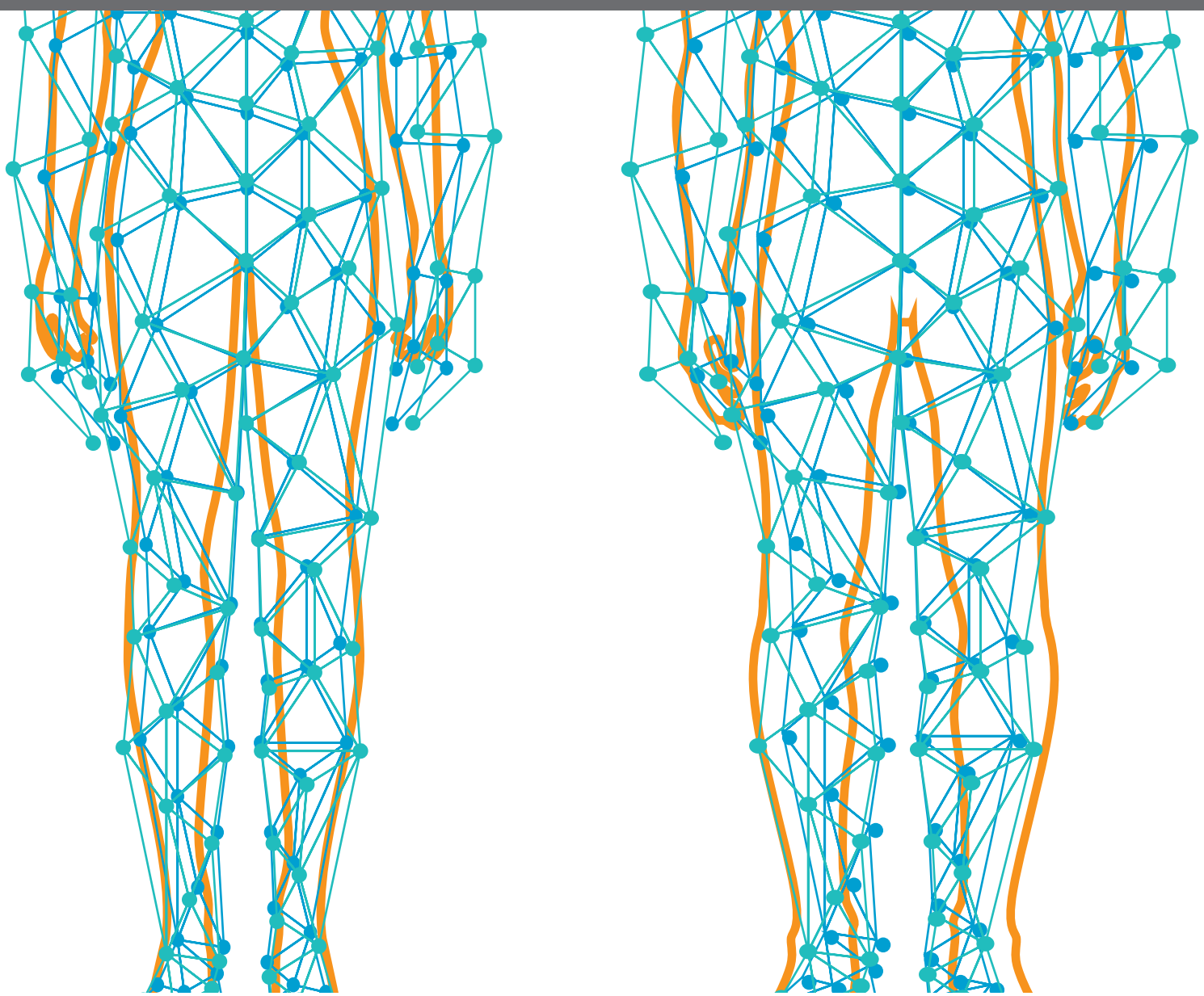
UPDATE ON STEVENS JOHNSON SYNDROME

EDITED BY: Jodhbir Mehta, Mayumi Ueta and Shigeru Kinoshita
PUBLISHED IN: Frontiers in Medicine



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ISSN 1664-8714
ISBN 978-2-88974-314-8
DOI 10.3389/978-2-88974-314-8

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UPDATE ON STEVENS JOHNSON SYNDROME

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Citation: Mehta, J., Ueta, M., Kinoshita, S., eds. (2022). Update on Stevens Johnson Syndrome. Lausanne: Frontiers Media SA.
doi: 10.3389/978-2-88974-314-8

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frontiers in Medicine

EDITORIAL
published: 22 December 2021
doi: 10.3389/fmed.2021.811570

Editorial: The Updated Understanding of Stevens-Johnson Syndrome and Toxic Epidermal Necrolysis

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Keywords: Stevens-Johnson Syndrome (SJS), toxic epidermal necrolysis (TEN), severe ocular complications (SOC), human leukocyte antigen (HLA), international collaboration

Editorial on the Research Topic

The Updated Understanding of Stevens-Johnson Syndrome and Toxic Epidermal Necrolysis

Stevens-Johnson Syndrome (SJS) is an acute inflammatory vesiculobullous reaction of the skin and mucosa, including the ocular surface, oral cavity, and genitals. In SJS patients with extensive skin detachment and a poor prognosis, the condition is called toxic epidermal necrolysis (TEN). The treatment of both SJS and TEN is extremely difficult, and in fact, in our Ophthalmology Residency Program in the 1970s, we were instructed that there was currently no surgical or medical treatment for visual disturbance of patients afflicted with SJS/TEN. However, for corneal specialists, proper treatment of the devastating SJS/TEN-associated ocular surface disorder is vital. Depending on the drugs and infections involved, SJS/TEN is not always accompanied by severe ocular complications (SOC). However, the subgroup of SJS/TEN develops SOC due to corneal epithelial stem cell deficiency at the acute phase, thus resulting in severe visual impairment that prolongs into the chronic phase as well. The corneal opacity in SJS/TEN cases cannot be treated with regular corneal transplantation due to the ocular-surface stem cell deficiency and the proliferative changes caused by postoperative inflammation. Thus, when in search of a treatment for such devastating ocular surface disorders that cannot be treated with regular corneal transplantation, the use of several surgical strategies, such as keratoprosthesis (1), have been tried. In 2002, our team developed a new treatment method for cases with severe ocular surface disorders, known as Cultivated Oral Mucosal Epithelial Transplantation (COMET) (2). In SJS/TEN patients with severe visual impairment, treatment with COMET might provide a novel pathway toward the improvement of vision and overall quality of life. Recently, we developed a limbal-supported hard contact lens for use after the COMET procedure (3), which we found improved the patient's visual acuity. Hence, patients with SJS/TEN (which is an extremely rare disease) with SOC are now visiting the Department of Ophthalmology at Kyoto Prefectural University Hospital from all over Japan for treatment.

Previously, research on SJS/TEN was primarily conducted by dermatologists, as they are the clinical specialists who treat SJS/TEN patients in the acute phase in many countries, including Japan, Taiwan, Korea, and Europe. However, ophthalmologists also treated chronic SJS/TEN patients with ocular sequelae, such as the visual impairment that exists throughout their lives. Hence, we ophthalmologists have now joined with dermatologists in a nationwide Japanese SJS/TEN Study Group to deepen our understanding on SJS/TEN patients with and without SOC, complications that can lead to ocular sequelae in the chronic phase. Quite surprisingly, this partnership has allowed us to more deeply understand SJS/TEN-related ocular sequelae, as well

Edited and reviewed by:
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Specialty section:
This article was submitted to Ophthalmology, a section of the journal Frontiers in Medicine

Received: *09 November 2021*
Accepted: *17 November 2021*
Published: *22 December 2021*

Citation:
Kinoshita S and Ueta M (2021) Editorial: The Updated Understanding of Stevens-Johnson Syndrome and Toxic Epidermal Necrolysis. Front. Med. 8:811570. doi: 10.3389/fmed.2021.811570

as the overall condition and quality-of-life setbacks that SJS/TEN patients endure. Moreover, we discovered that not all SJS/TEN patients are afflicted with SOCs, such as severe conjunctivitis with ocular-surface persistent epithelial defects and pseudomembrane formation in the acute phase. To that regard, in collaboration with the Japanese Research Committee on Severe Cutaneous Adverse Reaction, our findings revealed that ∼80% of all SJS/TEN patients had experienced conjunctivitis, and that ∼50% of all SJS/TEN patients have experienced severe conjunctivitis with ocular surface epithelial defects and/or pseudomembrane formation (4).

A dermatological study revealed that anticonvulsants (i.e., carbamazepine, etc.) and anti-gout drugs like allopurinol were critical causative agents for SJS/TEN (5). However, when we performed detailed interviews with SJS/TEN patients with SOC who attended our hospital about their condition at the onset of SJS/TEN, we found that only about 5% of those patients had developed SJS/TEN after taking anticonvulsants, and that almost none of the patients had developed SJS/TEN after taking allopurinol. Moreover, our human leukocyte antigen (HLA) typing analysis findings of Japanese SJS/TEN patients with SOC, which showed that *HLA-A*02:06* and *HLA-B*44:03* was significantly associated with those complication (6), were also completely different from the HLA types reported in the above-mentioned dermatological study; i.e., carbamazepine-induced SJS/TEN manifested a very strong association with the *HLA-B*15:02* allele in Taiwanese Han Chinese patients (7), and with the *HLA-A*31:01* allele in Japanese (8) and European patients (9), and that allopurinol-induced SJS/TEN was strongly associated with *HLA-B* 58:01* in Han Chinese (10), Caucasian (11), and Japanese patients (12). Hence, we have now come to realize that SJS/TEN patients with SOCs might actually constitute a subgroup of all SJS/TEN patients treated by dermatologists, and have focused our attention on SJS/TEN patients with SOC at the acute phase and ocular sequelae at the chronic phase by investigating the epidemiology, causative agents, and associated pathogenesis.

Surprisingly, in 2009 we discovered that the average age at disease onset of the SJS/TEN patients with ocular sequelae treated at our hospital was 26 years (13), which is about 20 years younger than the average age at disease onset reported by dermatologists in 2007 (14). Moreover, disease onset in ∼80% of our SJS/TEN patients with SOC occurred after taking cold medicine, such as multi-ingredient medications including acetaminophen and non-steroidal anti-inflammatory drugs (NSAIDs), thus indicating that the causative drugs for SJS/TEN with SOC might be unique. Furthermore, in SJS/TEN patients in which the disease is caused by antiepileptic drugs or allopurinol, onset can occur 2 weeks after administration of the causative drug. In cold medicine-related SJS/TEN with SOC, onset can occur within 1 week after taking the medication. Thus, we now theorize that SJS/TEN with SOC might be a subgroup of the overall SJS/TEN population. However, it has been challenging to obtain an international consensus of our concept, because the world's leading dermatologists on SJS/TEN have yet to embrace of finding that cold medicine can cause SJS/TEN. Moreover, a leading dermatological group has argued that the onset of SJS/TEN within a few days after the administration of cold medicine was more likely due to an infection, and not the medication (5).

Hence, we subsequently developed an international collaboration with ophthalmologists who have treated SJS/TEN patients with SOC in order to demonstrate that our concept is both appropriate and acceptable. Fortunately, the COMET procedure developed by our group has now been used to some extent worldwide, and many ophthalmologists now perform the procedure for the treatment of SJS/TEN with SOC. Initially, we began collaboration on causative agents and genetic predisposition of SJS/TEN with SOC in Korea, followed by Brazil and India. As we proceeded with these international collaborations, we were selected for the International Research Center Formation Project Core-to-Core Program A; Advanced Research Networks, funded by JSPS (the Japan Society for the Promotion of Science). Using this research funding, we have now expanded our international collaborations and have been holding the annual "International Stevens-Johnson Syndrome Symposium" in Japan since 2016. At present, in addition to Korea, Brazil, and India, we collaborate on this project with Thailand, Taiwan, the United Kingdom, the United States, and Singapore. Moreover, we not only collaborate with ophthalmologists, but also basic scientists in the field of genomic analysis and immunologists to elucidate the genetic predisposition and pathogenesis of SJS/TEN. We also hold discussions with dermatologists to further elucidate the difference between SJS/TEN with SOCs and without SOCs.

In this way, the International Stevens-Johnson Syndrome Symposium has now brought together not only ophthalmologists and dermatologists, but also epidemiologists, genomic researchers, immunologists, and researchers from other medical fields. We discuss the advanced current clinical treatment, epidemiology, genetic predisposition, and pathogenesis of ophthalmic SJS/TEN, which now greatly enhances our knowledge and improves the level of understanding about ophthalmic SJS/TEN worldwide.

In conclusion, this special issue consists of many mini-reviews from our collaborators showing their advanced research results; i.e., the clinical aspect of SJS/TEN with SOCs in each country (i.e., in Japan, Korea, Taiwan, Thailand, Singapore, India, the United States, and the United Kingdom), from the pathological and genomic aspects of SJS/TEN with SOC. It is our hope that this special issue will raise the level of understanding of SJS/TEN throughout the world, and we hope that it will contribute to the further elucidation of the pathogenesis of ophthalmic SJS/TEN, including its genetic predisposition, and the future development of novel treatment modalities.

AUTHOR CONTRIBUTIONS

All authors listed have made a substantial, direct, and intellectual contribution to the work and approved it for publication.

FUNDING

This work was supported by grants-in-aid from the Ministry of Education, Culture, Sports, Science, and Technology of

the Japanese government, by the JSPS Core-to-Core Program, A. Advanced Research Networks, and partly supported by grants-in-aid for scientific research from the Japanese Ministry of Health, Labor, and Welfare.

ACKNOWLEDGMENTS

The authors acknowledge Mr. John Bush for his editing service.

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frontiers in Medicine

MINI REVIEW
published: 22 February 2021
doi: 10.3389/fmed.2021.640360

Clinical Aspects of Stevens-Johnson Syndrome and Toxic Epidermal Necrolysis With Severe Ocular Complications in South Korea

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OPEN ACCESS

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Specialty section:
This article was submitted to Ophthalmology, a section of the journal Frontiers in Medicine

Received: 11 December 2020
Accepted: 22 January 2021
Published: 22 February 2021

Citation:
Kim MK, Yoon KC, Yoon SH and Seo KY (2021) Clinical Aspects of Stevens-Johnson Syndrome and Toxic Epidermal Necrolysis With Severe Ocular Complications in South Korea. Front. Med. 8:640360. doi: 10.3389/fmed.2021.640360

This review describes the current knowledge regarding genetic susceptibilities and treatment strategies for Stevens-Johnson syndrome (SJS) and toxic epidermal necrolysis (TEN), with ocular complications, in Korea. In a case-control study, the gene frequencies of both HLA-A∗0206 (20.0%) and HLA-Cw∗0304 (15.0%) increased but the gene frequency of HLA-Cw∗0303 (1.3%) decreased with cold medicine (CM)-SJS/TEN with severe ocular complications (SOCs). In a case-series, positive genotyping of HLA-B∗5801 was 80.0% in allopurinol-induced SJS/TEN without SOCs. In a genome-wide association study, HLA-A∗0206 was substantially related to CM-SJS/TEN with SOCs. Both HLA-A∗0206 and prostaglandin-E receptor 3 (PTGER3) single nucleotide polymorphism (SNP) rs1327464 exert a synergistic effect on SOCs in CM-SJS/TEN. In the acute stage, conventional procedures, amniotic membrane transplantation or suture-less amniotic contact lenses are applied. Applications of intravenous Immunoglobulin (IVIG) or mega-dose steroids are attempted in patients with high acute ocular and systemic involvement scores. In the chronic stage, keratolimbal transplantation and penetrating keratoplasty are the standard procedures. Either autologous nasal or oral mucosal grafts, or biomaterial-free cultured oral mucosal epithelial cell sheets are transplanted as alternative therapies. Deep anterior lamellar keratoplasty is attempted. Combined photodynamic therapy with intrastromal bevacizumab injection or intense pulse laser are used to resolve chronic ocular complication. Corneoscleral contact lenses are available for a visual rehabilitation. As a last resort, Seoul-type keratoprosthesis had been transplanted. There are unmet needs to standardize nationwide ocular grading system and to correct tarsal scarring using mucosal grafting. This review provides a perspective on the current practices to treat ocular complications in SJS/TEN.

Keywords: HLA-A∗0206, HLA-B∗5801, HLA-Cw∗0303, HLA-Cw∗0304, South Korea, Stevens-Johnson syndrome

INTRODUCTION

Steven-Johnson syndrome (SJS) and its severe form, toxic epidermal necrolysis (TEN), are severe, inflammatory vesiculobullous reactions of the skin and mucous membranes. The mortality rate of SJS and TEN are estimated as 1–10%, and 30%, respectively. According to the Korean National Health Insurance Database, SJS and TEN are infrequent, yet they constantly occur throughout the year by showing 3.96 and 0.94 cases per million/year for SJS and TEN, respectively (1). The management of SJS/TEN imposes a considerable clinical and financial burden, which is comparable with that of other major health problems (1, 2). SJS/TEN may permanently damage the affected mucosa, inducing severe sequelae including the lungs, genitals and eye. During primary intervention, acute ocular involvement occurs in approximately 60–100% of SJS/TEN patients (3–5). In Korea, ocular complications are reported as the most common complication related to SJS/TEN (1). Patients with ocular complications spent a considerable amount of money even after their recovery (2).

It is well known that SJS/TEN can be induced by various infections or classes of pharmacological agents, such as antibiotics, anticonvulsants, nonsteroidal anti-inflammatory drugs (NSAIDS), or allopurinol (6). Among the culprit drugs, as reported in a nationwide study, anticonvulsants are most frequent, followed by allopurinol, amoxicillin/dorzolamide, and acetaminophen (6). Previous pharmacogenomic studies demonstrated that certain human leukocyte antigen (HLA) genotypes could induce T-cell activation in response to a specific drug (7, 8). In a nationwide study that enrolled 5,802 Korean patients, allele frequencies of HLA-A∗0206, HLA-B∗5801, HLA-Cw∗0303, and HLA-Cw∗0304 were reported to be 10.3, 7.0, 10.9, and 9.1%, respectively (9). Specific genetic risk factors play an important role in the development of SJS/TEN. Recently, a genome-wide association study (GWAS) with a single nucleotide polymorphism (SNP) microarray has been employed to detect an association between SNPs and SJS/TEN (10, 11).

This review describes the current knowledge on the clinical aspect and treatment strategies for SJS/TEN, with ocular complications, in Korea. We summarized the HLA genotypes and the associated drugs for Koreans responsible for severe ocular complications (SOCs) in the acute and chronic stage of SJS/TEN, and elaborated upon the treatment strategies.

OVERVIEW OF CAUSATIVE DRUGS AND GENETIC PREDISPOSITION IN KOREAN PATIENTS WITH SJS/TEN WITH SOCs

Regarding frequencies of the culprit medications related with SOCs in Korea, cold medicine is the highest frequency, but antibiotics, allopurinol, or anti-epileptic drugs are not related to SOCs (12).

Allopurinol

Allopurinol, a xanthine oxidase inhibitor, has been widely used to manage hyperuricemia and gout. Several studies report a strong association of the HLA-B∗5801 genotype and allopurinol-induced SJS/TEN among Koreans (7–13%) (13–15). A recent study revealed that HLA-B75, DR13 homozygosity, or DR-14 increased the risk of allopurinol-induced SJS/TEN when combined with HLA-B∗5801, especially in patients with impaired renal function (14, 16). Compared to other drugs, allopurinol-induced SJS/TEN was associated with longer and more severe systemic manifestations, resulting in a high mortality rate (15); however, allopurinol-induced SJS/TEN may not cause serious acute or chronic ocular surface complications (12, 17). In a case-series, HLA-B∗5801 genotype was observed in 80.0% of allopurinol-induced SJS/TEN without SOCs (17).

Anti-epileptic Drugs

In a nationwide registry-based study, the most common causative AEDs were carbamazepine, lamotrigine, and levetiracetam (18, 19). In the case of AEDs-induced SJS/TEN, aromatic AEDs (e.g., carbamazepine, lamotrigine) were greatly associated with a severe reaction than non-aromatic AEDs (e.g., valproic acids) (19). It may be caused that AEDs containing an aromatic ring can form an arene-oxide intermediate, resulting in a hypersensitivity reaction (19). HLA-B∗1502, which is closely related to SJS/TEN, is very rare in Koreans (7, 20). Several HLA genes are weakly associated with AEDs-induced hypersensitivity syndrome in the Korean population, but not with SJS/TEN (7, 20). Ocular manifestations are relatively mild in AEDs-induced SJS/TEN (12).

Cold Medicine

Cold medicine (CM), including NSAIDS and acetaminophen, is relatively safe; however, it can trigger SJS/TEN in patients with suspected viral infection mediated by T-cells and monocytes (12, 21). SJS/TEN with severe ocular complications (SOCs) are commonly associated with CM in the Korean population (10, 22–25). In GWAS, HLA-A∗0206 was considerably related to CM-SJS/TEN with SOCs (22). In addition, both HLA-A∗0206 and prostaglandin-E receptor 3 (PTGER3) single nucleotide polymorphism (SNP) rs1327464 exert synergistic effect in CM-SJS/TEN with SOCs (23). A recent multicenter case-control study suggested that HLA-Cw∗0304 may also be a positive marker for CM-SJS/TEN with SOCs; however, HLA-Cw∗0303 may be an indicator of protection against this disease in the Korean population (24). In a worldwide GWAS that enrolled Korean, Japanese, Indian, and Brazilian patients, *IKAROS family zinc-finger 1* (IKZF1) was revealed as a novel susceptibility gene (meta-analysis, rs4917047) for CM-SJS/TEN with severe mucosal involvement (25).

Carbonic Anhydrase Inhibitors

Surprisingly, both topical and oral formulations of CAIs, such as acetazolamide, methazolamide, and dorzolamide, can induce SJS/TEN (6, 26). HLA-B∗5901 genotype, which occurs in 2.1% of the Korean population, has been suggested as a genetic marker for CAIs-induced SJS/TEN (27, 28). CAIs-induced SJS/TEN results in more extensive cutaneous manifestations and frequent ocular sequelae when compared with SJS/TEN due to other

drugs including allopurinol, anticonvulsants, or anti-tuberculosis drugs (29).

Other Drugs

Antibiotics such as amoxicillin/clavulanate and cephalosporin are the most common causative drugs in pediatric patients with SJS/TEN (30). However, there is no report stating that antibiotics may be related to SOCs (12). The anti-human immunodeficiency virus agents including abacavir and nevirapine could induce a hypersensitive reaction associated with HLA-B∗5701 (7). However, HLA-B∗5701 is not a clinically critical allele, since it is rare in Koreans (31).

TREATMENT STRATEGY IN KOREAN PATIENTS WITH SJS/TEN WITH SOCs IN THE ACUTE STAGE

General supportive care with anti-inflammatory intervention is the mainstay to restore barrier function of the skin and mucous membrane, and fluid balance, and to treat the infection (3, 10). The Korean severe cutaneous adverse drug reactions (SCARs) registry includes patients who were diagnosed with SJS and TEN (18, 32). Ocular involvement was in the ranges of 34–43% in Korea (1, 30). Therefore, therapeutic approaches to SJS/TEN should be multidisciplinary (3, 10). In Korea, patients with SJS/TEN are usually referred to the ophthalmologists upon presenting with complaints of ocular symptoms during hospitalization. Given that there is window of time within which vision-saving treatments can be applied, ophthalmologic consultation upon admission or within 24–48 h after diagnosis is critical (3, 10). The concept of a multidisciplinary approach, including eye care, should be shared with a primary physician.

There are local and systemic interventions to treat ocular complications in the acute stage of SJS/TEN (3, 10, 33, 34). As local treatments, aggressive lubrication, mechanical membrane removal/synechiolysis, bandage contact lens (CL) placement, and topical antibiotics and steroid application are implemented (3). Preservative-free artificial tears are instilled every 1–2 h and eyedrops containing hyaluronate are preferred in epithelial defected ocular surface. All membranes should be mechanically removed (33). However, there is no consensus about how often either membrane removal or synechiolysis be conducted since cotton-tip application can induce mechanical trauma. The benefits of mechanical synechiolysis should be cautiously weighed against the intervention-induced inflammation. One percentage topical prednisolone acetate combined with antiseptic eyedrops containing fluoroquinolone are preferably applied. 0.5–1.5% levofloxacin or 0.5% moxifloxacin eyedrops are administered three to four times a day. Topical 1% prednisolone acetate is administered every 2–3 h depending on the severity. High-oxygen-transmissible silicone hydrogel CL with medium water content (35–46%) such as Acuvue Oasys, Acuvue Advance, and PureVision are available to cover corneal epithelial defects (35).

Although there is no worldwide consensus on a grading system to assess severity of acute ocular involvement in SJS/TEN, new grading systems are currently being proposed (34, 36, 37). Sotozono et al. proposed a grading scale of 0–3 using three parameters, including conjunctival hyperemia, ocular surface epithelial defect, and pseudomembrane (36). Gregory et al. proposed four grading scales based on the presence of epithelial defected area with three parameters, including conjunctiva, cornea, and lid margin (37). In French, they reached a nationwide consensus on a diagnostic grading system for acute ocular complications that consists of three stages of severity using seven parameters (34). In Korea, we have not reached a consensus yet on grading system for acute ocular complications. The authors working with the international collaboration network of ocular SJS/TEN led by Kinoshita currently use the grading scales proposed by Sotozono (17, 38). Therefore, a nationwide consensus on the grading system to evaluate acute ocular complications should be established.

Amniotic membrane transplantation (AMT) is a standardized procedure for the severe acute ocular complication. AMT within the first 7–10 days can potentially avoid vision-threatening chronic complications (33, 37, 39). The indication of AMT includes (1) any corneal epithelial defect, (2) staining of the eyelid margin > 1/3 of its length, or (3) any conjunctival staining >1 cm at its greatest diameter and/or (4) pseudomembrane formation (33, 37, 39). There are two studies reporting the effect of AMT on visual improvement or SOCs in SJS/TEN in Korea (38, 40). One of the reports had presented the beneficial effect of AMT on visual improvement and SOCs (40). On the contrary, the other report showed that AMT was related with a poor final visual outcome; however, it did not mention when the AM was transplanted (38). AMT in the latter study may not be a timely treatment. The AMT technique to cover the whole ocular surface including fornix and the eyelid was recently standardized using the symblepharon ring and lid bolsters (39, 41, 42). In Korea, a similar technique of AMT was adapted. For a bedside application, ProKera is available in western countries (43), whereas suture-less amniotic membrane patch with a silicone ring (44) or suture-less amniotic CL is available in Korea. Effect of amniotic CL on wound healing was comparable to that of AMT *in vivo* study (**Figure 1A**, **Supplementary Video 1**) (45). However, the size of the amniotic CL is just enough to cover the cornea.

Systemic anti-inflammatory treatment is of utmost importance in reducing inflammation for both the body and the eye. So far, the effect of systemic intravenous immunoglobulin (IVIG) or mega-dose steroids on SOCs has been the subject of debate (38). In Korea, IVIG or mega-dose steroids are sometimes used for treatment of patients with high acute ocular and systemic involvement (38). A recent SCAR registry-based study showed that most of the patients have been treated with systemic steroid with an average maximal dose of 60 mg/day (18). Additionally, 87.5, 0.6, and 11.8% of the patients were treated using systemic steroids, IVIG, and both systemic steroids and IVIG, respectively (18); whereas, 49, 17, and 28% of the pediatric patients received systemic steroids, IVIG, and both systemic steroids and IVIG, respectively (30). It revealed that pediatric patients were more treated with IVIG compared to adults (18, 30). Considering

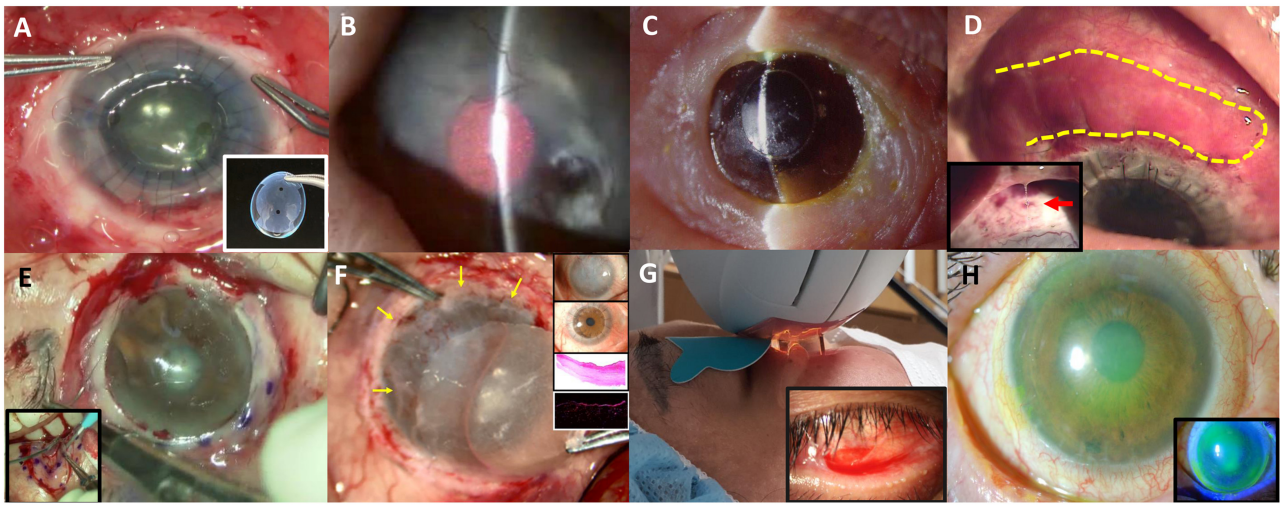

FIGURE 1 | Various non-surgical and surgical modalities to treat ocular complications in Stevens-Johnson syndrome or Toxic epidermal necrosis are introduced. **(A)** Commercially available suture-less amniotic contact lens. **(B)** Photodynamic therapy with verteporfin combined with intrastromal bevacizumab injection. **(C)** Seoul-type keratoprosthesis. **(D)** Autologous nasal mucosal grafting (yellow-highlighted) combined with penetrating keratoplasty and keratolimbal allografting. A thick mucus is often secreted by the nasal mucosal graft (red arrow).* **(E)** Circumferential autologous oral labial mucosal grafting. **(F)** Biomaterial-free cultured oral mucosal epithelial cell sheets (COMECs) transplantation (yellow arrows) with H&E and K13 immunofluorescent staining. **(G)** Intense pulsed light. **(H)** Corneoscleral contact lens.

that children with SJS/TEN have higher ocular and systemic complications than adults do (46, 47), such a treatment pattern may be reasonable. Combined treatment of IVIG and systemic steroids may be beneficial to reduce both SOCs and systemic complications.

TREATMENT STRATEGY IN KOREAN PATIENTS WITH SJS/TEN WITH SOCS IN THE CHRONIC STAGE

Complex ocular sequelae, such as symblepharon, lid malformation, trichiasis, conjunctival keratinization, limbal stem cell deficiency, corneal pannus, and dry eye occur in the chronic stage in patients with SJS/TEN. The goal of treatment in the chronic stage is the preservation of visual function, and reduction of the inflammation and persistent discomfort. Herein, surgical and medical interventions that have been currently practiced in Korea are presented (**Table 1** and **Figure 1**).

Medical Intervention Strategies

Chronic inflammation has been controlled by various medical interventions, such as serum eyedrops, topical or systemic steroid, and immunosuppressants. Autologous serum eye drops contain many anti-inflammatory molecules and are effective in reducing inflammation on the ocular surface (54); however, the components of serum eye drops may differ depending on the general condition of the patient. Steroid is effective but has undesirable adverse effects including glaucoma, cataract, infection, and delayed wound healing (55). Topical 0.02% tacrolimus ointment, originally approved for dermatologic purpose, is a good alternative to topical steroid (56). Topical 0.02% tacrolimus ointment was added to treat refractory chronic conjunctival inflammation in six SJS patients with tapering of the topical steroid (56). Topical tacrolimus decreased surface inflammation, corneal neovascularization, and intraocular pressure within 4 weeks (56).

Additionally, infection of the ocular surface should be closely monitored especially in SJS/TEN with SOCs. Unlike healthy people who show a high diversity of ocular microbiomes with prevalent streptococcus and lactobacillus, staphylococcus is a predominant bacteria with a less diversity with SJS, which can become easily pathogenic (57). A report in Korea presented higher rate of infective keratitis (35%) in LSCD with SJS than in those with a chemical burn (18%) (58). The higher the score of chronic ocular complications is, the more frequently infective keratitis develops in SJS (58).

Besides, tear film is unstable and meibomian gland is dysfunctional by the sequelae of SJS, and the degrees of meibomian gland disease tend to be correlated with the severity of SJS (59). Intense pulsed light is used to improve meibum expressibility (**Figure 1G**) (60). It contributes to decreased inflammatory cytokines such as IL-4,−6,−10, 17A, and TNF-α. IPL can be applied to stabilize tear film and reduce inflammatory cytokines, thereby treating severe meibomian gland obstruction in SJS.

Finally, corneoscleral CL with a total diameter of 14.0 mm is available for non-surgical visual rehabilitation in Korea (61). Fitting of a corneoscleral CL improved the vision by reducing corneal punctate erosions and reconstructing a new optical surface in six of eight SJS patients (**Figure 1H**) (61).

TABLE 1 | The clinical outcomes of various surgical interventions to treat chronic limbal stem cell deficiency in Korean SJS/TEN patients.

First author (reference)	Enrolled patients (*N*)	Indications	Surgery	Success* ≥ 6 Ms (%)	Visual improvement† (%)	Mean FU (Ms) after surgery
Han E. S. (48)	6	LSCD (± symblepharon)	KLAL (±PKP/AMT)	33.3	66.7	49.5
Choi S. E. (47)	3‡	LSCD	KLAL + PKP	33.3	NA	NA
Wee S. W. (49)	2	Failed previous PKP + corneal ulcer/opacification**	DALK + AMT (±additional PKP)	100	100	15
Kim M. K. (50)	6	Total LSCD + corneal opacity/symblepharon	S-KPro implantation	100	100††	46.8ξ
Chun Y. S. (51)	1	Total LSCD + corneal opacity/symblepharon	Autologous nasal mucosal grafting + PKP/KLAL	100	100	20
Choi H. R. (52)	4	Total or partial LSCD + corneal opacity (±symblepharon)	Autologous oral labial mucosal grafting (±PKP)	75	100	11
Kim Y. J. (53)	6	Total LSCD + corneal opacity	COMECs transplantation (±PKP)	83.3	66.7	8.8

AMT, Amniotic membrane transplantation; COMECs, Biomaterial-free cultured oral mucosal epithelial cell sheets; DALK, Deep anterior lamellar keratoplasty; FU, follow-up; KLAL, Keratolimbal allograft; LSCD, Limbal stem cell deficiency; Ms, Months; N, Number; NA, not available data; PKP, penetrating keratoplasty; SJS, Stevens-Johnson syndrome; S-KPro, Seoul-type keratoprosthesis; TEN, Toxic epidermal necrolysis.

**Success; Success has been defined as the cornea has been well maintained without persistent epithelial defect at least 6 months after the surgery.*

†*Visual improvement has been defined as at least one-line increase of post-operative best corrected visual acuity during the follow-up compared with pre-operative best corrected visual acuity.*

‡*Children SJS/TEN.*

***This study did not mention whether LSCD was present or not.*

††*The visual improvement has been assessed only in 3 SJS patients after exclusion of the other three patients who had a previous amblyopia, glaucoma, or retinal detachment.*

ξ*Primary retention time of S-KPro.*

The Outcome of Surgical Interventions

Intense immunologic reactions destruct limbal stem cells. Subsequently, corneal pannus occurs due to the loss of the limbal barrier function. Despite a high risk of rejection, keratolimbal allograft (KLAL) and penetrating keratoplasty (PKP) are standard procedures for visual rehabilitation. The clinical outcomes of various surgical interventions to treat chronic limbal stem cell deficiency (LSCD) in Korean SJS/TEN patients are shown in **Table 1**.

Eyes with SJS demonstrated a 33.3% of short-term success rate (≥6 months) and 16.7% of long-term success rate (≥2 years) in KLAL, which showed the least success rate among patients with LSCD (48). In children with SJS/TEN, LSCD developed in 32%, and combined PKP with KLAL failed in two (67%) out of three children (47). Deep anterior lamellar keratoplasty was attempted using acellular cornea with AMT in two eyes with previous failed PKP (49). One of them kept the cornea clear with epithelization. The other eye which needed additional PKP showed no additional corneal opacity (49). Photodynamic therapy with verteporfin combined with intrastromal bevacizumab injection was also applied to reduce corneal neovascularization (**Figure 1B**) (62). Within 6 months, five of eight eyes showed complete regression and the remaining eyes showed partial regression (62). In a few cases, Seoul-type keratoprosthesis (S-KPro) had been transplanted (**Figure 1C**) (50, 63). In the six S-KPro-implanted eyes of SJS, mean retention and visual preservation time was 46.8 and 35 months, respectively. To correct conjunctival keratinization with symblepharon or a LSCD, mucosal grafting has been attempted. A report presented successful reconstruction of the ocular surface and visual improvement by autologous nasal mucosal grafting accompanied with PKP and KLAL in a patient with SJS (**Figure 1D**) (51). Another report revealed visual improvement with a stable ocular surface by circumferential autologous oral labial mucosal grafting at the limbus in all four SJS patients (**Figure 1E**) (52). Recently, biomaterial-free cultured oral mucosal epithelial cell sheets (COMECs) transplantation has proven some efficacy on an LSCD in a clinical trial (**Figure 1F**) (53). Although the initial migration of the oral mucosal epithelial cells harvested from SJS patients (SJS-cells) was delayed with lower levels of epidermal growth factor and higher levels of vascular endothelial growth factor, compared to those of non-SJS cells, *in vivo* transplanted SJS-COMECs revealed similar expression of cytokeratin and stem cell markers as in non-SJS COMECs (64, 65). COMECs were transplanted in six SJS patients, and five eyes achieved complete reepithelization in a mean follow-up of 10.2 months (53). Among those five eyes, visual acuity was improved in four eyes with/without PKP (53).

Although the outcomes of various surgical interventions to treat LSCD cannot be directly compared due to different indications and follow-up periods (**Table 1**), autologous nasal or oral mucosal grafting, COMEC transplantation seem to show better successful outcome with visual improvement compared with that in KLAL. Meanwhile, first S-KPro implantation showed long-term successful outcome with visual improvement (50). However, due to skirt exposure, secondary exchange of S-KPro was mandatory in all S-KPro implanted patients (50). Given that retinal detachment developed in all S-KPro-exchanged eyes

within 2 months (50), S-KPro implantation can be considered as a last resort. In Korea, less attention is paid to correction of scarring of the tarsal conjunctiva and lid malformation in SJS patients. There have been no reports regarding the reconstruction of tarsal scarring using a mucosal grafting in SJS yet.

DISCUSSION

In Korea, about 40% of the SJS/TEN patients suffer from chronic ocular complications. HLA-A∗0206 combined with PTGER3 SNP rs1327464 enhances genetic susceptibility in CM-SJS/TEN with SOCs, whereas HLA-C∗03:03 may be an indicator of protection against CM-SJS/TEN with SOCs. For the timely treatment of acute ocular complications, a nationwide consensus on ocular grading system should be reached, and a multidisciplinary approach including ophthalmologists should be standardized in Korea. In the chronic stage, various innovative surgical and medical modalities have been attempted to restore vision and stable ocular surface. Notably, both oral and nasal mucosal grafting as well as COMECs transplantation hold the most promise in the treatment of LSCD of Korean patients with SJS/TEN at present. However, the enrolled patient numbers were too small and the follow-up was too short to verify the long-term clinical efficacy. Therefore, large scale study with long-term follow-up should be further conducted. This review provides insightful information about genetic predisposition and current strategies to treat ocular complications of SJS/TEN in Korean population and gives us a perspective on how to improve current practice.

AUTHOR CONTRIBUTIONS

MK: conceptualization, data curation, formal analysis, investigation, methodology, resources, visualization, and roles/writing—original draft. KY: conceptualization, data curation, formal analysis, investigation, methodology, resources, and roles/writing—original draft. SY: data curation, formal analysis, investigation, visualization, and writing—editing. KS: conceptualization, formal analysis, supervision, validation, and writing—review and editing. All authors contributed to the article and approved the submitted version.

FUNDING

This research was supported by Korea Mouse Phenotyping Project (NRF-2013M3A9D5072551) from the Ministry of Science and ICT through the National Research Foundation.

ACKNOWLEDGMENTS

Yeoun Sook Chun provided a photograph in **Figure 1D**. A photograph (**Figure 1A**, bottom) and the **Supplementary Video 1** were provided by MS bio Inc. (Seoungnam-si, Korea).

SUPPLEMENTARY MATERIAL

The Supplementary Material for this article can be found online at: https://www.frontiersin.org/articles/10.3389/fmed.2021.640360/full#supplementary-material

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Conflict of Interest: The authors declare that the research was conducted in the absence of any commercial or financial relationships that could be construed as a potential conflict of interest.

The handling editor declared a past co-authorship with several of the authors MK, KY, and KS.

frontiers in Medicine

MINI REVIEW
published: 24 March 2021
doi: 10.3389/fmed.2021.644154

Implementation of Pharmacogenomic Information on Stevens-Johnson Syndrome and Toxic Epidermal Necrolysis

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Drug-related Stevens-Johnson syndrome and toxic epidermal necrolysis (SJS/TEN) are rare but severe adverse drug reactions, termed as idiosyncratic reactions; however, predicting their onset remains challenging. Pharmacogenomic information associated with SJS/TEN has accumulated on several drugs in the last 15 years, with clinically useful information now included on drug labels in several countries/regions or guidelines of the Clinical Pharmacogenetics Implementation Consortium (CPIC) for implementation. However, label information might be different among countries. This mini-review summarizes pharmacogenomic information on drug labels of five drugs in six countries and compared descriptions of drug labels and CPIC guidelines. Finally, we discuss future perspectives of this issue. Pharmacogenomic information on drug labels is not well-harmonized across countries/regions, but CPIC guidelines are a scientifically sound goal for future pharmacogenomic implementation.

Keywords: Stevens-Johnson syndrome, toxic epidermal necrolysis, pharmacogenomics, implementation, drug label, guideline

OPEN ACCESS

Edited by:
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Specialty section:
This article was submitted to Ophthalmology, a section of the journal Frontiers in Medicine

Received: *20 December 2020*
Accepted: *18 February 2021*
Published: *24 March 2021*

Citation:
Tsukagoshi E, Tanaka Y and Saito Y (2021) Implementation of Pharmacogenomic Information on Stevens-Johnson Syndrome and Toxic Epidermal Necrolysis. Front. Med. 8:644154. doi: 10.3389/fmed.2021.644154

INTRODUCTION

Stevens-Johnson syndrome (SJS) and toxic epidermal necrolysis (TEN) are rare but life-threatening, severe adverse drug reactions. SJS and TEN are characterized as fever and mucosal disorders (such as at the mouth and ocular conjunctiva) and are reactions within the same spectrum (1, 2). Skin lesions often exhibit epidermal necrosis, resulting in skin detachment such as erosion and blisters. Top 5 common causative drugs were reported to be carbamazepine, allopurinol, phenytoin, lamotrigine and sulfamethoxazole in Asians and allopurinol, carbamazepine, sulfamethoxazole, phenytoin and phenobarbital in Europeans (3). In Japan, diagnostic classification is defined as follows: SJS; skin detachment area <10% of the body surface area; TEN, not <10% of the body surface area (4), with the associated mortality estimated at 1–5% and 20–30%, respectively (5, 6). Hence, they are considered the most important severe adverse reactions from a pharmacovigilance standpoint and in terms of patient relief. However, they are called idiosyncratic reactions, and predicting their onset has remained challenging.

In 2004, Chung et al. reported a markedly strong association between *HLA-B**15:02* and carbamazepine-related SJS (7). To date, pharmacogenomic information associated with SJS/TEN has accumulated on several drugs. Accordingly, clinically useful pharmacogenomic information, as well as and their application, are included on drug labels in several countries/regions or guidelines of the Clinical Pharmacogenetics Implementation Consortium (CPIC). However, label information

may differ among countries. This mini-review summarizes the pharmacogenomic information on drug labels of allopurinol, carbamazepine, oxcarbazepine, phenytoin, and fosphenytoin in six countries/regions.

ALLOPURINOL

Allopurinol is used as a urate-lowering drug and frequently causes severe cutaneous adverse reactions (SCARs), including SJS/TEN (8–10). The frequency of allopurinol-related SCARs is estimated to be 0.1–0.4%. The *HLA-B*58:01* allele is a strong predictor for allopurinol-related SCARs and the population/ethnic frequency of this *HLA* allele is relatively high among Asians and Africans (4–18%), but low in Hispanics, Europeans, and Japanese populations (<1.5%).

On the EU label, the Special Warnings and Precautions section describes that the *HLA-B*58:01* allele is associated with the risk of developing allopurinol-related hypersensitivity syndrome and SJS/TEN, and screening for *HLA-B*58:01* should be considered before initiating treatment in patient subgroups where the prevalence of this allele is known to be high (**Table 1**). A similar statement is presented in the (Special) Warnings and Precautions section of the Australian and Singaporean labels. The Japanese label shows only the facts from reported papers in the Other Precautions subsection of the Side-Effects section owing to the very low frequency of the variant allele when compared with that observed in Han Chinese. In contrast, no pharmacogenomic description is stated in the US and Canadian labels. The Warnings section of the US drug label states that the drug should be discontinued at the first appearance of skin rash or other signs that may indicate an allergic reaction. A similar description is presented in the Warnings section of the Canadian label.

The "CPIC Guideline for Allopurinol and HLA-B" recommends that allopurinol is contraindicated for *HLA-B*58:01* carriers [**Table 2**; (9, 10)]. Non-carriers of *HLA-B*58:01* are considered to have a low risk for SCARs. Several clinical non-genetic factors, including renal dysfunction and high-dose allopurinol, have also been associated with the risk of allopurinol hypersensitivity. Furthermore, the CPIC guideline warns that *HLA-B*58:01* predicts only allopurinol-related SCARs, not other skin reactions such as rash, and this allele marker does not predict the efficacy. Moreover, this guideline recommends that physicians should monitor patients closely, regardless of the genotyping results. Some candidate genetic factors, including *HLA-A*33:03* and *HLA-C*03:02*, may be associated with allopurinol-related SCARs, but CPIC did not include these factors in the guideline as the strength of evidence was not achieved for inclusion. Importantly, the guideline recommends that allopurinol should not be prescribed to patients who have tested positive for *HLA-B*58:01*. Moreover, patients positive for *HLA-B*58:01* should be treated with alternative drugs. This guideline suggests that a non-purine xanthine oxidase inhibitor, febuxostat, is available as an alternative to allopurinol hypersensitivity. The CPIC guideline also proposes that the patients' pharmacogenetic information must be incorporated into electronic health records to guide physicians' decisions, including drug selection.

CARBAMAZEPINE AND OXCARBAZEPINE

The antiepileptic carbamazepine is known to occasionally induce SCARs, with a markedly strong association observed between carbamazepine- and oxcarbazepine-induced SJS/TEN and *HLA-B*15:02* (11–14). *HLA-B*15:02* is common in East Asians (6.9%), Oceanians (5.4%), and South/Central Asians (4.6%), whereas these are <1% in individuals of other Asians, Caucasians and African Americans. *HLA-A*31:01* is another risk factor for carbamazepine-related SJS/TEN and other SCARs, including drug reactions with eosinophilia and systemic symptoms (DRESS), and even milder skin reactions such as maculopapular exanthema (MPE). The population frequency of *HLA-A*31:01* is relatively high in Japanese (8%), South Koreans (5%), and Hispanic/South Americans (6%), but relatively low in South/Central Asians (2%), Caucasians (3%), and African-Americans (1%). In addition to the above two *HLA* alleles, *HLA-B*57:01* was reported to confer genetic susceptibility to carbamazepine-induced SJS/TEN in Europeans (15).

The Boxed Warnings section of the US label shows that *HLA-B*15:02* is almost exclusively detected in patients with ancestry across broad areas of Asia (at-risk populations), who should be screened for *HLA-B*15:02* before initiating treatment. *HLA-B*15:02*-positive patients should not be treated with carbamazepine unless the benefit undoubtedly outweighs the risk. Regarding *HLA-A*31:01*, the Warnings section indicates that positive patients should weigh the risks and benefits before commencing treatment with carbamazepine. On the EU label, the Special Warnings and Precautions section indicate that prescreening for *HLA-B*15:02*, whenever possible, should be performed for populations with a high frequency of this allele, such as Han Chinese and Thai, and carbamazepine should not be prescribed to *HLA-B*15:02*-positive patients. Carbamazepine may be used in *HLA-A*31:01*-positive European and Japanese patients if the benefits outweigh the risks. On the Canadian label, the two *HLA* alleles are described in the Boxed Serious Warnings section presenting recommendations for physicians' consideration of *HLA-A*31:01* and *HLA-B*15:02* genotyping as a screening tool in genetically at-risk populations. On the Australian label, the Special Warnings and Precautions section states that prior testing for *HLA-A*31:01* and *HLA-B*15:02* alleles should be considered in patients with an ancestry of genetically at-risk populations. On the Singaporean label, testing for the *HLA-B*15:02* allele is highly recommended before initiation of carbamazepine therapy in new patients of Asian ancestry, whereas testing for the *HLA-A*31:01* allele should be considered in patients of these at-risk populations, which are described in the Warnings and Precautions section. Only the facts from the reported papers are described in the Japanese label for both alleles in the Other Precautions subsection of the Side Effects section.

Cross-sensitivity has been reported among various antiepileptic drugs and is commonly seen in patients receiving

TABLE 1 | Description of pharmacogenomic information in the five drug labels of the United States, European Union (EU) or the United Kingdom (UK), Canada, Australia, Singapore, and Japan.

Drugs	Biomarker	US	EU or UK	Canada	Australia	Singapore	Japan
Allopurinol	*HLA-B*58:01*	**(Warnings)** •This drug should be discontinued at the first appearance of skin rash or other signs which may indicate an allergic reaction. •In some instances a skin rash may be followed by more severe hypersensitivity reactions such as exfoliative, urticarial, and purpuric lesions, as well as SJS (erythema multiforme exudativum), DRESS and/or generalized vasculitis, irreversible hepatotoxicity, and, on rare occasions, death.	**(EU, Special Warnings and Precautions for Use)** •The *HLA-B*5801* allele is reportedly associated with the risk of developing allopurinol related hypersensitivity syndrome and SJS/TEN. •Screening for *HLA-B*5801* should be considered before starting treatment with allopurinol in patient subgroups where the prevalence of this allele is known to be high.	**(Warnings)** •Allopurinol should be discontinued immediately at the appearance of a skin rash, as the rash may be, in some instances, followed by a more severe hypersensitivity reaction, including SJS, DRESS, and TEN.	**(Special Warnings and Precautions for Use)** •The *HLA-B*5801* allele is known to be associated with the risk of developing allopurinol related hypersensitivity syndrome and SJS/TEN. •Screening for *HLA-B*5801* should be considered before starting treatment in patient subgroups where the prevalence of this allele is known to be high.	**(Warnings and Precautions)** •The *HLA-B*5801* allele is reportedly associated with the risk of developing allopurinol related hypersensitivity syndrome and SJS/TEN. •Screening for *HLA-B*5801* should be considered before starting treatment with allopurinol in patient subgroups where the prevalence of this allele is known to be high.	**(Side Effects/Other Precautions)** •A previous report has presented the association of *HLA-B*5801* and SJS/TEN in Han Chinese, Japanese and European populations. •Allele frequency of *HLA-B*5801* in Japanese and European population is very low (0.010–0.020) when compared with that in Han Chinese (0.20–0.30).
Carbamazepine	*HLA-B*15:02*	**(Boxed Warnings)** •*HLA-B*1502* is found almost exclusively in patients with ancestry across broad areas of Asia. •Patients with ancestry in genetically at-risk populations should be screened for the presence of *HLA-B*1502* prior to initiating treatment with carbamazepine. •Patients testing positive for the allele should not be treated with carbamazepine unless the benefit clearly outweighs the risk.	**(EU, Special Warnings and Precautions for Use)** •Whenever possible, these individuals should be screened for this allele before starting treatment with carbamazepine or chemically-related active substances. •If patients of these ethnic origins are tested positive for *HLA-B*1502* allele, the use of eslicarbazepine acetate may be considered if the benefits are thought to exceed risks.	**(Boxed Serious Warnings and Precautions)** •The *HLA-B*1502* allele is found almost exclusively in individuals with ancestry across broad areas of Asia. •Recommended that physicians consider *HLA-B*1502* genotyping as a screening tool in genetically at-risk populations. •Until further information is available, the use of carbamazepine and other antiepileptic drugs associated with SJS/TEN should be avoided in patients who test positive for the *HLA-B*1502* allele.	**(Special Warnings and Precautions for Use)** •Testing for the presence of *HLA-B*1502* allele should be considered in patients with ancestry in genetically at-risk populations, prior to initiating treatment with carbamazepine. •The use of carbamazepine should be avoided in tested patients who are found to be positive for *HLA-B*1502* unless the benefits clearly outweigh the risks.	**(Warnings and Precautions)** •Testing for the presence of *HLA-B*1502* allele is highly recommended prior to the initiation of carbamazepine therapy in new patients of Asian ancestry. •The use of carbamazepine should be avoided in tested patients who are found to be positive for *HLA-B*1502* unless the benefits clearly outweigh the risks.	**(Side Effects/Other Precautions)** •Citing a paper showing association of *HLA-B*1502* and SJS/TEN in Han Chinese populations. •Allele frequency of *HLA-B*1502* in Japanese population is very low (0.001) compared to that in Han Chinese (0.019–0.124)

(Continued)

TABLE 1 | Continued

Drugs	Biomarker	US	EU or UK	Canada	Australia	Singapore	Japan
	*HLA-A*31:01*	**(Warning)** •The risks and benefits of carbamazepine therapy should be weighed before considering carbamazepine in patients known to be positive for *HLA-A*3101*.	**(EU, Special Warnings and Precautions for Use)** •There are insufficient data supporting a recommendation for *HLA-A*3101* screening before starting carbamazepine or chemically-related compounds treatment. •If patients of European descent or Japanese origin are known to be positive for *HLA-A*3101* allele, the use of carbamazepine or chemically-related compounds may be considered if the benefits are thought to exceed risks.	**(Boxed Serious Warnings and Precautions)** •Recommending that physicians consider *HLA-A*3101* genotyping as a screening tool in genetically at-risk populations. •Until further information is available, the use of carbamazepine and other antiepileptic drugs associated with SJS/TEN should be avoided in patients who test positive for the *HLA-A*3101* allele.	**(Special Warnings and Precautions for Use)** •Testing for the presence of *HLA-A*3101* allele should be considered in patients with ancestry in genetically at-risk populations, prior to initiating treatment with carbamazepine. •The use of carbamazepine should be avoided in patients who are found to be positive for *HLA-A*3101*, unless the benefits clearly outweigh the risks.	**(Warnings and Precautions)** •Testing for the presence of *HLA-A*3101* allele should be considered in patients with ancestry in genetically at-risk populations prior to initiating treatment with carbamazepine. •The use of carbamazepine should be avoided in patients who are found to be positive for *HLA-A*3101*, unless the benefits clearly outweigh the risks.	**(Side Effects/Other Precautions)** •Citing a paper showing association of *HLA-A*3101* and severe cutaneous adverse reactions in Japanese. •Allele frequency of *HLA-A*3101* in Japanese population is relatively high (0.071–0.120).
Oxcarbazepine	*HLA-B*15:02*	**(Warnings)** •Patients who have had hypersensitivity reactions to carbamazepine should be informed that approximately 25–30% patients with reactions are known to experience hypersensitivity reactions with oxcarbazepine. •If signs or symptoms of hypersensitivity develop, oxcarbazepine should be discontinued immediately.	**(UK, Warnings and Precautions)** •The risk of serious skin reactions in patients of Han Chinese or Thai origin associated with carbamazepine or chemically-related compounds may be predicted by testing a blood sample from these patients. •Your doctor should be able to advise if a blood test is necessary before taking oxcarbazepine.	**(Boxed Warnings and Precautions)** •The *HLA-B*1502* allele is found almost exclusively in individuals with ancestry across broad areas of Asia. •It is therefore, recommended that physicians consider *HLA-B*1502* genotyping as a screening tool in genetically at-risk populations. •Until further information is available, the use of oxcarbazepine and other anti-epileptic drugs associated with SJS/TEN should be avoided in patients who test positive for the *HLA-B*1502* allele.	**(Special Warnings and Precautions for Use)** •As the chemical structure of oxcarbazepine is similar to that of carbamazepine, there is a possibility that patients carrying the *HLA-B*1502* allele also have an increased risk of SJS/TEN skin reactions with oxcarbazepine. •Testing for the presence of the *HLA-B*1502* allele should be considered in patients with an ancestry of genetically at-risk populations, prior to initiating treatment with oxcarbazepine. •The use of oxcarbazepine should be avoided in tested patients who are found to be positive for *HLA-B*1502* unless the benefits clearly outweigh the risks.	Not approved	**(Boxed Warnings/Side Effects/Other Precautions)** •Patients treated with oxcarbazepine may present the appearance of severe cutaneous adverse reactions such as TEN, SJS, and DIHS. •A report showing allele frequency of *HLA-B*1502* and *HLA-A*3101* in Japanese population.

(Continued)

TABLE 1 | Continued

Drugs	Biomarker	US	EU or UK	Canada	Australia	Singapore	Japan
	*HLA-A*31:01*	•Included in the above section.	•Included in the above section.	**(Boxed Warnings and Precautions)** •Retrospective genome-wide studies in Japanese and Northern European populations reported an association between severe skin reactions (SJS, TEN, DRESS, AGEP, and maculopapular rash) associated with carbamazepine use and the presence of the *HLA-A*3101* allele in these patients.	**(Special Warnings and Precautions for Use)** •As the chemical structure of oxcarbazepine is similar to that of carbamazepine, there is a possibility that patients carrying the *HLA-A*3101* allele also have an increased risk of SJS/TEN skin reactions with oxcarbazepine.		•Included in the above section.
Phenytoin	*HLA-B*15:02*	**(Warnings and Precautions)** •*HLA-B*1502* may be a risk factor for the development of SJS/TEN in patients of Asian ancestry taking other antiepileptic drugs associated with SJS/TEN, including phenytoin. •Consideration should be given to avoiding phenytoin as an alternative for carbamazepine in patients positive for *HLA-B*1502*.	**(UK, Special Warnings and Precautions for Use)** •*HLA-B* 1502* may be a risk factor for the development of SJS/TEN in patients of Asian ancestry taking drugs associated with SJS/TEN, including phenytoin. •Consideration should be given to avoiding the use of drugs associated with SJS/TEN, including phenytoin, in *HLA-B*1502* positive patients when alternative therapies are otherwise equally available.	**(Warnings and Precautions)** •The *HLA-B*1502* allele is found almost exclusively in individuals with ancestry across broad areas of Asia. •Physicians should consider *HLA-B *1502* genotyping as a screening tool in these patients. •The use of phenytoin and other anti-epileptic drugs associated with SJS/TEN should also be avoided in patients who test positive for the *HLA-B*1502* allele.	**(Special Warnings and Precautions for Use)** •*HLA-B*1502* may be a risk factor for developing SJS/TEN in patients of Asian ancestry taking drugs associated with SJS/TEN, including phenytoin. •Consideration should be given to avoiding the use of drugs associated with SJS/TEN, including phenytoin, in *HLA-B*1502*-positive patients when alternative therapies are otherwise equally available.	**(Special Warnings and Precautions for Use)** •*HLA-B*1502* may be a risk factor for the development of SJS/TEN in patients of Asian ancestry taking drugs associated with SJS/TEN, including phenytoin. •Consideration should be given to avoiding the use of drugs associated with SJS/TEN, including phenytoin, in *HLA-B*1502*-positive patients when alternative therapies are otherwise equally available.	**(Side Effects)** •Patients treated with phenytoin may present the appearance of severe cutaneous adverse reactions such as TEN and SJS.

(Continued)

TABLE 1 | Continued

Drugs	Biomarker	US	EU or UK	Canada	Australia	Singapore	Japan
Fosphenytoin	*HLA-B*15:02*	**(Warnings and Precautions)** •Consider avoiding fosphenytoin as an alternative to carbamazepine in patients who are positive for *HLA-B*1502* or in *CYP2C9*3* carriers. •Fosphenytoin should be utilized for *CYP2C9*3* carriers; consider starting at the lower end of the dosage range.	**(UK, Special Warnings and Precautions for Use)** •Fosphenytoin can cause SCARs such as AGEP, exfoliative dermatitis, SJS, TEN and DRESS which can be fatal. •Limited evidence suggests that *HLA-B*1502* may be a risk factor for the development of SJS/TEN in patients of Asian ancestry taking drugs associated with SJS/TEN, including phenytoin.	**(Warnings)** •The *HLA-B*1502* allele is found almost exclusively in individuals with ancestry across broad areas of Asia. •Physicians should consider *HLA-B *1502* genotyping as a screening tool in these patients. •Until further information is available, the use of fosphenytoin and other anti-epileptic drugs associated with SJS/TEN should also be avoided in patients who test positive for the *HLA-B*1502* allele.	Not approved	Not approved	**(Side Effects)** •Patients treated with fosphenytoin may present the appearance of severe cutaneous adverse reactions such as TEN and SJS.

AGEP, acute generalized exanthematous pustulosis; DIHS, drug-induced hypersensitivity syndrome; DRESS, drug reaction with eosinophilia and systemic symptoms; SCAR, severe cutaneous adverse reactions; SJS, Stevens-Johnson syndrome; TEN, toxic epidermal necrolysis.

TABLE 2 | Recommendations for therapy based on genotype in CPIC guideline.

Drugs	Genotype	Therapeutic recommendation
Allopurinol	*HLA-B*58:01*	Allopurinol is contraindicated.
Carbamazepine Oxcarbazepine	*HLA-B*15:02* positive	If a patient is carbamazepine- or oxcarbazepine-naïve, do not use both drugs. Optional If a patient has previously used carbamazepine or oxcarbazepine consistently for longer than 3 months without the incidence of cutaneous adverse reactions, cautiously consider the use of carbamazepine or oxcarbazepine.
Carbamazepine	*HLA-B*15:02* negative and *HLA-A*31:01* positive	If a patient is carbamazepine-naïve and alternative agents are available, do not use carbamazepine. Optional If the patient is carbamazepine-naïve and alternative agents are unavailable, consider the use of carbamazepine with increased frequency of clinical monitoring. Discontinue therapy at the first evidence of a cutaneous adverse reaction. If a patient has previously used carbamazepine consistently for longer than 3 months without the incidence of cutaneous adverse reactions, cautiously consider the use of carbamazepine.
Phenytoin Fosphenytoin	*HLA-B*15:02* positive	If the patient is phenytoin naïve, do not use phenytoin/fosphenytoin.
	*HLA-B*15:02* negative	
	CYP2C9 intermediate metabolizer (**1/*3*, **2/*2*)	Consider a 25% reduction of the recommended starting maintenance dose. Subsequent maintenance doses should be adjusted according to therapeutic drug monitoring and response.
	CYP2C9 poor metabolizer (**2/*3*, **3/*3*)	Consider a 50% reduction of the recommended starting maintenance dose. Subsequent maintenance doses should be adjusted according to therapeutic drug monitoring and response.

CPIC, Clinical Pharmacogenetics Implementation Consortium.

aromatic antiepileptic drugs. Oxcarbazepine is a keto-analog of carbamazepine, with a similar structure, sharing several therapeutic indications and adverse effects with carbamazepine. The *HLA-B*15:02* allele is strongly associated with a greater risk of SJS and TEN in patients treated with oxcarbazepine (14, 16). The Boxed Warnings and Precautions section of the Canadian label recommend that physicians consider *HLA-B*15:02* genotyping as a screening tool in genetically at-risk populations. For *HLA-A*31:01*, retrospective genome-wide studies in Japanese and Northern European populations reported an association between severe skin reactions (SJS, TEN, and other SCARs) related to carbamazepine use and the presence of the *HLA-A*31:01* allele in these patients. The Special Warnings and Precautions section of the Australian label states that prior testing for *HLA-B*15:02* alleles should be considered in patients presenting an ancestry of genetically at-risk populations. For *HLA-A*31:01*, as the chemical structure of oxcarbazepine is similar to that of carbamazepine, there is a possibility that patients carrying the *HLA-A*31:01* allele also possess an increased risk of SJS/TEN skin reactions with oxcarbazepine. In contrast, the Warnings section of the US label only states, without description regarding *HLA* alleles, that the drug should be immediately discontinued at the appearance of signs or symptoms of hypersensitivity, as ∼25–30% of patients who have had hypersensitivity reactions to carbamazepine will experience hypersensitivity reactions with oxcarbazepine. On the UK label, the Warnings and Precautions section indicates that patients with a risk of serious skin reactions, including Han Chinese and those of Thai origin, should be advised if a blood test is necessary before taking oxcarbazepine. The Boxed Warnings of the Japanese label describes that the drug may result in the appearance of SCARs such as TEN, SJS, and drug-induced hypersensitivity syndrome (DIHS) as the chemical structure of oxcarbazepine is similar to that of carbamazepine.

The CPIC guideline for carbamazepine and oxcarbazepine recommends carbamazepine- or oxcarbazepine-naïve patients who are *HLA-A*15:02*-positive should avoid both drugs owing to the high risk of SJS/TEN unless the benefits outweigh the risk [**Table 2**; (13, 14)]. Patients without *HLA-B*15:02* could be prescribed standard therapy according to standard dosing guidelines. For selecting other drugs, limited evidence is available regarding the association between *HLA-B*15:02* and other aromatic anticonvulsants, and caution is needed when selecting an alternative drug. *HLA-B*15:02* testing helps to reduce the incidence of carbamazepine- or oxcarbazepine-induced SJS/TEN and select an appropriate treatment. The positive predictive value for carbamazepine-related SJS/TEN was higher than that for oxcarbazepine, and the negative predictive values for both drugs were 100%. Thus, negative test results provide valuable information to determine the use

of carbamazepine or oxcarbazepine. *HLA-B*15:02* is included in HLA-B75 serotypes, with other haplotypes in the HLA-B75 serotype presenting similar structures; moreover, the CPIC guideline states the necessity to consider the potential risk if this information is available. Carbamazepine-naïve patients with *HLA-A*31:01* should avoid carbamazepine owing to the high risk of SCARs, including SJS/TEN (**Table 2**). Other anticonvulsants, including lamotrigine, oxcarbazepine, eslicarbazepine, phenytoin, fosphenytoin, and phenobarbital, present limited evidence regarding the association of SCAR onset with *HLA-A*31:01*. Therefore, these drugs are not recommended as alternative drugs in *HLA-A*31:01*. If alternative drugs are unavailable for patients with *HLA-A*31:01*, CPIC guidelines propose considering the use of carbamazepine with a high frequency of clinical monitoring, discontinuing therapy at the first evidence of a cutaneous adverse reaction. Carbamazepine- and oxcarbazepine-related SJS/TEN usually develops within the first 4–28 days of therapy, and patients who have been administering these drugs for more than 3 months are at low risk regardless of *HLA-B*15:02* and *HLA-A*31:01* status.

PHENYTOIN AND FOSPHENYTOIN

Phenytoin is a widely prescribed antiepileptic drug that can cause cutaneous adverse reactions, ranging from a mild rash to SCARs, including DRESS, SJS, and TEN. *HLA-B*15:02* is associated with phenytoin-related SJS/TEN in Asian populations (17–19). The *HLA-B*15:02* carrier increased the risk of SJS/TEN, and this association has reported a sensitivity of 36.6% and specificity of 87.2%. Instead, non-carriers of *HLA-B*15:02* are considered low risk but can potentially develop phenytoin-related SJS/TEN. The frequency of *HLA-B*15:02* is more common in Oceanic and Asian populations than in European and African populations (see above section). In addition to the *HLA* allele, the genotype of *CYP2C9*, a major metabolizing enzyme for phenytoin, is associated with phenytoin-related SJS/TEN. Some activity-decreasing or no function genetic variants of *CYP2C9*, i.e., **2* and **3*, increase the probability of phenytoin-related toxicities. *CYP2C9*2* is classified as a decreased function allele, and **3* is classified as a no function allele in the CPIC guideline (18, 19). In that, individuals with "one decreased or no function + one function alleles" or "two decreased function alleles" (**1/*2*, **1/*3*, and **2/*2*) are classified as intermediate metabolizers, and those with "two no function alleles" or "one no functional + one decreased function alleles (**2/*3* and **3/*3*) are classified as poor metabolizers. The frequencies of *CYP2C9*2* and **3* differ among racial and ethnic groups, commonly observed in European and Hispanic populations (>5%). Fosphenytoin, a prodrug of phenytoin, is mostly metabolized to phenytoin within 2 h.

The Warnings and Precautions section of the US label states that patients positive for *HLA-B*15:02* should avoid phenytoin and fosphenytoin as an alternative to carbamazepine as *HLA-B*15:02* may be a risk factor for the development of SJS/TEN in patients of Asian ancestry administering other antiepileptic drugs. In the UK, Canadian, Singaporean, and Australia, a similar description is present on phenytoin labels in the Special Warnings and Precautions section. The Warnings and Precautions section of the Canadian label recommends that physicians consider *HLA-B*15:02* genotyping as a screening tool. Only the reported facts are described in the Japanese label, stating that the drug may result in the appearance of SCARs such as TEN and SJS. No description for *CYP2C9* alleles was present on drug labels of any country/region. Regarding fosphenytoin, only the UK and Canadian labels describe *HLA-B*15:02*.

The CPIC guideline recommends that an *HLA-B*15:02* carrier should not use phenytoin and fosphenytoin if the patient is phenytoin-naïve (18, 19). The guideline also recommends the re-initiation of phenytoin with caution in patients who have previously used phenytoin/fosphenytoin for longer than 3 months without the incidence of cutaneous adverse reactions. The CPIC guideline recommends that the phenytoin/fosphenytoin starting dose is reduced by at least 25% for *CYP2C9*1/*3* and **2/*2* intermediate metabolizers and 50% for poor metabolizers (**2/*3* and **3/*3*), with subsequent maintenance dose adjustment based on therapeutic drug monitoring (**Table 2**). The guideline further shows the algorithm for the dose based on *HLA-B*15:02* and *CYP2C9* genotypes, recommending the decision of phenytoin/fosphenytoin use based on the *HLA-B*15:02* genotype, followed by adjusting the initial dose by the *CYP2C9* genotype. The guideline proposes that patients' pharmacogenetic information must be incorporated into electronic health records to guide physicians' decisions.

OTHER DRUGS

Sulfone drugs, e.g., dapsone, sulfamethoxazole, and salazosulfapyridine (sulfasalazine), are used for infectious and inflammatory diseases. These drugs sometimes cause hypersensitivity, and HLA alleles have been reported as the risk factors for hypersensitivity in Asian population. *HLA-B*13:01* was significantly associated with dapsone-related hypersensitivity syndrome in Chinese population (20). *HLA-B*13:01* was also significantly associated with salazosulfapyridine-induced DRESS in Chinese Han population (21). Co-trimoxazole (CTX), the sulfamethoxazole-trimethoprim combination drug, has been known to cause SCARs, and *HLA-B*15:02* and *HLA-C*08:01* were significantly associated with CTX-induced SJS/TEN, and *HLA-B*13:01* was associated with CTX-induced DRESS in Thai population (22). Moreover, genome-wide association study in CTX hypersensitivity in collaboration of Taiwan, Thai and Malaysia confirmed that *HLA-B*13:01* was strongly associated with its SCARs (23). Recently, association between *HLA*11:01* and sulfonamide-related SCAR was shown in Japanese patients (24). Unfortunately, neither the drug labels containing pharmacogenomic information in six investigated countries/region nor CPIC guideline for this drug class has not been released.

Acetaminophen and non-steroidal anti-inflammatory drugs are often included in cold medicine (CM), and CM is known to sometimes induce SJS/TEN. Furthermore, acetaminophen was reported to be significantly related to severe ocular

involvements in SJS/TEN patients (25). *HLA-A*02:06* and *HLA-B*44:03* were associated with CM-related SJS/TEN with severe ocular complications (SOCs) in Japanese (26). The associations with *HLA-A*02:06* and *HLA-B*44:03* were also shown in Korean, and Indian, Brazilian and Thai populations, respectively (27, 28). By meta-analysis, *HLA-A*02:06*, *HLA-A*33:03*, *HLA-B*44:03,* and *HLA-C*05:01* were significantly associated with CM-induced SJS/TEN with SOCs (29). However, at least for the acetaminophen/paracetamol, no pharmacogenomic information are included in the labels of the six countries/region (although mentioned the risks of SJS/TEN) and no CPIC guideline are released.

DISCUSSION

Pharmacogenomic information is an important factor for predicting the onset of SJS/TEN in the three discussed drug types. Based on the comparison of drug labels in the US, EU/UK, Canada, Australia, Singapore, and Japan, their description is not well-harmonized, possibly because of differences in the population frequencies of risk alleles, availability of genetic testing, and coverage policies of public/private health insurance. In Japan, genetic testing is not commonly available for SJS/TEN and, in principle, most medical costs are covered by the national health insurance. Although situations tend to vary, CPIC guidelines are a scientifically sound goal for pharmacogenomic implementation. Further and periodical investigations on drug labels and guidelines are important to understand the current worldwide situation, as well as for policy determination regarding the description/utilization of pharmacogenomic information of SJS/TEN in each country.

AUTHOR CONTRIBUTIONS

All authors listed have made a substantial, direct and intellectual contribution to the work, and approved it for publication.

FUNDING

This study was supported by AMED under Grant Number 20mk01011173.

ACKNOWLEDGMENTS

We thank Ms. Chie Sudo for her secretarial assistance.

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Conflict of Interest: The authors declare that the research was conducted in the absence of any commercial or financial relationships that could be construed as a potential conflict of interest.

frontiers in Medicine

MINI REVIEW
published: 26 March 2021
doi: 10.3389/fmed.2021.644871

Associations Between Stevens–Johnson Syndrome and Infection: Overview of Pharmacoepidemiological Studies

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Stevens–Johnson syndrome and toxic epidermal necrolysis (SJS/TEN) are classified as type B adverse drug reactions, and are severe, potentially fatal rare disorders. However, the pathogenesis of SJS/TEN is not fully understood. The onset of SJS/TEN is triggered by the immune system in response to antigens with or by drugs. As activation of the immune system is important, infection could be a risk factor for the onset of SJS/TEN. Based on the hypothesis that infections induce the onset of SJS/TEN, we conducted pharmacoepidemiological investigations using two spontaneous adverse drug reaction reporting databases (Japanese Adverse Drug Event Report database and Food and Drug Administration Adverse Event Reporting System) and Japanese medical information database. These data suggest that infection could be a risk factor for the development of SJS/TEN. In this mini-review, we discuss the association between infection and the development of SJS/TEN.

Keywords: Stevens–Jonhson syndrome, toxic epidermal necrolysis, infection, pharmacoepidaemiology, real world evidence

OPEN ACCESS

Edited by:
Mayumi Ueta,
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Reviewed by:
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Specialty section:
This article was submitted to Ophthalmology, a section of the journal Frontiers in Medicine

Received: *22 December 2020*
Accepted: *04 March 2021*
Published: *26 March 2021*

Citation:
Imatoh T and Saito Y (2021) Associations Between Stevens–Johnson Syndrome and Infection: Overview of Pharmacoepidemiological Studies. Front. Med. 8:644871. doi: 10.3389/fmed.2021.644871

INTRODUCTION

Stevens–Johnson syndrome (SJS) and the related disease toxic epidermal necrolysis (TEN) are two of the most serious adverse reactions caused by drugs. SJS is characterized by high fever, malaise, and a rapidly developing, blistering exanthema of macular papules and target-like lesions, accompanied by mucosal involvement. According to the World Allergy Organizations (WAO) definition of 2014, SJS/TEN are defined by the degree of skin detachment: SJS/TEN are defined as skin involvement of <10 and >30%, respectively, and that of SJS/TEN overlap as 10–30% skin involvement.

SJS/TEN are known as idiosyncratic drug reactions. They are rare and unpredictable. Therefore, serious idiosyncratic drug reaction is one of the cause of withdrawal of drug from the market. SJS/TEN are rare but life-threatening severe cutaneous adverse reactions, which are mainly induced by a variety of drugs. SJS/TEN occur in all ages, races, and sexes (1), with incidences ranging from 0.4 to 1.2 and 1.2 to 6 per million person-years. A USA-based study analyzing nationwide inpatient records from 2009 to 2012 calculated an incidence per million inhabitants of 8.61–9.69 for SJS, 1.46–1.84 for SJS/TEN overlap, and 1.58–2.26 for TEN (2). Epidemiological studies have calculated a TEN incidence rate of 1.2 per 1 million inhabitants per year for France (3) and of 0.93 per 1 million inhabitants per year for Germany (4). However, Frey et al. recently estimated that

Asian patients were at a two-fold higher risk of SJS/TEN when compared with Caucasian patients (5). The incidence of SJS ranged from 3.3–4.1 per million people per year in Taiwan between 2000 and 2008 (6). Approximately 800–1,000 cases of SJS and 500–700 cases of TEN are reported annually in Japan (7).

Some drugs have been associated with the onset of SJS/TEN. Phenytoin, carbamazepine, and phenobarbital have been reported as common causes of SJS in a previous case control study (8). Additionally, sulfamethoxazol/trimethoprim, sulfonamides (sulfasalazine, sulfadiazine, sulfadoxine, and sulfafurazole) and oxicam-type non-steroidal anti-inflammatory drugs (NSAIDs) (meloxicam, piroxicam, and tenoxicam) are known to have a high risk of inducing SJS/TEN. A large proportion of suspected drug is comprised cold medicines. In particular, SJS/TEN with severe ocular complications (SOC) associated with cold medicine were reported in several studies (9, 10). In addition to conventional drugs, herbal remedies and new biologicals have been considered as causative agents. Recently, lamotrigine and zonisamide have been reported as major causative drugs of SJS/TEN (7).

The pathogenesis of SJS/TEN is not yet fully understood, but it is thought to be immune-mediated. The role of the T-cell-mediated immune response in the pathogenesis of SJS/TEN has been firmly established. In particular, the human leukocyte antigen (HLA) system plays an important role in the pathogenesis of SJS/TEN, as some drugs may bind directly to the HLA-complex and cause self-reactivity due to the drug-modified HLA-peptide repertoire (11). There are numerous reported associations between some *HLA* alleles and SJS/TEN (12–14).

In this mini-review, we have focused to analyze on infections, that is, the role of the immune response to viruses and bacteria in SJS/TEN. Previous studies have reported associations between some infections and the onset of SJS/TEN. However, most were clinical studies and case reports (15–19) with very few pharmacoepidemiological studies. Therefore, we conducted a pharmacoepidemiological study to elucidate the association between infection and SJS/TEN using the Japanese Adverse Drug Event Report (JADER) database. We also used the Food and Drug Administration (FDA) Adverse Events Reporting System (FAERS) database to compare these associations in the US, Europe, Japan, and other countries. Based on these findings, we discuss the association between infection and the development of SJS/TEN.

Results of a Pharmacoepidemiological Study Using the JADER Database

First, to elucidate the association between infection and SJS/TEN, we conducted a pharmacoepidemiological study using the JADER database (20).

JADER is a large published spontaneous reporting database for drug adverse reactions that was established by Japan's Pharmaceuticals and Medical Device Agency (PMDA) for pharmacovigilance activities. The dataset can be accessed directly on: http://www.info.pmda.go.jp/fukusayoudb/CsvDownload.jsp (available in Japanese only), and compose of four relational tables: DEMO, DRUG, REAC, and HIST. The tables contain the following information: demographic information of patients including, sex and age (DEMO table), drug information used in patients (DRUG table), adverse drug information that have occurred in patients (REAC table) and primary disease information (HIST table). Each table was connected using the ID number of each recorded case.

We used the November 2014 version of JADER and extracted the records of 177,659 cases of ADRs reported from 2009–2013. The reported cases were classified into three categories (anti-infectious drug group, concomitant infection group, and non-infection group) based on the presence of anti-infectious drugs (either as primary suspected drug or concomitant drug) and infectious disease. We defined the cases whose clinical outcome was "death," "unrecovered," or "with sequela" as severe. We assessed the association between SJS/TEN and the presence or seriousness of infection using logistic regression analysis. Logistic regression analysis showed a significant positive association between the infection status and onset of SJS/TEN compared to the non-infection group. Odds ratios (OR) were 2.04 [95% confidence interval (CI) (1.85–2.24)] for the anti-infectious drug group and 2.44 [95% CI (2.21–2.69)] for the concomitant infection group, respectively. Moreover, a significantly positive association between infection and SJS/TEN severity was observed [OR 1.48; 95% CI (1.10–1.98)]. These results suggest that SJS/TEN is strongly associated with infection in this Japanese dataset.

Results of a Pharmacoepidemiological Study Using a Japanese Medical Information Database

Spontaneous drug adverse reaction databases have considerable biases. Limited information is available in standardized spontaneous reports (21) and only a fraction of adverse drug events are identified and reported (22). There is a growing need for real-world data in medical and healthcare research. Big data in healthcare may be comprised of massive amounts of information from various sources, including electronic health records (EHRs), administrative or claims data, and data from self-monitoring devices. The utilization of electronic medical record databases for drug safety assessment has been extensively discussed (23–25). In Japan, a new medical information database network (designated MID-NET®) to provide real-world data for drug safety assessments was officially launched in April 2018 (26). This network was designed and developed by the Ministry of Health, Labor and Welfare, and the PMDA in collaboration with 23 hospitals of 10 healthcare organizations across Japan. Thus, real-world data is an important source of information for the detection of adverse drug reactions.

We used a medical information database in Japan to confirm the association between infection and the onset of SJS/TEN (27). We used commercial medical information data collected by Medical Data Vision (MDV Co., Ltd). The medical information database covers more than 30 million patients in more than 400 Japanese hospitals and includes health claims, pharmacy claims and the diagnosis procedure combination (DPC) data.

TABLE 1 | Odds ratios for the combination between antipyretic analgesics and infection in matched nested case control analysis of SJS/TEN.

			Cases		Controls		Crude		Adjusted*	
			n	%	*n*	%	OR	95% CI	OR	95% CI
Antipyretic analgesics/Infection	−	−	42	32.1	183	46.6	1.00	(Reference)	1.00	(Reference)
	−	+	18	13.7	58	14.8	1.61	(1.03–2.52)	1.13	(0.43–2.95)
	+	−	41	31.3	119	30.3	1.76	(0.75–4.11)	1.61	(1.00–2.61)
	+	+	30	22.9	33	8.4	7.42	(3.10–17.79)	5.59	(2.01–15.51)
CCI	Low (0–1)		77	58.8	294	74.8	1.00	(Reference)	1.00	(Reference)
	Medium (1–3)		37	28.2	68	17.3	2.22	(1.35–3.67)	1.55	(0.88–2.75)
	High (3+)		17	13.0	31	7.9	2.17	(1.14–4.13)	1.14	(0.42–2.49)
Corticosteroid use	No		65	49.6	308	78.4	1.00	(Reference)	1.00	(Reference)
	Yes		65	49.6	60	15.3	6.30	(3.80–10.44)	5.46	(3.20–9.32)

OR, odds ratio; 95% CI, 95% confidence interval; CCI, Charlson comorbidity index.

**Adjusted for Charlson comorbidity index and corticosteroid use.*

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Since antipyretic analgesics, including acetaminophen and loxoprofen sodium, are widely prescribed and are known as major suspected drugs for SJS/TEN (28), we conducted a matched nested case-control study to elucidate the association between concurrent infection and the onset of SJS/TEN in patients prescribed antipyretic analgesics. We used the data of 4,112,055 patients prescribing antipyretic analgesics between January 2014 and December 2015. The presence of International Classification of Diseases, 10th revision (ICD-10) codes for SJS/TEN (L511, L512) was defined as SJS/TEN. 553 (0.01%) were diagnosed with SJS/TEN. Among them, 131 patients who had been prescribed antipyretic analgesics during the month prior to the defined date of SJS/TEN onset were identified. Moreover, to minimize the impact of antibiotics agents, we excluded the patients who had been prescribed top 10 suspected antibiotics and viral and fungal agents (levofloxacin, clarithromycin, amoxicillin, galenoxacin, sefkapen, sulfamethoxazole/trimethoprim, azithromycin, ceftriaxone, cefditoren and vancomycin) during the month prior to the index date.

In a matched nested case-control study, for each case, three controls were randomly matched with the case for age at index date (onset of SJS/TEN) and sex. Infection was defined the diagnosis of infection (bacterial, viral, and fungal infection) during the month prior to the index date, which co-existed with one or more prescription claims for antibiotic agents (antibiotics-bacterial, virus, and fungal infection agents) in the same month. We calculated odds ratios and 95% CIs using conditional logistic regression to estimate the association between SJS/TEN and infection on patients prescribing antipyretic analgesics.

According to conditional logistic regression analysis, patients with infection and prescribing antipyretic analgesics had significantly increased the risk of onset of SJS/TEN [adjusted OR 5.59, 95% CI (2.01–15.51)] (**Table 1**). Similar to the results of our study using the JADER, It suggests that infection may increase the risk for the onset of SJS/TEN in patients taking antipyretic analgesics.

Results of a Pharmacoepidemiological Study Using FAERS

Based on both JADER and Japanese medical information databases, an association was found between infection and the onset of SJS/TEN. We next conducted a pharmacoepidemiological study using FAERS to elucidate the association between infection and the onset of SJS/TEN in other countries.

The FAERS database contains >14 million adverse event reports, medication error reports and product quality complaints resulting in adverse events that were submitted to the FDA in the USA and other countries and has increased to over 1.8 million reports per year. Case report information is separated into seven tables, which contain details on patient demographics and administrative information (DEMO), medication and biological products used (DRUG), adverse drug reactions (REAC), patient outcomes (OUTC), report sources (RPSR), drug therapy start and end dates (THER), and indication (INDI). The database is made publicly available as a quarterly download on the FDA website.

We obtained data from case reports received by the FDA between January 1, 2007 and June 30, 2017. Duplicate reports were removed, and drug names were modified based on modified World Health Organization (WHO) drug dictionaries. To identify infections, we used the DRUG and INDI files, which include two drug variables and an indications variable, defined as follows: (1) DRUG_CODE: code of medicinal product; (2) ROLE_COD: code for drug's reported role in event, and (3) INDI_PT: PT code of indications. We categorized infection into three categories, defined as follows: (1) primary suspected anti-infectious drug group, (2) concomitant infection group, and (3) non-infection group. We identified individual SJS/TEN based on the MedDRA (version 20.1) preferred terms in the FAERS database. The ORs and 95% CIs were calculated using logistic regression analysis.

We observed significant associations between infections and SJS/TEN in the US and England (**Table 2**). In particular, a strong association was observed in the US. [US: OR for primary suspected anti-infectious drug group 8.21, 95% CI

TABLE 2 | Odds ratios for the association between infection and SJS/TEN in the FAERS database.

		Cases	Non-cases	Odds ratio	(95% CI)
Japan	Anti-infectious drug	403	27,513	2.05	(1.81–2.33)
	Concomitant infection	361	23,517	2.04	(1.80–2.32)
	Non-infection	1,146	177,082	1.00	(Reference)
The United States	Anti-infectious drug	1,302	203,782	8.21	(7.60–8.87)
	Concomitant infection	526	182,813	3.69	(3.32–4.10)
	Non-infection	4,134	4,617,902	1.00	(Reference)
England	Anti-infectious drug	268	28,227	3.30	(2.82–3.87)
	Concomitant infection	215	21,021	3.35	(2.82–3.98)
	Non-infection	599	230,352	1.00	(Reference)
China	Anti-infectious drug	21	5,125	0.89	(0.53–1.48)
	Concomitant infection	13	2,019	1.13	(0.59–2.18)
	Non-infection	121	30,864	1.00	(Reference)
All countries (except Japan)	Anti-infectious drug	3,430	383,970	6.92	(6.59–7.28)
	Concomitant infection	2,129	318,665	4.73	(4.66–5.24)
	Non-infection	8,832	6,535,291	1.00	(Reference)

Adjusted for age (by 20-year-old class) and sex.
95% CI, 95% confidence interval.

(7.60–8.87), OR for concomitant infection group 3.69, 95% CI (3.32–4.10); England: OR for primary suspected anti-infectious drug group 3.30, 95% CI (2.82–3.87), OR for concomitant infection group 3.69, 95% CI (2.82–3.98)]. However, there was no association between infection and SJS/TEN in China. [OR for primary suspected anti-infectious drug group 0.89, 95% CI (0.53–1.48), OR for concomitant infection group 1.13, 95% CI (0.59–2.18)].

DISCUSSION

We consulted three medical databases JADER, a medical information database in Japan, and FAERS, to analyze the association between infection and SJS/TEN. Based on the available information, there appears to be a strong statistical association between infection and the onset of SJS/TEN, in Western countries, as well as in Japan.

Cutaneous diseases, including drug reactions, are increased up to 100-fold in persons with human immunodeficiency virus (HIV) (29). Infectious agents, such as a variant of Coxsackie virus A6 and *Mycoplasma pneumoniae*, have been previously reported to cause SJS/TEN (16, 30, 31). Furthermore, 56% of SJS patients had an antecedent upper respiratory tract infection or non-specific viral infection (19, 32). Recently, a study using microbiological analysis reported that a higher proportion of pathogenic microorganisms, including *Pseudomonas* spp., *Staphylococcus* spp., *Streptococcus* spp., and *Acinetobacter* spp., was observed in the SJS patient group (33). Meanwhile, several pharmacoepidemiological studies have reported that some classes of antibiotics are associated with the occurrence of SJS/TEN (3, 5, 34). Previous studies that used EHRs have reported that more than half of the SJS/TEN cases are attributed to antibiotics (35).

We found that the association between infection and SJS/TEN differed between countries. The frequency of HLA alleles differs among ethnicities. For example, HLA-B*1502 is common in East Asians (6.9%) (36), and the FDA recommends screening this allele in individuals of Asian ancestry before initiating treatment with carbamazepine.

SJS/TEN is thought to be a type IV hypersensitivity reaction, in which a drug or its metabolite stimulates cytotoxic T-cells and helper T cells. The specific molecular mechanisms driving this reaction have only been elucidated in a handful of cases, and the pathogenesis of SJS/TEN is not completely clear. Numerous studies have reported that HLA and T-cell receptors play an important role in the immune mechanisms of SJS/TEN. Several concepts have been proposed to explain the pathogenesis of severe cutaneous adverse drug reactions. In the hapten concept, small molecules called haptens elicit an immune response only when attached to proteins. The "p-i" concept postulates that the suspected drugs can stimulate cells by binding directly and reversibly to immune receptors. The altered peptide repertoire model suggests that drugs alter the antigen by binding to the human leukocyte antigen pocket. Recently, White et al. proposed that some T-cell mediated hypersensitivity reactions likely represent another example of heterologous immunity (37). Another possibility is that innate immunity-related molecules such as toll-like receptors might be activated by the infections and their involvement of specific immune reactions to the drug for SJS/TEN onset. The pathogenesis of SJS/TEN clearly requires further investigation.

There are many case reports and small sample-size clinical studies regarding the association between infection and SJS/TEN. Epidemiological studies with larger sample sizes are extremely rare. Although large-scale epidemiological studies have been performed in the United States, Europe, and Korea (5, 38, 39), little has been reported on the association between infection and SJS/TEN. We conducted large-scale epidemiological studies using Japanese medical data from spontaneous reporting adverse databases and medical information databases. While JADER or FAERS are useful to investigate the risk factors for adverse drug reactions, as the incidences of SJS and TEN are very rare, these databases have some inherent limitations. These limitations include underreporting, biased reporting rates, incomplete patient information, and indeterminate population exposure, and create the need for complementary data sources and methods (40). There are two major limitations that are unique to the FAERS database. First, the drug nomenclature consists of medication brands and trade names, generic or non-proprietary names, and chemical or scientific names with frequent misspellings. Second, there are a lot of duplicates and multiple follow-up reports

(41). Consequently, the interpretation of these findings requires careful consideration.

We also conducted an epidemiological study using a Japanese medical information database. The limitations of real-world evidence studies can include low internal validity, lack of quality control surrounding data collection, and susceptibility to multiple sources of bias for comparing outcomes. As these database were collected retrospectively, there may be some potential confounding factors that were not analyzed. In our medical information database study, even though the patients prescribing top 10 suspected antibiotics and viral and fungal agents in SJS/TEN were excluded, the significant association remained. However, it was not possible to completely distinguish whether the associations were caused by the infection, or were a direct consequence of the antibiotic agents. Hence, additional evidence is needed to elucidate the association between infection and SJS/TEN.

In summary, we reviewed our pharmacoepidemiological studies on the association between infection and SJS/TEN. These studies indicated that there is a strong association between infection and the onset of SJS/TEN, in Japan and other countries analyzed. Overall, infection may be an important risk factor for SJS/TEN worldwide.

AUTHOR CONTRIBUTIONS

All authors listed have made a substantial, direct and intellectual contribution to the work, and approved it for publication.

FUNDING

This study was supported by AMED under Grant Number 19mk0101085j0503.

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Conflict of Interest: The authors declare that the research was conducted in the absence of any commercial or financial relationships that could be construed as a potential conflict of interest.

frontiers in Medicine

MINI REVIEW
published: 07 May 2021
doi: 10.3389/fmed.2021.645053

The Ocular Microbiome in Stevens-Johnson Syndrome

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The ocular surface microbiome is an essential factor that maintains ocular surface homeostasis. Since the ocular surface is continuously exposed to the external environment, its microbiome, tears, and local immunity are vital for maintaining normal conditions. Additionally, this microbiome helps prevent pathogen colonization, which commonly leads to opportunistic infection. The abnormal ocular surface microbiome has previously been reported in several conditions, including dry eyes, allergy, blepharitis, graft-versus-host disease (GVHD), and Stevens-Johnson syndrome (SJS). Several approaches were applied to identify the ocular microbiome, including conventional culture techniques and molecular sequencing techniques. By using 16s rRNA sequencing, alterations in the type, proportion, and composition of bacterial communities, described by alpha (α)-and beta (β)-diversity, were observed in SJS patients compared to the healthy group. Conventional culture techniques indicated a higher number of positive bacterial cultures in the SJS group, with a predominance of gram-positive cocci and gram-positive bacilli. Besides, there are increased variations and multiple detections of bacterial genera. Taken together, SJS causes structural changes in the ocular surface and significantly affects its microbiome. Further studies into the area of temporal relationship, metagenomics, proteomics, and metabolomics analysis of the microbiome will lead to a better understanding of this disease. Finally, the treatment using prebiotics and probiotics to re-establish the normal ocular ecosystem and bring back a healthy ocular surface await confirmation.

Keywords: Stevens-Johnson syndrome, ocular surface, ocular surface disease, microbiome, microbial community

OPEN ACCESS

Edited by:
Mayumi Ueta,
Kyoto Prefectural University of Medicine, Japan

Reviewed by:
Jun Kunisawa,
National Institutes of Biomedical Innovation, Health and Nutrition (NIBIOHN), Japan
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Specialty section:
This article was submitted to Ophthalmology, a section of the journal Frontiers in Medicine

Received: *22 December 2020*
Accepted: *06 April 2021*
Published: *07 May 2021*

Citation:
Kittipibul T and Puangsricharern V (2021) The Ocular Microbiome in Stevens-Johnson Syndrome. Front. Med. 8:645053. doi: 10.3389/fmed.2021.645053

INTRODUCTION

The ocular surface appears to be the most anterior part of the eye, exposed to the external environment. Several barriers, such as tear film, local immunity, and commensal bacteria, play essential roles on the ocular surface to protect and maintain homeostasis. In a healthy ocular surface, the microbiome is an essential factor that maintains ocular surface homeostasis and strengthens innate immunity by increasing immune effectors, particularly IgA, in tear films (1).

Microbial communities in human bodies are commonly specific in each body site. Differences in the microbial composition are associated with health and disease. In healthy subjects, a predominance of Bacteroidetes was observed in the gastrointestinal system, while Actinobacteria was a major phylum isolated from the skin. Besides, alteration of microbial communities may

be related to the pathogenesis of some diseases. *Lactobacillus,* which commonly colonizes and stabilizes pH in the vagina, is shifting in bacterial vaginosis. Thus, the relationship between microbial communities and human bodies is another essential factor that regulates health status (2, 3).

Previous studies have shown a low bacterial load on a healthy ocular surface. There were 10–13% of positive cultures (4, 5) with a predominance of coagulase-negative *staphylococci*, *Corynebacterium*, and *Propionibacterium* (6, 7). Although conventional culture techniques can detect bacteria, the technique is limited for conditions such as slow-growing and unculturable microorganisms. Genome sequencing was recently applied for microbial detection, which showed a higher sensitivity by reporting several prominent bacterial genera, including *Propionibacterium, Corynebacteria, Staphylococcus*, and *Streptococcus* in healthy subjects (8, 9). Furthermore, Doan et al. identified 42 genera from conjunctival samples of healthy with highest confidence genera of *Corynebacteria, Propionibacteria*, and *Staphylococcus* (10).

Several conditions, such as contact lens, topical medications, dry eyes, meibomian gland dysfunction (MGD), allergy, trachoma, blepharitis, graft-versus-host disease (GVHD), and Stevens-Johnson syndrome (SJS), can disrupt the ocular surface microbiome. Shin et al. studied the impact of the contact lens on the ocular microbiome. They reported an increased proportion of *Methylobacterium, Lactobacillus, Acinetobacter*, and *Pseudomonas* in lens wearers compared with non-wearers (11). This study also reported a more remarkable similarity in the ocular microbiome and skin microbiome in contact lens wearers (11). Further, Graham et al. reported altering the ocular microbiome in patients with dry eyes, detecting atypical bacterial genera such as *Rhodococcus, Klebsiella,* and *Erwinia* (12). The shifting of colonized genera was also reported in MGD with an increased number of potentially pathogenic strains, including *Staphylococcus epidermidis, Propionibacterium acne, Coryneform bacteria*, and *Staphylococcus aureus* (13). Similar trend of shifting colonization was also identified in GVHD patients. Higher ratio of culture-positive and multiple microbial detection were observed in GVHD compared to non-GVHD. In addition, *Alpha-haemolytic Streptococcus, Haemophilus influenza, and Enterobacter cloacae,* which were defined as pathogenic species, were mostly isolated from GVHD (14).

STEVENS-JOHNSON SYNDROME AS A SEVERE OCULAR SURFACE DISORDER

SJS is a rare but severe disorder that affects the skin, mucous membrane, genitals, and eyes. The etiology is immune-mediated and can be triggered mostly by drugs, followed by viral or Mycoplasma infections. About 20–79% of survivors will experience severe ocular complications from chronic inflammation, desiccation, and scarring leading to blindness (15, 16).

Ocular infection occurs quite common in chronic SJS, most of which is severe, recurrent, and challenging to treat due to the occurrence of multidrug-resistant organisms. Nouri et al. reported incidences of endophthalmitis after keratoprosthesis transplantation in 13 of 108 patients. SJS was identified as a significant cause of endophthalmitis, which accounted for 39% of this report (17). Gunasekaran et al. reported ocular surface flora in chronic limbal stem cell deficiency and found culture-positive in all 13 specimens. Ten of thirteen cases were diagnosed as SJS, which were positive for *Staphylococcus epidermidis* (6 cases), *Staphylococcus aureus* (3 cases), and multiple microorganisms (1 case) (18). Furthermore, SJS was probably associated with multiple drug-resistant microorganisms. Sotozono et al. found 6 of 10 cases of methicillin-resistant *Staphylococcus aureus* (MRSA) keratitis in SJS patients (19). These findings, taken together, imply that ocular infection in SJS may be associated with abnormal microbial colonization on the ocular surface.

ROLE OF THE OCULAR SURFACE MICROBIOME IN SJS

The normal ocular microbiota helps preventing colonization by pathogenic species, which associated with various pro-inflammatory states. The analysis of the ocular microbiome composition is crucial for understanding the pathophysiology of various ophthalmic diseases. The ocular surface innate immune system recognizes and responds to this microbiota through different pathways, including the "Pattern Recognition Receptors" (PRRs) through Toll-Like Receptors (TLRs), which are the transmembrane receptors expressed on different cells (20). Under normal state, the ocular surface immune system maintains the "immune silence" condition when several unique mechanisms prevent the unnecessary inflammatory response to the normal bacterial flora (21).

In SJS, the viral infection, genetic factors, or other environmental factors trigger the innate immune system via the TLR pathway, leading to the expression of different pro-inflammatory cytokines, chemokines, or other molecules as proposed by Ueta et al. (22). These conditions lead to inflammation that can compromise visual function in patients. The same authors also proposed that abnormal host mucosal immunity will affect the normal polyclonality of the commensal bacteria, resulting in the monoclonality of bacteria that can become pathogenic (23).

Thus, the ocular surface problem in SJS potentially causes microbiome changes in terms of the bacterial load, characteristics of prominent microorganisms, the proportion of each genus or species, and diversity of microbial communities, which can lead to a greater risk of infections and chronic inflammation. Furthermore, the ocular surface microbiome may be another indicator of the severity of ocular surface diseases.

STUDIES ON THE OCULAR MICROBIOME IN SJS PATIENTS

Due to the rarity of SJS, there is still little information regarding the characteristics of the ocular surface microbiome and its impact on ocular SJS. Previous studies mostly demonstrated the microbial community with conventional culture techniques. According to culture condition and duration, which affect each bacteria's growth differently, these techniques detected

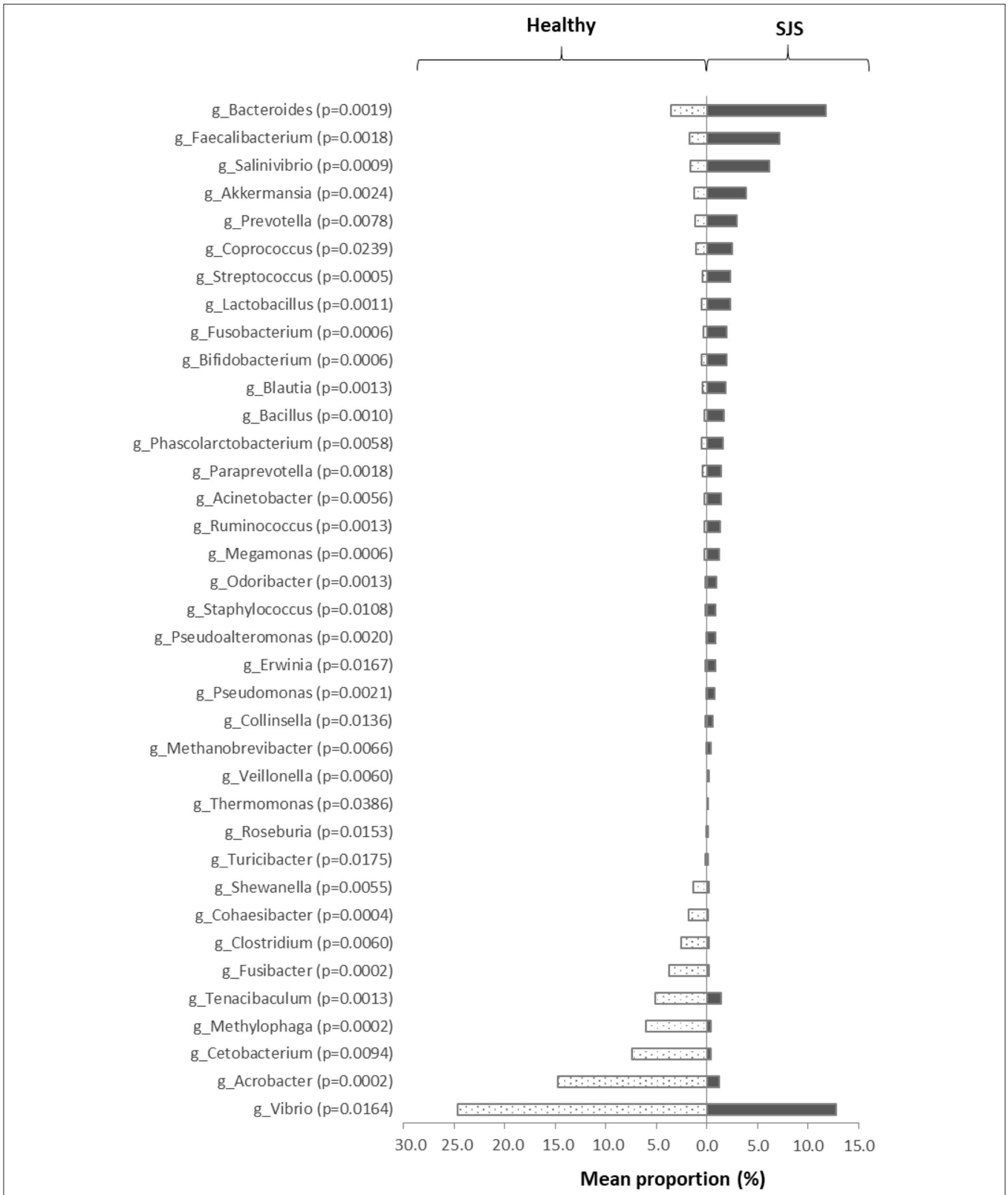

FIGURE 1 | The significant difference in taxa abundance. This figure represents the significant difference in each genus' taxonomic level compared between SJS patients and healthy subjects. We analyzed the proportion of each genus by Mann–Whitney *U*-test. The $p < 0.05$ was defined as statistically significant difference.

only a fraction of the microbial community (7, 24). The 16s rRNA assays and newer genomic sequencing techniques were introduced for microbiome analysis to improve microbial detection effectiveness. This novel analyses demonstrated efficient identification of microbiota, especially in uncultivable and lower abundance genera (25).

Recently, the new 16s rRNA sequencing, named Next-Generation Sequencing (NGS) technique gave unbiased results together with high-throughput data analysis, and performed massively parallel sequencing in a shorter time (26).

We aimed to review the ocular microbiome in SJS patients and compared them with healthy subjects. We referred to both conventional culture techniques and molecular sequencing techniques to get comprehensive data.

Conventional Culture Techniques

In our recent study (5), we collected specimens by swabbing conjunctiva and placing them in transport media. After dissolving specimens, we devided each specimens into 2 parts. The first part was placed on chocolate agar for bacterial isolation. Bacterial identification was performed by biochemical tests and the API system. We found significantly higher culture-positive rates in the SJS group. While 60% (12 of 20 eyes) of the SJS patients were culture-positive, only 10% (2 of 20 eyes) of the healthy individuals were culture-positive. Besides, multiple bacterial detections were reported only in the SJS group, similar to a previous report (4). Venugopal et al. (4) found that the most common isolates in the SJS group were *Corynebacterium spp.* (4 of 12 eyes) and *Streptococcus spp.* (4 of 12 eyes) followed by *Staphylococcus spp.* (3 of 12 eyes). Compared to healthy groups, gram-positive species are still predominant on the ocular surface. Frizon et al. also reported the microbial detection in SJS with the highest number of *Staphylococcus spp.,* followed by *Corynebacterium spp*. These results showed that gram-positive are still predominant species in SJS patients with a higher rate of culture-positive (27). Our study's conventional culture results also discovered atypical bacteria in SJS, including *Streptococcus agalactiae* and *Proteus mirabilis* (5). Frizon et al. (27) found several atypical species colonizing on the ocular surface of SJS, such as *Serratia non-liquefaciens*, *Escherichia coli*, and *Proteus mirabilis*, *Haemophilus spp*. However, there is not only an alteration of microbial colonization but also a change in the antimicrobial susceptibility. Venugopal et al. (4) reported antibiotic resistance to second-generation fluoroquinolones, similar to Frizon et al. (27) who reported antibiotic resistance to chloramphenicol and second-generation fluoroquinolones. Conversely, such resistant strains were not found in our study.

In summation, SJS, which affects anatomical structures and immune modulation (28), also commonly disrupted ocular surface homeostasis and caused dysbiosis. This condition may result in the amplification of several bacteria, which increases the possibility of bacteria detection by conventional cultures.

Molecular Sequencing Techniques

Conventional culture techniques may not demonstrate the overall composition of the microbial community. Dong et al. observed a disparity between microbiologic and molecular approaches. Molecular methods by 16s rRNA sequencing demonstrated 59 distinct bacterial genera, which was more than three times higher diversity than culture methods. They concluded that these newer approaches might provide better pieces of knowledge (7).

In our study (5), residual specimens from conventional cultures were extracted for 16s rRNA amplification with V3-V4 regions targeting. After genome products were prepared, analysis of sequences was performed by Illumina miseq platform.

We reported SJS's core microbiome, identified as 100% of core OTUs samples matching, consisted of *Pseudoalteromonadaceae*, *Vibrionaceae*, *Burkholderiaceae*, *Enterobateriaceae* (5). Microbiome diversity was demonstrated by α- diversity, which showed a higher number of bacterial species (represented by observed operational taxonomic units or OTUs) in SJS (**Supplementary Figure 1**). Similarly, the Shannon index also demonstrated a higher species abundance in the SJS group (**Supplementary Figure 2**). These findings indicate a more significant variation in the microorganisms existing on the ocular surface of SJS patients. However, Zilliox et al. reported the ocular microbiome of SJS in different ways. They found that 7 SJS patients had lower diversity compared to healthy (29). The disparity among studies may be from different baseline characteristics, including geographic distribution, lifestyle, antimicrobial administration pattern, etc. Regarding geographic distribution, Deng et al. reported a difference in ocular surface microbiome from Guangzhou, Beijing, and Wenzhou. Predominance of *Propionibacterium acne* was observed in Guangzhou's subjects, while *Pseudomonas aeruginosa* was predominantly seen in Beijing's subjects. Besides, the diversities of the conjunctival microbiome were different among the three districts (30).

We also compared each specific genera between SJS and healthy. There was a higher relative proportion of *Lactobacillus, Bacteroides, Pseudomonas, Staphylococcus, Streptococcus, Bacillus,* and *Acinetobacter* in the SJS group (**Figure 1**). Similarly, Zillox et al. reported a higher proportion of *Staphylococcus* in their study. Furthermore, our study showed an increased number of potentially pathogenic bacteria, including *Pseudomonas spp.* and *Acinetobacter spp.* in the SJS group, which may increase the risk of opportunistic infections.

Regarding the severity of SJS, we analyzed the correlation between the severity of the disease and culture-positive specimens. We found a significantly higher severity score in the culture-positive group ($p = 0.016$) (5). However, we could not demonstrate a correlation between the number of OTUs and the severity grading (**Supplementary Figure 3**). Further study in a larger group may illustrate the definite correlation between microbiome and disease severity.

FUTURE RESEARCH AND APPLICATIONS

Current knowledge of ocular microbiome change in SJS has mostly been uncovered. However, it remained unclear whether the microbiome's change plays a role in increasing inflammation in SJS or the disease alters the microbiome. Further studies trying to assess the temporal relationship between the two is undoubtedly warranted. Further assessments, including

metagenomic profiling, protein expression, and metabolic activity, may bring us to a better perception of this disease's microbiome (31). Future studies should also be directed to identify other factors' roles in this change, such as aging, systemic diseases, surgical interventions, and antimicrobial treatment. Finally, various treatments aiming to restore the healthy ocular ecosystem should also be explored. Although probiotics and prebiotics are still not directly applied in ocular treatment, a report shows the improvement of dry eye after initiating oral prebiotic supplement (32). This new treatment may pave the way for better control of this devastating ocular surface disease.

AUTHOR CONTRIBUTIONS

TK and VP contributed to the writing of this review and have read and approved the final version.

ACKNOWLEDGMENTS

We want to thank the staff of Cornea and Refractive Unit, Department of Ophthalmology, Faculty of Medicine, Chulalongkorn University, for providing patients' information. We would also like to thank Dr. Tanittha Chatsuwan from the Department of Microbiology, Faculty of Medicine, Chulalongkorn University, for her contribution and collaboration.

SUPPLEMENTARY MATERIAL

The Supplementary Material for this article can be found online at: https://www.frontiersin.org/articles/10.3389/fmed.2021.645053/full#supplementary-material

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Conflict of Interest: The authors declare that the research was conducted in the absence of any commercial or financial relationships that could be construed as a potential conflict of interest.

The handling Editor declared a past collaboration with one of the authors VP.

frontiers in Medicine

ORIGINAL RESEARCH
published: 12 May 2021
doi: 10.3389/fmed.2021.661891

Clinical Aspects of Stevens-Johnson Syndrome/Toxic Epidermal Necrolysis With Severe Ocular Complications in Taiwan

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Specialty section:
This article was submitted to Ophthalmology, a section of the journal Frontiers in Medicine

Received: *31 January 2021*
Accepted: *08 April 2021*
Published: *12 May 2021*

Citation:
Ma DH-K, Tsai T-Y, Pan L-Y, Chen S-Y, Hsiao C-H, Yeh L-K, Tan H-Y, Lu C-W, Chen C-B and Chung W-H (2021) Clinical Aspects of Stevens-Johnson Syndrome/Toxic Epidermal Necrolysis With Severe Ocular Complications in Taiwan. Front. Med. 8:661891. doi: 10.3389/fmed.2021.661891

Purpose: Over the last decade, there has been tremendous progress in the treatment of Stevens-Johnson syndrome (SJS) and toxic epidermal necrolysis (TEN). To understand whether this has resulted in better ophthalmic outcomes, we aimed to study the incidence of severe ocular complications (SOCs) in the acute and chronic stage among SJS/TEN patients, major causative medications, and therapeutic effect of medical and surgical treatment.

Methods: Using electronic medical records review of patients of Chang Gung Memorial Hospital Linkou Branch from 2010 to 2020, 119 patients (236 eyes) received ophthalmic consultation during the acute stage and were retrospectively studied. Sotozono's grading score systems for acute and chronic SJS/TEN were employed for accessing correlation between acute and chronic presentations, the therapeutic effect of systemic etanercept treatment, and outcome of early amniotic membrane transplantation (AMT) performed in patients with severe acute SOCs.

Results: There were 46 male and 73 female patients with a mean age of 45.6 ± 22.7 years old (2–90 years), and follow-up time of 408.3 ± 351.0 (116–1,336) days. The numbers of patients with SJS, overlap syndrome, and TEN were 87, 9, and 23, respectively. In total, 109 eyes (55 patients) had acute SOCs, which comprised 46.2% of patients who underwent ophthalmic examination. Antiepileptics were the most common category of culprit drugs causing SOCs in the acute stage. At the end of follow-up, there were 14 eyes (9 patients) with chronic SOCs (5.9%), and non-steroidal anti-inflammatory drugs and cold medicine were the most common causative medications that were associated with severe chronic sequela. The correlation between Sotozono's acute

and chronic grading score showed a positive relationship [Spearman's rank correlation coefficient (r) = 0.52, $p < 0.001$]. The average chronic grading scores in patients receiving systemic corticosteroid combined with etanercept treatment were significantly lower than those receiving corticosteroid only, Finally, the average chronic grading scores in patients receiving AMT <7 days after onset were significantly lower than those performed beyond 7 days.

Conclusion: Our study implies that acute manifestation can be an indicator for chronic sequelae. Additional early etanercept treatment and early AMT showed beneficial effect in reducing chronic ocular sequela.

Keywords: Stevens-Johnson syndrome, toxic epidermal necrolysis, ocular complication, amniotic membrane transplantation, etanercept, Taiwan

INTRODUCTION

Stevens-Johnson syndrome/toxic epidermal necrolysis (SJS/TEN) is a potentially life-threatening and vision-impairing immune-mediated disease with an estimated annual incidence of 1–5 per 1,000,000 individuals globally (1). The incidence differs among countries. A study from Korea reported incidences of 3.96–5.03 for SJS and 0.94–1.45 for TEN per million individuals from 2010 to 2013 (2). An incidence rate of 5.76 SJS/TEN cases per million person-years were reported from the UK (database between 1995 and 2013) (3).

Two studies from the US reported similar incidences. The annual SJS spectrum incidence rate reported by White et al. was 12.35 per million people per year (database between 2010 and 2012) (1), and Hsu et al. reported that the mean estimated incidences of SJS, SJS/TEN, and TEN were 9.2, 1.6, and 1.9 per million adults per year, respectively (database between 2010 and 2012) (4).

In Taiwan, utilizing data from the National Health Insurance Research Database (NHIRD) of Taiwan from 2000 to 2008, Syu et al. reported that the overall SJS incidence rate was 3.6 per million people per year (study database between 2000 and 2008) (5). These data may potentially reveal a considerable number of patients affected by ocular complications. Severe ocular complications (SOCs) in chronic SJS/TEN include dry eye, chronic inflammation and neovascularization of the cornea, symblepharon and keratinization of the conjunctiva. If not properly handled, SOCs often result in permanent visual loss.

Because of severe dry eye, SOCs in SJS/TEN are more difficult to treat by surgery; therefore, prevention is the key to reduce the incidence of SOCs in SJS/TEN.

Although Taiwan was the first country to report an intense association of human leukocyte antigen (HLA)-B*15:02 and carbamazepine-induced SJS/TEN (6), and the first to implement HLA-B*15:02 screening for carbamazepine users (7), reports focusing on ocular manifestations of SJS/TEN from Taiwan are limited. In 2007, Chang et al. reported a total of 207 patients with 213 episodes/attacks of SJS/TEN. The most frequent causative drugs were carbamazepine and allopurinol. Dry eye was the most frequent ocular sequelae identified within 3 months after hospital discharge (17.2%) followed by symblepharon (4.7%) and corneal scarring (4.7%) (8).

Over the last decade, there has been considerable progress not only in diagnostic methods but also in treatment protocols, especially the early application of amniotic membrane transplantation (AMT) (9–12), and it has been shown that the long-term outcomes of AMT to be quite favorable (9, 13). In this article, we aim to study the incidence of SOCs among SJS/TEN patients, major causative medications, the final outcome of affected patients, therapeutic effect of systemic corticosteroids combined with etanercept treatment, and beneficial effect of early AMT.

MATERIALS AND METHODS

This retrospective study to collect and analyze electronic medical records of SJS/TEN was approved by the Institutional Review Boards of Chang Gung Medical Foundation (IRB approval No. 202100092B0). All experimental procedures were conducted in accordance with the principles set forth in the Helsinki Declaration.

The list of SJS/TEN patients who were admitted to Chang Gung Memorial Hospital, Linkou Branch from January 2010 to July 2020 was retrieved from the database maintained by the Department of Dermatology. The electronic medical records were retrospectively reviewed, and the recorded data included information on gender, presenting age, causative medications/diseases, and systemic treatments. Regarding disease chronicity, Shanbhag et al. have defined the acute phase as the period between symptom onset of SJS/TEN up to 2 months later; the subacute phase was defined as 2–6 months after symptom onset; and the chronic phase was defined as more than 6 months after symptom onset (14). Ocular manifestations in the acute stage were retrieved from ophthalmic consultation records. To record the severity of ocular involvement at the first time of consultation in the acute stage (within 1 week from the first manifestation), the Sotozono acute stage ocular surface grading score (OSGS) was employed (15). OSGS ranges from grade 0 to 3, with grade 0 indicating no ocular surface involvement, grade 1 indicating mild involvement with conjunctival hyperemia, grade 2 indicating severe involvement with accompanying

pseudomembrane formation or ocular surface epithelial defects, and grade 3 indicating very severe involvement with both pseudomembrane formation and ocular surface epithelial defects. The eyes with greater than grade 2 ocular involvement were considered to have acute severe ocular complications (SOCs). The initial VA and ophthalmic medical and surgical treatments were also reviewed. Visual acuity (VA) was evaluated in naked-eye with standard Snellen E chart. Regarding the causative medications, those with acute SOCs (grade 2 and grade 3) were analyzed and compared in percentage.

In the chronic stage (defined as at least 6 months from the first manifestation), ocular involvement was assessed according to the scoring system proposed by Sotozono et al. (16). Complications were broadly defined as corneal, conjunctival, and eyelid complications. There are a total of 13 categories of findings, such as superficial punctate keratopathy (SPK), hyperemia, trichiasis, and symblepharon. Each category scored from 0 to 3, and the maximal score was 39. Treatment in the chronic stage, Schirmer test values and vision were also recorded. Because there was a high portion of missing data for Schirmer test values, the diagnosis of dry eye was made if the patient's Schirmer's test I value (without topical anesthesia) was < 10 mm and/or the cornea showed greater than grade 1 SPK. To judge the severity of the ocular manifestation in the chronic stage, the patient's last electronic medical records with a detailed eye examination was used as a reference (**Table 1**). Patients with Sotozono's chronic stage grading scores 0–5 were considered to have non- or minimal ocular involvement. Patients with scores 6–10 exhibited mild involvement, scores 11–15 indicate moderate involvement, and scores > 16 were considered to have severe involvement.

Based on published therapeutic benefits of steroid therapy at disease onset in preventing ocular complications (17), systemic treatment with steroid pulse therapy (1–1.5 mg/kg/day prednisolone by intravenous injection until the skin lesions were healed), intravenous methylprednisolone or hydrocortisone has also been commonly administered to SJS/TEN patients admitted to dermatology wards (17, 18). Based on the conclusion from a randomized and controlled trial from our hospital (2009–2015) (19), additional subcutaneous etanercept (Enbrel; Pfizer) has been prescribed for recalcitrant SJS/TEN patients with progression of blistering or erythema even after methylprednisolone (>1 mg/kg/day) treatment for 3–5 days. To investigate the effect of additional systemic etanercept on long-term ocular outcome, we focused on patients whose medical records showed treatment with intravenous corticosteroids with or without additional subcutaneous etanercept. Demographics of the patients in each group such as age, gender, and distribution of top 5 culprit drugs were compared, and we found no significant difference in these parameters (**Table 5**). Thereafter, the acute and chronic stage severity grading scores were compared between these two groups.

In the acute stage, we used topical balanced salt solution (BSS, Alcon) for lubrication, levofloxain (Cravit, Santen) as a prophylactic antibiotic, Tobradex ointment (Alcon) as topical corticosteroid ointment for eyelid wounds, and preservative-free 0.1% betamethasone (Fusone, AIM Medicine, Taiwan) qid to q3h when conjunctival congestion was evident. Conjunctival pseudomembranes were removed every 2–4 days. If grade 3 and sometimes grade 2 ocular involvement was noted, amniotic membrane (AM) dressing using cryopreserved AM was performed to protect the entire ocular surface. Before 2019, suture-fixated AM dressing was performed (20–22). Since 2020, sutureless AM dressing using cyanoacrylate glue to fixate AM at the lid margin has been adopted (23). This novel technique significantly reduced the time and discomfort of the surgery. To study the influence of timing of AM transplantation (AMT; AM grafting or AM dressing) on the outcome, we compared the Sotozono's chronic grading score of patients who received AMT less than or more than 7 days after onset.

TABLE 1 | Demographics and grading of patients receiving ophthalmic examination in acute and chronic stage of SJS/TEN from 2010 to 2020.

Demographics/characteristics	
Number of patients	119
Total eye number	236
Mean age ± SD (range)	45.6 ± 22.7 (2–90)
Gender, n (%)	
Male	46 (38.7)
Female	73 (61.3)
Laterality, n (%)	
Bilateral	117 (98.3)
Unilateral	2 (1.7)
Diagnosis, n (%)	
SJS	87 (73.1)
Overlap syndrome	9 (7.6)
TEN	23 (19.3)
Mean follow-up time (days)	408.3 ± 351.0 (116–1,336)
Sotozono's acute stage grading scores, *n* = eyes (%)	
Grade 0	30 (12.7)
Grade 1	97 (41.1)
Grade 2	79 (33.5)
Grade 3	30 (12.7)
Mean OSGS in acute stage (range)	1.46 ± 0.87 (0–3)
Sotozono's chronic stage grading scores, *n* = eyes (%)	
0–5	195 (82.6)
6–10	22 (9.3)
11–15	5 (2.1)
>16	14 (5.9)
Mean OSGS in chronic stage (range)	3.54 ± 5.50 (0–33)

SJS, Stevens-Johnson syndrome; TEN, toxic epidermal necrolysis; OSGS, ocular surface grading score.

Statistics

All statistics were calculated using SPSS software version 23.0 for Windows (SPSS, Inc., Chicago, IL, USA). Continuous variables are presented as the mean and standard deviation (SD). Spearman's rank correlation was used to present the association between Sotozono's acute and chronic grading score. Correlation coefficients (ρ) were also calculated. Student's *t*-test was used

to compare the difference in demographics, follow-up duration, acute and chronic grading scores between patients treated with or without additional etanercept, and chronic grading scores in patients receiving AMT before or beyond 7 days after onset. Chi-squared test was used to compare distribution of causative medications between patients treated with or without additional etanercept. A $p < 0.05$ was deemed to be statistically significant.

RESULTS

From January 2010 until July 2020, a total of 294 patients were registered in the Department of Dermatology database. Among them, 119 patients (236 eyes) received ophthalmic consultation during the acute stage and were recruited in this study. There were 46 male and 73 female patients with a mean age of 45.6 +/– 22.7 years old (2–90 years). The numbers (percentages) of patients with SJS, overlap syndrome, and TEN were 87 (73.1%), 9 (7.6%), and 23 (19.3%), respectively. When the number of involved eyes was calculated, using Sotozono's acute OSGS, there were 30 eyes without ocular involvement (grade 0, 12.7%), 97 eyes with mild involvement (grade 1, 41.1%), 79 eyes with severe involvement (grade 2, 33.5%), and 30 eyes with the most severe involvement (grade 3, 12.7%). Given that patients with greater than grade 2 ocular involvement were considered to have SOCs, there were 109 eyes (55 patients) in total with acute SOCs, comprising 46.2% of patients who had ophthalmic examination, and 18.6% of total patients (**Table 1**). In the chronic stage, when the assessment was done at an averaged 408.3 ± 351.0 (116–1,336) days after onset, there were 195 eyes (82.6%) with Sotozono's chronic grading scores 0–5 (non- or minimal ocular involvement). Twenty-two eyes (9.3%) with scores 6–10 (mild involvement), 5 eyes (2.1%) with scores 11–15 (moderate involvement), and 14 eyes (5.9%) with scores >16 (severe involvement) (**Table 1**).

Among 67 identifiable drugs that were associated with acute SOCs, antiepileptics (carbamazepine, phenytoin, lamitrogine, etc.) was the category of drugs that were associated with most acute SOCs ($n = 15$, 22.4%) followed by antibiotics ($n = 12$, 17.9%), allopurinol ($n = 8$, 11.9%), non-steroidal anti-inflammatory drug (NSAID; $n = 7$, 10.4%), and sulfa drugs ($n = 6$, 9.0%) (**Table 2**). In terms of a single drug, allopurinol was the drug that was associated with most acute SOCs. In 14 eyes of the 9 patients with chronic SOCs, NSAID and cold medicine were the most common causative medications that were associated with chronic SOCs (44.4%, **Table 2**).

The average grading score for all patients in the acute stage was 1.46 ± 0.87. The value in the chronic stage (at the end of follow-up) was 3.54 ± 5.50. For patients whose grading score ranged from 0 to 3 during the acute stage, their corresponding chronic stage grading scores were 0.67 ± 0.80, 1.62 ± 1.99, 4.70 ± 6.38, and 9.60 ± 7.73, respectively. The correlation between Sotozono's acute and chronic grading score showed a moderately correlated relationship [Spearman's rank correlation coefficient (ρ) = 0.52, $p < 0.001$] (**Figure 1**). This finding implies that patients who presented with more severe acute ocular manifestations tended to suffer from sequelae in the chronic stage.

TABLE 2 | Top 5 causative drug categories responsible for acute and chronic SOCs in SJS/TEN patients.

Name of causative drugs	No. of patients (%)
Acute SOCs	***N* = 67**
Antiepileptics	**15 (22.4)**
Phenytoin	2 (3.0)
Carbamazepine	4 (6.0)
Oxcarbazepine	5 (7.5)
Lamotrigine	2 (3.0)
Zonisamide	2 (3.0)
Antibiotics	**12 (17.9)**
Cephalexin	1 (1.5)
Cefuroxime	1 (1.5)
Ceftazidime	1 (1.5)
Ceftriaxone	1 (1.5)
Norfloxacin	1 (1.5)
Levofloxacin	1 (1.5)
Moxifloxacin	1 (1.5)
Amoxicillin	3 (4.5)
Vancomycin	2 (3.0)
Allopurinol	**8 (11.9)**
NSAIDs	**7 (10.4)**
Diclofenac	3 (4.5)
Ibuprofen	1 (1.5)
Mefenamic acid	3 (4.5)
Sulfa drugs	**6 (9.0)**
Sulfasalazine	3 (4.5)
Sulfonamide	3 (4.5)
Miscellaneous	**19 (28.4)**
Chronic SOCs	***N* = 9**
NSAIDs	**4 (44.4)**
Diclofenac	2 (22.2)
Mefenamic acid	1 (11.1)
Cold medicine	19 (11.1)
Anti-epileptics	**2 (22.2)**
Carbamazepine	1 (11.1)
Lamotrigine	1 (11.1)
Antibiotics	
Cefuroxime	1 (11.1)
Sulfa drugs	
Sulfasalazine	1 (11.1)
Tenofovir	**1 (11.1)**

SOCs, Severe ocular complications.
NSAIDs, Non-steroidal anti-inflammatory drugs.

Judging from Sotozono's chronic stage ocular complication category, hyperemia was the most common chronic stage ocular complication, followed by SPK, meibomian gland dysfunction, mucocutaneous junction involvement, and trichiasis. Judged from the Schirmer test value and the presence of corneal staining, the incidence of dry eye in the chronic stage was estimated to be 49.2% (116 eyes) (**Table 3**).

When best corrected vision in the chronic stage was measured, data were available from 174 eyes. Among them, 112 eyes (64.4%) had vision better than 20/40, and 43 eyes (24.7%) had vision between 20/40 and 20/200. Nine eyes (5.2%) had vision between

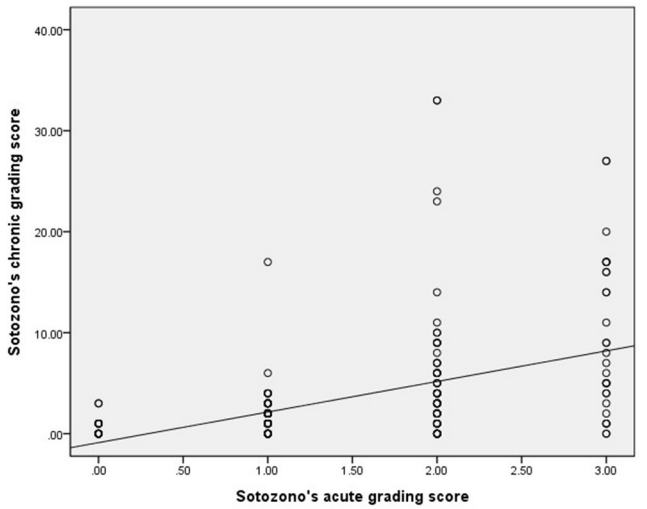

FIGURE 1 | Correlations between Sotozono's acute (15) and chronic (16) stage grading score of SJS/TEN patients evaluated during the acute and chronic stage, respectively.

TABLE 3 | Ocular manifestations in chronic stage of SJS/TEN patients.

Characteristic	Number of eye	Percentage (%)
Corneal complication		
Superficial punctate keratitis	117	49.58
Epithelium defect	29	12.29
Loss of POV*	9	3.81
Conjunctivalization	13	5.51
Neovasculization	22	9.32
Opacification	19	8.05
Keratinization	14	5.93
Conjunctival complication		
Hyperemia	122	51.69
Symblepharon	8	3.39
Eyelid complication		
Tichiasis	49	20.76
MC* junction involvement	62	26.27
Meibomian gland involvement	90	38.14
Punctal damage	7	2.97

POV, Palisades of Vogt; MC, Mucocutaneous.

20/200 and 20/2,000, and 10 eyes (5.7%) had vision worse than 20/2,000.

To study the effect of additional systemic etanercept on long-term ocular manifestations, there was no significant difference in gender, age, distribution of culprit drugs, and follow-up time between patients receiving corticosteroid treatment only and patients receiving corticosteroid plus etanercept treatment (**Table 4**). The average acute stage score for patients who received additional systemic etanercept was 1.32 ± 0.76 (0–3). The value for patients who received systemic corticosteroid only treatment was 1.49 ± 0.90 (0–3; $p = 0.171$). In the chronic stage, the average score for additional etanercept treated patients was 1.64 ± 2.47 (0–14), which was significantly lower than the score for corticosteroid only treated patients (3.95 ± 5.76; range 0–33, $p < 0.001$) (**Table 4**).

TABLE 4 | Comparison between corticosteroid with or without additional etanercept treatment on Sotozono's acute and chronic stage grading score.

	Corticosteroid + etanercept	Corticosteroid only	*p*-value
Number (patient/eye)	31/62	82/164	
Gender (M/F)	15/16	32/50	0.126
Age (years old)	48.00 ± 18.72	45.79 ± 24.06	0.601
Mean follow up time (days)	485.00 ± 502.42	360.82 ± 319.64	0.319
Time to intervention (days)	1.96 ± 1.49	0.78 ± 0.64	0.003
Major causative drugs			
Anti-epileptics	24 (38.71%)	48 (29.27%)	0.264
Antibiotics	11 (17.74%)	26 (15.58%)	
Allopurinol	6 (9.68%)	10 (6.10%)	
NSAID	6 (9.68%)	26 (15.58%)	
Sulfa drugs	2 (3.23%)	18 (10.98%)	
Others	13 (20.97%)	36 (21.95%)	
Sotozono's grading score			
Acute stage			
Mean	1.323	1.488	0.171
Std. deviation	0.763	0.903	
Std. Error Mean	0.097	0.071	
Chronic stage			
Mean	1.645	3.951	<0.001
Std. deviation	2.470	5.765	
Std. error mean	0.314	0.450	

Finally, for surgical treatment, during the acute stage (<2 months after onset), 7 patients (13 eyes) received AM grafting (AMG) and 7 patients (14 eyes) received AM dressing (AMD) at an averaged 8.15 ± 4.5 days and 4.93 ± 4.6 days, respectively, after onset. During the chronic stage, seven patients (12 eyes) received oral mucosal transplantation to correct lid margin keratinization, 4 patients (7 eyes) received punctal occlusion to treat dry eye, and 2 patients (4 eyes) received correction of entropion (**Table 5**). When we compare the Sotozono's chronic stage grading scores in patients receiving AM transplantation (AMG + AMD) less than or more than 7 days after onset, we found that in AMG group and combined AMG and AMD group, the scores were significantly lower when the operation was performed <7 days (2.17 ± 2.63 vs. 15.6 ± 12.94, $p = 0.031$; 6.29 ± 4.69 vs. 13.60 ± 11.22, $p = 0.025$; Chi-squared test). This implies that patients receiving earlier AM transplantation were associated with less severe chronic SOCs (**Table 5**).

DISCUSSION

In multiple-country epidemiological studies of medication risk related to SJS/TEN in Asian populations (1998–2017), Wang et al. reported that antiepileptic drugs/antipsychotics (53%) were the most common category of drugs that caused SJS/TEN followed by antibiotics/antiviral agents (20%), allopurinol (19%), and

TABLE 5A | Surgical intervention in the acute and the chronic stage of SJS/TEN.

Type of surgery	Patient (%)	Eye (%)	Time to intervention (days)
Acute stage			
AMG*	7 (5.88)	13 (5.51)	8.15 ± 4.5 (3–15)
AMD*	7 (5.88)	14 (5.93)	4.93 ± 4.6 (0–14)
Chronic stage			
OMT*	7 (5.88)	12 (5.08)	
Punctum suture	4 (3.36)	7 (2.97)	
Correction of entropion	2 (1.68)	4 (1.69)	

TABLE 5B | Comparison of Sotozono's chronic stage grading score in patients receiving AM transplantation more than or < 7 days after onset.

Type of surgery	Onset to intervention (in days)	Chronic stage grading score	*p*-value
AMG	≧7 day ($n = 7$)	15.6 ± 12.94 (4∼33)	0.031
	<7 day ($n = 6$)	2.17 ± 2.63 (0∼6)	
AMD	≧7 day ($n = 3$)	8.33 ± 2.08 (6∼10)	0.904
	<7 day ($n = 11$)	8.55 ± 3.98 (5∼16)	
AMG + AMD	≧7 day ($n = 10$)	13.60 ± 11.22 (4∼33)	0.025
	<7 day ($n = 17$)	6.29 ± 4.69 (0∼16)	

**AMG, Amniotic membrane graft; *AMD, Amniotic membrane dressing; *OMT, Oral mucosal transplantation.*

NSAIDs (4%) (24). In Taiwan, Chang et al. previously reported that carbamazepine was the most common medication that caused SJS/TEN followed by allopurinol and phenytoin (8). With the ground-breaking finding that the human leukocyte antigen HLA-B*15:02 was intensively associated with carbamazepine-induced SJS/TEN in Han Chinese individuals (6), subsequent government health insurance covering HLA-B*15:02 screening dramatically reduced the incidence of carbamazepine-induced SJS/TEN (7). When all registered patients within the last 10 years were reviewed, antiepileptics were still the most common category of drugs that caused acute SOCs followed by antibiotics and allopurinol. However, allopurinol was the most common single culprit drug that caused acute SOC followed by oxcarbazepine and carbamazepine. Recently, cold medicine (antipyretic or analgesic but not antibiotics a patient takes when catching cold) was thought to be the most common drug that induces SOCs in chronic SJS/TEN (25–29). We also had similar observations in our recent study based on patients from outpatient clinics, and identified HLA B*0207 to be associated with cold medicine-induced SJS/TEN with SOCs (30). In this study, NSAID and cold medicine were found to be the most common causative medications that were associated with chronic SOCs. A significant association was noted between HLA-B*15:02 and oxcarbazepine-induced SJS/TEN; however, the incidence and severity were lower than those of carbamazepine-induced STS/TEN (31). On the other hand, although a strong association of HLA-B*5801 with allopurinol-induced SJS/TEN has been reported (32, 33), the relatively lower incidence of allopurinol-induced SJS/TEN does not support the implementation of gene screening.

One may think that patients with more severe dermatological involvement also have more severe ocular involvement. However, Morales et al. reported that although ocular damage in the acute stage was more frequent in patients with epidermal detachment >10% of the total body surface area, the SCORTEN value did not correlate with the severity of eye involvement in the acute stage (34). Heng et al. reported that the grading of acute ocular disease severity does not correlate with systemic disease severity but is significantly associated with the time to resolution of ocular involvement in TEN (35). Yip et al. also stressed that the severity of acute ocular disease and abnormal laboratory tests were not found to be significant risk factors for late complications (36).

To identify predictors for the development of chronic ocular complications, Gueudry et al. retrospectively reviewed the records for demographics, cause of the condition, and severity of ocular involvement. They found that (1) Patients with TEN had more frequent but not more severe acute ocular involvement; (2) Dry eye syndrome was the most common late complication; (3) The severity of acute ocular disease was found to be the only significant risk factor for late complications. Although late complications are more frequent in patients with severe initial eye involvement, these complications may also develop in patients without initial ocular symptoms (37). In this study, we found a good correlation between the severity of acute ocular manifestations and chronic ocular sequelae; nevertheless, we also observed that some patients with only minimal ocular involvement in the beginning deteriorated over the years due to insults from chronic inflammation, dry eye, trichiasis and lid margin keratinization. Therefore, we agree with Shanbhag et al. that patients with any acute ocular involvement regardless of severity should be seen by an ophthalmologist for life given that severe and irreversible complications can occur at any time, even decades after acute disease (38).

There are several different grading systems to define the severity of ocular involvement in chronic SJS/TEN (16, 39, 40). We chose to use Sotozono's 2007 grading system because the system includes the most observation features, each with a score range, which facilitates quantitative comparison between different groups (16). We found hyperemia to be the most common chronic stage ocular complication followed by dry eye, SPK, and meibomian gland dysfunction. However, in our hospital, not all acute SJS/TEN patients (294 patients in the last decade) were seen by ophthalmologists. It was only when patients presented with red eye or other ophthalmic symptoms that dermatologists sent out a consultation request (119 patients, 236 eyes in total). This is the major drawback in the study as this might overestimate the SOC rate given that many non-consulted patients were in fact patients without any ocular involvement. For example, the percentages of patients with acute SOCs, chronic SOCs, and late severe vision impairment (< 20/200) were 46.2, 5.9, and 10.9%, respectively, among consulted patients, but the value could be as low as 18.7, 2.4, and 3.4%, respectively, if non-examined patients were all considered free of eye involvement. This projected value would be very similar to the report by Power

et al. which indicates that 16% of patients with SJS-spectrum will experience severe ocular involvement (41), and the report by Shanbhag et al. which indicates that only 3% eyes had vision worse than 20/200 after aggressive treatment (14).

Previously, a high portion of SJS/TEN patients often suffered from chronic debilitating sequelae. In 2007, Sotozono et al. reported that greater than half of their patients had final vision worse than 20/200 (74 eyes, 53.6%) with an average chronic SJS grading score of 25.66 (16). With the awareness that early and aggressive intervention in the acute stage is key to prevent long-term complications, a specific protocol for acute ocular care in SJS/TEN, including aggressive use of AMT (22, 23), was instituted at Massachusetts Eye Infirmary in January 2008, which was highly successful in reducing corneal blindness and severe vision-threatening complications (14). In the report of Shanbhag et al. after adapting the protocol, only 3% (2/78) of eyes had vision worse than 20/200 in contrast to 50% (9/18) before the protocol (14). In this study, systemic corticosteroids were administered to all but 5 patients in the acute stage, and 27 of the 30 eyes with acute grade 3 involvement received either AMG or AMD. We believe that in the last decade, aggressive systemic immunosuppressives and early AM transplantation have already contributed to reduced long-term ocular complications. In this study, the average chronic grading scores in patients receiving AMT <7 days after onset were significantly lower than those performed beyond 7 days, suggesting the beneficial effect of early AMT in reducing chronic SOCs (9, 13).

In addition to systemic corticosteroids (17, 39), other immunomodulatory medications, such as intravenous immunoglobulin (IVIG) (39, 42) and cyclosporine A (43, 44), have been used to treat acute SJS/TEN. Although IVIG was found to be ineffective, the use of cyclosporine may offer a greater mortality benefit (45) in the treatment of SJS/TEN, and cyclosporine and glucocorticosteroids were shown to be the more promising systemic immunomodulating therapies (43). Recently, our dermatology colleagues reported the beneficial effect of systemic etanercept treatment in promoting epidermal regeneration and reducing the incidence of gastrointestinal hemorrhage and mortality in acute SJS/TEN in a randomized, controlled study (19). The use of subcutaneous etanercept is generally safe, but we need to pay attention to whether there is tuberculosis, hepatitis B, hepatitis C, and serious infections before the injection. In the present study, we also found that patients receiving additional systemic etanercept exhibited better final vision and significantly lower chronic SJS/TEN grading scores. This encourages us to conduct a study to trace the long-term ocular condition in the original cohort of patients (manuscript in preparation).

In summary, we found that patients with severe acute ocular manifestations in SJS/TEN tend to suffer from chronic ocular involvement. Antiepileptics were the category of drugs that caused most acute SOCs, whilst NSAIDs and cold medicines were associated with most chronic SOCs. With aggressive medical and surgical treatment, eyes suffering from chronic complications of SJS/TEN have decreased in the last decade. Finally, systemic etanercept given in the acute stage showed promise in reducing long-term ocular morbidity; however, the efficacy and long-term benefit still await further investigation.

DATA AVAILABILITY STATEMENT

The original contributions presented in the study are included in the article/supplementary material, further inquiries can be directed to the corresponding author/s.

ETHICS STATEMENT

The studies involving human participants were reviewed and approved by Institutional Review Boards of Chang Gung Medical Foundation. Written informed consent from the participants' legal guardian/next of kin was not required to participate in this study in accordance with the national legislation and the institutional requirements.

AUTHOR CONTRIBUTIONS

DM: writing of the manuscript, patient care and surgery. T-YT: review of electronic medical records, statistical analysis, and making of tables and figure. L-YP: review of electronic medical records, statistical analysis, and making of tables. S-YC: patient care and surgery. C-HH, H-YT, and L-KY: ophthalmic consultation. C-WL: dermatological care of patients. C-BC: dermatological care of patients and provides patient list. W-HC: dermatological care of patients and inventor of systemic etanercept treatment. All authors contributed to the article and approved the submitted version.

FUNDING

The study was supported by research grants from the Ministry of Science and Technology, Taiwan (MOST) 106-2314-B-182A-043-; and Chang Gung Memorial Hospital, Taiwan (CMPRPG1J0011) to DM.

ACKNOWLEDGMENTS

The authors are grateful to Biostatistical Section, Clinical Trial Center, Chang Gung Memorial Hospital (MOHW110-TDU-B-212-123005) for the statistical support.

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Conflict of Interest: The authors declare that the research was conducted in the absence of any commercial or financial relationships that could be construed as a potential conflict of interest.

The handling Editor declared a past collaboration with several of the authors DM, W-HC, and S-YC.

frontiers in Medicine

PERSPECTIVE
published: 21 May 2021
doi: 10.3389/fmed.2021.656998

Understanding Immune Responses to Surgical Transplant Procedures in Stevens Johnsons Syndrome Patients

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Stevens Johnsons syndrome (SJS) is a mucocutaneous disorder caused by an autoimmune response most commonly to medications. Unless it is properly managed in the acute setting, this entity can affect the ocular surface causing chronic cicatrizing conjunctivitis with limbal stem cell deficiency and lid anomalies which ultimately result in corneal opacities that may limit patients' visual acuity. When this stage is reached, some patients might need to undergo some form of corneal and/or limbal stem cell transplantation that exposes an already sensitized immune system to a new alloantigen. While the innate immunity plays a role in corneal graft survival, adaptive immune responses play a major part in corneal graft rejection and failure, namely through CD4+ T cell lymphocytes. Hence, the management of the immune response to surgical transplant procedures in SJS patients, involves a dual approach that modulates the inflammatory response to a new alloantigen in the context of an autoimmune sensitized patient. This review will explore and discuss current perspectives and future directions in the field of ocular immunology on how to manage SJS immune responses to ocular surgical procedures, reviewing systemic and local immunosuppressive therapies and protocols to adequately manage this debilitating condition.

Keywords: Stevens Johnsons, corneal transplant, immunosuppression, limbal stem cell transplant, high risk corneal transplantation

OPEN ACCESS

Edited by:
Mayumi Ueta, Kyoto Prefectural University of Medicine, Japan

Reviewed by:
Sayan Basu, L V Prasad Eye Institute, India
James Chodosh, Massachusetts Eye and Ear Infirmary and Harvard Medical School, United States

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Specialty section:
This article was submitted to Ophthalmology, a section of the journal Frontiers in Medicine

Received: *21 January 2021*
Accepted: *23 April 2021*
Published: *21 May 2021*

Citation:
Soifer M, Mousa HM, Levy RB and Perez VL (2021) Understanding Immune Responses to Surgical Transplant Procedures in Stevens Johnsons Syndrome Patients. Front. Med. 8:656998. doi: 10.3389/fmed.2021.656998

INTRODUCTION

Stevens Johnsons syndrome (SJS) is a vesiculobullous disorder that affects the mucocutaneous tissues, which are generally triggered by an autoimmune response to different medications, commonly cold medications, anticonvulsants, and sulfa drugs (1). This condition has classically been defined as a spectrum of disease, called SJS when there is <10% of skin involvement and toxic epidermal necrolysis (TEN) when it is more than 30%. For the purposes of this review, SJS will account for the entire spectrum of the disease. The overall incidence for this disorder has been estimated as 0.5-1.89 per million inhabitants (2–4). SJS is diagnosed clinically as a skin reaction with epidermal necrolysis in conjunction with the histopathological findings of subepidermal blisters and apoptotic keratinocytes. This is presumed to occur as a result of T-cell mediated type IV hypersensitivity reaction (5), on which CD14+ monocytes and CD4 T cells contribute to the activation of the effector CD-8+ T cells (5–7), which mediate cell death through induction

of apoptosis. This entity affects the ocular surface with a frequency of 40-75% of cases acutely (8), and about 63% of SJS patients present late symptoms of ocular surface involvement (9). During the acute episode, the classical finding is a bilateral conjunctivitis that ranges from simple hyperemia to widespread sloughing of the ocular surface, tarsal conjunctiva, and lid margins. The acute complications typically resolve within 2-4 weeks; however, conjunctival scarring may result from the initial inflammatory course. In order to prevent this, it is important to perform an early amniotic membrane transplantation (AMT) to the ocular surface, since this procedure has been shown to be associated with better outcomes (10). Importantly, a longitudinal 10 year review of 284 pediatric patients with SJS, revealed that 99% did not receive AMT during the acute setting, and 60% of these developed low vision or blindness (11). Common chronic sequelae from ocular SJS are entropion, trichiasis, and instability of the tear film that set up a vicious cycle of slow persistent inflammation, which provokes constant injuries to the ocular surface leading to corneal scarring, keratinization, and blink related trauma, further damaging the cornea, conjunctiva, and limbal stem cells, which ultimately may limit patients' visual acuity. Because of the corneal opacification resulting from the described mechanisms, some patients might need to undergo corneal transplant to increase visual acuity, in combination with another allogeneic stem cell transplant, keratolimbal allograft (KLAL). These procedures represent a challenge in SJS patients, since the corneal transplants are considered high risk due to their corneal neovascularization, dry ocular surface, and lid anomalies. Moreover, since the involvement is often bilateral, there is no possibility of performing an autologous "non-allogeneic" transplant from the contralateral eye. Therefore, the ocular surface reconstruction of SJS patients with allogeneic tissue, represents an immunological challenge as they have already had an autoimmune response to ocular surface "auto-antigens." Hence, the management of the immune response to transplant procedures in SJS patients involves a dual approach that modulates the inflammatory response to a new alloantigen in the context of an autoimmune sensitized patient. These procedures require a thoughtful and targeted systemic immunosuppression to avoid graft rejection, which includes modulation of the alloimmune and autoimmune responses. In order to understand the current perspectives on the immunologic approach to limbal and corneal transplants on SJS we conducted a literature review of publications from prestigious journals based on updated studies of ocular Stevens Johnsons and the immunologic management of corneal transplants and ocular surface reconstruction.

SJS PATIENTS ARE HIGH RISK CORNEAL TRANSPLANT RECIPIENTS

In a low-risk PK, defined as a naive transplant on a cornea without neovascularization on a non-inflamed host bed, only a minority of transplants will experience an immune reaction and these may rarely lead to graft failure. These successful outcomes are based on a quick inhibition of the vascular sprouting following surgery, that restores the normal angiogenic privilege of the cornea (12), which explains the excellent prognosis of low-risk PK with a survival of 90% of grafts at 1 year (13). Importantly, management of these corneas does not require systemic immunosuppression and tapered topical steroid therapy are generally enough to avoid graft rejection. This is not the case for SJS patients. These patients are considered to be high-risk PK recipients, not only because of corneal neovascularization but also because the lymphatic system invades the cornea. These offer a continuous delivery of immune effector cells to the graft and favors migration of antigen presenting cells to lymphoid tissues, particularly in the neck, activating T cell lymphocytes and ultimately causing transplant rejection (14, 15). Hence, on SJS patients undergoing corneal transplants, systemic immunosuppression is required to dampen the aggressive inflammatory response. Fundamentally, the anti-inflammatory therapy must be directed toward the adaptive immunity, essentially T cell lymphocytes, which have been shown to participate in allografts rejection in other organs (16) and the cornea (17). Therefore, similarly to solid organ transplantation, SJS high risk corneal transplants associated with limbal stem cell grafting requires the use of three groups of medications to prevent graft rejection: these are mainly the use of a systemic T-cell inhibitor in combination with an antimetabolite, and an early short course of steroid.

TARGETING OCULAR ALLOIMMUNE RESPONSES IN SJS

To inhibit the immunologic response directed to and elicited by the antigens carried in the donor graft, the pivotal elements of a chronic immunomodulation are the calcineurin inhibitors, which inhibit T cells activation. These are Cyclosporine, Tacrolimus, and Sirolimus and should be started at the time of transplantation (**Figure 1**). The rationale for their use is to provoke an immunosuppression that stops one or many steps in the path that is started when the donor antigens from the transplant are presented to the T-cell receptor and trigger the immune response that involves interleukin-2 (IL-2) and other factors, eventually leading to T-cell proliferation, migration, and attack on the corneal or limbal graft. Cyclosporine has been studied on patients with total limbal stem cell deficiency (LSCD) undergoing KLAL with a mean of 34 months of follow up. Fifty three eyes, of which nine had a history of SJS, received 5 mg/kg of oral cyclosporine daily. On follow up, the overall ambulatory vision (vision >20/200) decreased with time, being 44.6% at 5 years. Notably, SJS was the group with worse survival of ambulatory vision and survival of PK (18). This suggests that for SJS patients, cyclosporine is not an optimal choice for immunosuppression. In contrast, Tacrolimus success has been reported in KLAL in six patients with LSCD with 11 months of mean follow up (19). A group from the Cincinnati Eye Institute Cincinnati presented an immunosuppression protocol to address limbal transplantation (20), on which they administered high-dose oral corticosteroids, in addition to oral tacrolimus initiated at 4 mg twice daily and oral mycophenolate mofetil 1 g twice daily. With

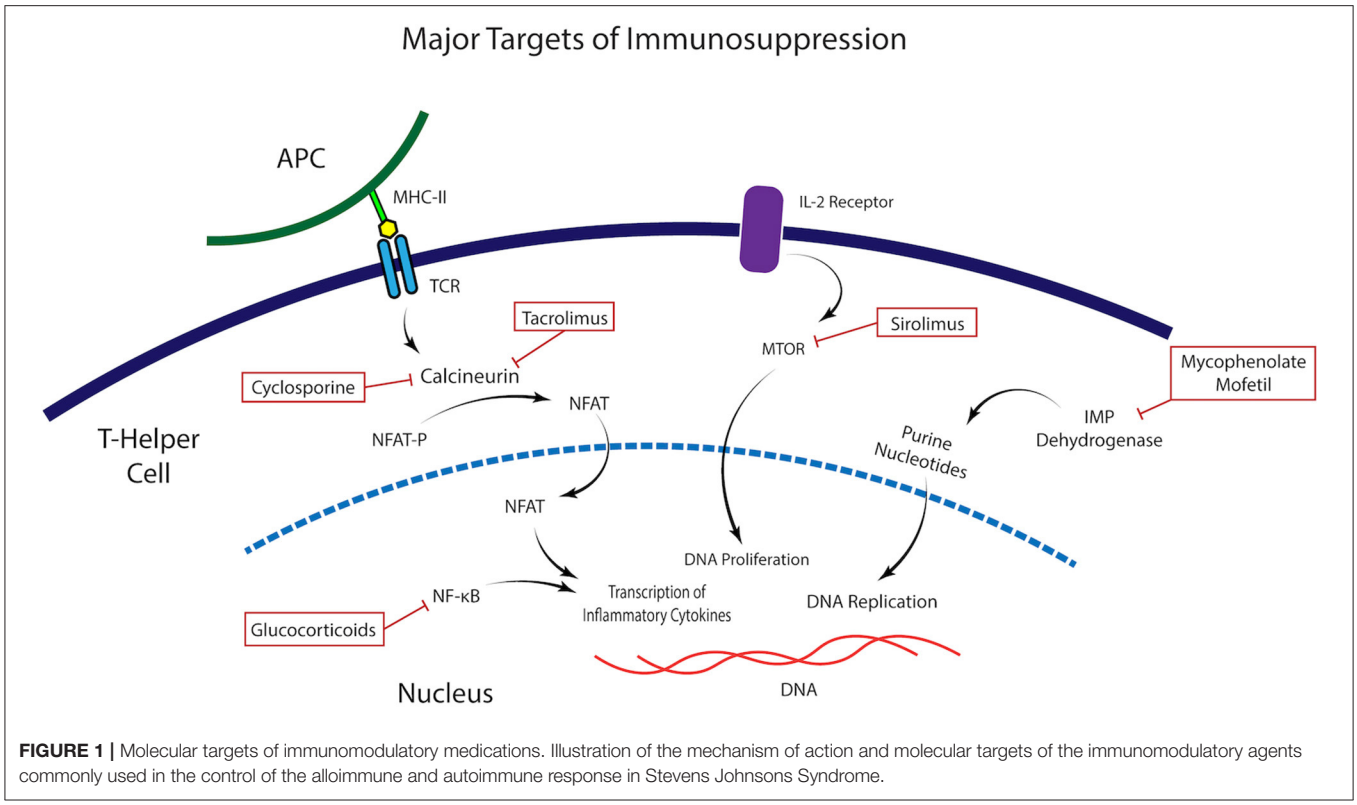

FIGURE 1 | Molecular targets of immunomodulatory medications. Illustration of the mechanism of action and molecular targets of the immunomodulatory agents commonly used in the control of the alloimmune and autoimmune response in Stevens Johnsons Syndrome.

this protocol, after a mean follow-up of 62.7 months, the authors achieved an incidence of rejection of 31.1% which was lower to other studies using only oral cyclosporine (18, 20). This same group evaluated their protocol in 19 patients with severe ocular surface disease undergoing living related conjunctival limbal allograft (CLAL) and KLAL, of which the most prevalent etiology was SJS. After 43.4 months of mean follow-up, almost 80% of patients required a subsequent keratoplasty to improve visual acuity (21). These findings suggest that even though SJS is a condition with poor ocular prognosis, combined corneal and limbal transplant require an aggressive and diligent immunosuppression with a group of drugs that includes a T cell inhibitor, and that Tacrolimus is favored over Cyclosporine as a T cell inhibitor.

TARGETING OCULAR AUTOIMMUNE RESPONSES IN SJS PATIENTS

Ocular autoimmune inflammatory disorders tend to present a chronic course. The correct management of these conditions involves the use of a steroid sparing agent that modulates B cell lymphocytes effectively with antimetabolites. In 2000, a consensus panel established that there is good evidence for the use of systemic immunosuppressive medication for various ocular inflammatory disorders, including mucous membrane pemphigoid (MMP) (22). This is an autoimmune disorder characterized by antibody deposition on the cell basement membrane that commonly attacks the mucocutaneous tissues. In particular, ocular cicatricial pemphigoid (OCP) is the variant that causes a cicatricial conjunctivitis that ranges from subepithelial fibrosis to ankyloblepharon with severe loss of visual acuity, similarly to SJS. OCP is another immunobullous disorder caused by an adaptive immune component that functions as an analog to explain the management of the autoimmune component of SJS patients, since there is scarce literature concerning the ocular management of the autoimmune responses of SJS patients. The treatment of MMP/OCP is through systemic immunosuppression, and the medications most frequently used are Dapsone, Mycophenolate, Methotrexate, Cyclophosphamide, and Rituximab (23). A proposed scheme is to start with tapered oral Steroids for 3 months, along with Mycophenolate 1-g BID. The use of mycophenolate is advised for its good efficacy at inhibiting not only T cells, but also B lymphocytes, in addition to presenting a safe toxicity profile and an easy dosing for the patient (24). For management of high-risk PK, a prospective, randomized trial compared the use of topical and systemic steroids with or without addition of 2 g of Mycophenolate/day for 6 months. At 1 year, the authors observed a statistical difference in the rate of immune reactions in 11% of those treated with MMF as opposed to 33% in the control group ($P = 0.03$) (25, 26). After 3 years of mean follow up no immune reactions were seen in 83% of MMF treated patients, in contrast to 64.5% in the control group ($P = 0.04$), and the rate of corneal rejection was much higher in the control group (78%), than the MMF group (20%) (25, 26). This data supports that MMF is a safe and effective drug to attenuate the autoimmune responses that OCP and SJS patients commonly present.

DUAL IMMUNOMODULATORY APPROACH FOR SJS PATIENTS UNDERGOING SURGERY

In total, an immunologic approach for corneal or limbal stem cell transplants on SJS requires modulation of the alloimmune and autoimmune response in order to fully attenuate the inflammatory response to the corneal graft and avoid failure of therapy (**Figure 1**). As described, one component is the auto antigen surface disease, which is controlled with Mycophenolate and on the other hand one has to address the allotransplant immune response that attacks the living related and/or cadaveric KLAL. For this, a T cell inhibitor, preferably Tacrolimus should be used. The proposed immunosuppression regimen for SJS patients, as depicted by the Cincinnati group, should be as follow (21): At the time of surgery, solumedrol 500-1,000 mg, with immediate implementation of Tacrolimus 4 mg twice a day, and MMF 1 g twice a day. Prophylactic drugs such as valacyclovir and trimethoprim-sulfamethoxazole must be strongly considered. Tacrolimus levels must be measured at 3 months, and the optimal serum concentration is 8-10 ng/ml. Systemic prednisone is started with high initial doses at time of surgery, typically with intravenous Solumedrol 500-1,000 mg, followed by prednisone 1 mg/kg/day in the post-operative. Once inflammation is fully suppressed, at about one to 2 months, tapering of the steroid can begin. Importantly, steroid sparing therapy should be kept for a long period of time, similarly to a solid organ transplant.

CONSIDERATIONS FOR SYSTEMIC IMMUNOSUPPRESSION MEDICATIONS

Of the presented groups of drugs, corticosteroids are a tempting resource to manage these patients, since these are highly effective, however they carry a myriad of adverse effects. For immunosuppressive outcomes on graft transplantation, the usual dose is 60 ± 20 mg of oral prednisone, which are highly effective; though the side effects are hyperglycemia, bone damage, weight gain, altered cognition, amid many others that should be screened at every clinic visit. In order to tackle the adverse effects, alternate day corticosteroids dosing is a possible solution, but corticosteroid-sparing agents should always be pondered. The T cell inhibitors function by inhibiting calcineurin activation, *via* binding to different proteins to block T cell proliferation. Cyclosporine A (CsA) works by binding to cyclophilin. It is generally dosed from 2 to 5 mg/kg. Known side effects are nephrotoxicity, high blood pressure, gingival hyperplasia and hirsutism. Tacrolimus binds to FK506-binding protein 12 (FKBP12) to form a complex that inhibits calcineurins. Thus, the initial phase of T cell activation is blocked, resulting in inhibition of T-lymphocyte signal transduction and IL-2 transcription (27). Tacrolimus has been reported to entail fewer systemic side effects than CsA, and these include nephrotoxicity in addition to high blood pressure and dyslipidemias as well but, unlike cyclosporine, these are more rare (28). Tacrolimus may cause diabetes and peripheral neuropathies, as well. It is generally dosed with 4-5 mg daily and monitoring should include creatinine; complete blood count (CBC); liver functions testings (LFT), blood pressure and cyclosporine/tacrolimus serum levels, which should range from 70 to 180 ug/L and 8-10 ng/mL, respectively, and ought to be strictly controlled. Finally, Mycophenolate mofetil inhibits the synthesis of guanosine nucleotides, resulting in selective inhibition of T- and B-lymphocyte proliferation. MMF is generally dosed with 2.0-3.0 g per day and its main side effects are diarrhea and bone marrow suppression. Therefore, monitoring is advised with CBC and LFT.

PERIOPERATIVE MANAGEMENT OF SJS PATIENTS

It is important to note that the management of the ocular surface of SJS patients is complex since lid anomalies, such as trichiasis, distichiasis, and/or lid entropion can be present and should be addressed prior to the corneal or limbal stem cell transplant. Two additional characteristics should be investigated: whether the bulbar conjunctiva is lubricated or significantly dry and if there is posterior eyelid margin keratinization. These difficulties can be resolved with mucous membrane grafting (MMG) if the eye is significantly dry and there is posterior eyelid margin keratinization. This procedure also helps improve severe dry eye, since the minor salivary glands that are present in the labial mucosa can be harvested and increase tear production. A recent multicentre study presented satisfactory long-term outcomes for 17 patients with SJS (29). Another series of SJS patients with lid related keratopathy observed that MMG and prosthetic replacement of the ocular surface ecosystem (PROSE) placement significantly increased long term vision, as compared to conservative treatment with medical management (30). Consequently, prior to performing the ocular surface reconstruction, a multidisciplinary approach should be considered with a nephrologist and an oculoplastic team. Post-operative management encompasses the use of topical steroids to reduce the ocular surface inflammation and prevent rejection from the graft, as well. Frequent tear substitution should be implemented with preservative free artificial tears or ideally serum tears or plasma rich in growth factors, since these have a myriad of growth factors and contribute to stabilization and nurturing of the ocular surface (31). Unfortunately, KLAL procedures in SJS have a high rate of failure due to different complications that may lead to a poor visual acuity, and these should be communicated with the patient.

THE FUTURE OF LOCAL TARGET ORIENTED IMMUNE REGULATION FOR SJS PATIENTS

In 1995, Sakaguchi et al. discovered a population of CD4+ cells, which were termed regulatory T-cells (T-regs) (30, 31). CD4+FoxP3+ Tregs play integral roles in maintaining immune homeostasis, particularly through suppressing the immune response and modulating effector inflammatory cells (32–34). Importantly, identification of T-regs in organ transplants have implicated them as being important in graft tolerance (35).

Downregulation of the inflammatory mechanisms is achieved *via* stimulation of inhibitory cytokines (34–36), reduction of effector inflammatory molecules (34, 37), and inhibition of dendritic cells (34, 38). Regulation of IL-2 reduces the levels of this cytokine to limit availability for conventional T-cell activation, since low doses of IL-2 selectively favor activation of T-regs over effector/conventional T cells (34, 39). Infusion of T-regs have shown promising results in different types

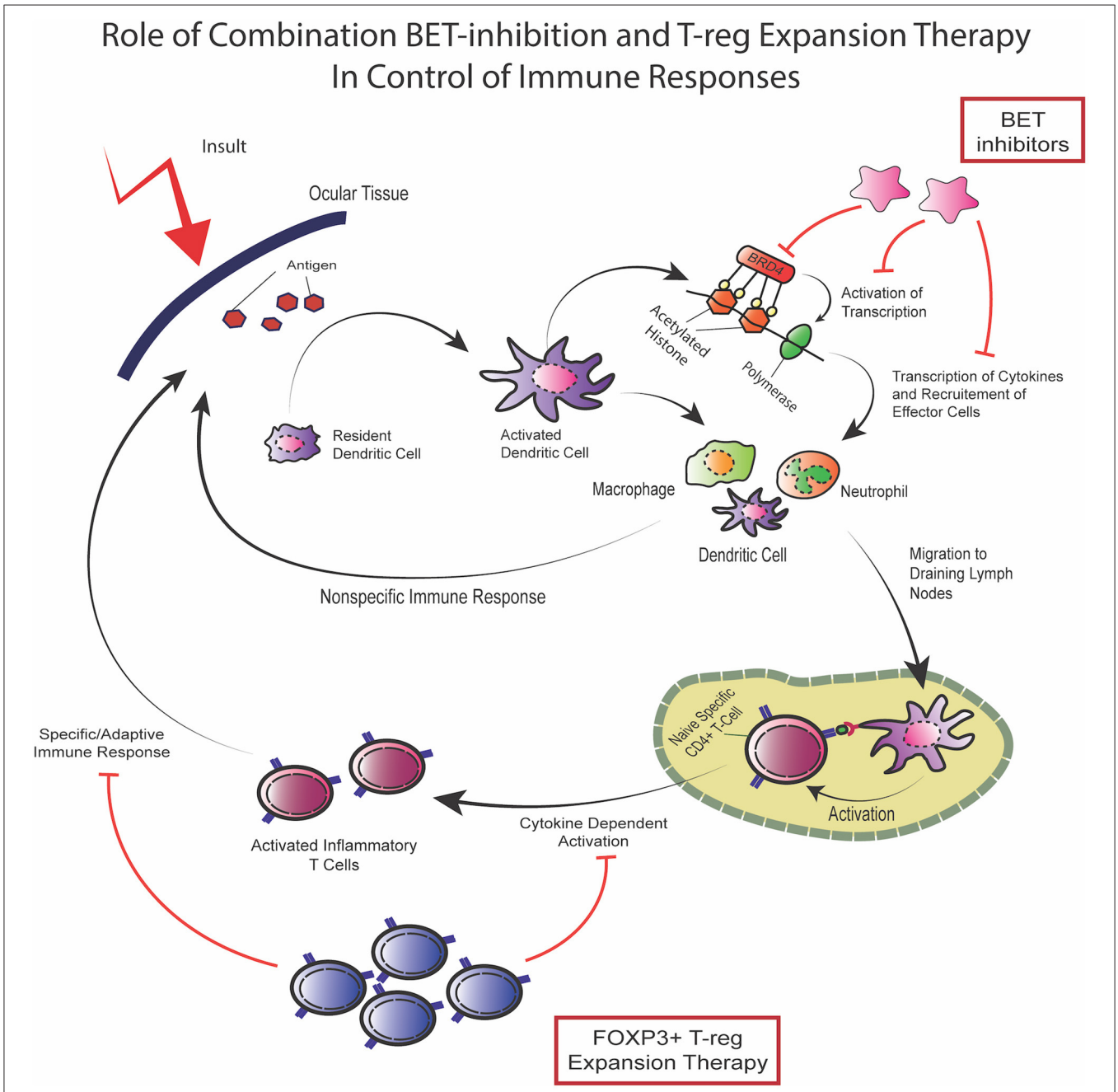

FIGURE 2 | Combination of BET inhibition and T-reg expansion to target immune responses. In response to the presentation of novel antigens, as in the case of an ocular surface transplant, the resident immune cells activate and, through bromodomain-regulated activation of transcription, produce inflammatory cytokines which leads to recruitment of effector cells which carry out non-specific innate immune response. In addition, activated immune cells may also function as antigen presenting cells through MHC-II expression and migrate to draining lymph nodes where activation of antigen specific CD4+ T-cells takes place resulting in cytokine dependent specific immune response activation of the adaptive immune response. Dual therapy using BET-inhibitors mainly targeting the cytokine-dependent innate response along with T-reg expansion therapy targeting the activation of the adaptive response can potentially control immune responses and suppress inflammatory disease. The two modalities have been shown to not interfere with one another and can effectively provide a compound strategy for inflammatory control.

of solid organ transplantation (40–42). Recently, our group developed a new approach to expand T-regs *in vivo* by targeting TNF receptor superfamily 25 (TNFRSF25) and CD25 using a TL1A-Ig fusion protein together with low dose IL-2 (43, 44). This strategy showed promise by demonstrating an impressive T-reg expansion in donor mice which ameliorated graft vs. host disease (GVHD) in pre-clinical models (45, 46). Epigenetic readers of histone acetylation can regulate transcription of genes involved in inflammation (43). Bromodomain and extra-terminal (BET) proteins which affect acetylation can be targeted using bromodomain and extra-terminal protein inhibitors (BETi). The BETi I-BET762 and JQ1 showed anti-inflammatory properties by disrupting the expression of pro-inflammatory cytokines in macrophages and suppressing genes involved in T cell-mediated pro-inflammatory functions (47). These have shown efficacy in a variety of inflammatory conditions (48–52). There have also been recent studies to investigate the use of bromodomain inhibitors to suppress responses against allo-antigens in transplantation (43). Such approaches provide the promise for developing novel platforms for new therapeutic options. Our group recently proposed a combinational strategy of BETi combined with T-reg expansion therapy and in murine models of allogeneic hematopoietic stem cell transplant, did not interfere with one another but together suppressed GVHD (43). In the future, this combinatorial platform could be considered for application to SJS patients to downregulate allo and auto immune responses following transplant (**Figure 2**).

CONCLUSION

SJS is a rare, but highly morbid disease. Although new genetic associations of drugs are being recognized, the incidence of SJS has not dramatically changed, and its consequences are severe. On the eye, it commonly affects the ocular surface to the extent that it may need to undergo corneal surface reconstruction, with possible corneal or limbal stem cell transplantation to improve visual acuity. This presents an immunologic challenge, which should be managed with a dual approach to down regulate the immune response by using a T cell inhibitor and an antimetabolite (Tacrolimus and Mycophenolate are effective and safe choices) in addition to tapered systemic steroids. Further studies with diverse drugs, including monoclonal antibodies, are warranted to improve graft rejection outcomes. The future of immunosuppression for graft transplant involves local target oriented immune regulation *via* T-reg modulation and epigenetic mechanisms. These offer SJS patients and others promising opportunities to tackle the high risk of corneal rejection.

DATA AVAILABILITY STATEMENT

The original contributions generated for the study are included in the article/supplementary material, further inquiries can be directed to the corresponding author/s.

ETHICS STATEMENT

Written informed consent was obtained from the individual(s) for the publication of any potentially identifiable images or data included in this article.

AUTHOR CONTRIBUTIONS

MS: collection, analysis and interpretation of data, manuscript preparation, and critical reading, edition of figures. HM: manuscript preparation and critical reading. RBL: interpretation of data and manuscript preparation. VLP: senior author of the review, involved in all aspects of this study. All authors contributed to the article and approved the submitted version.

FUNDING

This work was supported by Gillingham Pan-American Scholarship, Pan-American Association of Ophthalmology (to MS), National Institutes of Health/National Eye Institute grants: R01EY030283 and R01EY024485 (to VLP and RBL), and Duke NIH Center Core Grant and Duke Research to Prevent Blindness Unrestricted Grant (to VLP and RBL).

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Conflict of Interest: RBL is a compensated consultant/advisory board member for and equity holder in Heat Biologics. VLP has worked as a compensated consultant for Alcon, Eyegate, Oculis, Novartis, Trefoil, Quidel, Dompe and is a board member of OBTears.

The remaining authors declare that the research was conducted in the absence of any commercial or financial relationships that could be construed as a potential conflict of interest.

frontiers in Medicine

ORIGINAL RESEARCH
published: 24 May 2021
doi: 10.3389/fmed.2021.644795

Clinical Characteristics of Patients With Chronic Stevens-Johnson Syndrome Treated at a Major Tertiary Eye Hospital Within the United Kingdom

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The purpose of this study is to provide a comprehensive review of the clinical characteristics in chronic Stevens-Johnson syndrome (SJS) patients within the United Kingdom population, their causative factors, treatment profile and prognosis. This retrospective series included 91 patients with chronic SJS treated at Moorfields Eye Hospital (London, United Kingdom). A chart review included visual acuity and presence of clinical findings (including lid abnormalities and ocular surface findings). All medical and surgical treatments were also recorded. Approximately a half of patients were White British but there were significant numbers of patients from other ethnic groups, South Asian and Black in particular. Oral antibiotics were the causative agent in almost a half of the patients with SJS, systemic infections in 14%, non-steroidal anti-inflammatory drugs in 8% and anticonvulsants in 7%. The age of onset was varied but a significant proportion of patients developed acute SJS in childhood. There was a significant correlation between visual acuity at initial referral to final recorded vision. Vision was found to continue to significantly deteriorate over time despite therapeutic interventions. Our regression model shows that ∼62% of the variance in final vision can be explained by the initial vision and duration disease. The majority of our patients were on advanced ocular surface treatments including serum drops, topical ciclosporin and retinoic acid drops. Of particular significance, approximately a third of our patient cohort was also on systemic immune suppression. In conclusion, chronic SJS within the UK population under tertiary care remains an area of unmet clinical need. Current medical and surgical modalities prevent worsening of vision in severe ocular disease from SJS.

Keywords: Stevens Johnson syndrome, toxic epidermal necrolysis, Limbal stem cell failure, ocular surface disease, symblepharon

OPEN ACCESS

Edited by:
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Reviewed by:
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Seoul National University, South Korea
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Specialty section:
This article was submitted to Ophthalmology, a section of the journal Frontiers in Medicine

Received: *21 December 2020*
Accepted: *03 May 2021*
Published: *24 May 2021*

Citation:
Jabbour S, Din N, Logeswaran A, Taberno Sanchez S and Ahmad S (2021) Clinical Characteristics of Patients With Chronic Stevens-Johnson Syndrome Treated at a Major Tertiary Eye Hospital Within the United Kingdom. Front. Med. 8:644795. doi: 10.3389/fmed.2021.644795

INTRODUCTION

Stevens-Johnson syndrome is an immune mediated mucocutaneous disease that induces widespread sloughing of the skin and mucosal surfaces, and mortality can be as high as 35% (1). The estimated annual incidence of SJS is 1.2–12.35 new cases per million (2). SJS is a type IV hypersensitivity reaction and leads to a characteristic vesiculo-bullous reaction. Whilst the

pathogenesis is unclear, it appears to be mediated by a cell-mediated keratinocyte apoptosis via the Fas signaling cascade (3). In survivors of the disease, the unremitting chronic inflammation, dessication and scarring lead to blindness, with 20–79% of survivors experiencing chronic ocular surface disease (4–6).

There are numerous potential causes for the development of SJS. The commonest is an idiosyncratic reaction to systemic medications, such as antibiotics, anti-epileptic medications and non-steroidal drugs. In 15% of cases, no causative drug agent can be found (1, 7). However, other causes include viral infections and vaccines (8). Ethnicity also plays a role and it is estimated that Asian patients are at a 2-fold increased risk of SJS compared to Caucasian patients (9).

To our knowledge, there is a lack of published literature on SJS in the United Kingdom. One study by Radford et al. in collaboration with the British Ophthalmic Surveillance Unit in 2012, reported 16 cases of SJS/TEN across the United Kingdom (10). They identified the incidence to range between 0.1 and 1.2 per million, with the highest in the West Midlands, fitting with a higher Indian sub-continent ethnicity. Greater London had an incidence of 0.2 per million. Fifty nine percent (59%) of patients had visual acuities < 6/18 at presentation which fell to 55% on their final 12-month follow-up.

The aim of the work described in this manuscript is to provide a comprehensive review of the clinical characteristics in chronic SJS patients within the United Kingdom population, their causative factors, treatment profile and prognosis. While some papers have reported cicatricial conjunctivitis as whole, we aim to provide a spotlight on ocular SJS and its sequalae. We believe this paper has the highest number of cases of ocular SJS reported in the United Kingdom, shedding some light on this rare condition.

METHODS

Patients

This retrospective clinical was conducted at Moorfields Eye Hospital in London, UK. The study adhered to the tenets of the Declaration of Helsinki and was approved by our institution's review board (IRAS 119170). All patients referred to Moorfields Eye Hospital (London, UK) for the management of their chronic SJS related ocular surface disease were selected using our medical archives diagnosis code and were included in the study.

Evaluation Method of Clinical Data

A thorough chart review was conducted. Demographic details were collected and included age at disease onset, ethnicity (as self-identified by the patient and following national census categories), age at presentation and precipitating agent of SJS (if known). Clinical findings included laterality and Snellen best corrected visual acuity (BCVA) at initial referral visit and at last clinical visit follow-up. The presence of lid abnormalities (e.g., entropion, distichiasis/trichiasis, and symblepharon), and ocular surface findings (e.g., dry eyes, persistent epithelial defect, keratinization and limbal stem cell deficiency) were noted. These were documented as either present or absent throughout the follow-up period. For example, the presence of any keratin on the lid margin, conjunctiva or cornea was noted as a positive finding. Limbal stem cell deficiency was defined as corneal conjunctivalization in presence of late fluorescein staining. No grading system of clinical findings was conducted given the heterogeneity of the reviewed notes and the retrospective nature of this study. All medical treatments (e.g., topical drops, systemic medications and contact lens use) and surgical treatments (e.g., lid surgery, amniotic membrane transplantation, and limbal stem cell transplantation) were also recorded. **Supplementary Material 1** provides all the data collected. Given that acute care of SJS was carried out at several burn units nationally at different location sites, details of early ocular care were not available for review.

Statistical Analysis of Clinical Data

Statistical analysis was conducted using SPSS version 24 (IBM Corp, Armonk, New York). To negate the effect of inter-eye correlation, data from only from one eye per patient was used for statistical analysis. This can be achieved through many methods, but we used the left eye for the purpose of this analysis (11, 12). Correlations were measured using the data collected, with particular focus on the association with chronic complications i.e., dry eye, symblepharon and LCSD. The strength of association between continuous variables (e.g., initial and final visual acuity) was determined using a Pearson correlation (r). The strength of association between binary and continuous variables (e.g., final visual acuity and presence of symblepharon) was determined using a point-biserial correlation. The strength of association between binary variables (e.g., presence of trichiasis and corneal graft) was determined using a Phi coefficient. An association (x) was considered strong when $x \geq |0.6|$, moderate when $|0.3| \leq x < |0.6|$ and weak when $x < |0.3|$. The Bonferroni correction was not applied due to its inconclusive value and to minimize Type II error in the study of this rare disease (13, 14). To calculate which variables could independently predict the final VA, a stepwise linear regression was performed. A p-value of <0.05 was considered to be statistically significant.

RESULTS

Demographics

There was an almost equal gender split in our patient cohort (47 female and 44 male). The mean age of acute SJS onset was 25.4 years with a range of 3 months to 82 years (**Figure 1**). **Table 1** provides the demographics details of our patient population. There are two peaks of disease onset, those younger than 10 years of age and those between 21 and 30 years of age. Our patients had suffered from SJS for a mean of 26.7 years (defined from the time of acute disease to last encounter) with a range of 0–81 years (**Figure 2**). The causative agents in almost half of our patients were antibiotics (43 patients; 48%) including penicillins, sulfa drugs and tetracyclines (**Figure 3**). Other common causes were systemic infections (13 patients; 14%), non-steroidal anti-inflammatory drugs (7 patients; 8%), anti-epileptics (6 patients; 7%) and allopurinol (4 patients; 4%). Almost half of our patients were White British (40 patients; 44%) but the other half was

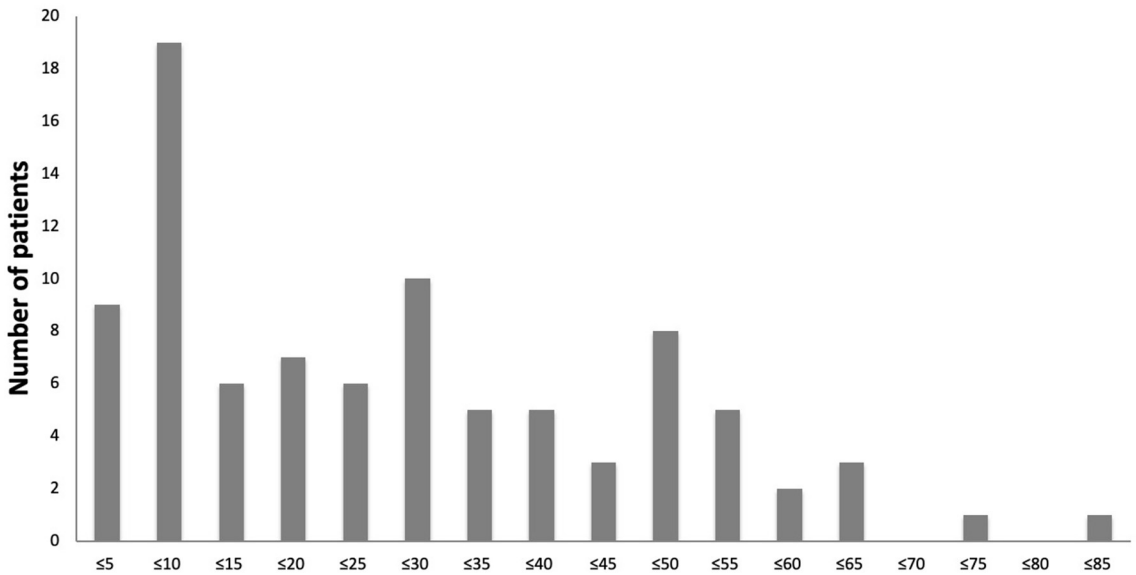

FIGURE 1 | A bar chart showing age of patients at onset of acute SJS. Number of patients in every 5-year age range from ≤5 years to ≤85 years are shown.

TABLE 1 | Patients' demographics and Snellen decimal best-corrected visual acuity.

	Mean (range)	Standard Deviation
Age at disease onset (years)	24.9 (0.0–82.0)	19.9
Age at presentation to our center (years)	52.0 (8.0–90.0)	18.4
Duration of disease (time from onset to last follow-up) (years)	0.49 (0.00–1.50)	19.44
BCVA at presentation (decimal)	0.49 (0.00–1.50)	0.39
BCVA at last follow-up (decimal)	0.44 (0.00–1.50)	0.47

BCVA, best-corrected visual acuity.

represented by different ethnicities, mostly South Asian (16 patients; 17%) and Black African or Black Caribbean (14 patients; 16%) patients (**Figure 4**).

Vision

When each eye is evaluated separately, the majority had decimal vision worse than 0.33 (6/18 or worse) (**Figure 5**). The initial visual acuities between the right eye and left eye on presentation were correlated ($p = 0.001$), and there was no statistically significant difference in the initial vision between each eyes ($p = 0.754$). The final visual acuities between the right eye and left eye were also correlated ($p = 0.001$) and there was no statistically significant difference in the final vision between each eye ($p = 0.975$). For both right and left eyes, poor vision remained poor at most recent follow-up despite clinical input and interventions. Vision continued to deteriorate for most eyes despite treatment. This is demonstrated in the scatter plot between initial BCVA and final BCVA (**Figure 6**).

Correlation of Signs

There was evidence of moderate correlation between the presence of symblepharon and misdirected lashes ($p = 0.001$, Phi coefficient), and a weak correlation with dry eye ($p = 0.008$, Phi coefficient). There was a moderate correlation between the presence of limbal stem cell deficiency and misdirected lashes ($p = 0.003$, Phi coefficient) and weak correlation with the formation of lid margin keratin ($p = 0.012$, Phi coefficient), conjunctival keratin ($p = 0.015$, Phi coefficient) and corneal keratin ($p = 0.008$), Phi coefficient. There was a moderate correlation between the presence of corneal keratin and conjunctival keratin ($p = 0.001$, Phi coefficient), and weak correlations with the formation of lid margin keratin ($p = 0.015$, Phi coefficient) and limbal stem cell deficiency ($p = 0.008$, Phi coefficient). **Supplementary Material 2** provides the table of all correlations evaluated in this study.

Treatment

All medical and surgical interventions are presented in **Table 2**. Of the therapies used in our cohort of patients, 82.2% were using steroid drops, 41.1% were on Ciclosporin A drops, 22.2% were using serum drops (either autologous or allogeneic serum) and 32.2% were on topical retinoic acid. A third of our patient cohort were prescribed systemic immune suppression (mostly Mycophenolate). In patients who have used RGP or scleral lenses, final decimal visual acuity was 0.21 ± 0.10 (0.00 to 1.20) compared to 0.01 ± 0.00 (0.00 to 1.20) with those with no RGP or scleral lenses ($p = 0.001$). In patients who have undergone mucous membrane grafting (MMG) for lid keratinization, final

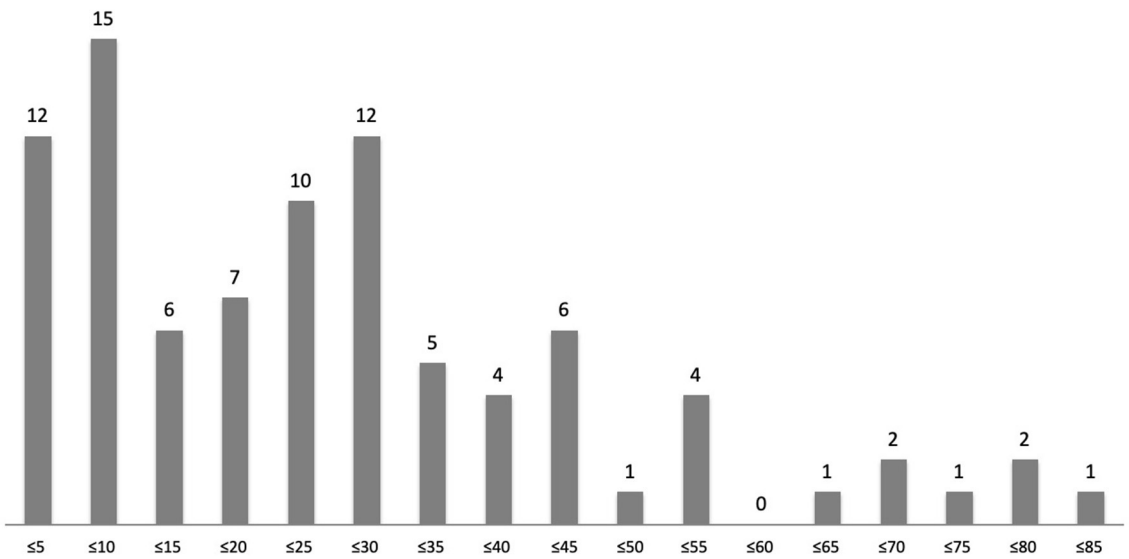

FIGURE 2 | A bar graph showing duration of ocular SJS in years. Number of patients in each 5-year range category from ≤5 years to ≤85 years are shown.

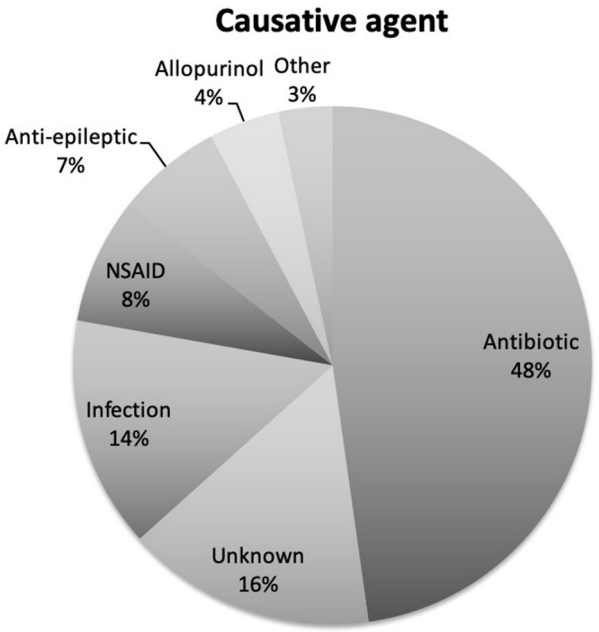

FIGURE 3 | A pie chart showing the causative agent for SJS in our patient cohort. Antibiotics are the commonest cause being in almost half of our patients.

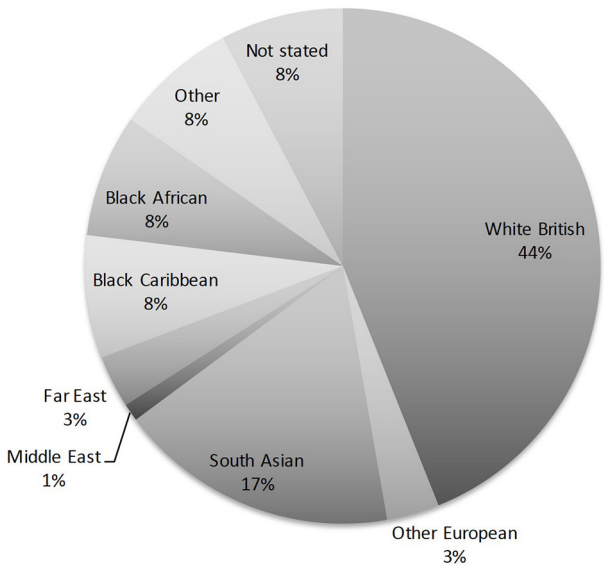

FIGURE 4 | A pie chart showing the breakdown of ethnicities amongst our patients. Although most of our patients were White British (44%), over a half belonged to various other ethnic groups.

decimal visual acuity was 0.31 ± 0.58 (0.00 to 1.50) compared to 0.56 ± 0.57 (0.01 to 1.20) at first visit ($p = 0.236$).

Signs Associated With Poor Vision

Our regression model predicted variance in final vision [$F_{(4,78)} = 31.93$, $p < 0.001$, $R^2 = 0.62$]. Parameters of significance included initial vision ($B = 0.697$, $p < 0.001$), corneal keratin ($B = -0.239$, $p = 0.004$), duration of disease ($B = -0.004$, $p = 0.019$) and limbal stem cell deficiency ($B = -0.176$, $p = 0.024$). There was no evidence of auto-correlation (Durbin-Watson <2.5) or multicollinearity (VIF<10), and the assumption of homoscedasticity was met. This model shows that ∼62% of the variance in final vision can be explained by the initial

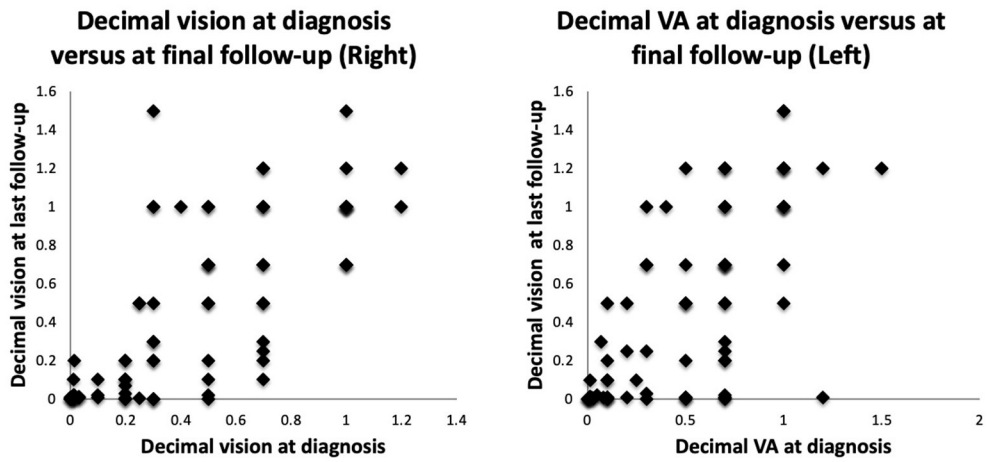

FIGURE 5 | Dot plots showing decimal vision in the right eye (RE) and the left eye (LE) at presentation against most recent vision.

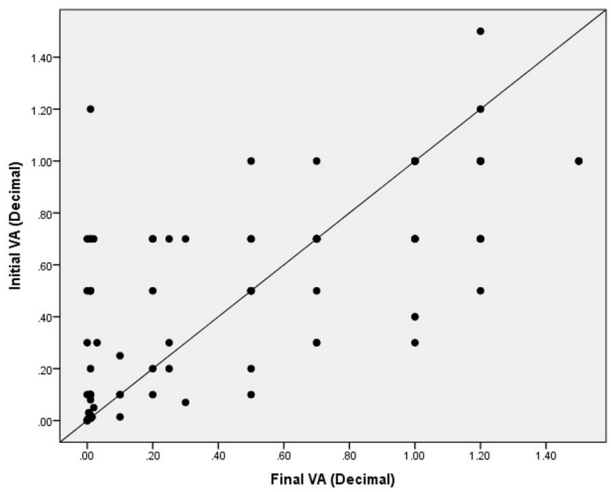

FIGURE 6 | Scatter plot demonstrating the relationship between initial visual acuity and final visual acuity, as compared to a plot with a slope =1. Most eyes demonstrate a deteriorating vision throughout the follow-up.

TABLE 2 | Percentage of patients undergoing specific medical and surgical ocular interventions.

	Percentage of patients (%)
Topical steroids	82.2
Topical ciclosporin A	41.1
Topical serum drops (autologous or allogeneic)	22.2
Topical retinoic acid	32.2
Contact lens wear (RGP or SCL)	49.5
Amniotic membrane transplantation	18.7
Punctal closure	25.3
Systemic immunosuppression	33.3
Lid surgery (entropion, trichiasis)	80.2
Mucous membrane grafting	10.0
Corneal transplantation (penetrating or lamellar keratoplasty, keratoprosthesis)	13.2
Limbal stem cell transplantation	5.5

RGP, rigid-gas permeable; SCL, scleral contact lens.

vision, corneal keratin, duration disease and presence of limbal stem cell deficiency.

DISCUSSION

In this manuscript we describe our findings from the retrospective analysis of our large cohort of patients in the chronic ocular phase of SJS. The chronic ocular features of SJS include limbal stem cell deficiency and ocular surface keratinisation which lead to blindness. Our cohort is of importance partly because of the large number of patients with this rare disease but also because it shows a varied ethnic (and therefore likely genetic) spectrum with approximately a half being White British but significant numbers of South Asian and Black patients. London has a diverse ethnic mix owing to its cosmopolitan global city status and hence provides a closer representation of global epidemiological patterns. Unlike some other published cohorts, the commonest trigger in our patients was antibiotics rather than anticonvulsants (15), allopurinol (16), or non-steroidal anti-inflammatory drugs (17), although they were also represented in the trigger data. As in other published cohorts, over one third of our patients (33 patients) developed SJS in childhood (18).

Long-term visual impairment is a major problem in chronic SJS, and this is reflected in our cohort. In one case series of 89 patients, Jongkhajornpong et al. found 26% of their patient cohort developed severe visual impairment during both the acute and chronic phases of the disease, and this is also seen in other published reports (19–21). However, when further subgroup

analysis was performed and chronic ocular complications were focused upon, the rate of severe visual impairment rose to 52.27%. As in our cohort, it was found that corneal neovascularisation, symblepharon and corneal opacification were the key determinants of severe visual impairment. In our model the major predictors of final VA were the initial VA duration and LCSD and keratin. As a result of these chronic complications, management of the acute stage is critical. In a recent study by Basu et al. almost 66% of children with SJS/TEN who did not receive appropriate care in the acute phase were blind 1 year after the acute episode of SJS/TEN (22). Hence, immediate acute ophthalmic assessment and intervention, and appropriate follow-up by corneal specialists is critical to prevent these significant vision compromising sequelae.

Long-term visual rehabilitation remains an area of unmet need. Very few interventions demonstrate an improvement in final visual acuity in patients with chronic SJS. The wear of scleral contact lenses, mainly the PROSE (Prosthetic Replacement of the Ocular Surface Ecosystem) lens has been shown to improve final visual acuity, similar to our outcomes with scleral or RGP lenses (22–25). Mucous membrane grafting, a newer procedure, targets lid margin keratinization. It has been shown in some studies to improve overall visual outcomes in SJS (23). Ten eyes in our cohort underwent MMG, but there was no statistically significant change in vision. More studies are warranted on the proper technique and timing of MMG in halting progressive keratinization and deterioration of vision.

This is an exploratory study of a rare disease. Correlations were ascertained to explore the relationship between a range of clinical signs with advanced sequelae of the disease. This does not explain a causal relationship nor any potential confounding between these variables. However, it does provide valuable information on potential associations that could help guide further research and management of SJS. The initial vision at a tertiary referral center does not reflect the initial vision at the time of disease onset. While this may introduce an element of Berkson bias, the strength of this study is real-world outcome data that reflects referral pathways from secondary to tertiary referral centers.

At Moorfields Eye Hospital, for all patients with severe ocular surface disease (SJS, mucous membrane pemphigoid and limbal stem cell deficiency), our management protocol is based on a treatment stepladder approach. This includes management of dryness, epithelial defects, and limbal stem cell deficiency; lid disease (trichiasis, lid malposition and meibomian gland dysfunction); and inflammation. Treatments will include the use of topical treatments (lubricants, mucolytics, preservative free steroids, ciclosporin drops, and serum drops); lid surgery (excision of lash follicles, lid split and anterior lamellar repositioning, mucous membrane grafts); the use of scleral contact lenses; amniotic membrane transplantation and surface reconstructive surgery; and systemic immune suppression.

One third of the patients in our cohort were prescribed systemic immunosuppression. This is a significant number and proportion of patients. The use of systemic immunosuppression in chronic SJS remains a controversial and poorly studied topic. In most cases with SJS, late surface failure has been associated with the destruction of corneal limbal stem cells during the acute inflammatory phase of the disease. Chronic cicatricial sequelae, such as trichiasis, entropion and exposure also contribute to progressive surface failure. Abating the acute inflammatory response with systemic immunosuppression, including corticosteroids, and addressing cicatricial lid disease can prevent and halt surface failure in patients. In a small subset of patients, disease progression can still occur despite appropriate treatment, believed to be due to endogenous recurrent conjunctival inflammation (26). A recent retrospective study described seven tertiary referrals of SJS with chronic inflammation that required systemic immunosuppression including steroids and steroid-sparing agents. Five out of these seven patients demonstrated improved outcome with therapy (27). Although specific outcomes and indications of the use of systemic immunosuppression in SJS is beyond the objectives and scope of this retrospective study, further studies are currently being conducted in our center examining outcomes in this subgroup of patients.

Compared with other international studies, our study remains one of the largest to date to record on chronic SJS findings with the Australia study reporting three cases, 95 cases in India and 70 cases in a Chinese study (28–30). In the Australian study, the incidence of SJS was reported to be 0.1 per million. Patients with SJS had a younger mean age of 43 +/−10 years (range 28–53 years). The diagnosis of SJS was found to be shorter, with a mean duration of 12.8 days (range 2–28 days), which was in keeping with the UK study (10, 28). The predominant signs seen in the Indian study was 75% of SJS patients had a BCVA of <6/18, with predominant signs being symblepharon formation, fornix shortening, ocular surface keratinisation with limbitis and corneal scarring. This contrasts with the Indian study where 57% of patients were between 21 and 40 years old (29). The duration from initial onset to time of presentation ranged from 6 days to 18 years. Intakes of drugs was the principle cause with sulfonamides being cited as the most frequent cause of SJS. Thirty three percent (33%) of patients has VA better than 6/12. The major complications cited in the Indian study were: corneal superficial punctate epitheliopathy, scarring and vascularization. Conjunctival xerosis and lid oedema were also commonly cited signs (29). By contrast, the Chinese study describes a mean age of 43.4 age, with 64% diagnosed in males, 36% in females. The commonest cause offending drugs were antibiotics (29.5%) and anticonvulsants (24.1%). Carbamazepine, allopurinol, and penicillins were the most common single offending drugs (17.5, 9.6, and 7.2%, respectively) (30).

Our study presents several limitations. First, all patients are referred to our center following acute care at different hospitals. The unique aspect of Moorfields Eye Hospital as a tertiary national center for ophthalmic care is that it receives complex SJS/TEN referrals across the country. Many of the patients are examined and managed by dermatologists or burns units according to local guidelines, and only those with ocular involvement resistant to first line treatment are referred for specialist opinion (1). As a result, we were unable to capture the acute ocular complications and management of the disease. This limitation is relevant to demonstrate differences in long term

outcomes of SJS that received specific treatments such as AMT on the lid margin and ocular surface during the acute phase of the disease, which has been shown to improve outcomes and clinical prognosis. Second, we considered a wide range follow-up periods which can limit different time point of measurement in visual acuity and chronic complications. Third, given the heterogeneity of documentation of clinical findings, it was not possible to grade clinical findings as per chronic SJS grading system. Such data would have allowed us to stratify overall outcomes depending on severity of the disease and the presence and severity of specific clinical findings. Fourth, visual acuity as a metric of disease in chronic SJS and severe ocular disease is limited as many patients are unable to cooperate due to severe photophobia. Other visual metrics, such as visual function test surveys (NEI VFQ-25 or OSDI) or contrast sensitivity would portray a clearer image of visual outcomes in these patients. Finally, our case series presents only data from one large tertiary center and cannot represent the whole situation in the UK directly.

In conclusion, chronic SJS remain a poorly studied inflammatory disease in which prognostic factors are yet to be identified to guide better management. Our findings suggest that visual acuity at presentation is an important prognostic sign for long-term visual acuity, regardless of management and clinical course. Visual acuity continues to deteriorate with time in most cases. Early intervention could be mandated in some patients to prevent disease progression, particularly in patients with recurrent and chronic inflammation. The care of patients with chronic SJS remains an area of unmet clinical needs in which better algorithm based treatment modalities are needed.

DATA AVAILABILITY STATEMENT

The raw data supporting the conclusions of this article will be made available by the authors, without undue reservation.

ETHICS STATEMENT

The studies involving human participants were reviewed and approved by IRAS. The ethics committee waived the requirement of written informed consent for participation.

AUTHOR CONTRIBUTIONS

All authors listed have made a substantial, direct and intellectual contribution to the work, and approved it for publication.

SUPPLEMENTARY MATERIAL

The Supplementary Material for this article can be found online at: https://www.frontiersin.org/articles/10.3389/fmed.2021.644795/full#supplementary-material

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Conflict of Interest: The authors declare that the research was conducted in the absence of any commercial or financial relationships that could be construed as a potential conflict of interest.

frontiers in Medicine

MINI REVIEW
published: 18 June 2021
doi: 10.3389/fmed.2021.649369

Clinical Aspects of Stevens-Johnson Syndrome and Toxic Epidermal Necrolysis With Severe Ocular Complications in Brazil

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OPEN ACCESS

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Specialty section:
This article was submitted to Ophthalmology, a section of the journal Frontiers in Medicine

Received: 04 January 2021
Accepted: 19 April 2021
Published: 18 June 2021

Citation:
Wakamatsu TH, dos Santos MS, Barreiro TP, Sant'Anna AEBPP, Murta F, da Costa AX, Marculino LGC, de Alcântara RJA, de Farias CC and Gomes JÁP (2021) Clinical Aspects of Stevens-Johnson Syndrome and Toxic Epidermal Necrolysis With Severe Ocular Complications in Brazil. Front. Med. 8:649369. doi: 10.3389/fmed.2021.649369

Stevens-Johnson syndrome (SJS) and toxic epidermal necrolysis (TEN) are acute and potentially fatal inflammatory vesiculobullous reactions that affect the skin and mucous membranes, and which are most often triggered by particular medications and infections. In Brazil, the drugs most frequently associated with TEN and SJS include cold medicine such as dipyrone and NSAIDs, followed by carbamazepine, phenobarbital, penicillin, and allopurinol. Genetic variations have been found to increase the risk of SJS/TEN in response to triggering factors such as medications. The most closely associated genes found in Brazilian cold-medicine-related SJS/TEN patients with severe ocular complications are HLA-A*66:01 in those of mixed African and European ancestry and HLA-B*44:03 and HLA-C*12:03 in those of solely European ancestry. Our classification system for grading ocular surface complication severity in SJS/TEN patients revealed the most severe complications to be limbal stem cell deficiency and dry eye. Changes to the conjunctival flora have also been observed in SJS/TEN patients. Our group identified bacterial colonization in 95% of the eyes (55.5% of which were gram-positive cocci, 25.5% of which were gram-negative bacilli, and 19% of which were gram-positive bacilli). Several new treatment options in the acute and chronic ocular management of the SJS/TEN patients have been described. This article highlights some Brazilian institutions' contributions to ocular surface care in both the acute phase (including the use of amniotic membrane transplantation) and the chronic phase (such as eyelid margin and fornix reconstruction, minor salivary gland transplantation, amniotic membrane and limbal transplantation, scleral contact lenses, anti-angiogenic eyedrops for corneal neovascularization, *ex-vivo* cultivated limbal epithelium transplantation, conjunctival-limbal autografting, oral mucosa transplantation, and keratoprosthesis).

Keywords: Stevens-Johnson syndrome, toxic epidermal necrolysis, Brazil, clinical aspects, treatment, genetic predisposition

INTRODUCTION

Stevens-Johnson syndrome (SJS) and toxic epidermal necrolysis (TEN) are rare but life-threatening hypersensitivity reactions characterized by inflammatory vesiculobullous reaction of the skin and mucous membrane (1, 2). They are considered two of the most devastating ocular surface diseases in that they cause corneal damage and threaten vision. SJS and TEN are estimated to affect two to ten million people each year (3, 4). The mortality rate of SJS is estimated as 16.7% in Brazil (5). Several aspects of SJS and TEN are considered to be unmet needs in terms of management in different regions of the globe. In this review, we will highlight some clinical aspects of these diseases in Brazilian patients.

CLINICAL ASPECTS OF BRAZILIAN PATIENTS

Epidemiology

In Brazil, ocular complications are reported to be the most common complication related to SJS/TEN (5). We retrospectively reviewed a total of 108 patients (61 females and 47 males) with SJS and TEN who were treated in the Ophthalmology Department of Paulista School of Medicine. Mean age at onset was 22.81 years of age (range of 7 months−58 years). Acute ocular manifestations consisted of corneal erosions and conjunctivitis. The prevalence of severe ocular complications (SOCs) varied, with the most common chronic presentation represented by dry eye syndrome, limbal stem cell deficiency (LSCD) and trichiasis (6).

Etiology

SJS and TEN are commonly associated with pharmaceuticals and infectious agents. Of the 108 patients with SJS and/or TEN included herein, cold symptoms were reported by 73 patients (67.59%), and symptom onset was reported after the use of implicated medications in 98 patients (90.74%). The medications mostly commonly taken by the patients prior to symptom onset were dipyrone (41 patients; 37.96%), penicillin (13 patients; 12.04%), phenobarbital (9 patients; 8.33%), sulphonamides (8 patients; 7.41%), phenytoin (seven patients; 6.48%), and carbamazepine (six patients; 5.56%), followed by aspirin (four patients; 3.70%), allopurinol (three patients; 2.78%), amoxicillin (two patients; 1.85%), paracetamol (two patients; 1.85%), and lamotrigine (two patients; 1.85%). Cephalexin, ciprofloxacin, ibuprofen, ofloxacin, piroxicam, ipilimumab, zidovudine, and theophylline were each recorded in one patient (0.93% each). Finally, eight patients (7.41%) had taken an unknown pharmaceutical prior to symptom onset.

Human leukocyte antigens (HLAs) are highly polymorphic proteins that start the immunity process by introducing pathogen-derived peptides into T-cells (7). HLA typing in large patients samples involving different autoimmune diseases has revealed the occurrence of HLA alleles at higher frequencies in patients with certain diseases than in the general population; these studies have also demonstrated that carries of a specific HLA allele experience an increased risk of developing SJS and/or TEN. In a study of Japanese patients, Ueta et al. (8, 9) found that HLA-A*02:06 is closely associated with and HLA-A*11:01 is inversely associated with cases of SJS and TEN with SOCs. These same authors later found close to 80% of the reactions to be associated with cold medicine (CM) (10). In another study, they found HLA-A*02:06 and HLA-B*44:03 to be closely and independently associated with CM-related SJS and TEN (CM-SJS/TEN) with severe mucosal involvement, including SOCs (8). The association between CM-SJS/TEN and theses alleles was confirmed in a study that organized results by ethnicity in the consideration of Indian, Brazilian, and Korean populations (9). These findings support genetic predispositions for CM-SJS/TEN with SOCs. CM represents a group of medications marketed to help relieve symptoms of common cold. They include analgesics and antipyretics (such as dipyrone and acetaminophen) and non-steroidal anti-inflammatory drugs (NSAIDs), such as salicylates, propionic acid, acetic acid, enolic acid, anthranilic acid derivatives, selective cyclooxygenase-2 inhibitors, and sulphonamides).

We conducted a case-control study to determine any associations between HLA class I genes and CM-SJS/TEN with SOCs. Thirty-nine Brazilian patients with CM-SJS/TEN, 74 patients with SJS/TEN with SOCs, and 133 healthy Brazilian volunteers were enrolled. We found different alleles to be associated with CM-SJS/TEN with SOCs in Brazilians of mixed African and European and of solely European ancestry. The HLA-A*66:01 allele may be a marker for CM-SJS/TEN with SOCs in individuals of mixed African (OR, 12.2; 95% CI, 1.19–125.0; $P = 0.03$) and European ancestry (OR, 21.2; 95% CI, 0.97–465.0; $P = 0.04$), while HLA-B*44:03 (OR, 5.50; 95% CI, 1.47–20.50; $P = 0.01$) and HLA-C*12:03 (OR, 8.79; 95% CI, 1.83–42.20; $P = 0.008$) were found to be likely markers in those of solely European ancestry. We suggest that HLA-A*11:01 is a universal marker of resistance to CM-SJS/ TEN with SOCs (11).

In a recent study, we determined the association of HLA class I and II with dipyrone-related SJS/TEN with severe ocular complications in a Brazilian population. We found that *HLA-B*44:03* (carrier frequency: $p = 0.002$, Pc = 0.02, OR = 8.8; gene frequency: $p = 0.001$, Pc = 0.01, OR = 7.5) and *HLA-DQB1*04:02* (carrier frequency: $p = 0.01$, Pc = 1.08, OR = 11.4; gene frequency: $p = 0.003$, Pc = 0.03, OR = 12.6) were significantly associated with cases of dipyrone-related SJS/TEN with SOCs in the Brazilian population of European ancestry. *HLA-C*05:01* (carrier frequency: $p = 0.001$, Pc = 0.01, OR = 19.4; gene frequency: $p = 0.002$, Pc = 0.02, OR = 15.0) was significantly associated with cases of dipyrone-related SJS/TEN with SOCs in the Brazilian population of mixed raced ancestry (12).

Classification

A classification system provides a quantitative tool to compare outcomes in SJS/TEN. It is important to identify disease progression, documenting patient follow up, and helps to monitor the response to a specific treatment.

Sotozono et al. graded the severity of corneal, conjunctival and eyelid complications totalizing 13 components on a scale from 0 to 3. They showed that severity of chronic ocular manifestations in SJS/TEN is significantly correlated with the final visual outcome (13). Sharma et al. scored 12 ocular surface

parameters ranging from 0 to 5 and demonstrated that correlated significantly with corrected distance visual acuity (14). Ong et al. analyzed 12 components of the ocular surface divided in three functional categories (inflammation, scarring and ocular morbidity) and validated this tool of clinical assessment for cicatrizing conjunctivitis (15).

To assess and grade the extent and severity of ocular surface manifestations of SJS, we proposed a grading system for assessing ocular surface manifestations. Ocular surface manifestations were separated into corneal complications, conjunctival complications, eyelid-related complications, and the presence or absence of dry eye disease. Nine components were graded on a scale from 0 to 3 based on their severity. This grading system also separated the complications into those of the cornea (epitheliopathy, opacity and LSCD), conjunctiva (inflammation and wound healing), and eyelid (keratinization and eye lash abnormalities), as well as dry eye status (Schirmer's test and corneal wound healing).

Microbiome

Microbial communities and their genes—understood together as the microbiome—are spread throughout different areas of the human body. They maintain homeostasis and aid immunity against disease (16). The microbiome is affected by interactions with both environmental antigens and drugs, including antimicrobials. The bacterial genome of some mucosal surfaces alone is more than 100 times the size of the human genome (17). Other mucosal sites, such as the ocular surface, are paucibacterial, with less than a single bacterium per human cell (18, 19).

There seems to be an immunological relationship between the gut and other organs such as the eye. Gut microbiome abnormalities have been linked to a variety of ocular conditions including dry eye, diabetic retinopathy, glaucoma, macular degeneration, and infectious keratitis (20, 21). In an experimental model of Sjögren's syndrome, a dysbiotic intestinal microbiome was associated with worse presentation of ocular mucosal disease (21).

The microbiome in cases of SJS has also been investigated. Two studies found that the frequency of conjunctival culture positivity was much higher than that which was reported in healthy patients (22, 23). Coagulase-negative *staphylococci* and *Corynebacterium spp*. were the most commonly found species (22, 23). Half of the patients had multiple bacterial species in their flora, including pathogenic bacteria such as *Enterobacter spp*, *Serratia nonliquefaciens*, *Escherichia coli*, *Morganella morganii*, *Proteus mirabilis*, and *Haemophilus spp* (22). A more recent study compared the microbiomes from SJS patients to those of healthy subjects using conventional cultures and sequencing methods (24). Positive-cultured specimens were found in 60% of the SJS patients and in only 10% of the healthy subjects (24). *Corynebacterium* and *Streptococcus* were the bacteria genera detected most frequently. rRNA sequencing confirmed a wider diversity of microbial species and a greater proportion of pathogenic microorganisms in the eyes of SJS patients; the genera detected included *Pseudomonas*, *Staphylococcus*, *Streptococcus*, and *Acinetobacter* (24).

This altered microbiome found in SJS cases is likely associated with severe ocular surface abnormalities, including chronic epitheliopathy and reduction of the mucin layer of the tear film (24). In addition, it has been reported that SJS produces an abnormal innate immune response that may affect the balance between mucosal immunity and microorganism pathogenicity, inducing chronic-recurrent ocular surface inflammation (25). These changes can predispose patients to severe ocular infections that might impact the results of surgical procedures for ocular surface reconstruction, thus jeopardizing visual rehabilitation of these patients (26). In their prevention and control of infection in SJS patients, physicians are advised to start these patients on appropriate antibiotics prior to relevant procedures (24–26).

Acute Phase Treatment

In the acute phase of SJS, patients exhibit a critical state of involvement of multiple organs and thus require the support of a multidisciplinary team. Ocular treatment in the acute phase consists of maintaining eye hygiene, intensive lubrication, the mechanical removal of membranes, prophylactic topical antibiotics, corticosteroids, and therapeutic contact lenses.

Amniotic membrane transplantation (AMT) to treat acute SJS is an option for severe cases. It can aid in epithelization, in addition to decreasing inflammation and the consequences thereof (entropion, symblepharon, and dry eye) (27, 28). If the procedure is not performed within 10 days of the beginning of this condition, severe vision-threatening complications can occur. In these cases, however, LSCD is inevitable and will require limbal stem cell transplantation (LSCT) or other surgeries used for ocular surface reconstruction (29). In AMT, the amniotic membrane covers the entire bulbar surface up to the fornices. Nylon sutures (10-0) can be used to secure the edge of the membrane to the lid margin, and the larger silk sutures can be passed through the eyelid as a mattress stitch to secure the membrane reflected into the fornix; fibrin glue can also be used (29).

Chronic Phase Treatment

Ocular treatment during the chronic phase of SJS is considered one of the most substantial challenges in ophthalmology. The goals of treatment include restoration of eyelid function, dry eye management, and restoration of the ocular surface.

Eyelid Complications

Eyelid Margin Reconstruction

Mucous membrane transplants have been used for the reconstruction of fornices damaged by symblepharon formation, a common condition in chronic SJS patients (30). Nevertheless, some keratin accumulates on the eyelid margin, causing inflammation and irritation of the ocular surface.

Iyer et al. (31) reported on the use of the oral mucosa to reconstruct the eyelid margin by removing the keratinized area and grafting a mucous membrane from the lip using fibrin glue. They studied 54 eyes of 31 patients, with an improvement in 92.6% of patients (31). In our department, we prefer to use this technique by removing the lip mucosa with a mucotome to

produce a thinner graft more similar to the conjunctiva and to suture it with 8-0 polyglactin suture.

Adnexal complications

Minor Salivary Gland Transplantation

Severe dry eye is known to be one of the main sequelae experienced by patients with SJS. The minor salivary glands located in the submucosa of the oral cavity can be used in the visual rehabilitation of patients with SJS. These glands are classified as labial, buccal, glossopalatine, and palatine. The minor labial salivary glands, which are present on the inner surface of the upper and lower lips, are the glands most commonly used in severe dry eye treatment.

Several authors have successfully described the transplantation of minor salivary glands for the treatment of severe dry eye in patients with SJS and severe eye burns (32–34). A thin labial mucosal graft removed with a mucotome (35) can be used to correct the symblepharon in association with the minor salivary gland transplantation, providing the eye not only with labial mucosa to serve as a lining, thus reestablishing the ocular surface, but also with the minor salivary glands which increase the amount of tear film (36).

In 2012, Sant'Anna et al. reported on 19 patients with SJS and severe symblepharon treated simultaneously with symblepharon correction through labial mucosal grafting obtained using a mucotome and autologous transplantation of minor salivary glands attached to the submucosa (36) and not full thickness mucosa as previously described by Murube et al. (37). The glandular tissue attached to the submucosa was implanted nasally in the lower and upper sacs. The results were satisfactory, and Schirmer's test results improved in all patients. Results were superior in patients in whom more than 10 glands were implanted. Therefore, this procedure managed to simultaneously treat severe symblepharon and implant minor salivary glands (36). Wakamatsu et al. also demonstrated the viability of minor salivary glands transplanted into the fornices of patients with dry eye by performing immunohistochemistry on graft biopsies with antibodies against lactoferrin, lysozyme, MUC1, and MUC16. The salivary gland units were found to be functional, with local production of proteins, enzymes, and mucins (38).

Vazirani et al. reported the transplantation of a complex consisting of mucosa, minor salivary glands, and muscle that removed and implanted en bloc in 19 patients (21 eyes) with cicatricial conjunctivitis. During the surgeries, the minor salivary glands were attached to the upper bulbar surface and anchored to the superior rectus muscle. Patients' visual acuity and Schirmer's test results improved (39).

Corneal complications

Anti-VEGF Treatment for Corneal Neovascularization

Corneal neovascularization is a common consequence of ocular manifestations and is associated with significant visual morbidity. Neovascularization triggers tissue scarring, stromal hemorrhage, lipid deposition, and corneal edema, which all have severely negative effects on visual acuity. Several factors, including vascular endothelial growth factor (VEGF) and platelet-derived growth factor (PDGF), regulate angiogenesis. Recent findings suggest that VEGF and PDGF inhibition may be effective treatment options for corneal neovascularization (40).

Our team performed a prospective, randomized, double blind, placebo-controlled study to evaluate the safety, efficacy, and stability of topical bevacizumab and sunitinib in the treatment of corneal neovascularization in patients with SJS (manuscript in preparation).

Scleral Contact Lenses

In recent years, several studies have considered the use of different scleral contact lenses (SCLs) to treat dry eye disease (DED). SCLs are typically indicated for severe DED in cases when conventional treatment fails. SCLs protect the cornea and conjunctivae because the covering they provide controls evaporation and maintains direct contact between fluid and the corneal epithelium. SCLs also protect the cornea from the mechanical trauma and abrasions that commonly result from irregular eyelid scarring and misdirected eyelashes that SJS patients often exhibit (41).

Weber et al. evaluated the efficacy of SCL treatment and how this treatment affects clinical tests used to determine severe SJS with DED. The SCL treatment positively impacted SJS patients' tear osmolarity and vital staining scores; it also improved their visual acuity, DED symptoms, and overall quality of life (42, 43).

Limbal Stem Cell and Amniotic Membrane Transplantation

Conjunctival-limbal grafting combined with AMT is a surgical procedure currently available for reconstruction of the ocular surface in cases of total LSCD (26, 44–48).

In 2003, Gomes et al. studied 10 eyes of 10 patients with LSCD secondary to SJS who were treated with AMT and a living-related conjunctival-limbal allograft. As we noted in our previous study, which relied on a follow-up period that averaged 16.7 months, "satisfactory ocular surface reconstruction was obtained in 2 eyes (20%), with reduced inflammation and vascularization and a mean epithelialization time of 3 weeks. Surgical failure was observed in four cases (40%), and complications (infection) occurred in four cases (40%). Visual acuity improved in four eyes (40%), remained stable in five eyes (50%), and decreased in one eye (10%)" (26).

In 2005, Santos et al. prospectively evaluated the survival of conjunctival-limbal grafts associated with AMT for LSCD and assessed the role of different effects and symptoms associated with LSCD, eyelid abnormalities, keratinization, dry eye, systemic immunosuppression, HLA compatibility, and keratoplasty (PKP) on surgical outcomes in a prospective, non-comparative, interventional study (47). Of the 31 patients with total LSCD who received conjunctival-limbal grafts and AMT, 11 of the cases (33%) were secondary to SJS. Ten eyes (30%) received a conjunctival-limbal autograft, and 23 (70%) received a conjunctival-limbal allograft from living HLA-matched donors; these counts represented all of the SJS patients included in the study. Grafts survived in 13 eyes (40%) at 1 year and in 11 eyes (33.3%) at 2 years; the cumulative graft survival rate was 33% at a mean follow-up time of 33 months. Among the SJS patients, the graft survival rate decreased significantly over time, with a survival rate of only 10% after 1 year (47).

Other researchers have found this type of procedure to have a substantial effect on graft survival in patients with SJS, dry eye, eyelid abnormalities, keratinization, and/or allogeneic conjunctival-limbal transplantation, regardless of HLA compatibility ($p < 0.05$). The researchers found preoperative dry eye to be the parameter that most highly predicted surgical outcome ($p < 0.001$) (47).

Corneal Transplantation

In aggressive and prolonged ocular surface morbidities, such as those caused by SJS/TEN, keratoplasty is employed largely to attempt to preserve of the ocular globe (49). Improvement in final visual function by corneal transplantation is a challenge in SJS patients. The prognosis is typically poor (50) due to the patients' high risk of immune rejection, persistent epithelial defection, infection, graft melting, and corneal perforation (22). Today, keratoplasty is considered for visual rehabilitation only after ocular surface restoration is completed (41, 51). Moreover, almost all SJS patients require systemic immunosuppression after corneal transplantation (26, 52).

In our department, we follow the same protocols described previously for keratoplasty in patients with acute and chronic SJS/TEN.

Keratoprosthesis

Patients with neovascularization, severe corneal opacity, and LSCD may have part of their vision restored for varying lengths of time through keratoprosthesis. The risks of operative and postoperative complications are greater in SJS/TEN patients than in other groups who undergo keratoprosthesis, and rates of both anatomical success (retention of the prosthesis) and functional success (improved visual acuity) are lower than among patients with other types of diseases. Corneal necrosis, infectious keratitis, microbial endophthalmitis, and glaucoma are some of the complications experienced by SJS/TEN patients at rates substantially higher than among patients with other conditions (53). Oliveira et al. reported the experience of our department in performing Boston Kpro type I. They evaluated and compared the results in subgroups distinguished by previous diagnosis (SJS/TEN, chemical burn and multiple graft failure). There was a tendence of lower retention rate in the SJS/TEN group and no statistically differences in visual acuity outcomes among the three groups was found (54).

Type I and II Boston keratoprosthesis devices and modified osteo-odonto keratoprosthesis (MOOKP) are the treatment options currently available. Boston Kpro type I may be indicated for some patients with relatively healthy ocular surfaces and eyelids, while Boston Kpro type II and MOOKP are reserved for cases with major abnormalities of the eyelid, keratinization of the conjunctiva, and/or severe dry eye. More recently we started to perform salivary gland transplantation before the implantation of Boston type I keratoprosthesis in a few selected SJS patients presenting severe dry eye with encouraging results. The decision between the latter two options depends on the surgical conditions available, the surgeon's experience, and local regulations (41).

Artificial corneal implants in SJS/TEN patients should be seen as a surgery of last resort and should be preceded by other visual rehabilitation methods.

Systemic Immunosuppression

The importance of continued immunosuppression for graft survival after ocular surface stem cell transplantation has been discussed previously. The systemic immunosuppression protocols used by our team to prevent rejection after allogenic LSCT is based on the combination of 1 mg/kg prednisone and 3 to 5 mg/kg cyclosporine administered orally and daily and, more recently, 1 mg/kg oral prednisone once daily, 4mg tacrolimus twice daily, and 1 g mycophenolate mofetil (MMF) twice daily. Oral prednisone is tapered progressively and discontinued after 8 weeks. Cyclosporine, tacrolimus, and MMF dosages are tapered after 8 to 12 weeks but are administered indefinitely. Blood cell counts, kidney function, and liver function, are tested monthly (47, 55–57).

DISCUSSION AND CONCLUSIONS

SJS and TEN commonly involve ocular complications. The acute conjunctival inflammation seen in SJS and TEN patients leads to chronic scarring of the ocular surface, often the most devastating long-term sequela in these patients. The sequelae experienced required that the initial treatments being instituted within windows of opportunity. Prevention of complications is the most reliable way to minimize vision loss. Despite improvements in the understanding of these issues in recent decades, SJS and TEN continue to create substantial challenges, and unmet needs remain in the management of this disease.

AUTHOR CONTRIBUTIONS

TW and JG: conception and design, data collection, writing—original draft review and editing, analysis and interpretation, obtained funding, overall responsibility. CdF, RdA, LM, AdC, FM, and AS'A: data collection, writing—original draft, analysis and interpretation. TB and MdS: conception and design, data collection, writing—original draft, analysis and interpretation. All authors contributed to the article and approved the submitted version.

FUNDING

This work was supported by São Paulo Research Association (FAPESP) grant nos. 2012/09816-0 and 2018/08344-4.

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Conflict of Interest: The authors declare that the research was conducted in the absence of any commercial or financial relationships that could be construed as a potential conflict of interest.

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PERSPECTIVE
published: 07 July 2021
doi: 10.3389/fmed.2021.670643

USA: Ophthalmologic Evaluation and Management of Acute Stevens-Johnson Syndrome

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Stevens-Johnson syndrome (SJS) and toxic epidermal necrolysis (TEN) can cause significant damage to the ocular surface and eyelids. The sloughing and inflammation of the ocular mucosal epithelium during the acute phase may lead to scarring sequelae of the eyelids and ocular surface, resulting in pain and vision loss. Amniotic membrane transplantation (AMT) to the eyes and eyelids during the initial 1–2 weeks of the disease can decrease the chronic sequelae. The main development in the ophthalmologic treatment of SJS/TEN in the USA over the last 15 years has been the use of AMT on the ocular surface and eyelids during the acute phase. The evolution of AMT techniques, refinement of the evaluation of the eyes in acute SJS, and the efforts to increase the use of AMT in the USA are discussed.

Keywords: Stevens-Johnson syndrome, toxic epidermal necrolysis, amniotic membrane, ocular surface, USA

OPEN ACCESS

Edited by:
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Reviewed by:
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Specialty section:
This article was submitted to Ophthalmology, a section of the journal Frontiers in Medicine

Received: *22 February 2021*
Accepted: *21 May 2021*
Published: *07 July 2021*

Citation:
Gregory DG (2021) USA: Ophthalmologic Evaluation and Management of Acute Stevens-Johnson Syndrome. Front. Med. 8:670643. doi: 10.3389/fmed.2021.670643

INTRODUCTION

Stevens-Johnson syndrome (SJS) and its more severe variant, toxic epidermal necrolysis (TEN), are rare diseases that cause acute blistering of the skin and mucous membranes. Both diseases are most commonly drug-induced and the effects on the ocular surface can be devastating, potentially yielding severe scarring, and dry eye problems, as well as debilitating photophobia and decreased vision. The acute phase of the illness can vary in length, but essentially corresponds to the period of active blistering and epithelial sloughing (1). This period can range from a few days in mild cases up to a few weeks in severe cases. In 2002 the first case report was published describing the use of amniotic membrane transplantation (AMT) to treat the ocular surface inflammation in acute SJS (2). Since then numerous other investigators have shown that when it is applied to the ocular surface during the early portion of the acute phase of the illness, AMT can minimize the damage that leads to the late-phase chronic cicatricial problems.

At the University of Colorado we began using AMT to treat acute SJS in 2005 and soon realized the benefits it provided. In 2008 we published a "how to" guide for the ophthalmologic management of acute SJS (3). Many of our chronic SJS patients used customized scleral contact lenses (PROSE devices, Boston Foundation for Sight, Needham, Mass) as a treatment for their severe dry eye problems. Through the Boston Foundation for Sight and the network of ophthalmologists who used their devices, an interest group of ophthalmologists who care for acute SJS patients developed. All were at large ophthalmology training centers with an affiliated burn intensive care unit (ICU). The bulk of the publications and advances in the care of acute SJS patients in the USA have come from the efforts of this group. Principal members are from the University of Colorado, The Massachusetts Eye and Ear Infirmary/Harvard University in Boston, Loyola University Medical Center/Loyola University of Chicago, the University of Miami, Weill-Cornell Medical Center in New York City, and Brooke Army Medical Center in San Antonio. This group, along with

numerous international experts, published a consensus paper in 2016 regarding the ophthalmologic evaluation and management of SJS/TEN (1). The current article will review the rationales for the current evaluation and management of the acute ocular manifestations of SJS and TEN in the USA.

EVALUATION

With an incidence of just over 12 cases per million persons per year, SJS/TEN seems to be more common in the USA than older reports have suggested (4). The eyes are affected in a majority of SJS/TEN patients (5, 6). The epithelial sloughing and inflammation that is characteristic of the disease can involve the eyelid margins and eyelashes, the palpebral and bulbar conjunctiva, and the corneas. Even in cases where the extent of the skin sloughing on the rest of the body is limited, the extent of the ocular surface epithelial sloughing can be significant (7, 8). It is therefore important that all acute SJS/TEN patients have an urgent evaluation of the eyes by an ophthalmologist, regardless of the severity of the overall skin involvement. Damage to the ocular surface begins with widespread necrosis in the deep epidermal layers and the intense inflammation that follows. Areas that experience extensive epithelial necrosis will tend to heal in with scar tissue rather than normal mucosa. The mucosal damage that begins in the first few weeks of the illness leads to the relentless cascade of challenging ocular surface problems that characterize the chronic phase of the disease months and years after the acute episode. The extent of the epithelial sloughing of the conjunctiva and cornea (delineated by fluorescein staining) is the key exam finding that determines the severity of the acute eye involvement and helps guide management (9). Inspection of the fornices is crucial, as there may be extensive sloughing of the palpebral conjunctiva even in cases where there is relatively mild bulbar conjunctival sloughing. Simply sweeping for symblephara is not sufficient. Controlling the intense inflammation that is leading to the symblepharon formation should be the priority.

In the acute phase, mild eye involvement is characterized by a conjunctivitis that may be accompanied by small, well-demarcated conjunctival epithelial defects that are easily appreciated with fluorescein staining done at the bedside. In seemingly mild cases it is still important to inspect the fornices and palpebral conjunctiva for sloughing that would not otherwise be seen (**Figure 1A**). Inspection and saline rinsing of the ocular surface (including the fornices) should be performed daily at least until there are signs of improvement. Enlargement of epithelial defects, corneal epithelial sloughing, or the formation of symblephara indicate worsening that should prompt consideration of more significant ophthalmologic treatments, such as AMT.

Severe cases have more diffuse, destructive conjunctival inflammation with pseudomembranous and membranous conjunctivitis. Fluorescein staining is extensive, involving much of the ocular surface (**Figure 1B**). These raw surfaces can lead to adhesion formation between the palpebral and bulbar conjunctiva. Although this symblepharon formation is concerning, the larger problem is the underlying intense inflammation that is leading to the symblepharon in the first place. This inflammation can damage both goblet cells and accessory lacrimal glands on the ocular surface, as well as the secretory ductules of the main lacrimal gland (10). In such cases, urgent AMT is indicated to suppress the destructive inflammation and to limit the formation of cicatrized epithelium.

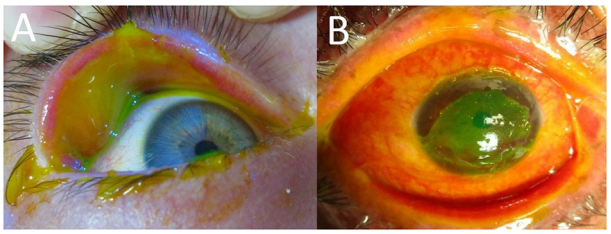

FIGURE 1 | (A) Fluorescein staining in an acute SJS patient showing extensive palpebral conjunctival sloughing despite limited bulbar conjunctival sloughing. **(B)** Severe eye involvement in an acute SJS patient (extensive sloughing of the corneal epithelium, bulbar conjunctiva, palpebral conjunctiva, and lid margins).

Damage to the eyelids in the acute phase can also be a significant source of longer term visual morbidity. Inflammation of the lid margins can cause occlusion of meibomian gland orifices and damage to the meibomian glands (11, 12). Cicatricial changes may alter eyelid and eyelash anatomy, resulting in entropion, trichiasis, and distichiasis. The abnormal eyelashes can rub the already compromised ocular surface and cause irritation, corneal abrasions, corneal ulceration, and corneal scarring. Keratinization of the lid margins and palpebral conjunctiva can also add to the discomfort and corneal damage in the chronic phase of the disease, so sloughing of the palpebral conjunctiva and lid margin ulceration in the acute phase is particularly concerning (13).

Severe cases may also yield limbal stem cell failure. There is probably some direct injury to the stem cells during the acute phase combined with ongoing damage from the abnormal tear film and mucosal surfaces in the years following the acute illness. The limbal stem cell damage can lead to opacification and "conjunctivalization" of the cornea, decreased vision, and chronic pain and photophobia. All of these ocular surface abnormalities make the prognosis for corneal transplantation poor. Prevention of the damage in the acute phase of the illness can greatly decrease the risk for these long-term, debilitating sequelae (14, 15). Early AMT (ideally in the first week of the illness) has been shown to be an effective means of suppressing the inflammation of the ocular mucosal membranes and minimizing the acute phase damage to these tissues (1).

MANAGEMENT

Medical Management

The extensive loss of skin and mucous membranes in SJS/TEN puts patients at risk for sepsis and pneumonia, with mortality rates approaching 40% in some series (16). Early referral to a facility experienced in the care of burn patients significantly decreases mortality rates (17–19). In the USA, this is commonly

a regional burn ICU. The life-threatening nature of the disease, however, can initially cause the eye involvement to be overlooked or deprioritized, even at facilities specialized in the care of burn patients. A 2015 survey of North American burn centers found that only 66% routinely include ophthalmology consultation as part of the initial evaluation and care of SJS/TEN patients (20). It is crucial for ophthalmologists to help establish evaluation and treatment protocols in burn centers so that the urgent ophthalmologic evaluation of all SJS/TEN patients becomes the standard practice. Additionally the consulting ophthalmologist must be well-versed in the current evaluation and treatment recommendations for the SJS/TEN. Patients with mild skin involvement may still have significant mucosal inflammation and need urgent ophthalmologic evaluation during the acute phase. The clinical severity can progress quickly in the first few days of the illness, so daily eye exams are needed until it is clear that the mucosal inflammation is subsiding. Failure to appreciate the severity of eye involvement in patients with less severe skin involvement can lead to delays in transfer to a facility experienced in the care of SJS patients. Such delays can potentially cause worse visual outcomes for the patients. As part of an overall effort to improve awareness of AMT's benefits in acute SJS, Loyola University Medical Center convened a free, virtual national educational symposium specifically for burn centers in March 2021. Continued collaboration with burn centers is planned.

The ophthalmologic management of acute SJS/TEN should focus on infection prophylaxis, symblepharon prevention, and minimization of destructive inflammation. In the USA, systemic treatments are generally directed by the burn surgeons and medical specialists in charge of the overall care of the patient. Unfortunately there are few studies that examine the effects of systemic acute phase treatments on the eyes. In 2009 it was reported that high dose systemic and topical corticosteroids within the first 4 days after the onset of illness could decrease the severity of the ocular surface damage (21). The use of systemic corticosteroids in the acute phase has historically been controversial due to concerns over possible increased mortality (22, 23). Multiple reports suggest that with close monitoring, however, intensive topical corticosteroid drops may be safely used to help decrease the ocular surface damage during the acute phase (21, 24). Subconjunctival triamcinolone injections have also been utilized in combination with AMT (25). Although they may play a beneficial role in decreasing the ocular surface inflammation in acute SJS, topical steroids alone are not sufficient treatment in severe cases.

Studies of other systemic treatments have mostly looked at mortality as the main outcome measure. Other than possibly corticosteroids, no other systemic treatments have been shown to have a benefit for the ocular surface (26, 27). This may be more due to a lack of studies specifically investigating this, rather than studies showing an actual lack of benefit. In a recent review of studies examining the use of systemic cyclosporine, however, no statistically significant benefit for the eyes was found (28).

Milder cases with non-membranous conjunctivitis and no lid margin or corneal involvement may be managed with daily exams, topical antibiotics, and topical steroid medications. Mild cases have a low risk for developing cicatricial sequelae and many will not progress to more severe involvement. Close monitoring is still required, however, until it is clear that no worsening is occurring. If membranous conjunctivitis, mucosal adhesions, or lid margin sloughing do develop, then urgent AMT should be considered.

Surgical Management

Cryopreserved AMT to the ocular surfaces during the acute phase of SJS and TEN has been described by multiple groups (1, 24, 29–33). The use of AMT in this setting has also been summarized in multiple reviews (2, 3). Additionally, a randomized control trial has established that AMT is more effective than medical management in the prevention of longer term cicatricial sequelae (34). The evidence supporting the early use of AMT in SJS/TEN cases with severe ocular involvement is increasingly strong. AMT seems to be most beneficial if applied during the first week of illness, the earlier the better (9). After the first 2weeks the process of scarring becomes more prominent in severe cases. Minimizing the inflammation and mucosal damage in the early phases of the disease decreases the severity of this scarring. The amniotic membrane (AM) degrades within 7–10 days following application, however, and may need to be reapplied in more severe cases with persistent mucosal sloughing.

Numerous techniques have been described for the application of AMT. It can be performed under local anesthesia at the bedside or under general anesthesia in an operating room. Regardless of the exact technique, however, the AMT should ideally cover the lid margins, palpebral conjunctiva and ocular surface, including the cornea. The bedside methods use a single large sheet of cryopreserved AM which is initially positioned over the eyelids and eye. It is then sutured (35) or glued (36) to the eyelid skin of the lower lid then folded up and over the lid margin into the fornix where it is held in place by a custom-made, ring-shaped conformer constructed from pliable, small-bore intravenous tubing. The superior portion of the AM sheet covering the globe is then reflected out of the superior fornix and over the upper eyelid margin and then fixated to the skin just beyond the lid margin and lashes using glue or sutures. The main advantage of these techniques is the logistical simplicity, allowing effective AM coverage of the lid margins and all conjunctival surfaces without the need for an operating microscope or a trip to the operating room. Transporting these critically ill patients to an operating room may be challenging or even impossible, so having bedside options is beneficial. Additionally, increasing the simplicity and ease of AMT may allow more widespread adoption of the procedure.

Whenever possible, at our facility we still prefer to perform AMT under an operating microscope in an operating room. We use one half of a 3.5 cm^2 sheet of cryopreserved AM (Amniograft, Bio-Tissue, Miami, FL) on each eyelid and a full 3.5 cm^2 AM sheet or a Prokera (Bio-Tissue, Miami, FL) on the ocular surface. A Prokera is a 16 mm diameter thin plastic ring with a sheet of AM stretched across the lumen of the ring (**Figure 2A**). It is placed over the cornea like a contact lens. The amniotic membrane portion only covers the cornea and perilimbal conjunctiva, however, so it should only be used in cases that have limited bulbar conjunctival sloughing.

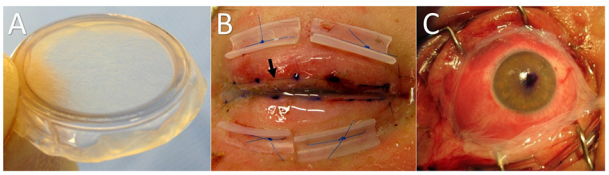

FIGURE 2 | (A) Prokera self-retaining amniotic membrane. Useful only when bulbar conjunctival sloughing is limited. Amniotic membrane grafting to the lid margins and palpebral conjunctiva is still necessary even when a Prokera has been used on the surface of the globe. **(B)** Lid margin and palpebral conjunctival amniotic membrane. The black arrow shows the running 8–0 nylon suture 1–2 mm peripheral to the lid margin. Once fixated to the external lid skin by the 8–0 nylon, the membrane is reflected over the lid margin and onto the palpebral conjunctiva where it is fixated with a pair of double-armed 6-0 polypropylene sutures. Both needles of each suture are passed full-thickness through the membrane and the eyelid and then tied externally over bolsters. **(C)** SJS patient with significant bulbar conjunctival sloughing treated with a sheet of cryopreserved amniotic membrane rather than a Prokera. The running perilimbal 10-0 nylon suture and oblique quadrant interrupted sutures have not yet been placed.

For the eyelid treatment, the eyelashes are trimmed close to the skin. Then a long edge of the AM sheet is placed along the eyelid margin with the stromal surface against the skin. An 8-0 nylon running suture fixates the membrane edge along the eyelid skin ∼2 mm from the lid margin. Then the rest of the AM sheet is reflected over the lid margin and into the fornix. A muscle hook is helpful for spreading the membrane out and keeping it in the proper position along the back of the eyelid while further sutures are being placed. Both ends of a double-armed 6-0 polypropylene suture are passed through the AM as deep in the fornix as possible and then full-thickness through the eyelid to be tied over a bolster on the external eyelid skin surface. Two such sutures and bolsters are used on each eyelid to fixate the sheet of AM to the palpebral conjunctiva (**Figure 2B**).

Following the application of AM to the lid margin and palpebral conjunctiva of each eyelid, we then simply place a Prokera on the ocular surface in most cases. The Prokera can be used in place of sutured AMT for the ocular surface, but only in cases with very limited sloughing of the bulbar conjunctiva. If there is extensive bulbar conjunctival sloughing we recommend suturing a sheet of AM to surface of the globe instead of placing a Prokera since a Prokera provides incomplete coverage of the bulbar conjunctiva. When complete coverage of the bulbar conjunctiva is needed, a full 3.5 cm^2 piece is centered over the cornea and sutured to the conjunctiva using a 10-0 nylon suture running circumferentially around the cornea 1–2 mm posterior to the limbus. An ink mark is placed on the center point of the AM sheet to help keep it properly centered during positioning and suturing (**Figure 2C**). Epinephrine drops (1:1,000) applied to the ocular surface prior to suturing help to decrease bleeding. After the perilimbal running suture is completed, single interrupted 10-0 nylon sutures are placed in each oblique quadrant and at the medial and lateral canthi. The suture tails are left long so they will lay flat on the ocular surface. A symblepharon ring is then placed on the eye to help maintain the fornices and to optimize the apposition of the amniotic membrane to the mucosal surfaces.

Postoperative Care

Postoperative care starts with showing the nursing staff how to properly apply the eye medications, particularly the eyelid ointment. Combination tobramycin/dexamethasone ointment is applied to the eyelid margins and eyelashes 4 times per day to minimize inflammation and to prevent desiccation of the lid margin amniotic membrane. The importance of this needs to be stressed to the nurses caring for the patient. An ophthalmologic exam is performed daily and includes rinsing the eyes with sterile saline to remove the buildup of ointment and serosanguinous debris, which can be significant. The corneas are evaluated for the presence of infiltrates under the AM. Topical quinolone drops and corticosteroid drops are applied 4 times per day. The amniotic membranes degrade after about a week in most cases and should be reapplied if there are areas of persistent, severe inflammation.

DISCUSSION

SJS and TEN are among the worst diseases of the ocular surface and their incidence is likely higher than previously reports have suggested. The long-term cicatricial sequelae of the diseases can be devastating to patients, and efforts to correct these chronic problems are prone to failure. Applying cryopreserved amniotic membrane to the eyes and eyelids during the acute phase of the disease greatly decreases the occurrence of severe cicatricial sequelae and the resultant visual problems. Early intervention with AMT during the acute phase is crucial in severe cases because the window of opportunity is short and the potential consequences of the disease are significant. Although early AMT is the recommended treatment for severe cases, the management of SJS in the United States remains quite variable. Severe cases are often transferred to intensive care units specializing in the care of burn patients, but not always. The decisions on the systemic management of the disease are made by burn surgeons and other medical specialists. Ophthalmologists may consult on the specific treatment of the eyes, but generally play no role in the systemic management. There is still no national consensus on what systemic anti-inflammatory agents, if any, should be used in the acute phase of the disease.

Although the ophthalmologic use of AMT in the acute phase appears to be slowly increasing, delays in the referral of patients to tertiary care burn centers where AMT can be performed still occur. Additionally, consulting ophthalmologists outside of large teaching centers may only rarely see cases of acute SJS and, thus, may not be aware that AMT can be an effective treatment in the acute phase. Not all ophthalmologists use AM on a regular basis and most facilities do not keep the necessary AM in stock. Getting the necessary AM delivered presents both a hurdle and a delay for treatment. As a result, AMT remains underutilized in acute SJS.

Increasing the awareness and utilization of AMT as a treatment option remains a top priority for American ophthalmologists who regularly care for patients with acute SJS and TEN. Delivering lectures to burn centers and publishing

guidelines for the eye care of acute SJS in burn journals as well as ophthalmology journals are key steps in the awareness campaign. Additionally, educating cornea surgical trainees on the use of AMT in acute SJS is increasing awareness each year. Unfortunately there is still no national database to monitor treatment and outcomes, nor is there a national treatment guideline that is adhered to. As a result the ophthalmologic management of acute SJS remains quite variable throughout the United States. Urgent AMT is commonly performed at large academic institutions with affiliated burn centers, but is less widely used outside of those settings.

DATA AVAILABILITY STATEMENT

The original contributions presented in the study are included in the article/supplementary material, further inquiries can be directed to the corresponding author/s.

AUTHOR CONTRIBUTIONS

The author confirms being the sole contributor of this work and has approved it for publication.

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Conflict of Interest: The author declares that the research was conducted in the absence of any commercial or financial relationships that could be construed as a potential conflict of interest.

frontiers in Medicine

MINI REVIEW
published: 12 July 2021
doi: 10.3389/fmed.2021.662897

Acute and Chronic Management of Ocular Disease in Stevens Johnson Syndrome/Toxic Epidermal Necrolysis in the USA

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Stevens Johnson syndrome and toxic epidermal necrolysis are on a spectrum of a severe, immune-mediated, mucocutaneous disease. Ocular involvement occurs in the vast majority of cases and severe involvement can lead to corneal blindness. Treatment in the acute phase is imperative in mitigating the severity of chronic disease. Advances in acute treatment such as amniotic membrane transplantation have shown to significantly reduce the severity of chronic disease. However, AMT is not a panacea and severe chronic ocular disease can and does still occur even with aggressive acute treatment. Management of chronic disease is equally critical as timely intervention can prevent worsening of disease and preserve vision. This mini-review describes the acute and chronic findings in SJS/TEN and discusses medical and surgical management strategies.

Keywords: Stevens-Johnson syndrome, toxic epidermal necrolysis, keratoprosthesis, amniotic membrane transplantation, ocular SJS, mucous membrane graft

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Specialty section:
This article was submitted to Ophthalmology, a section of the journal Frontiers in Medicine

Received: *01 February 2021*
Accepted: *31 May 2021*
Published: *12 July 2021*

Citation:
Metcalfe D, Iqbal O, Chodosh J, Bouchard CS and Saeed HN (2021) Acute and Chronic Management of Ocular Disease in Stevens Johnson Syndrome/Toxic Epidermal Necrolysis in the USA. Front. Med. 8:662897. doi: 10.3389/fmed.2021.662897

INTRODUCTION

Overview

Stevens-Johnson syndrome (SJS) and toxic epidermal necrolysis (TEN) are severe and potentially lethal multisystem, mucocutaneous, immune-mediated, adverse drug reactions (IM-ADR), with significant long-term ocular and systemic morbidity (1–6). Medications trigger SJS/TEN in >80% of adults, typically occurs within the first few weeks after first administration or upon a dose adjustment of an inciting agent (culprit drug) (7). Secondary complications include sepsis, blindness, respiratory, and genitourinary scarring and dysfunction.

Severe cicatrizing ocular surface disease is one of the most significant and debilitating sequelae of SJS/TEN and can profoundly impact the patient's quality of life (QOL) (8, 9). There is a short window of opportunity during the acute stage where intervention may potentially avoid these lifelong complications including severe vision loss and blindness.

Etiology and Culprit Drugs

Although the induction of SJS/TEN may be multifactorial, medications are the most common culprit (10–12). A large study of 377 patients in the US between 2000 and 2015 found that antibiotic agents were the most common class of culprit drug with trimethoprim-sulfamethoxazole in 26.3% of cases (13). Anti-epileptics, particularly carbamazepine, lamotrigine, and phenytoin as well as allopurinol are other common causes of SJS/TEN (10, 14, 15).

TREATMENT STRATEGY FOR SJS/TEN WITH SEVERE OCULAR COMPLICATIONS IN THE ACUTE STAGE (0–6WEEKS)

Presenting Signs and Symptoms

The clinical presentation often begins with a prodrome of fever, malaise, cough, rhinorrhea, and anorexia followed by mucositis and a painful generalized erythematous vesiculobullous rash with skin sloughing (2, 5, 16). Early ocular disease is highly variable and can range from conjunctival hyperemia, sometimes as early as the prodromal phase, to near total sloughing of the entire ocular surface and eyelid margin epithelium.

Initial Eye Exam

An initial ocular examination on *all SJS/TEN patients* should occur within 24 h of admission. However, only 66% of burn ICUs in the United States consult ophthalmology for SJS/TEN patients (17, 18). A standardized EMR template may be useful to facilitate and prompt the documentation of key clinical signs on a daily basis. Examination should include the upper and lower eyelid skin, eyelid margins, and meibomian gland orifices. Fluorescein dye should be used to assess epithelial breakdown of the eyelid margins and ocular surface (cornea and conjunctiva). The entire conjunctiva including the forniceal and tarsal conjunctiva should be examined by everting the eyelids, with special attention to the presence of membranes (5, 19, 20). Saline rinses can aid in removal of mucous and tear film debris that may hide corneal or conjunctival epithelial defects (18).

Subsequent Examinations

Following initial ocular examination, patients should be monitored every 24–48 h during the first week of admission due to the potential for clinical signs and symptoms to rapidly progress (5). Daily evaluation is needed for any patient with the following: eyelid margin involvement, conjunctival pseudomembranes, opposing bulbar and tarsal conjunctival defects, or corneal epithelial defects. Upper and lower fornices need to be inspected daily. Degree of eyelid margin staining (location, size) should also be documented. The length and width of any corneal epithelial defect(s) should be measured and recorded.

The position of the eyelid should also be noted, as lagophthalmos, either from intubation/sedation or early cicatricial changes, can lead to corneal exposure with blinding complications (5, 19). A Desmarres retractor is useful in facilitating the examination and rotating the upper eyelid. See **Figures 1A–C** for examples of ocular involvement in acute SJS/TEN.

MANAGEMENT PROTOCOLS FOR ACUTE OCULAR SJS/TEN

Ocular Surface Disease Severity Grading and Treatment Overview

Several grading systems have been developed to assess disease severity in the acute stage. Sotozono et al. developed a grading system in 2007 to classify the severity of acute ocular disease (8). Their grading scheme lacked eyelid margin involvement, which has become an important risk factor for chronic surface disease (21). An updated grading system and algorithm for the initiation of ocular therapy in SJS/TEN is presented in **Supplementary Figure 1** (5, 22, 23). Beneficial long-term outcomes following the use of this standardized protocol has been recently published (17, 23).

Suppression of exogenous and endogenous causes of inflammation, avoidance of treatment toxicity, and preservation of the ocular surface are essential to halt disease progression (1, 5, 19). Resolution of conjunctival injection, epithelial defects, and eyelid margin ulceration are signs of resolution of acute disease.

Medical Management

Ocular treatment should start on admission as it is critical to maximally inhibit the ocular immune response to minimize long-term scarring. Ocular disease may actually precede the severe skin changes and treatment should not be delayed for skin biopsy results. Coordinated effort with burn unit/ICU nursing staff with written protocols is essential.

For Grades 0–1, daily saline (NaCl 0.9%) flushes should be performed and pseudomembranes debrided with a cotton tipped applicator. Medical treatment should include moxifloxacin 0.5% drops three times a day, topical steroid eye drop six times a day, and a steroid or antibiotic-steroid combination ointment to the eyelid margins 4–6 times a day. Cyclosporine 0.09% drops (Cequa, Sun Pharma) four times a day should also be considered. Preservative-free artificial tears should be used every 1–3 h in between the other drops.

In addition to topical antibiotics, small corneal epithelial defects may be managed initially with lubrication and/or soft therapeutic contact lenses to aid healing and minimize trauma. Larger defects may require amniotic membrane (ProKera) (see below).

All cases of cicatricial lagophthalmos and associated exposure should be aggressively managed with frequent lubricant ointment, humidity goggles, and/or plastic wrap to address evaporative dry eye. Definitive management includes surgical release of the cicatrix. Sedation-induced lagophthalmos (non-cicatricial) can be effectively managed with Tegaderm (3M, Saint Paul, MN) placement (19). For prevention of exposure keratopathy, scleral contact lenses have also been effective (19, 24, 25). External photography is very helpful to follow disease if available.

For Grades 2–3 with significant eyelid margin involvement +/– bulbar conjunctiva, amniotic membrane should be applied in addition to the above medical management (see below).

Surgical Management: Amniotic Membrane Transplantation (AMT)

All patients with eyelid margin involvement, pseudomembranes, and/or corneal and conjunctival epithelial defects within 4–7 days from index day, should receive AM (19, 23, 26, 27). Better visual acuity and reduced incidence of corneal haze, limbal stem cell deficiency (LSCD), symblepharon, ankyloblepharon, or eyelid-related complications have been reported in the long-term (17,

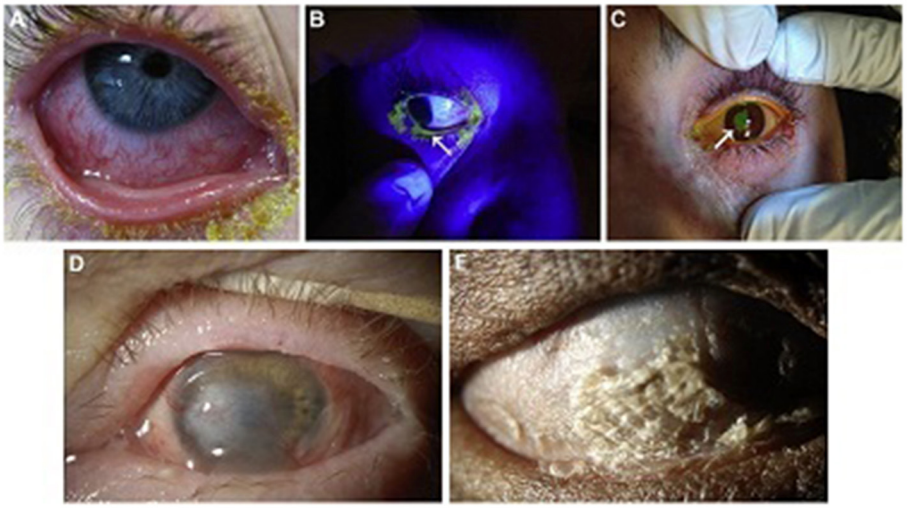

FIGURE 1 | Ocular surface involvement in acute SJS/TEN and severe chronic SJS/TEN. **(A)** Acute conjunctival hyperemia and membrane. **(B)** Acute eyelid margin sloughing (arrow) as evident with fluorescein staining under cobalt blue light. **(C)** Acute corneal epithelial defect (arrow) stained with fluorescein. **(D)** Chronic dense corneal neovascularization and opacity in a wet, blinking eye. This eye might be a candidate for a Boston keratoprosthesis type I. **(E)** Complete ocular surface keratinization in an eye devoid of aqueous tears. This eye would not be a candidate for a Boston keratoprosthesis type I, but might be for a Boston keratoprosthesis type II. Reproduced with permission from Elsevier (19).

28). Although AM has not been shown to affect mild dry eye, it has been shown to affect the incidence of moderate to severe dry eye (17).

Timing for AM placement is crucial, as its anti-inflammatory and anti-scarring properties are more beneficial when used early on in the acute phase. Previous studies have reported timeframes between 5 and 10 days after symptom onset as the ideal window for prevention of serious long-term ocular complications (20, 23). AM can dissolve anywhere from 3 days to 2 weeks post placement (5, 19) and can be repeated as necessary in patients with persistent inflammation. Complications are exceedingly rare (17, 29–32).

AM can be used either as a large single sheet of AM or in the form of a ProKera device (Biotissue, Miami, FL), but a ProKera by itself is insufficient. Prokera is an AM that is stretched across a polycarbonate ring and is placed on the eye similar to a contact lens (26). Although it can be inserted at the bedside without sedation and quickly replaced, it does not cover peripheral conjunctiva, fornices, and eyelid margins and leaves these areas susceptible to complications (26, 27, 33). Single sheet AMT utilizes a single 5 × 10 cm sheet of AM that is secured to the upper and lower eyelids, by suture or glue, and a large symblepharon ring that is inserted to ensure contact of the membrane to the upper and lower fornix. A recent study by Shanbhag et al. describes a sutureless AMT technique involving cyanoacrylate glue to secure the AM to the eyelids (34). It has been shown to speed up AMT placement as well as cause less discomfort allowing for bedside treatment without general anesthesia.

If a patient is already scheduled for a procedure in the OR, ophthalmologists should consider placement of AMT within the same scheduled time. If bedside or operative room AMT placement are not possible due to instability of the patient's condition, patient declining treatment, or due to issues of comfort/patient cooperativity, ProKera can be placed but it will not prevent later eyelid margin keratinization. It is important to note that AMT is also not a panacea and severe chronic disease can still occur despite aggressive acute phase treatment and all SJS/TEN patients must be followed closely for the development of complications (17, 23).

Systemic Treatment

Systemic treatment may provide benefit in managing the ocular disease in acute SJS/TEN. Suggested therapies as reported include the use of corticosteroids, intravenous immunoglobulin (IVIG), plasmapheresis, cyclosporine, granulocyte-stimulating factor, TNF-alpha inhibitors, and cyclophosphamide but published results are equivocal at best (5, 19, 35–40). In addition, these treatments are not without systemic risks. An FDA approved prospective randomized clinical trial (NATIENS) is planned in the US comparing etanercept, cyclosporine and supportive therapy (https://clinicaltrials.gov/ct2/show/NCT02987257?term=natiens&draw=2&rank=1).

TREATMENT STRATEGY FOR SJS/TEN WITH SOC IN THE CHRONIC STAGE

Overview of Management Strategy for Chronic Disease

Thirty-50% of patients who survive SJS/TEN in the acute setting develop some form of chronic ocular disease and all patients should have a follow-up ophthalmologic exam (41). The initial follow up visit should be performed within the first month after discharge and should be repeated every 2–4 months in

the first year and then at least every 6 months thereafter, dependent upon the patient's ocular condition (19). Chronic complications for which these acute management strategies are designed to prevent and treat include those related to dry eye disease (DED), eyelid malposition (ectropion, entropion, lagophthalmos), misdirected lashes (trichiasis, distichiasis), posterior eyelid margin keratinization, conjunctival disease (keratinization, symblephara, ankyloblephara), and corneal disease (epithelial defects, thinning, scarring, neovascularization, LSCD). There is no standardized timepoint at which SJS/TEN is considered to be chronic, but in general this is related to stabilization of any acute inflammation and de-epithelialization. This may be between the 3–6 months post-SJS-onset range.

Ocular Surface Stabilization

Ocular surface inflammation can persist and/or recur episodically during the chronic phase (42). Failure to stabilize the ocular surface can result in postoperative inflammatory and infectious complications (43, 44). Topical antibiotics and low potency topical corticosteroids may be needed for treatment of brief bouts of inflammation. High potency topical corticosteroids can be associated with infection and/or keratolysis and long-term use is ill-advised (19). Oral doxycycline or azithromycin may help in controlling inflammation (45). Systemic immunosuppressive therapy with cyclosporine, azathioprine and others may have a role in stabilization, although studies were performed without controls (42, 46).

Ocular surface inflammation may be due in part to changes in the ocular surface microbiome (44, 47–49). SJS/TEN eyes may have a more diverse microbiome than healthy eyes and may be due to deficiencies in the innate immune response (50). This imbalance may result in inflammation leading to ulceration and infection (51–53). These results raise interesting possibilities for clinical management of the disease including probiotics to promote the growth of a healthy microbiome or targeted antibiotics to kill pathogenic bacteria that may be causing inflammatory symptoms. Further investigation is warranted to better understand the immunopathophysiology and potential targets for intervention.

Ocular Xerosis and Dry Eye Disease (DED)

DED is a common complication of SJS/TEN, occurring in more than 50% of patients secondary to deficiencies in all three components of tear film: aqueous, mucin, and lipid (19, 54–56). Topical cyclosporine has had equivocal success in improving goblet cell density, possibly due in part to self-withdrawal due to side effects (57). For aqueous deficiency, preservative-free artificial tears may be used but require frequent dosing and can be expensive. Punctal occlusion (cautery or plugs) can improve ocular surface health; many patients may already have closed puncta from scarring related to SJS/TEN (58). Minor salivary gland transplantation can increase ocular surface wetting and corneal clarity (3, 19, 59–61). Serum tears have also been reported to improve clinical signs and symptoms (3, 19, 62).

Abnormalities of the Eyelid and Lashes

Malposition of the eyelids and misdirection of the eyelashes is a common chronic sequela of SJS/TEN. Trichiasis and distichiasis can be temporarily treated with mechanical epilation, whereas long-term treatment involves hyfrecation, cryotherapy, and/or extirpation (19). Ectropion or entropion can be treated with lateral canthoplasty or tarsal strip, anterior lamellar repositioning, tarsal fracture, posterior lamellar tightening, or tarsoconjunctival advancement (19). Tarsorrhaphy and cicatricial release can be used to treat lagophthalmos as well. In the setting of posterior eyelid margin keratinization or scarring resulting in entropion, mucous membrane grafting (MMG) or scleral lenses such as the PROSE lens are most appropriate (5, 63, 64).

Primary and Secondary Corneal Complications

Corneal infection and perforation are severe consequences that can occur as a result of persistent, untreated corneal epithelial defects during the acute and subacute phase of SJS/TEN. Recommended standard treatments for persistent defects include those that modulate tear film (lubrication with artificial tears and ointment, serum tears, punctal occlusion), those that protect the ocular surface [discontinuation of toxic medications, bandage contact lens, AMT (ProKera)], and those that correct eyelid abnormalities (tarsorrhaphy) (19, 62, 65–67).

Posterior eyelid margin keratinization is itself a primary cause of corneal disease from repetitive mechanical microtrauma which can induce corneal epithelial defects, infection, perforation, and stromal melting as well as LSCD and ultimately corneal blindness (21, 68, 69). Treatment for posterior eyelid margin keratinization includes all-trans retinoic acid ointment (70, 71), scleral contact lenses such as PROSE therapy (63, 72) and MMG (41, 60, 73).

PROSE is a treatment that utilizes a gas-permeable, large-diameter contact lens which provides a protective barrier over the cornea and submerges the entire corneal surface in a pool of oxygenated artificial tears creating an environment which supports healing and maintenance of the corneal epithelium (63, 74). It also improves visual acuity and comfort and reduces corneal complications (41, 64, 75). Symblephara may need management before a lens can be fitted properly (21). Newly developed limbal rigid contact lenses may be indicated in eyes with a short fornix and/or symblepharon (76, 77).

Definitive treatment for posterior eyelid margin keratinization is MMG (41, 60, 62). By replacing the keratinized mucosal surface with healthy, viable mucosa, typically from the oral cavity, the procedure removes the microtrauma associated with a keratinized eyelid. MMG has been shown to restore ocular surface integrity and improve visual function, particularly when used in conjunction with PROSE devices, in both children and adults (41, 78, 79). MMG can be performed in conjunction with autologous cultivated oral mucosal epithelial transplantation (COMET), a technique that utilizes host oral mucosa as a graft and transplants it onto the corneal surface (80, 81). Allogeneic simple limbal epithelial transplantation (SLET) may also be used

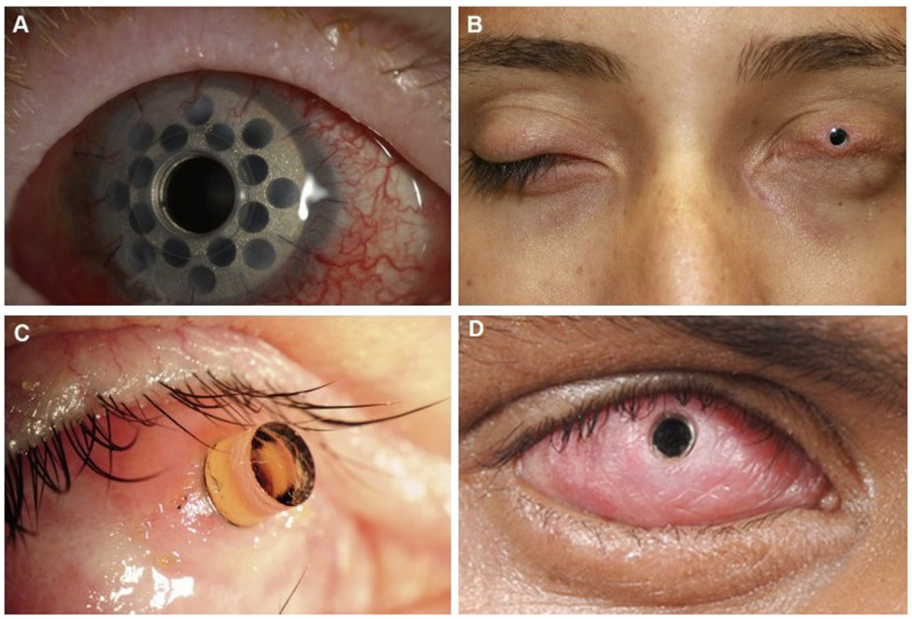

FIGURE 2 | Keratoprosthesis implantation in patients post SJS/TEN. **(A)** Boston keratoprosthesis type I. **(B)** Boston keratoprosthesis type II. **(C)** Osteo-odonto-keratoprosthesis. This image is taken from an oblique view. **(D)** LVP Keratoprosthesis. Reproduced with permission from Elsevier and BMJ Publishing Group Ltd. (19, 109).

in conjunction with MMG to address LSCD in eyes without extensive cicatrization and with a wet surface (82).

MANAGEMENT PROTOCOLS FOR END-STAGE THERAPY

Globe Salvage and Ocular Surface Stabilization

Ocular surface keratinization from SJS/TEN can actually be protective of the ocular surface but at the cost of severely reduced vision. Once disease has progressed to this stage, it is unlikely that ocular surface reconstructive surgery alone will restore visual function. See **Figures 1D,E**. However, there may be a short window prior to this point at which some globe salvaging therapy remains viable. This includes scleral contact lenses for non-healing epithelial defects, cyanoacrylate glue with a bandage contact lens for small perforations or keratolysis, and Gunderson conjunctival flap (19). Penetrating keratoplasty may be utilized for severe corneal thinning/perforation or corneal infection with thinning but leaves patients at further risk for complications such as graft ulceration and perforation and reactive inflammatory response (19).

Ocular surface stabilization procedures should be considered in order to restore normal eyelid/globe anatomy and improve tear film before consideration of reconstruction. These include punctal occlusion to improve tear film, MMG for posterior eyelid margin keratinization, and AMT with/without MMG, or COMET to restore conjunctival fornices (19, 70). Most reports on limbal stem cell transplantation in the setting of SJS/TEN, either show poor outcomes or are series with limited follow up. Short-term improvement in vision and the ocular surface is most often not sustained in the long-term (83). Allogeneic SLET may be an option in select eyes with LSCD and may have better outcomes compared to other forms of limbal stem cell transplantation in this population (82).

Reconstructive Management

Keratoprosthesis (KPro) is the mainstay of visual rehabilitation in end-stage ocular SJS/TEN as it has been shown to restore normal to near normal visual function after surgery, although not indefinitely as complications and the need for repeat procedures often arise (41, 84–91). Unfortunately, relative to other populations, patients with SJS/TEN tend to have worse post-operative complications, device retention, and visual prognosis after KPro; KPro should be considered an option of last resort (92–95). Common complications include melt and leaks, endophthalmitis, microbial keratitis, and glaucoma (96–102). The different types of keratoprostheses include Boston KPro (types I and II), the LVP KPro, and the modified osteo-odonto-keratoprosthesis (MOOKP). Boston KPro type I can only be done in eyes with a wet ocular surface and intact eyelid function. The Boston KPro type II, MOOKP, and LVP KPro may be done in eyes with a dry, keratinized surface and with significant eyelid abnormalities (103–109) (see **Figure 2**).

CONCLUSIONS AND FUTURE DIRECTION

SJS/TEN is a severe multisystem, immune-mediated mucocutaneous disease commonly involving the ocular surface that has the potential to result in corneal blindness. The

ophthalmologist is a critical caretaker in the acute and long-term treatment of these patients. Early aggressive intervention using a standardized protocol as that proposed is vital to reduce and/or prevent chronic ocular morbidity. As chronic disease may still arise regardless of early treatment, interventions such as PROSE and MMG in the chronic phase, and keratoprosthesis at end-stage disease, may be necessary. Prevention of significant disease should be the mainstay of future research and includes more targeted acute ocular and systemic therapy; identification of biomarkers for early diagnosis of disease and for prognostic assessment; and education and training of healthcare personnel on early referral to tertiary burn care centers, standardized treatment protocols, and windows of treatment opportunity. To truly mitigate the occurrence of ocular surface and systemic disease from SJS/TEN, personalized medicine in the form of genetic screening is needed to identify at-risk individuals and prevent rather than treat the occurrence of disease.

AUTHOR CONTRIBUTIONS

DM, OI, CB, and HS contributed to conception and design of this review. DM did the literature review and organized the structure of the review. DM, CB, and HS wrote the first draft of the manuscript. OI and JC wrote sections of the manuscript. All authors contributed to manuscript revision, read, and approved the submitted version.

FUNDING

This work was supported by National Eye Institute, National Institutes of Health, K23EY028230.

SUPPLEMENTARY MATERIAL

The Supplementary Material for this article can be found online at: https://www.frontiersin.org/articles/10.3389/fmed.2021.662897/full#supplementary-material

Supplementary Figure 1 | Flow diagram outlining the protocol for management of ocular manifestations in acute SJS/TEN. MF [moxifloxacin 0.5%; PA [prednisolone acetate 1%; FML [fluorometholone 0.1%; AT [artificial tears; AMT [amniotic membrane transplantation. *Decision to perform AMT was based on feasibility (intubation status, cooperation, etc.). ProKera is acceptable only with limited bulbar conjunctival or corneal involvement or when AMT is not feasible. Reproduced with permission from Elsevier (23).

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Conflict of Interest: HS and JC are employed by Mass Eye and Ear which manufactures and distributes the Boston keratoprosthesis and is discussed in this article.

The remaining authors declare that the research was conducted in the absence of any commercial or financial relationships that could be construed as a potential conflict of interest.

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REVIEW
published: 15 July 2021
doi: 10.3389/fmed.2021.652091

Genetics of Severe Cutaneous Adverse Reactions

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Severe cutaneous adverse reactions (SCARs) including Stevens-Johnson syndrome (SJS), toxic epidermal necrolysis (TEN), and drug rash with eosinophilia and systemic symptoms (DRESS) are T cells-mediated life-threatening immune reactions, most commonly induced by drug. The last decade has seen significant progress in SCARs research. Recent studies have unveiled the pathogenesis of SCARs involved in susceptible genes, including human leukocyte antigens (HLA) and drugs-T cell receptor (TCR) interaction that may trigger T cell activation with downstream immune signaling of cytokines/chemokines and specific cytotoxic proteins releases. Advances in identification of multiple genetic alleles associated with specific drugs related SCARS in different populations is an important breakthrough in recent years for prevention of SCARs. This article summarized the findings on genetic factors related to SJS/TEN, especially for HLA.

Keywords: genetic screen, Stevens–Johnson syndrome, toxic epidermal necrolysis, pharmacogenomic, severe cutaneous adverse drug reactions

OPEN ACCESS

Edited by:
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Reviewed by:
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Specialty section:
This article was submitted to Ophthalmology, a section of the journal Frontiers in Medicine

Received: *11 January 2021*
Accepted: *11 May 2021*
Published: *15 July 2021*

Citation:
Yang S-C, Chen C-B, Lin M-Y, Zhang Z-Y, Jia X-Y, Huang M, Zou Y-F and Chung W-H (2021) Genetics of Severe Cutaneous Adverse Reactions. Front. Med. 8:652091. doi: 10.3389/fmed.2021.652091

INTRODUCTION

Cutaneous reactions are most common manifestations seen in hypersensitivity reactions of drugs, named cutaneous adverse drug reactions, and among those with risk of life-threatening are classified into severe cutaneous adverse reactions (SCARs), mediated by drug-specific T lymphocytes, including drug rash with eosinophilia and systemic symptoms (DRESS)/drug-induced hypersensitivity syndrome (DIHS), Stevens–Johnson syndrome (SJS), and toxic epidermal necrolysis (TEN). The mortality rates for SJS/TEN are ∼5–10% in SJS and 30–50% in TEN (1), and the common leading culprit drugs around the world are antibiotics, antiepileptics, allopurinol, and cold medicine (2–4). In this article, we reviewed the updated molecular mechanism and susceptible genes related to SCARs.

Immune Mechanisms and Clinical Manifestations of Severe Cutaneous Adverse Reactions

SCARs belonged to type IV hypersensitivity reaction and are T cell-mediated immune responses with different effector cells and cytokines, resulting in further subtypes with specific clinical features.

SJS/TEN is characteristic for cutaneous and mucosal detachment, commonly including oral, ocular, and genital or anal mucosae. Internal epithelial organs are rarely involved, concerning mainly in the respiratory and gastrointestinal tract (5). SJS/TEN is one of the representative SCARs with high mortality and complications, where CD8+ cytotoxic T lymphocytes (CTLs) play a role, acting as effector cells with nature killer cells, causing cell death by the participant of perforin/granzyme B, granulysin, and/or Fas-Fas ligand (6). Besides, cytokines/chemokines, including interleukin (IL)-6, IL-8, IL-15, C-C chemokine receptor 10, tumor necrosis factor-α, interferon-γ, etc., also contribute to these severe immune reactions (7). The messenger RNA expression and level of 15-kDa granulysin were found much higher than others in SJS/TEN blister cells, suggesting it is the key mediator of disseminated keratinocyte apoptosis (8).

Another severe phenotypes of SCARs is DRESS, presenting as long-lasting, widespread, and infiltrated skin rash with internal organ involvement and hematological abnormalities, most frequently as eosinophilia and atypical lymphocytes (9). The immune mechanism involved in DRESS is majorly the Th2 immune response. Th2 cells involved in DRESS secrete ILs, including IL-5, IL-4, and IL-13, promoting immunoglobulin E and immunoglobulin G4 production and macrophage deactivation, leading to mast cell and eosinophil activation (6). Perforin/granzyme B, tumor necrosis factor-α, interferon-γ, C-C chemokine receptor 4, and thymus and activation-regulated chemokine (10) are also engaged.

Molecular Mechanism and Susceptible Genes Related to Severe Cutaneous Adverse Reactions

Roujeau et al. firstly reported the relationship between human leukocyte antigen (HLA) and SJS in 1986 (11) and HLA and TEN in 1987 (12). The association of HLA and SCARs are drug-specific and ethnicity-specific (13). Specific HLA is not only a genetic marker but also plays an important role in the pathogenesis of SCARs by presenting drug antigen to T cell receptor (TCR) and causing T cell-dependent immune response (14).

Recent advance in the technology of pharmacogenomic studies have showed more genetic risk factors associated with SCARs, not only in genes of HLA and other immune pathways, but also in drug metabolism or elimination. The genetic approach for the pharmacogenomics studies for SCAR has been evolved from sequencing based genotyping with polymerase chain reaction (PCR), such as HLA genotypes (15) to more comprehensive approaches, including genome-wide association study (GWAS) and next-generation sequencing (NGS), in discovering the relationship between adverse drug reactions (ADRs) and genotyping, and discovered more non-HLA loci (15–17).

Genetic Susceptibility to Aromatic Antiepileptic Drug-Induced Severe Cutaneous Adverse Reactions

Aromatic antiepileptic drugs (AEDs) are commonly used mainly in treating epilepsy and neuralgia, including carbamazepine (CBZ), oxcarbazepine (OXC), lamotrigine (LTG), phenytoin (PHT), and phenobarbital (PB). A strong association of *HLA-B*15:02* with CBZ-induced SJS/TEN was first found in Han Chinese (18). This relationship was also proved in Southeast Asians, including Thais (19), Malaysians (20), Indians (21).

AEDs had the same chemical structure, an aromatic ring, thus sharing the same risk allele. The susceptibility of *HLA-B*15:02* with AED-induced SJS/TEN was also found in PHT (22) and OXC (23), causing SJS/TEN in Han Chinese and Southeast Asians (24–26) (**Table 1**).

By using GWAS approach, our previous study found that *CYP2C9*3* was significantly related to PHT-induced SCARs in Han Chinese, Japanese and Malaysian, and by adding HLA-B*15:02 to this variant could increase sensitivity for preemptive test (35). In addition to *HLA-B*15:02, HLA-B*13:01*, and *HLA-B*51:01* were also found strong association with PHT-induced SCARs in Han Chinese, Thai and Japanese (37). Another genetic variant for PHT-induced SCARs was HLA-B*15:13, which majorly found in Malaysian (24) (**Table 1**).

The *HLA-DRB1*15:01* allele had been reported to be associated with AED-induced SJS/TEN in Han Chinese (68). Besides, *HLA-A*33:03, HLA-B*58:01, HLA-B*40:01*, and HLA-DRB1*03:01 alleles had also been reported to be associated with AED-induced SJS/TEN (68, 69).

There were differences of susceptible genes among ethnic groups. The same susceptible genotype of HLA-B*15:02 of CBZ-induced SJS/TEN was not found in Northeast Asians like Japanese and Korean, but HLA-B*15:11 instead (27, 28, 63). Interestingly, association between *HLA-B*15:21* and CBZ-induced SJS was found in an *HLA-B*15:02* negative Thai patient (29). The relationship of *HLA-B*15:11* and *HLA-B*15:21*, member of HLA-B75 serotype, and CBZ-induced SJS/TEN was found in *HLA-B*15:02* negative patients with pooled-data of Southeast Asian (29) (**Table 1**).

As for other AEDs in Northeast Asians, *HLA-B*51:01* was found to be related to PHT- and PB-induced SJS/TEN, and HLA-A*02:07 was found to be relevant with PB- and zonisamide-induced SJS/TEN (36) (**Table 1**).

Caucasians also revealed less relevant of AEDs and *HLA-B*15:02*, instead, they were commonly found with *HLA-A*31:01*, and developed CBZ-induced DRESS (31, 32). This relationship also existed in Han Chinese and Japanese (31, 70), however, not only DRESS but also SJS/TEN were related with this gene in Japanese (70). Another Caucasian-specific gene was HLA-B*57:01 and was found to be strongly associated with CBZ-induced SJS/TEN in Europeans (30). A limited number also showed a relationship with HLA-B*38 and LTG-induced SJS/TEN (34) (**Table 1**).

TABLE 1 | Genetic associations with SCARs in different populations.

Causative drug	Genetic associations	SCAR	Ethnicity	Reference	Clinical implementations and recommendations
Antiepileptic drug					
Carbamazepine	B*15:02	SJS/TEN	Han Chinese	(18, 25)	1. Labeled by Taiwan FDA, Hong Kong Department of Health, Singapore Ministry of Health, Thailand HITAP, India MOHFW, US FDA, Canada HCSC, EMA.
			Southeast Asian	(19, 20)	2. National health insurance subsidized in Taiwan, China, Hong Kong, Singapore, and Thailand.
	B*15:11	SJS/TEN	Northeast Asian	(27, 28)	
			Southeast Asian	(29)	
	B*15:21	SJS/TEN	Southeast Asian	(29)	
	B*57:01	SJS/TEN	Caucasians	(30)	
	A*31:01	DRESS	Han Chinese	(31)	1. Labeled by US FDA, Canada HCSC, Japan, and Taiwan.
			Caucasians	(31, 32)	
		SCARs	Japanese	(33)	
Oxcarbazepine	B*15:02	SJS/TEN	Han Chinese	(23, 25)	1. Labeled by US FDA, EMA and Taiwan FDA. 2. Ongoing clinical trial in Taiwan and China.
Lamotrigine	B*15:02	SJS/GEN	Han Chinese	(25)	Ongoing clinical trial in Taiwan and China.
	B*38	SJS/TEN	Caucasians	(34)	
Phenytoin	B*15:02	SCARs	Han Chinese	(22, 25, 35)	1. Labeled by Canada HCSC, US FDA, and Taiwan FDA.
			Southeast Asian	(24, 26)	2. Ongoing clinical trial in Taiwan and China.
	B*13:01	SCARs	Asian	(35)	Ongoing clinical trial in Taiwan and China.
	B*15:13	SJS/TEN	Japanese	(36)	Ongoing clinical trial in Taiwan and China.
	B*51:01	SCARs	Han Chinese	(37)	
	CYP2C9*3	SCARs	Asian	(35)	Ongoing clinical trial in Taiwan and China
Phenobarbital	B*51:01	SJS/TEN	Japanese	(36)	
	A*02:07	SJS/TEN	Japanese	(36)	
Zonisamide	A*02:07	SJS/TEN	Japanese	(36)	
Antiinfection drugs					
Antibiotics					
Co-trimoxazole	B*13:01	SCARs	Han Chinese Southeast Asian	(17)	
Piperacillin/tazobactam	B*62	DRESS	Caucasians	(38)	
Sulfamethoxazole	B*38	SJS/TEN	Caucasians	(34)	
Vancomycin	A*32:01	DRESS	Caucasians	(39)	
Anti-virus					
Abacavir	B*57:01	HSR	Caucasians	(40, 41)	Labeled by US FDA, US HHS, EMA, Canada HCSC, and multiple international HIV/AIDS organizations
			Hispanic	(42)	
			Indian	(43)	
Nevirapine	B*35:05	HSR	Thai	(44)	
	C*04:01	SJS/TEN	African	(45)	
	Cw*04	cADRs	All	(46)	
	Cw*08	HSR	Sardinian	(47)	
			Japanese	(48)	
	DRB1*01:01	HSR	Caucasians	(49)	
	CYP2B6	cADRs	All	(46)	
	CCHCR1	HSR	Thai	(44)	
Raltegravir	B*53:01	DRESS	African	(50)	
Anti-leprosy					
Dapsone	B*13:01	DHS	Han Chinese	(51)	Prospective screening in China.
			Korean	(52)	
			Indonesian	(53)	
		SCARs	Thai	(54)	

(Continued)

TABLE 1 | Continued

Causative drug	HLA allele	SCAR	Ethnicity	Reference	Clinical implementations and recommendations
Cold medicine					
	A*02:06	SJS/TEN	Japanese	(55)	
			Korean	(56, 57)	
	A*66:01	SJS/TEN	Brazilian	(58)	
	B*44:03	SJS/TEN	Japanese	(55)	
			Indian	(56)	
			Thai	(59)	
			Brazilian	(56, 58)	
	C*03:04	SJS/TEN	Korean	(57)	
	C*12:03	SJS/TEN	Brazilian	(58)	
	TLR3	SJS/TEN	Japanese	(60)	
	PTGER3	SJS/TEN	Japanese	(60)	
	IKZF1	SJS/TEN	Japanese	(61)	
Others					
Allopurinol	B*58:01	SJS/TEN	Thai	(62)	1. Recommendation in the American College of Rheumatology guidelines for allopurinol initiation in Asians. 2. National health insurance subsidized in Taiwan, China, Korea, and Thailand.
			Japanese	(63)	
		SCARs	Han Chinese	(64)	
			Korean	(65)	
			Caucasians	(34)	
Methazolamide	B*59:01	SJS/TEN	Northeast Asian	(66)	
			Han Chinese	(67)	

DHS, Dapsone hypersensitivity syndrome; HSR, hypersensitivity reaction.

Genetic Susceptibility to Antibiotics Induced Severe Cutaneous Adverse Reactions

Antibiotics are one of the most widely used medications, being responsible for one-fifth to one-third of ADRs (71, 72). The most common cause of SCARs induced by antibiotics are beta-lactams; others include sulphonamide antibiotics, fluoroquinolones, macrolides, tetracyclines, and glycopeptides (71). Above all, vancomycin is notable for causing DRESS. The relevant susceptible gene found with vancomycin-causing DRESS was HLA-A*32:01, with a strong association in Caucasians (39). Other possible genes as a risk factor in Caucasian were *HLA-B*38* with sulfamethoxazole-induced SJS/TEN (34) and HLA-B*62 with piperacillin/tazobactam-induced DRESS (38), yet further research is still needed due to number limitation (**Table 1**).

Antibiotics, AEDs, and allopurinol are the most common offending drugs causing SJS/TEN in China from our previous study (4). Although the finding of genetic susceptibility with antibiotic-induced SCARs was limited, our recent study by using whole genome sequencing (WGS) approach showed *HLA-B*13:01*, not metabolism enzymes, was strong associated with co-trimoxazole-induced SCARs in Asians, including Han Chinese, Thai, and Malaysian (17) (**Table 1**).

Dapsone is mainly used in the treatment of leprosy and can also apply in other dermatological inflammatory diseases due to the ability of anti-infection and anti-inflammation. Dapsone hypersensitivity syndrome is the potentially fatal adverse effect of dapsone, presenting as fever, skin rash, lymphadenopathy, and multiple systemic involvements. By using GWAS approach, the susceptible gene of DHS was first found in Han Chinese with HLA-B*13:01 (51), which mainly exists in Asians. The same result was validated in Koreans (52) and Indonesians (53). This gene was also susceptible in Thai with dapsone-induced SCARs (54), including DRESS and SJS/TEN (**Table 1**).

Genetic Susceptibility to Antivirus Induced Hypersensitivity Reactions

Abacavir is a nucleoside reverse transcriptase inhibitor and is used as one of the combination treatment of human immunodeficiency virus (HIV) infection. Hypersensitivity reactions induced by abacavir appear in ∼5–8% of Caucasians (73), which presented as fever, rash, gastrointestinal tract, and respiratory symptoms during the first 6 weeks of initiation. These symptoms are non-specific; however, being a delayed-type immune reaction, a patch test can easily help to distinguish hypersensitivity reactions (73). The relevant susceptible gene HLA-B*57:01 was found in white and black population (40, 41), especially white (74), and also Hispanic (42) and Indian children (43). A study in Hong Kong found a 0.5% positive rate with HLA-B*57:01 in HIV-positive patients of Han Chinese, thus suggesting that screening in this population is unnecessary (75) (**Table 1**).

Nevirapine is a nun-nucleoside reverse transcriptase inhibitor (NNRTI), and is also a medication treating HIV infection.

The association of susceptible gene was first found with *HLA-DRB1*01:01* in nevirapine-induced HSR in Western Australian (49). However, this gene was later proven more associated with hepatotoxicity rather than cADRs in Caucasian (46). Other susceptible gene found in nevirapine-induced hepatotoxicity were *HLA-Cw*08* in Japanese (29), *HLA-Cw*04* in Han Chinese (76), and *HLA-DQB1*05* in Caucasian (46). Both *HLA-Cw*08* and *HLA-Cw*04* were found relevant to nevirapine-induced HSR and hepatoxicity. Relationships between *HLA-Cw*08* and HSR were found in Sardinian (47) and Japanese (29). *HLA-Cw*04* was found commonly in nevirapine-induced cADRs in Han Chinese, Thai, Spain, African and Caucasian, especially African and Asian (46). *CYP2B6* was also participated due to affecting delayed plasma clearance of nevirapine (46). Besides, *HLA-B*35:05* was found to be predictable with nevirapine-induced skin rash in Thai (44), whereas the same relationship was found weak in Han Chinese and Caucasian (46). In addition to HSR, SJS/TEN was found in patients using nevirapine, associated with *HLA-C*04:01* in African (45), and recently, the association between genetic variations in CCHCR1 and nevirapine-induced HSR was also found in Thai (77). GWAS approach was used in both studies (**Table 1**).

Raltegravir is an integrase inhibitor that is also used in the treatment of HIV infection, and HLA-B*53:01 was found strongly associated with raltegravir-induced DRESS in Africans (50) (**Table 1**).

Genetic Susceptibility to Cold Medicine Induced Stevens–Johnson Syndrome and Toxic Epidermal Necrolysis

The term cold medicine comprises non-steroidal anti-inflammatory drugs and other multi-ingredient medications. Due to the high prevalence of cold and the use of cold medicine, SJS/TEN developed after patients using cold medicines is not uncommon, and a series of susceptible genes had been reported to be related to cold medicine-induced SJS/TEN, especially with severe ocular complications. The association of HLA-A*02:06 and HLA-B*44:03 was found to be associated with cold medicine-induced SJS/TEN in Japanese (55), and the same susceptible genes were verified in patients of other populations, such as HLA-B*44:03 in Indian and Brazilian, and HLA*02:06 in Korean (56). Besides, HLA-C*03:04 was also reported to be associated with cold medicine-induced SJS/TEN in Korean (57). Furthermore, HLA-A*66:01 and HLA-C*12:03 was found related in Brazilian (58) and HLA-B*44:03 and HLA-C*07:01 found in Thai (59). In summary, HLA-B*44:03 seems to be a cross-ethnic susceptible gene with a strong association in Japanese, Brazilian, Indian, and Thai, whereas *HLA-A*02:06, HLA-B*44:03, toll-like receptor 3 (TLR3), prostaglandin-E receptor 3 (PTGER3*), and IKZF1, by using GWAS approach, were identified as primary association to cold medicine-induced SJS/TEN with severe ocular involvement in Japanese (55, 60, 61, 78) (**Table 1**).

Genetic Susceptibility to Allopurinol-Induced Severe Cutaneous Adverse Reactions

By inhibiting xanthine oxidase and then reducing the synthesis of uric acid, allopurinol is a first-line drug used to treat hyperuricemia and gout and also remains to be one of the leading causes of SCARs. HLA-B*5801 was first found as an important genet marker of allopurinol-induced SCARs in Han Chinese (64). The same associations were validated in Thai (62), Japanese (63), Korean (65), and Caucasians (34). However, the pharmacogenomic associations varied from different ethnic populations, 50–60% in Caucasians and Japanese, and 80–100% in Korea, Thai, and Han Chinese (79). Other non-genetic factors may also contribute to allopurinol-induced SCARs, especially impaired renal function, cardiovascular diseases, and higher drug initiating dosages (80) (**Table 1**).

Genetic Susceptibility to Methazolamide-Induced Stevens–Johnson Syndrome and Toxic Epidermal Necrolysis

Carbonic anhydrase inhibitor methazolamide is a medication applied in lowering intraocular pressure, for example, as a patient with glaucoma. Despite the low frequency, methazolamide may potentially induce SJS/TEN. Strong association of HLA-B*59:01 and methazolamide-induced SJS/TEN in Korean and Japanese had been reported (66) and also in Han Chinese (67) (**Table 1**).

Jackpot Theory and Importance of Specific T Cell Receptor for the Development of Severe Cutaneous Adverse Reactions

Although previous studies proved the association of specific HLA genotypes with SCARs, the positive predictive values were mostly low (81). Our previous study showed CBZ-specific T cells expressing specific TCR from peripheral blood mononuclear cells and causing activation of granulysin release in HLA-B*15:02-positive CBZ-induced SJS/TEN but was not found in CBZ-tolerant individuals or other drug-related SJS/TEN (82). Similarly, preferential usage of TCRβ variable gene and clonal expansion of specific third complementarity-determining region (CDR3) was identified in blister cells of patients with allopurinol-induced SJS/TEN (83). More recently, our further study showed a public αβTCR was further identified from CTLs of patients with CBZ-induced SJS/TEN, with a paired TCRβ CDR3 clonotype "ASSLAGELF" and TCRα CDR3 clonotype "VFDNTDKLI," which react to CBZ and its structural analogs by its structural analogs and bind affinity and mediate immune response (84). Importantly, the specific CDR3 clonotype was present in CTLs of CBZ-induced SJS/TEN of patients from different populations (Chinese or Europeans) with or without the HLA-B*1502 genotype. The finding of clonotype-specific T cell and drug-specific public TCR in patients illustrated the essential molecular role of shared and restricted TCR that interacted with specific HLA and drugs for the development of SCARs (Jackpot theory).

Pharmacogenomic Test for Prevention of Severe Cutaneous Adverse Reactions

The burden of developing SCARs was life-threatening. Not only public health but also medical resources were affected. A team in Singapore observed higher laboratory costs in the residency of patients with ADRs (85).

Considering the mortality rate and economic burden of SCARs, an easy and effective method for the prevention of SCARs would be greatly needed. The development of a strong correlation of preemptive genetic tests for high-risk medications related to SCARs is therefore very helpful. By screening relevant genes before using susceptible culprit drugs, we should be able to prevent the occurrence of SCARs and the consequent cost for sequalae.

Genetic testing of HLA-B*15:02 before CBZ was warned by The Food and Drug Administration (FDA) of the United States, Taiwan, and similar agencies of other countries (86), and genetic testing of HLA-B*58:01 before allopurinol initiation was warned by the FDA of Taiwan or other Asian countries (**Table 1**). Recommendations of relative gene testing before culprit drugs in case of developing SCARs were noticed in various studies (87). The first prospective screening test was applied in patients with HIV infection needed for abacavir and demonstrated a significantly lower incidence in the HLA-B*57:01 screening group (74). For proof of concept and clinical implementation, the Taiwan SJS Consortium had conducted a clinical trial to prevent CBZ-induced SCARs by genotyping DNA with HLA-B*15:02 allele of 4,877 candidates before CBZ therapy and found no SJS/TEN with negative subjects (88). The other one of the most commonly used drugs and cause of SCARs in Taiwan was allopurinol. Prospective screening with HLA-B*58:01 enrolled 2,926 patients before initiation of allopurinol in Taiwan, and the result showed none of the negative subjects developed SCAR (89). Recently, a prospective study of 1,539 patients diagnosed with leprosy underwent HLA-B*13:01 genotyping before using dapsone in China, and the result showed no SCARs developed in non-carrier (90) (**Table 1**).

Implementation of Precision-Based Use of Antiepileptic Drug Therapy by Screening Multiple Risk Alleles Related to Aromatic Antiepileptic Drugs for Prevention of Severe Cutaneous Adverse Reactions

With a similar aromatic ring structure, the first line AEDs, such as CBZ, OXC, LTG, PHT, and PB, have potential and share similar risk alleles predisposing to SCARs. For consideration of efficacy and safety for clinical selection of AEDs, a piece of pharmacogenomics information is important for decision making for patients with epileptic or neurologic disorders. Therefore, pharmacogenomic panel testing for multiple risk alleles related to all AEDs has its clinical necessity and demand; for clinical implementation and to evaluate the feasibility and efficacy of a pharmacogenomic panel of AEDs, we have developed a rapid testing panel of multiple risk alleles, including HLA-B*15:02, CYP2C9*3, HLA-B*13:01, HLA-B*51:01, and HLA-A*31:01, which are strongly related to aromatic AED-induced SCARs (**Table 2**) for decision making before initiating AEDs. A clinical trial has started since 2018 in Taiwan and China of multiple medical centers, by enrolling patients with need of antiepileptic drugs without history of using, and performing the testing panel by quantitative polymerase chain reaction (qPCR). With avoiding relevant drugs with positive susceptible genes, a preliminary evaluation of 231 patients with negative corresponding risk alleles received aromatic AEDs therapy, no SCARs have been observed, although five patients developed milder maculopapular eruption or itchy skin lesions.

TABLE 2 | Pharmacogenomic panel linked to AED-related SCARs in Asians.

	Risk alleles	Sensitivity (%)	Specificity (%)	Reference
CBZ-SCARs	HLA-B*15:02 HLA-A*31:01	74.6	90.3	(31)
OXC-SCARs	HLA-B*15:02	70.6	92.1	(23)
PHT-SCARs	HLA-B*15:02 HLA-B*13:01 HLA-B*51:01 CYP2C9*3	71.9	77.7	(37)
LTG-SCARs	HLA-B*15:02	29.4	89.7	(69)

CONCLUSIONS

SCARs are rare but life-threatening. The findings of the relationship with susceptible genes and drugs lead to clinical applications of prevention. By screening the known relevant genes before prescribing potentially culprit drugs in corresponding ethnicities would be an effective method to avoid the development of SCARs.

AUTHOR CONTRIBUTIONS

S-CY, M-YL, Z-YZ, X-YJ, MH, Y-FZ, C-BC, and W-HC wrote the original draft. X-YJ, MH, and Y-FZ provided the resources. S-CY, M-YL, Z-YZ, C-BC, and W-HC reviewed and edited the draft. C-BC and W-HC conceptualized the review and acquired funding. All authors contributed to the article and approved the submitted version.

FUNDING

This study was supported by research grants from the Xiamen Science and Technology Bureau, China (3502Z20180411), Xiamen Chang Gung Hospital (3502Z20180411), the Ministry of Science and Technology, Taiwan (MOST 108-2314-B-182A-006-MY3 to C-BC; MOST 103-2321-B-182-001, MOST 104-2314-B-182A-148-MY3, MOST 104-2325-B-182A-006, MOST 105-2325-B-182A-007, MOST 106-2314-B-182A-037-MY3, MOST 106-2622-B-182A-003-CC2, MOST 107-2622-B-182A-001-CC2, MOST 108-23 14-B-182A-104-MY3, MOST 108-2320-B-182A-023-MY3,

MOST 108-2320-B-182A-024-MY2, MOST 109-2320-B-182A-008 -MY3, MOST-108-2314-B-182A-104 -MY3, and MOST-109-2326-B-182A-001 to W-HC), and Chang Gung Memorial Hospital, Taiwan (CMRPG2H0081, CMRPG2J0221, CMRPG2J0222, NMRPG2J6012, NMRPG2J6013, CIRPG2I0011, CIRPG2I0012, CIRPG2I0013 to C-BC; CIRPG3I0022, CIRPG3I0023, CIRPG3I0042, CIRPG3I0043, CLRPG3E0036, CLRPG3J0012, CMRPG3I0382, CORPG3J0322, CLRPG2E0053, CMRPG3D0363, CORPG3F0042∼3, NCRPG3G0023, NCRPG3GS023, NMRPG3G6293, NMRPG3J6062, NMRPG3J6063, NMRPG3K0521, and OMRPG3E0041 to W-HC).

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Conflict of Interest: The authors declare that the research was conducted in the absence of any commercial or financial relationships that could be construed as a potential conflict of interest.

frontiers in Medicine

MINI REVIEW
published: 28 July 2021
doi: 10.3389/fmed.2021.657327

Japan: Diagnosis and Management of Stevens-Johnson Syndrome/Toxic Epidermal Necrolysis With Severe Ocular Complications

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In 2005, the "Japanese Research Committee on Severe Cutaneous Adverse Reaction" (J-SCAR) presented the official "Diagnostic Criteria" for SJS/TEN, and the specific ocular findings are included in these very important criteria. In SJS/TEN cases involving ocular disorder, conjunctivitis often occurs prior to the onset of the high fever. In a Japanese survey, ocular involvement was observed in 77% of the cases, and the incidence of ocular sequelae increased depending on the score of the acute ocular severity findings. Pseudo-membrane formation and epithelial defects are considered to be high-risk signs of ocular sequelae. At the chronic stage, limbal stem cell deficiency, visual disturbance, and severe dryness of the ocular surface are the primary disease characteristics. In 2002, we started performing Cultivated Oral Mucosal Epithelial Transplantation (COMET) for the treatment of severe ocular disorders, including SJS/TEN. As an additional treatment method, we developed a new type of rigid contact lens (CL) that is 13 to 14.0-mm in diameter, known as the "Limbal Rigid Contact Lens (Limbal CL)." Our Limbal Rigid CL greatly enhances the postoperative outcome of COMET. The detection rate of ocular surface bacteria is high in SJS/TEN cases. Thus, appropriate use of topical antibiotics reduces the risk of ocular surface inflammation. Moreover, rebamipide is an ophthalmic solution for dry eye that was developed in Japan, and it also has the effect of suppressing ocular surface inflammation. From disease onset until the chronic stage, the control of inflammation and stem cell loss is key to successfully treating eyes afflicted with SJS/TEN.

Keywords: Stevens-Johnson syndrome, toxic epidermal necrolysis, cultivated oral mucosal epithelial transplantation, Limbal-Rigid contact lens, Japan

OPEN ACCESS

Edited by:
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Reviewed by:
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Specialty section:
This article was submitted to Ophthalmology, a section of the journal Frontiers in Medicine

Received: *22 January 2021*
Accepted: *17 June 2021*
Published: *28 July 2021*

Citation:
Sotozono C, Ueta M and Kinoshita S (2021) Japan: Diagnosis and Management of Stevens-Johnson Syndrome/Toxic Epidermal Necrolysis With Severe Ocular Complications. Front. Med. 8:657327. doi: 10.3389/fmed.2021.657327

INTRODUCTION

Stevens-Johnson syndrome (SJS), and its more severe variant, toxic epidermal necrolysis (TEN), are acute systemic disorders that can affect anyone, and at any age (1–3). A variety of drugs can be the cause of SJS/TEN. At the onset of the disease, a definitive diagnosis of SJS and TEN is often complex and confusing.

In Japan, the "Japanese Research Committee on Severe Cutaneous Adverse Reaction" (J-SCAR) has been conducting diligent and extensive work on the diagnosis and treatment of SJS/TEN over the past two decades. In 2005, J-SCAR presented the official "Diagnostic Criteria and Systemic Severity Index Score" for SJS/TEN (4). Since then, SJS/TEN has been diagnosed based on these criteria. Importantly, the disease-specific ocular characteristics are now included as one of the supportive findings, and these criteria has enabled ophthalmologists to be a valued clinical "team member" for the diagnosis and treatment of SJS/TEN at the acute stage.

Both SJS and TEN are systemically self-limited lasting 6–8 weeks after onset. However, in SJS/TEN cases with severe ocular complications (SOC), persistent epithelial defects (PED) on the ocular surface can linger, ultimately resulting in ulceration and perforation (5). Finally, visual impairment and severe dryness of the eye remain as ocular sequelae (6, 7). At present, there is no standardized treatment strategy for SJS/TEN-related blindness worldwide. Patients with SJS or TEN require life-long management for ocular discomfort and morbidity. Our group has now developed both surgical and non-surgical therapeutic methods for the successful treatment of SJS/TEN.

In this review article, we describe the current diagnostic and therapeutic strategies for SJS/TEN with SOC now practiced in Japan, and provide a detailed summary of the multi-year clinical research and comprehensive Japanese survey on SJS/TEN conducted by Kyoto Prefectural University of Medicine, Kyoto, Japan.

SJS/TEN WITH OCULAR INVOLVEMENT AT THE ACUTE STAGE

At disease onset, ocular involvement in SJS/TEN is often easily overlooked due to the serious general symptoms and high lethality. Thus, the clinical characteristics of SJS/TEN with SOC need to be well-understood for early diagnosis and successful treatment.

Characteristic Findings

Our findings revealed that among 94 SJS/TEN patients with SOC, 75 (82%) experienced common cold-like symptoms (general malaise, slight fever, sore throat, etc.) that preceded the skin eruptions. In all patients, except one, the disease was accompanied by very high fever (above 39°C) at onset. Acute conjunctivitis and oral involvement (blisters, erosions, and bleeding of the mouth and lips) occurred in all patients who could recollect their symptoms in detail. Fingernail loss at the acute stage or deformation at presentation existed in all patients, thus suggesting that paronychia occurred in all patients at the acute phase (**Figures 1A–C**). Other mucous-membrane involvements included those of the pharynx, respiratory tract, or ear canal (8). Forty-two patients reported episodes of acute conjunctivitis from several hours to 4 days prior to the skin eruptions, and 21 patients reported that skin eruptions and conjunctivitis occurred simultaneously. Only 1 patient reported the occurrence of conjunctivitis post skin eruption. All patients reported remembering their eye symptoms such as bilateral red eye or ocular pain at disease onset. Surprisingly, 11 patients were diagnosed with acute conjunctivitis by ophthalmologists prior to the development of systemic eruptions. Thus, ophthalmologists should be aware that acute conjunctivitis can occur prior to skin eruptions (8).

Acute Ocular Severity Score

Typically, pseudomembrane formation with corneal and/or conjunctival erosions occurs at the acute stage of SJS/TEN. Hence, we speculated that inflammation and epithelial defects are key aspects of the ocular findings at the acute stage and developed the "Acute Ocular Severity Score" on a scale from 0 to 3 (none, mild, severe, and very severe) according to the existence of hyperemia, corneal or conjunctival epithelial defect, and pseudomembrane formation (**Figures 1D–F**) (4). In a Japanese survey, ocular involvement was seen in 104 (77%) of 135 SJS/TEN cases (87 SJS and 48 TEN cases arising between 2005 and 2007), and pseudomembrane formation and/or epithelial defects were seen in 62 of those cases (46%) (4). The incidence of ocular sequelae increased depending on the score of the acute ocular severity. Thus, pseudomembrane formation and epithelial defects are considered to be high-risk signs of ocular sequelae.

As shown in our previous study, patient age and NSAIDs or cold remedies as the exposed drugs were the predictive factors for the increase of acute ocular severity (4) (**Table 1**). In our previously published retrospective studies on SJS/TEN cases at the chronic phase, mean patient age was between 20 and 30 years at disease onset and cold remedies were the exposed drugs that were used in more than 24% of the cases (7, 8) (**Table 2**).

Treatment Strategy

The use of systemic corticosteroids for acute SJS and TEN is controversial (9–11). Thus, the timing and dose of the administered steroid may be key to obtaining beneficial outcomes.

As a prospective study, we used systemic steroid-pulse and topical betamethasone treatments in five cases diagnosed within 4 days from disease onset (11). All 10 eyes successfully healed without visual dysfunction. In our retrospective analysis, visual prognoses were significantly better in the group receiving topical steroids at the acute stage compared with the no-treatment group (8). In the Japanese treatment guideline, steroid-pulse therapy and topical betamethasone have been recommended in SJS/TEN cases with severe ocular involvement; i.e., an Acute Ocular Severity Score of 2 or 3. In tears obtained from SJS cases at the acute stage with pseudomembrane and epithelial defects, IL-6, IL-8, and MCP-1 were found to be dramatically upregulated (12). Thus, it is important to suppress the ocular surface inflammation. Moreover, initiating treatment with systemic and topical steroids from the onset of the disease appears to be important for the improvement of the visual prognosis.

Subacute Phase With PED

PEDs occurring in the subacute phase of SJS/TEN are very difficult to treat. Massive inflammation on the ocular surface is often uncontrollable, even with the use of systemic and/or local

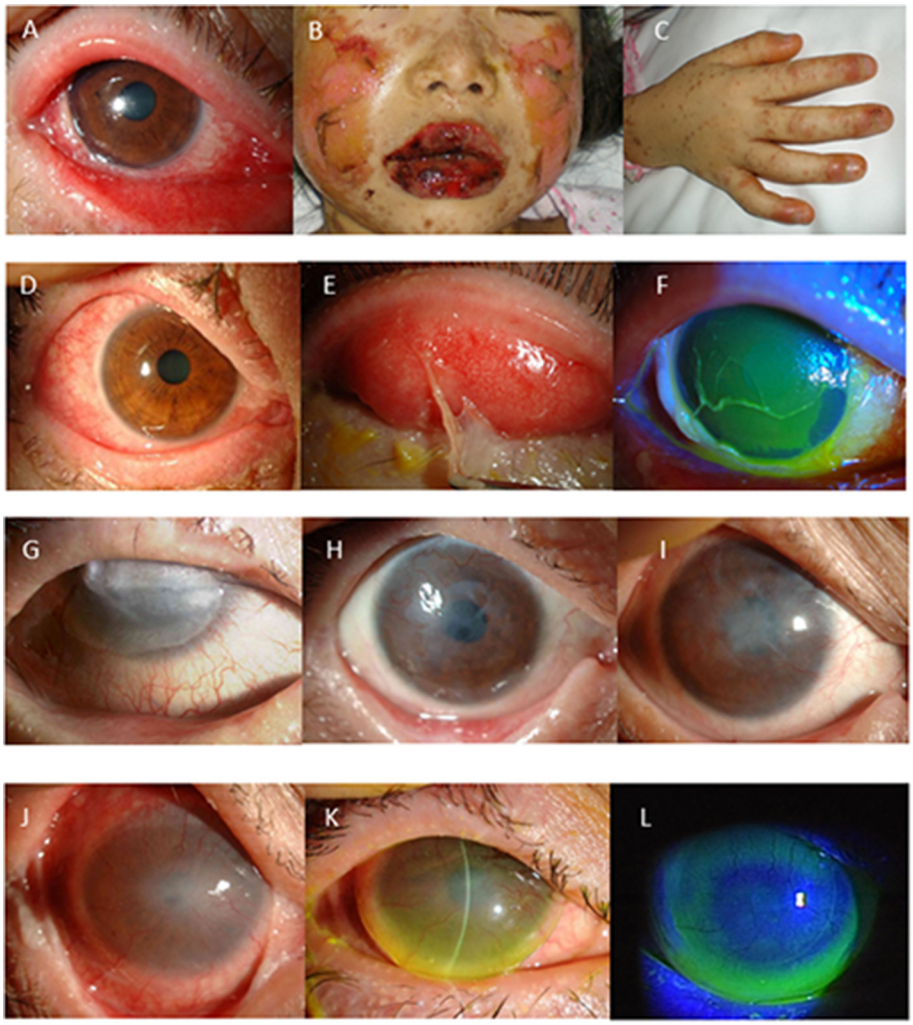

FIGURE 1 | (A–F) Representative photographs showing Stevens-Johnson syndrome/toxic epidermal necrolysis (SJS/TEN) at disease onset with severe ocular complications (SOC). **(A)** Conjunctivitis, which was accompanied by extensive loss of corneal and conjunctival epithelium. **(B)** Swollen and crusted lips. **(C)** Paronychia. In 66% of the patients, conjunctival hyperemia **(D)** preceded skin eruption. Pseudomembrane formation **(E)** and corneal or conjunctival epithelial defect **(F)** develop at the acute stage. **(G–I)** Long-term effect of cultivated oral mucosal epithelial transplantation (COMET). Images of SJS/TEN cases obtained at before **(G)** and at 2-years **(H)** and 5-years postoperative **(I)**. **(J–L)** Use of a limbal-supported rigid-type contact lens (Limbal-Rigid CL; Sun Contact Lens) for the treatment of SJS/TEN with ocular disorders. Representative appearances of the eyes with SJS/TEN at before **(J)** and after 3-months use of the Limbal-Rigid CL **(K,L)**.

steroids. Exposure of the corneal stroma can induce infectious or non-infectious corneal stromal thinning and perforation. Long-lasting inflamed PEDs eventually result in symblepharon, as well as conjunctivalization and neovascularization of the cornea, which can lead to blindness.

In such severely inflamed eyes, limbal transplantation and amniotic membrane transplantation (AMT) do not guarantee epithelialization (13–15). Both cultivated corneal limbal epithelial transplantation (CLET) (16, 17) and cultivated oral mucosal epithelial sheet transplantation (COMET) (5) resulted in complete epithelialization of subacute PED in SJS/TEN cases, thus preventing end-stage cicatrization and vision loss. We hypothesize that one of the mechanisms by which COMET has a positive treatment effect on subacute PED is the decrease of massive inflammation on the ocular surface post surgery. While conventional limbal transplantation requires several weeks for the limbal epithelium from the donor cornea to migrate and cover the corneal surface, transplantation of cultivated epithelium covers the entire cornea during surgery and works to resolve the ocular surface inflammation.

Management at the Chronic Phase

In the chronic stage of SJS/TEN, ocular surface disease arising from the acute stage encompasses a spectrum of ocular manifestations and complications that are often associated with significant visual morbidity (7, 18, 19). Visual impairment and ocular discomfort continue throughout the life of the patient,

and usually require long-term medication for optimal control of the disease.

Ocular Surface Grading Score

To elucidate the profile of chronic ocular-disorder manifestations, we developed an OSGS as an objective method for grading the extent and severity of ocular complications in SJS/TEN (7). Ocular surface findings were classified as corneal complications (i.e., superficial punctate keratopathy, epithelial defect, loss of the palisades of Vogt, conjunctivalization, neovascularization, opacification, and keratinization), conjunctival complications (i.e., hyperemia, and symblepharon formation), and eyelid complications (trichiasis, mucocutaneous junction involvement, meibomian gland involvement, and punctal damage). In the OSGS, these 13 components are graded from 0 to 3.

Among 138 SJS/TEN eyes treated, the most prevalent severe complications were loss of the palisades of Vogt (114 eyes, 82.6%) and meibomian gland involvement (102 eyes, 73.9%). Moreover, visual acuity in 74 of those 138 eyes (53.6 %) was worse than 20/200. Eyes with a higher total score for the three complication categories had poorer vision ($R = 0.806$, $p < 0.0001$). Multivariable regression analysis showed that corneal neovascularization, opacification, keratinization, and cataracts significantly affected logMAR findings ($p < 0.0001$, $p < 0.0001$, $p = 0.0142$, and $p = 0.0375$, respectively) (7).

Recently, our work using OSGS clearly demonstrated the long-term progression of ocular surface cicatrization in chronic-phase SJS/TEN eyes, and in 35 (33.3%) of 105 eyes, the total OSGS worsened during follow-up periods of over 5 years (20). Partial conjunctivalization progressed toward total conjunctivalization, and eyes with total conjunctivalization with partial keratinization progressed toward total keratinization. Thus, strict attention should be paid to eyes with partial conjunctivalization and partial keratinization.

TABLE 1 | Univariate Logistic Regression Analysis Of The Association Between Variables At Onset And Acute Ocular Severity In The Patients with Stevens-Johnson syndrome (SJS) and toxic epidermal necrolysis (TEN) [modified version of the table presented in (4)].

Variable at the onset $n = 135$	Univariate logistic regression		
	OR	95%CI	*P*-value
Disease: TEN (vs. SJS)	1.47	0.72–2.98	0.287
Gender: Male (vs. Female)	0.78	0.39–1.54	0.466
Age at the onset (years)	0.97	0.96–0.99	0.004
Age at onset (years): >50 (vs. 50≤)	0.36	0.18–0.72	0.004
NSAIDs	2.04	1.02–4.1	0.045
Cold-remedies	5.51	1.72–17.62	0.004
NSAIDs or cold-remedies	2.68	1.33–5.38	0.006
Antibiotics	0.66	0.27–1.63	0.363
Anticonvulsants	0.72	0.33–1.58	0.415

OR, odds ratio; CI, confidence interval; NSAIDs, non-steroidal anti-inflammatory drugs.

Management of the Ocular Surface

In the management of chronic SJS/TEN cases, it is important to control ocular surface inflammation. In most cases, topical steroids are considered adequate treatment. However, since

TABLE 2 | Demographics of the Stevens-Johnson syndrome and toxic epidermal necrolysis cases seen at the acute and chronic phase.

		Acute Phase Cases				Chronic Phase Cases	
		Acute Ocular Severity Score				Multi-center	KPUM
		0	1	2	3		
No of cases		31	42	39	23	73	94
Disease category	SJS	19	31	22	15		
	TEN	12	11	17	8		
Age at onset (years)	SJS	57.1 ± 18.2	52.3 ± 18.7	54.4 ± 19.1	39.2 ± 19.2	28.4 ± 18.2	26.2 ± 18.8
Mean ± SD	TEN	62.0 ± 14.5	64.6 ± 25.5	47.9 ± 19.0	39.6 ± 14.6		
Duration of illness (years)						18.8 ± 15.5	16.1 ± 15.2
Mean ± SD							
Exposed drug: No of cases (%)							
NSAIDs	Yes	12 (38.7%)	12 (28.6%)	18 (46.2%)	13 (56.5%)	10 (13.7%)	19 (20.2%)
Cold-remedies	Yes	1 (3.2%)	3 (7.1%)	9 (23.1%)	6 (26.1%)	18 (24.7%)	30 (31.9%)
Antibiotics	Yes	4 (12.9%)	11 (26.2%)	7 (17.9%)	2 (8.7%)	21 (28.8%)	23 (24.5%)
Anticonvulsants	Yes	6 (19.4%)	15 (35.7%)	10 (25.6%)	4 (7.4%)	6 (8.2%)	5 (5.3%)

SJS, Stevens-Johnson syndrome; TEN, toxic epidermal necrolysis; SD, standard deviation; NSAIDs, non-steroidal anti-inflammatory drugs.
The Acute Ocular Severity Score was defined as Score 0 (none) = no ocular involvement, Score 1 (mild) = conjunctival hyperemia, Score 2 (severe) = either ocular-surface epithelial defect or pseudomembrane formation, and Score 3 (very severe) = both ocular-surface epithelial defect and pseudomembrane formation (4). Chronic phase cases were summarized from our multi-center study in Japan (7) and our retrospective analysis for cases seen at Kyoto Prefectural University of Medicine (8).

steroid-induced glaucoma can develop during the long-term use of topical steroids, strict attention should be paid to secondary glaucoma in SJS/TEN.

Decreasing the number of bacteria on the ocular surface is the key to obtaining complete stabilization of the ocular surface. Thus, appropriate use of topical antibiotics reduces the risk of ocular surface inflammation. Due to the high detection rate of methicillin-resistant *Staphylococcus aureus* (MRSA) and methicillin-resistant *Staphylococcus epidermidis* (MRSA), 0.5% chloramphenicol is often prescribed, and 1% vancomycin eye ointment is known to be effective for MRSA/MRSE conjunctivitis or keratitis (21, 22).

Severe dry eye in SJS/TEN cases is comprised of three important mechanisms: (1) aqueous tear deficiency, (2) decreased wettability of the corneal surface, and (3) increased evaporation. The lacrimal punctum may be closed from scarring or cauterization, which can lead to a high tear meniscus and underestimation of the dry eye severity (23). Thus, it is important to suppress chronic inflammation on the ocular surface. The administration of 2% rebamipide ophthalmic solution reportedly helps to obtain ocular surface stabilization (24–26), and it often reduces or replaces topical steroid use.

Surgical Interventions

AMT

In Japan, AMT was first performed in the mid 1990s (27, 28). Since then, AMT has been performed for recurrent pterygium, severe ocular surface disorders, and ocular surface neoplasia. Amniotic membrane is used after the release of symblepharon as the substrate of epithelial cells. However, in end-stage SJS/TEN cases, the effect of AMT is limited.

COMET

In 2002, we started performing COMET for the treatment of severe ocular disorders, including SJS/TEN (29–34). Our retrospective analysis of 86 COMET surgeries revealed that COMET is effective for visual improvement in eyes with chronic SJS/TEN (35). In end-stage cases with severe conjunctivalization, keratinization, and symblepharon, visual improvement was obtained, and the re-constructed ocular surface in those cases was maintained for a long time-period (**Figures 1G–I**) (36).

Based on the above results, a prospective clinical study of COMET for the treatment of severe ocular surface disorders (i.e., SJS, OCP, and severe thermal/chemical injury) was performed between September 2014 and March 2017 as part of a prospective clinical study under the Advanced Medical Care System in Japan. Thereafter, an investigator-initiated phase 3 clinical trial was started in 2018 to obtain regulatory approval for COMET. In both prospective clinical trials, COMET provided beneficial effects for the release of symblepharon and visual improvement (manuscript in preparation).

Post-surgical management is the key to obtaining favorable results. In our retrospective and prospective clinical studies, systemic corticosteroid (betamethasone, 1 mg/day) and cyclosporine (2–3 mg/kg/day) were administered to prevent postoperative inflammation and immunological response, and then tapered depending on the clinical findings. Nearly all patients required frequent administration of artificial tears, and a therapeutic soft contact lens was used for at least 1-month post surgery to protect the transplanted epithelium from mechanical ablation.

Eye Lid Surgery

Trichiasis is a common complication of SJS/TEN at the chronic stage. Double eyelashes and/or entropion are also seen in severely cicatrized cases. Eyelashes touching the cornea induce ocular surface inflammation, and might promote the deterioration of chronic SJS/TEN. Thus, it is optimal to correct these problems, and tarsal wedge resection, gray-line splitting or an autograft of hard-palate are considered depending on the severity of eyelid cicatrization. Interestingly, in a clinically "quiet" chronic SJS/TEN case, folliculitis reportedly existed (37). It should be noted that ocular surface stabilization can be obtained after the successful intervention of these surgeries.

Visual Rehabilitation Using Limbal-Rigid Contact Lenses

With the aim of reducing the symptoms related to corneal irregularity and dry eye observed in severe OSD cases, we developed a limbal-supported rigid-type CL (Limbal-Rigid CL; Sun Contact Lens Co., Inc., Kyoto, Japan) with a diameter ranging from 13 to 14 mm. When our new CL is worn, a fluid layer exists at the peripheral zone of the lens, and the tears beneath the lens exchange at each blink.

A clinical study of the new Limbal-Rigid CL demonstrated significant improvement in VA and quality of life, particularly in SJS patients (38), and an investigator-initiated study for chronic SJS/TEN cases showed favorable results, the same as in the clinical study (**Figures 1J–L**) (39). We obtained regulatory approval for the Limbal-Rigid CL in 2016. Moreover, the Limbal-Rigid CL has good wettability, thus reducing eye pain related to severe dryness of the ocular surface, and it provides long-term maintenance of the ocular surface once stabilized.

It should be noted that use of the Limbal Rigid CL greatly enhances the postoperative outcome of COMET. The first step is COMET, followed by initiating Limbal Rigid CL wear (40).

SUMMARY

Ocular, oral, and nail manifestations are essential for a definitive diagnosis of SJS/TEN with ocular involvement. Acute conjunctivitis followed by skin eruptions with high fever indicates the initial sign of SJS/TEN, and early intervention with systemic and topical steroids at the acute stage appears to be important for the improvement of the visual prognosis. Although it remains impossible to fully restore the ocular surface to its normal healthy state (i.e., that of before disease onset), COMET alone, Limbal Rigid CL use alone, or the combination of both can greatly improve the vision and overall quality of life of patients with chronic-stage SJS/TEN.

AUTHOR CONTRIBUTIONS

CS and MU drafted the manuscript. CS, MU, and SK revised the final version of the manuscript. All authors contributed to the article and approved the submitted version.

FUNDING

Supported in part by a Grant-in-Aid for Scientific Research from the Japanese Ministry of Health, Labour and Welfare (20FC1035), a Research Grant from the Japan Agency for Medical Research and Development (20ek0109377h), and a Research Grant from the Japanese Ministry of Education, Culture, Sports, Science and Technology (19H03809).

ACKNOWLEDGMENTS

We would like to thank for the Japanese Research Committee on Severe Cutaneous Adverse reaction for their understanding of the ocular sequelae caused from SJS/TEN, and also thank for Mr. Masanori Fukushima and the Foundation for Biomedical Research and Innovation, at Kobe, Kobe, Japan, for their continuous support to translational research of COMET.

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frontiers in Medicine

MINI REVIEW
published: 29 July 2021
doi: 10.3389/fmed.2021.636924

Recent Dermatological Treatments for Stevens-Johnson Syndrome and Toxic Epidermal Necrolysis in Japan

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Stevens-Johnson syndrome (SJS) and toxic epidermal necrolysis (TEN) are serious conditions characterized by necrosis of the skin and mucus membranes, and are mainly caused by medication and infections. Although the exact pathomechanism of SJS/TEN remains unclear, keratinocyte death is thought to be triggered by immune reactions to these antigens. While there is no established therapy for SJS/TEN, corticosteroids and intravenous immunoglobulin (IVIG) have been utilized as immunomodulator. We previously conducted a study to evaluate the efficacy of IVIG therapy in Japanese patients with SJS/TEN. IVIG was administered at a dosage of 400 mg/kg/day for 5 consecutive days as an additional therapy with systemic steroids. Prompt amelioration was observed in seven of the eight patients. All patients survived without sequelae. Recently, we retrospectively analyzed 132 cases of SJS/TEN treated in our two hospitals. The mortality rates in the patients treated with methylprednisolone pulse were 0% (0/31) for SJS and 7.0% (3/43) for TEN, and 0% (0/10) in the TEN patients treated with methylprednisolone pulse in combination with IVIG. These results suggest that early treatment with high-dose steroids, including methylprednisolone pulse therapy, and IVIG together with corticosteroids are possible therapeutic options to improve the prognosis of SJS/TEN.

Keywords: intravenous immunoglobuline, methylprednisolone pulse therapy, Stevens-Johnson syndrome, toxic epidermal necrolysis, treatment

OPEN ACCESS

Edited by:
Jodhbir Mehta, Singapore National Eye Center, Singapore

Reviewed by:
Alessandro Meduri, University of Messina, Italy
Chonlaphat Sukasem, Mahidol University, Thailand

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Specialty section:
This article was submitted to Ophthalmology, a section of the journal Frontiers in Medicine

Received: *02 December 2020*
Accepted: *05 July 2021*
Published: *29 July 2021*

Citation:
Hsieh M-H, Watanabe T and Aihara M (2021) Recent Dermatological Treatments for Stevens-Johnson Syndrome and Toxic Epidermal Necrolysis in Japan. Front. Med. 8:636924. doi: 10.3389/fmed.2021.636924

INTRODUCTION

Stevens-Johnson syndrome (SJS) and toxic epidermal necrolysis (TEN) are rare but serious conditions characterized by necrosis of the skin and mucus membranes, and are most frequently caused by medication, and less frequently by infections, mainly *Mycoplasma pneumoniae*. The symptoms of SJS and TEN are high fever, necrosis of the skin and mucous membranes resulting in erythema, blisters/erosions and enanthema including severe eye lesions, and oral and genital bleeding erosions (1). Because TEN mostly occurs in patients with SJS, followed by rapid progression, these two disorders have been defined as the same disease spectrum and are classified on the basis of the percentage of body surface area (BSA) affected: <10% of BSA in SJS, between 10 and 30% of BSA in SJS/TEN overlap, and >30% of BSA in TEN (2). In addition to mucocutaneous lesions, SJS/TEN affects various organs and can induce life-threatening complications such as multiorgan failure. Severe mucosal involvement of the ocular epithelium and respiratory tract is accompanied by serious sequelae. The global mortality rates for SJS and TEN are as high as 5–10 and 20–40%, respectively (3–6).

The exact pathomechanism of SJS/TEN remains unclear. Keratinocyte death is thought to be caused by cytotoxic T cells and natural killer (NK) cells, and triggered by soluble Fas ligand (FasL), perforin/granzyme B, and granulysin produced by such activated cells (7–10). TNF-α, a major proinflammatory cytokine is highly expressed in the skin of SJS/TEN and suggested to be responsible for extensive skin necrosis (11). It was also demonstrated that the necroptosis pathway contributes to keratinocyte death in SJS/TEN through the interaction between monocyte-derived annexin A1 and formyl peptide receptor 1 expressed on keratinocytes (12). A number of pharmacogenetic studies of human leukocyte antigen (HLA)-associated drug hypersensitivity have recently been performed. In SJS/TEN induced by some drugs, such as anticonvulsants and allopurinol, T cell activation may be caused by the binding of specific drug antigens and HLA molecules with higher binding affinities to the antigens (11).

Treatment for SJS/TEN is the prompt cessation of the causative agent and supportive therapy. Many studies have described the efficacy of immunomodulator for SJS/TEN. Among them, systemic corticosteroids and intravenous immunoglobulin (IVIG) have been utilized in clinical practice (10, 13, 14). Previous reports discuss the drawback of corticosteroid therapies from the point of increased infection such as sepsis and no benefit at mortality. However, a recent systematic review and meta-analysis of systemic immunomodulating therapies for SJS/TEN concluded that the treatment of systemic corticosteroids significantly improved the prognosis of TEN compared to supportive care (13). In addition, Liu et al. reported a significantly lower mortality rate in the steroid treatment group than the mortality rate predicted by the SCORTEN (14). Treatment with IVIG increased after Viard et al. reported favorable outcomes with IVIG (10). In addition, a combination of corticosteroids and IVIG was reported as a more promising strategy than corticosteroids and IVIG alone (15). In the ophthalmologic field, it has been reported that treatment with steroid pulse therapy (500 mg to 1 g/day for 3 days) and topical corticosteroid in the early stage of onset is effective for acute severe ocular involvement with corneal ulceration associated with TEN (16). Furthermore, Kim et al. demonstrated that early administration of IVIG or high dose systemic corticosteroids could improve acute ocular involvement (17). However, the effects remain controversial.

Recently, cyclosporine administration was reported as a new therapeutic approach. Some studies have shown that cyclosporine reduces mortality in patients with TEN in combination with systemic corticosteroids in SJS/TEN patients (13). In another study, a comparison of the observed vs. expected mortality risk ratio of 49 cyclosporine-treated patients was performed (18) using the severity-of-illness scoring system for TEN (SCORTEN), which is widely used as a standard prognostic tool (19). The analysis showed a reduction in mortality risk with cyclosporine administration. On the other hand, the results of an epidemiological study including 174 patients did not show any beneficial effect of cyclosporine (3 mg/kg/day) in patients with SJS/TEN (20). Therefore, further studies are needed to evaluate the efficacy of cyclosporine for SJS/TEN treatment.

More recently, a randomized controlled trial was conducted to compare the effects of TNF-α antagonist (etanercept) vs. traditional corticosteroids in 96 SJS/TEN patients. The results showed that both etanercept and corticosteroids decreased the SCORTEN-based predicted mortality rate, but etanercept further reduced the skin-healing time in moderate-to-severe SJS/TEN patients compared with corticosteroids (21). This result shows the possibility that anti-TNF-α biological agents are an alternative for the treatment of SJS/TEN. There are presently insufficient data to discuss the efficacy of TNF-α antagonists.

Herein, we review the efficacy of treatments for SJS/TEN, focusing on IVIG and high-dose corticosteroids, and outline our previous study of IVIG treatment additionally administered with corticosteroids, and our recent retrospective analysis of the efficacy of methylprednisolone pulse therapy for SJS/TEN. Finally, we discuss treatments for SJS/TEN recently introduced in Japan.

IVIG THERAPY FOR SJS/TEN

IVIG Therapy in SJS/TEN Treatment in the World

In 1998, Viard et al. found that IVIG preparations containing Fas-blocking antibodies inhibit Fas-FasL interaction from keratinocyte apoptosis by blocking Fas receptors, and the capacity abrogated after the depletion of antibodies (10). They also reported an open, uncontrolled pilot study of 10 SJS and TEN patients receiving IVIG (0.2∼0.75 g/kg per day for 4 consecutive days). Disease progression was interrupted within 24 to 48 h, and rapid skin healing with favorable outcomes was also noted, proving their *in vitro* study (10). Because IVIG provides inhibition of Fas-FasL-mediated keratinocyte apoptosis and other multiple immune modulators that are still under investigation, the application of IVIG in the treatment of SJS/TEN increased over time and gradually become the main approach, even though the effects are still controversial. We summarized previous reports on the efficacy of IVIG (**Table 1**). A prospective non-comparative evaluation was performed from 1999 to 2000 in 34 patients (26% SJS, 15% SJS/TEN overlap, 59% TEN) under a total dose of 2 g/kg of IVIG within 2 days. The predicted death from SCORTEN was 8.2 deaths, and the actual mortality was 11 deaths without significant difference from prediction. They also pointed out that the progression of skin lesions was not arrested after IVIG administration (22). These negative results suggest that the destruction of epidermal cells is provoked by several apoptotic pathways and the blockage of Fas-FasL interaction is insufficient.

Although the efficacy of IVIG remains uncertain, several case series or reviews suggested that high-dose IVIG (more than 2 g/kg total dose) is associated with a tendency for better improvement. A recent retrospective review in Australia

Abbreviations: HLA, Human leukocyte antigen; IVIG, Intravenous immunoglobulin; NK, Natural killer; SJS, Stevens-Johnson syndrome; TEN, toxic epidermal necrolysis: JSCAR, the Japanese Research Committee on Severe Cutaneous Adverse Reaction; SCORTEN, the severity-of-illness scoring system for TEN.

TABLE 1 | IVIG and systemic corticosteroids therapy for SJS/TEN in the world.

References	Study design	Sample size and classification, study period	Treatment	Author conclusion
IVIG therapy for SJS/TEN				
Viard et al. (10)	Prospective, open, uncontrolled, multicenter	1 SJS, 4 SJS/TEN overlap, 5 TEN, N/A	IVIG (0.2∼0.75 g/kg per day for 4 consecutive days)	Effective, response within 24–48 h
Bachot et al. (22)	Prospective non-comparative SCORTEN based comparison	9 SJS, 5 SJS/TEN overlap, 20 TEN, 1999∼2000	IVIG (total dose of 2 g/kg within 2 days)	Ineffective
Tran and Sidhu (23)	Retrospective chart review	18 SJS, 6 SJS/TEN overlap, 18 TEN, 2000∼2009, 2010∼2017	(1) Skin and supportive, (2) Oral corticosteroids (3) IVIG alone (4) Oral corticosteroids and IVIG IVIG doses (1–3 g/kg/day)	Effective, improvement in mortality in IVIG groups
Lee et al. (24)	Retrospective, a single referral center	28 SJS/TEN overlap, 36 TEN 1. 2003-12, 2010	IVIG dosage (1) <3 g/kg (2) larger than 3 g/kg	Ineffective in mortality between dosage
Antoon et al. (25)	Retrospective Cohort Study, multicenter data from the Pediatric Health Information System	774 SJS, 124 TEN (IVIG only: 56 TEN) (IVIG and steroid: 15 TEN) (Steroid only: 12 TEN) 2008∼2015	167 steroids only, 229 IVIG only, 153 both IVIG and steroids	Ineffective, bias in distribution of severity
Yang et al. (26)	Retrospective, SCORTEN based comparison	(1) 10 SJS, 35 TEN, 1993∼2001 (2) 8 SJS, 12 TEN, 2001∼2007	(1) 1–1.5 mg/kg/day methylprednisolone (2) 2 g/kg of IVIG (0.4 g/kg/day for 5 days) with a combination of corticosteroids	Effective in mortality, disease progression and time of hospitalization in combined group
Chan and Cook (27)	Retrospective, a single referral center	10 SJS, 6 SJS/TEN overlap, 26 TEN, 2006∼2016,	(1) Skin and supportive 3 SJS, 1 SJS/TEN, 2 TEN (2) Corticosteroids alone 2 SJS, 0 SJS/TEN, 5 TEN (3) IVIG alone 1 SJS, 4 SJS/TEN, 11 TEN (4) corticosteroids and IVIG 4 SJS, 1 SJS/TEN, 8 TEN	Effective in mortality in combined group
Micheletti et al. (15)	Retrospective, multicenter of 18 academic medical centers	110 SJS, 158 SJS/TEN overlap, 79 TEN, 2000∼2015	(1) Skin and supportive, (2) Corticosteroids, mean (148 mg prednisone for 9.8 days) (3) IVIG alone, mean (1 g/kg/day for 3 days) (4) Oral corticosteroids and IVIG (5) Cyclosporine or tumor necrosis factor inhibitor	Ineffective. However, concluded co-administration of corticosteroids and IVIG deserving further prospective trials
Yang et al. (28)	Retrospective, SCORTEN based comparison, a single referral center	141 SJS, 19 SJS/TEN overlap, 53 TEN, 2008∼2018	Systemic corticosteroids and IVIG (mainly 0.4 g/kg/day for 5 days)	Effective in mortality without significance
Pham et al. (20)	Retrospective, a single institution	13 SJS/TEN, N/A	(1) Etanercept alone (2) IVIG for 3 days and Etanercept (3) Without Etanercept (Etanercept 50 mg)	Effective under Etanercept treatment without statistical significance
An open-label, multicenter, single-arm study of IVIG therapy in Japan				
Aihara et al. (29)	Prospective, open-label, multicenter, single-arm study	5 SJS, 3 TEN, N/A	Systemic corticosteroids and IVIG (400 mg/kg/day for 5 consecutive days, total 2 g/kg)	Effective without mortality in all patients
Systemic corticosteroid therapy for SJS/TEN				
Yamane et al. (5)	Retrospective, two university hospitals	52 SJS, 35 TEN, 2000∼2013	Steroid pulse therapy in combination with plasmapheresis and/or IVIG	Effective, lower than SCORTEN based mortality

(Continued)

TABLE 1 | Continued

References	Study design	Sample size and classification, study period	Treatment	Author conclusion
Liu et al. (14)	Retrospective, SCORTEN based comparison, a single referral center	18 SJS, 23 SJS/TEN overlap, 29 TEN, 2008∼2015	(1) Low-dose group (≤2 mg/kg/d) (2) High-dose group >2 mg/kg/d (5 mg prednisone or 4 mg methylprednisolone or 5 mg hydroprednisone or 0.75 mg dexamethasone).	Supporting the use of systemic corticosteroids for SJS/TEN.
Araki et al. (16)	Prospective, observational case series	4 SJS, 1 TEN, N/A	Steroid pulse therapy; 500 or 1000 mg/day for 3 to 4 days. Additional steroid (prednisolone 40∼60 mg/day)	Effective, early steroid pulse therapy improving ocular symptoms
Hirahara et al. (30)	Retrospective	3 SJS, 2 SJS/TEN overlap, 3 TEN, 2008∼2015	Methylprednisolone pulse therapy (1,000 mg/d for 3 consecutive days), Oral prednisolone at 0.8–1 mg/kg/d	Effective, reduction in the mean levels of IFN-γ, TNF-α, and IL-6
Watanabe et al. (31)	Retrospective	75 SJS, 53 TEN, 2000∼2019	Methylprednisolone pulse therapy (500–1,000 mg/day of methylprednisolone for 3 days), prednisolone equivalent 1 mg/kg/day, part of patients combined with IVIG and/or plasmapheresis	Effective, the mortality rate are lower than the global mortality rates
Sunaga et al. (32)	Retrospective, a nationwide survey in Japan,160 institutions	315 SJS, 174 TEN, 2016∼2018	(1) 37.8 % high-dose steroid alone (2) 29.2% pulse therapy followed by tapering (3) 11.7% high-dose steroid plus IVIG (4) 13.7% steroid pulse therapy plus IVIG (5) High-dose steroid (0.80–1.21 mg/kg) (6) IVIG (0.36–0.43 g/kg for 5 days)	Effective in mortality in high-dose steroid followed by pulse group

IVIG, intravenous immunoglobulin; N/A, no data; SJS, Stevens–Johnson syndrome; TEN, toxic epidermal necrolysis; SJS/TEN, SJS-TEN overlap. The classification was made according to the original study. If there was no classification in the study, we classified according to the classification of Roujeau and Stern, 1999 from the raw data as SJS:detachment of TBSA <10%, 10% < SJS/TEN < 30%, and <30%: TEN.
Review articles were not listed in this table.

comparing data between 2000–2009 (mainly corticosteroid) and 2010–2017 (mainly IVIG) of 42 SJS/TEN patients revealed improvement in mortality in IVIG groups (50 vs. 27.3%) (23). However, not every study shows positive results for high-dose IVIG. A retrospective review divided 64 patients (44% with SJS/TEN overlap, 56% with TEN) into IVIG dosage <3 g/kg and larger than 3 g/kg groups from 2003 to 2010, and the mortality was 31% without significant differences in mortality between high and low dosage groups (24).

Since better progression and less mortality tendency were reported after the administration of IVIG in some studies, physicians tend to give severe patients IVIG under the expectation of good progression, and thus may indirectly cause bias in the results of retrospective studies. A 7-year retrospective review of children with SJS/TEN evaluated 898 pediatric patients from the Pediatric Health Information System between 2008 and 2015. They reported longer length of stay in the IVIG alone and IVIG combined corticosteroid groups, and an increasing odds risk of mechanical ventilation use in the IVIG alone group. In that article, they also pointed out the deviation of distribution of severity in that more patients were diagnosed with TEN in the IVIG and combined groups (25).

For the suppression of multiple apoptotic pathways that cause keratinocyte death, the combination of IVIG with other immunomodulators is an emerging issue for researchers. A 14-year retrospective review from China evaluated 45 patients (35 with TEN, 10 with SJS) treated with 1–1.5 mg/kg/day methylprednisolone between 1993 and 2001, and 20 patients (12 with TEN, 8 with SJS) receiving a total dose of 2 g/kg of IVIG (0.4 g/kg/day for 5 days) with a combination of corticosteroids from 2001 to 2007. The combination group of patients with TEN presented a tendency for decreased mortality rate in comparison with the corticosteroid alone group. The time to interrupt the disease progression and time of hospitalization were reduced significantly in the IVIG combined with corticosteroid group, but the time of tapering off steroids did not differ

between the SJS and TEN groups (26). A 10-year retrospective review from Australia evaluated 42 patients with SJS/TEN from 2006 to 2016, and divided the patients into IVIG alone, IVIG combined with corticosteroid, corticosteroid alone, and supportive care groups. Although the dosage of IVIG and corticosteroid and the start of treatment deviated, there was no death in the group of IVIG combined with corticosteroid group with statistically significance. There was no statistically significant difference between different doses of IVIG in survival outcome (27). Favorable results without significance were also revealed in recent studies. In the United States, a multicenter study of 18 academic medical centers reviewed 377 adult patients with SJS/TEN between 2000 and 2015. Although there was no significant difference in mortality between all the subgroups of treatment, the authors concluded that co-administration of corticosteroids and IVIG (10.7% mortality) deserves further prospective trials (15). A similar conclusion was also mentioned in a retrospective review between 2008 and 2018 in a Chinese hospital, which included corticosteroid with IVIG as the first-line treatment. A total of 213 SJS/TEN patients receiving systemic corticosteroids and IVIG (mainly 0.4 g/kg/day for 5 days, for progressive condition) had lower mortality (3.8%) than the prediction of SCORTEN (8.6%) without significance (28). The latest network meta-analysis of review articles in the Journal of the American Academy of Dermatology evaluated 66 studies, involving 2,079 SJS/TEN overlap and TEN patients from 1999 to 2019. Although it was reported that none of the included systemic immunomodulating therapies reduced mortality rates in patients with SJS/TEN overlap and TEN, based on standardized mortality ratio, the combination of corticosteroids and IVIG significantly reduced the standardized mortality ratio and hinted at the synergistic effects of targeting different pathways (33).

In addition to corticosteroids, accompanied by the use of the TNF-α antagonist, IVIG combined with etanercept (50 mg) was evaluated at a single institution in California from 2005 to 2018. Although there was no difference in mortality (15.4 vs. 10%), and lower ICU stay (6.9 vs. 15.1 days) and lower total LOS (9.8 vs. 16.4 days) were without statistical significance, compared with their previous cohort review of IVIG alone, the SCORTEN, affected total body surface area and disease presentation were worse than those in the IVIG alone group. This indicates that there is also little improvement in the treatment effect of a combination of IVIG and other immunomodulators (34).

The history of the application of IVIG in SJS and TEN spans only 20 years, and most of the literature is limited to case series or retrospective reviews because of the rarity of SJS/TEN. IVIG still has its position in the treatment of SJS/TEN and further prospective evaluation of its application deserves to perform in combination with other immunomodulators.

An Open-Label, Multicenter, Single-Arm Study of IVIG Therapy in Japan

To evaluate the efficacy of IVIG therapy, we previously conducted an open-label, multicenter, single-arm study in Japanese adult patients with SJS/TEN (29). Enrolled patients showed progressive or unchanged symptoms with systemic steroids and judged not to respond sufficiently to systemic steroids. IVIG therapy was administered at a dosage of 400 mg/kg/day for 5 consecutive days (total 2 g/kg) as an additional therapy to systemic steroids in patients (five patients with SJS and three patients with TEN). All patients were observed on day 20 of IVIG treatment. The primary efficacy end-point was the response on day 7 of IVIG treatment, and ophthalmic lesions, lip/oral lesions, cutaneous lesions, and general condition were evaluated using our rating scale system. As a result, all of the patients survived and the efficacy on day 7 of the IVIG was 87.5% (seven out of eight patients). Prompt amelioration was observed in skin lesions and mucocutaneous lesions in patients in whom IVIG therapy was effective. Ophthalmic lesions were observed in seven patients at baseline and improved in six patients without sequelae, but little in one non-responder with TEN on day 7. No serious side effects were reported in any patient. In the seven responders, IVIG was started from 3 days to 13 days after the onset of cutaneous symptoms, while 23 days after the onset in the non-responders treated with steroids during the time. This time difference suggests that it is important to perform additional IVIG therapy promptly when a patient does not respond well to corticosteroid therapy. Analysis of the clinical course showed the possibility that early treatment with IVIG (400 mg/kg/day) administered for 5 consecutive days together with corticosteroids is effective in refractory SJS/TEN patients. Since only eight SJS/TEN patients participated, we could not show a significant difference between the predictive number of deaths (one patient) and our study (all survived).

In conclusion, we suggest that IVIG together with corticosteroids should be considered as a treatment modality for SJS/TEN patients, although a larger trial is needed to define the therapeutic efficacy of IVIG. After this study was performed in 2014, IVIG therapy was covered by health insurance for refractory SJS/TEN with steroid use in Japan.

HIGH-DOSE SYSTEMIC CORTICOSTEROID THERAPY FOR SJS/TEN

Review of Systemic Corticosteroid Therapy for SJS/TEN

Steroids bind to glucocorticoid receptors in the cytoplasm and act on the promoter regions of target genes to promote transcription of the related genes. In addition, steroids bind to transcription factors such as AP-1 and NF-κB and suppress the transcription of inflammatory cytokines (35). Because the glucocorticoid receptor in the cytoplasm is saturated in a dose-dependent manner and is 100% saturated at doses of prednisolone (PSL) over 100 mg/day, further escalation of PSL doses does not change the effect in the genomic mechanism (36). On the other hand, in the non-genomic mechanism, steroids bind to glucocorticoid receptors in the membrane and inhibit the arachidonic acid cascade via signaling, resulting in the suppression of enzyme activity and inflammatory responses. This function is fast-acting and has a steroid dose-dependent effect, such as in steroid pulse therapy and high-dose systemic corticosteroid therapy (36).

To evaluate the efficacy of systemic corticosteroid therapy, we summarized previous reports (**Table 1**). In the treatment of SJS/TEN, multiple previous studies reported that there was no difference in prognosis between supportive care and corticosteroid therapy because of the infection by immunosuppression of steroids (4, 37). On the other hand, in a systematic review and meta-analysis of 96 studies performed between 1990 and 2012, it was reported that three studies suggested the benefit of steroid treatment in prognosis, of which, one study significantly improved the prognosis of TEN compared with supportive care (13). Recently, a significantly lower mortality rate in the steroid treatment group than the mortality rate predicted by the SCORTEN has been reported (14). Furthermore, there are multiple previous studies that showed the possible usefulness of combination therapy with corticosteroids and IVIG as mentioned above (15, 26–28, 33, 38), even though steroid use alone did not show sufficient effects in those studies. Therefore, the therapeutic effect of steroids remains controversial.

In Japan, systemic steroid treatment has been mainly used for the treatment of SJS and TEN. Despite not being used worldwide, the use of methylprednisolone pulse therapy is increasing for severe and rapidly progressive cases based on the accumulation of individual case reports and epidemiological studies in Japan (5, 30). Skin lesions and enanthema usually start to recover within 3 days after initiating steroid pulse when the therapy is effective. Notably, it has been reported that steroid pulse therapy with concomitant use of topical betamethasone at disease onset greatly prevented ocular complications in Japanese patients with SJS/TEN (16). In the future, a randomized clinical trial of steroid pulse therapy compared with other treatments for SJS and TEN is required, although the rarity of these diseases precludes large-scale studies.

Current Retrospective Analysis of Efficacy of Methylprednisolone Pulse Therapy for SJS/TEN

To evaluate the efficacy of steroid pulse therapy, we retrospectively analyzed 132 cases of SJS and TEN treated at Yokohama City University Hospital and Yokohama City University Medical Center between January 2000 and March 2019 (31).

A total of 128 patients with SJS and TEN including overlap (75 patients, 96.2% for SJS; 53 patients, 98.1% for TEN) were treated with corticosteroids. The mean age was 52.2 years for SJS (median, 54.0 years) and 57.3 years for TEN (median, 61.5 years). Of these, methylprednisolone pulse therapy (500–1,000 mg/day of methylprednisolone for 3 days) was performed in 31 (41.3%) patients with SJS and 43 (78.0%) for TEN to prevent the rapid progression of severe skin and mucocutaneous lesions. Other patients were treated with prednisolone or betamethasone (mostly prednisolone equivalent 1 mg/kg/day). In addition to systemic corticosteroids, patients with rapidly expanding skin detachment were treated with IVIG and/or plasmapheresis therapy. Plasmapheresis, mostly plasma exchange, was performed to remove the causative drugs and metabolites, and proinflammatory cytokines. Two patients with SJS were treated with IVIG in combination with steroid pulse therapy, while 13 patients with TEN were treated with IVIG and systemic corticosteroids, including 10 with steroid pulse therapy. Of these TEN patients treated with pulse and IVIG, the four most serious patients were added plasmapheresis therapy before IVIG, and as a result, all four patients recovered. Finally, the mortality rates for SJS and TEN were 1.3% (1/78) and 12.5% (6/54), respectively. These values are lower than the global mortality rates for SJS and TEN (3–6).

We further focused on the efficacy of methylprednisolone pulse therapy on mortality. The mortality rates in the patients treated with steroid pulse therapy with or without IVIG and/or plasmapheresis were 0% (0/31) for SJS and 7.0% (3/43) for TEN. In addition, the mortality rate was 0% (0/10) in patients with TEN treated with steroid pulse therapy in combination with IVIG or IVIG and plasmapheresis. Next, we evaluated the difference between the expected and actual numbers of deaths in patients with TEN using SCORTEN. There was no statistically significant difference in the SCORTEN score between the methylprednisolone pulse therapy group (2.14 ± 1.04) and other groups (except methylprednisolone pulse therapy) (2.67 ± 1.49). However, the actual number of dead cases in the steroid pulse therapy group (three cases) was lower than the predicted dead cases (9.3 cases), while the actual and predicted dead cases were almost equivalent in the other group (3 cases vs. 2.6 cases). As a result, the actual mortality rate (7.0%) was lower than the predicted mortality rate (21.6%) in the pulse group, although the difference was not statistically significant (Chi-squared test, $P = 0.102$) (**Table 2A**). Furthermore, in the methylprednisolone-treated cases, differences between the numbers of predicted and actual dead cases were observed in both the pulse group (3 cases vs. 5.8 cases) and pulse in combination with IVIG group (0 cases vs. 1.6 cases) (**Table 2B**) without statistical significance. Of note, sequelae of eye lesions were not observed in any surviving patients. In two TEN patients who died of sepsis, steroid pulse therapy started more than 7 days after the onset (13 and 14 days, respectively). This delay in the initiation of treatment might attenuate the effect of steroid pulse therapy and affect the prognosis. These results suggest that early steroid pulse therapy may be effective and contribute to the improved prognosis of SJS and TEN. The limitations of this study include various combinations of treatment with steroid pulse and a small number of cases treated with steroid pulse combined with IVIG.

RECENT TREATMENTS FOR SJS/TEN IN JAPAN

Since randomized control studies are rarely performed due to the severity and rarity (3, 6) of STS/TEN, none of the abovementioned treatments have been established as the standard. Therefore, no evidence-based standardized guidelines for SJS/TEN treatment are currently available in the world. In Japan, guidelines for the management of SJS and TEN were established in 2009 and revised in 2016 by the Japanese Research Committee on Severe Cutaneous Adverse Reaction

TABLE 2A | Comparison of actual and predicted mortality in the treatment of methylprednisolone pulse.

SCORTEN	Predicted mortality, %	Patients, *n*	Predicted death	Actual death
0–1	3.2%	12	0.38	0
2	12.1%	14	1.69	0
3	35.3%	13	4.59	1
4	58.3%	3	1.75	2
≥ 5	90.0%	1	0.90	0
Total		43	9.32	3
SMR			0.32	

The comparison of actual and predicted mortality rates associated with the treatment of TEN showed the predicted mortality to be 9.32 cases (21.7%) in all patients and the actual mortality to be three cases (6.98%). In this study, there were no significant differences between predicted and actual mortality ($p = 0.1017$, X^2 test with Yates' continuity correction). SMR, standardized mortality ratio.

TABLE 2B | Comparison of actual and predicted mortality between methylprednisolone pulse only and methylprednisolone pulse+IVIG.

SCORTEN	Predicted mortality, %	Methylprednisolone pulse only			Methylprednisolone pulse+IVIG		
		Patients, *n*	Predicted death	Actual death	Patients, *n*	Predicted death	Actual death
0–1	3.2%	10	0.32	0	1	0.03	0
2	12.1%	9	1.09	0	7	0.85	0
3	35.3%	10	3.53	1	2	0.71	0
4	58.3%	0	0.00	2	0	0.00	0
≥5	90.0%	1	0.90	0	0	0.00	0
Total		30	5.84	3	10	1.59	0

The comparison of actual and predicted mortality rates associated with methylprednisolone pulse with/without IVIG. Methylprednisolone pulse only group showed the predicted mortality to be 5.84 cases (17.7%) and the actual mortality to be 3 cases (9.1%). Methylprednisolone pulse+IVIG group showed the predicted mortality to be 1.59 cases (15.9%) and the actual mortality to be 0 cases (0%). IVIG, intravenous immunoglobulin.

(JSCAR) supported by the Ministry of Health, Labor, and Welfare of Japan (39). In the guideline, high-dose systemic corticosteroids are recommended to start within 7 days after onset under appropriate infection control. Methylprednisolone pulse therapy is the first line of therapy, especially for highly progressing and more serious cases. Even though skin lesions are not widespread in SJS, high-dose systemic corticosteroids are recommended for patients with serious eye lesions to prevent ocular sequelae. After administration, steroids should be reduced gradually to prevent a return of the condition, especially eye lesions. On the other hand, continuation of the same amounts of corticosteroid without remarkable efficacy is not recommended because of uselessness and prevention of steroid side effects. Moreover, combination therapy with corticosteroids and IVIG is suggested as an additional therapy in patients with more serious conditions, progressing even with steroid therapy. Cyclosporine and TNF-α antagonists are not yet positively recommended in the guidelines because of insufficient empirical data.

The nationwide epidemiological survey (2016–2018) in Japan revealed that mortality rate was 4.1% for SJS and 29.9% for TEN, respectively (32). High-dose systemic corticosteroid therapy followed by steroid pulse therapy contributed to the greatest reduction in mortality when comparing the ratio of expected mortality to actual mortality (32). Furthermore, the incidence of ocular sequelae of SJS/TEN was 7.6% for SJS and 8.0% for TEN, which were less than previously reported (40).

CONCLUSION AND PERSPECTIVE

In the current review, we describe the efficacy of IVIG treatment and IVIG in combination with corticosteroids as immunomodulating therapies for SJS/TEN. In addition, we demonstrated our recent epidemiological study of SJS/TEN patients treated in our hospitals during the past 19 years that showed the possible effects of methylprednisolone pulse therapy, and that in combination with IVIG in more serious cases it had an effect on mortality and sequelae, although the difference was not statistically significant. Therefore, we suppose that methylprednisolone pulse therapy and also in combination with IVIG therapy are possible modalities in patients with refractory and rapidly progressing SJS/TEN if they are performed at an early stage under appropriate infection control. A limitation of this study is that randomized control studies were not performed. In the future, administration of cyclosporine and a TNF-α antagonist with or without steroids may be considered as alternative treatment modalities for SJS/TEN. Further trials are required to define the therapeutic efficacies of these treatments in SJS/TEN.

AUTHOR CONTRIBUTIONS

MA contributed to determine the content of each section and edited the manuscript. All authors collected the data, wrote each section of the manuscript, and approved the submitted version.

FUNDING

This work was partly supported by Health and Labor Sciences Research Grants from the Ministry of Health, Labor and Welfare of Japan.

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Conflict of Interest: The published IVIG study (28) was funded by Nihon Pharmaceutical, but none of the authors was financially supported by the company. The authors declare that the other SJS/TEN research was conducted in the absence of any commercial or financial relationships that could be construed as a potential conflict of interest.

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frontiers in Medicine

MINI REVIEW
published: 10 August 2021
doi: 10.3389/fmed.2021.664572

A Review of Clinical Disease Scoring Systems for Cicatricial Diseases of the Conjunctiva

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Cicatricial conjunctival diseases (CCDs), are a diverse group of ocular surface diseases characterized by chronic scarring of the conjunctiva. These diseases can cause significant ocular morbidity. They are life-long once acquired and can be debilitating, painful diseases leading to visual loss. A recent international consensus of ocular surface disease experts have placed emphasis on the need of validated clinical disease scoring systems for CCDs, important for the objective evaluation of disease severity, outcomes of therapies, and longitudinal monitoring of disease. This review aims to describe the various published clinical disease scoring systems available for CCDs and evaluates the benefits and limitations of each system. It can be used as a guide for clinicians managing patients with CCDs and for researchers evaluating potential therapies in clinical trials.

Keywords: cicatrising conjunctivitis, cicatricial conjunctival diseases, conjunctiva, scarring, fornix depth, grading, mucous membrane pemphigoid, Stevens-Johnson Syndrome

OPEN ACCESS

Edited by:
Kyoung Yul Seo,
Yonsei University Health System, South Korea

Reviewed by:
Takefumi Yamaguchi,
Tokyo Dental College, Japan
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Keio University, Japan

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Specialty section:
This article was submitted to Ophthalmology, a section of the journal Frontiers in Medicine

Received: *05 February 2021*
Accepted: *15 July 2021*
Published: *10 August 2021*

Citation:
Ong HS, Dart JK and Mehta JS (2021) A Review of Clinical Disease Scoring Systems for Cicatricial Diseases of the Conjunctiva. Front. Med. 8:664572. doi: 10.3389/fmed.2021.664572

INTRODUCTION

Cicatricial conjunctival diseases (CCDs), are a diverse group of ocular surface diseases characterized by chronic scarring of the conjunctiva (1). As scarring is often the sequelae of chronic inflammation, these conjunctival conditions are thus also commonly known as cicatrising conjunctivitis (1). Severe CCDs can cause significant ocular morbidity. Patients with these diseases can suffer from chronic pain, which are often debilitating (1). Bilateral visual loss, caused by the complications of chronic ocular surface inflammation and scarring, has also been reported to affect as many as one in five patients with CCDs (1–4). As certain CCDs affect individuals of all ages, ranging from young children and healthy working adults to the older population, they can result in significant socio-economic burden (4).

Population based studies have indicated that ocular mucous membrane pemphigoid (OcMMP) is the major cause of CCDs in countries with predominantly Caucasian populations (4). The prevalence of OcMMP however, is relatively lower in Asian countries, where Stevens-Johnson Syndrome (SJS) / Toxic Epidermal Necrolysis (TEN) with ocular involvement is a common cause of CCD. In the developing world especially within the African continent, endemic *Chlamydia trachomatis* infections causing blinding cicatricial trachoma are common causes of CCD (5). It has been estimated that over 20 million people are actively affected by trachoma, with ∼2 million

suffering from severe visual impairment from the scarring complications of trachoma (5). There are over 30 other conditions reported to cause chronic conjunctival scarring (1). Other common causative conditions include traumatic injuries (e.g., chemical, thermal, and radiation), chronic allergic eye diseases, drug-induced conjunctival scarring, and other autoimmune diseases (e.g., Sjögrens syndrome, graft-versus-host disease) (1).

Scarring diseases of the conjunctiva pose significant diagnostic challenges (6). Although the pathogenic mechanisms through which different diseases result in CCDs vary significantly, most conditions result in similar consequent features at the ocular surface, which are often clinically indistinguishable (7). Examples of features of chronic conjunctival scarring include subepithelial fibrosis, forniceal foreshortening, symblepharon, ankyloblepharon, and loss of ocular motility. The effects of ocular surface damage caused by inflammation and scarring are also similar. These effects include dry eyes (punctate keratopathy), trichiasis or distichiasis, cicatricial entropion, lagophthalmos, recurrent corneal erosions or persistent epithelial defects, infectious keratitis, corneal opacification, corneal vascularisation, ocular surface keratinisation, corneal melts, and ocular surface failure. Although most ocular surface diseases can often be effectively managed through a systematic approach in identifying and treating these effects at the ocular surface (7), in CCDs, it can be important to identify the underlying disease (1). This is especially the case in progressive scarring diseases. An important example is OcMMP, which is a known progressive inflammatory and scarring disease (1, 8). Another example is a subset of patients with SJS / TEN, that develop autoantibody-positive or negative progressive conjunctival scarring similar to that in OcMMP, which may continue from the acute episode or develop years later (1). In these progressive CCDs, topical treatments are mostly inadequate and systemic immunosuppressive therapies are often required to control the disease process to avoid the development of sight-threatening complications (8). Due to diagnostic difficulties, delays in the commencement of treatment often occur, which can significantly affect the visual outcomes of these challenging diseases (4). Therefore, clinical assessment tools that are sufficiently sensitive to identify progressive CCDs and characterize the severity of disease are important to ensure the timely commencement of appropriate therapies.

Another challenge in the management of CCDs is the lack of effective therapies for these diseases. Current therapies for progressive CCDs are mostly reliant on empirical systemic immunomodulation. For example, depending on severity, the treatment of OcMMP include the use of corticosteroid therapies, immunosuppressive agents (e.g., dapsone, sulphapyridine, methotrexate, azathioprine, mycophenolate, and cyclophosphamide), biological therapies (e.g., rituximab), and intravenous immunoglobulins (8). However, adverse effects have been reported to occur in up to 30% of patients using these therapies (3, 8). Such adverse effects include life-threatening infections (e.g., activation of tuberulosis, viral hepatitis). Systemic corticosteroids are associated with loss of bone densities and Cushing's syndrome; various immunosuppressive agents can also result in blood dyscrasias, renal impairment, deranged liver function, and malignancies. Furthermore, treatment failures have been observed in up to 50% of patients, due to progression of scarring despite the control of inflammation (4, 8, 9). There is thus a need for more effective targeted therapies to treat CCDs.

Research in CCDs have been focused on the development of anti-inflammatory (10, 11) and more recently, anti-scarring therapies (12). For example, pre-clinical studies have reported the use of a repurposed drug disulfiram, an aldehyde dehydrogenase inhibitor, as a new potential therapy for the prevention and reversal of conjunctival scarring (12). To assess the therapeutic effects of such potential therapies for CCDs, a robust objective clinical assessment tool is required. Indeed, validated reproducible measurements of disease activity, conjunctival scarring, and the effects of ocular surface damage, are essential to evaluate the effects of new treatments in clinical trials (13).

This review aims to describe the various published clinical disease scoring systems available for cicatricial diseases of the conjunctiva and evaluates the benefits and limitations of each system. It can be used as a guide by clinicians managing patients with CCDs and by researchers evaluating potential therapies to treat such challenging conditions.

CLINICAL DISEASE SCORING SYSTEMS FOR CICATRICIAL DISEASES OF THE CONJUNCTIVA

Various methods have been described to assess the severity of conjunctival scarring (**Table 1**).

Early Methodologies for the Assessment of Conjunctival Scarring

The initial clinical assessments of CCDs were introduced for patients with OcMMP. In 1981, Mondino and Brown introduced a method to grade the percentage shrinkage of the lower fornix (14). Reporting on 20 patients (40 eyes) with OcMMP, they described a four-stage grading assessment: stage 1: $\leq$ 25% shrinkage of conjunctival fornix; stage 2: 25–50% shrinkage of conjunctival fornix; stage 3: 75% shrinkage of conjunctival fornix; stage 4 (end-stage): obliterated conjunctival fornix and keratinization of conjunctival and corneal surfaces (14). In 1986's, Foster described a method of evaluating subepithelial fibrosis and the extent of symblepharon formation (15). Through a case series of 130 patients with OcMMP, they defined stage I as the presence of chronic conjunctivitis with subepithelial fibrosis; stage II was characterized by inferior fornix foreshortening (with features of stage I); stage III was defined by the appearance of a symblepharon (with features of stage II); and stage IV was defined as end stage disease with ankyloblepharon, severe sicca syndrome, and extreme ocular surface keratinisation (15). By combining these two methods, Tauber et al. subsequently introduced a system of grading CC (17); this system included assessing the loss of fornix depth, counting the number of symblephara, and estimating the percentage horizontal obliteration of the lower fornix by symblephara. The staging system proposed by Tauber et al. uses Foster's stages of I to IV as described above, with additional sub-divisions within

TABLE 1 | Summary of clinical disease scoring systems for cicatricial diseases of the conjunctiva.

	Mondino et al. (14)*	**Foster (15)†**	**Francis et al. (16)‡**	**Tauber et al. (17)§**	**Schwab et al. (18)**	**Rowsey et al. (19)**	**Sotozono et al. (20)††**	**Kawakita et al. (21)**	**Williams et al. (22)**	**Reeves et al. (23)**	**Munyangango et al. (24)**	**Murrell et al. (25)§§**	**Sharma et al. (26)*****	**Ong et al. (27)**
Disease	OcMMP	OcMMP	OcMMP	OcMMP	Drug-induced cicatricial conjunctival disease and healthy controls	OcMMP	OcSJS	OcSJS and healthy controls	CCDs, and healthy controls	OcMMP	OcMMP	OcMMP	OcSJS	OcMMP and OcSJS
Study numbers	20 patients (40 eyes)	130 patients	17 patients (33 eyes)	75 patients (123 eyes)	Both eyes of 179 patients and 240 controls	4 patients (8 eyes)	73 patients (138 eyes)	5 patients and 20 controls	26 patients (51 eyes) with CCDs and 18 controls; 17 patients with identifiable causes: 10 OcMMP, 5 other dry eye diseases (3 Sjogren's syndrome), 2 OcSJS,	44 patients (79 eyes)	7 patients	-	200 patients (400 eyes)	109 OcMMP and 61 OcSJS
Validation	No	No	No	No	Yes	No	No	No	Yes	Yes	No	No	No	Yes
Parameters weighted	No	No	No	No	No	No	No	No	No	No	No	No	No	Yes
Inflammation														
Conjunctival hyperaemia			U				G				G	G	G	G
Limbitis														G
Scarring														
Subepithelial fibrosis		U	G	U							U	U		U^{++}
Lower forniceal foreshortening	G	U	G	G	$M^{||}$	M**		$M^{||}$	$M^{||}$	$M^{‡‡}$	G	U		$M^{||}$
Upper forniceal foreshortening			G					$M^{||}$	$M^{||}$			U		$M^{||}$
Nasal forniceal foreshortening								$M^{||}$						
Temporal forniceal foreshortening								$M^{||}$						
Symblepharon		U	G	G			G				G	U	G	G
Ankyloblepharon		U		U							U	U		G^{++}
Restriction in ocular motility			G											G^{++}
Effects of Inflammation and Scarring (morbidity)														
Conjunctival keratinisation	U	U	G#	U									G	G^{++}

(Continued)

TABLE 1 | Continued

	Mondino et al. (14)*	Foster (15)†	Francis et al. (16)‡	Tauber et al. (17)§	Schwab et al. (18)	Rowsey et al. (19)	Sotozono et al. (20)††	Kawakita et al. (21)	Williams et al. (22)	Reeves et al. (23)	Munyangango et al. (24)	Murrell et al. (25)§§	Sharma et al. (26)***	Ong et al. (27)
Corneal keratinisation	U	U		U			G						G	G++
Visual acuity			G											
Schirmer's test			G											
Lagophthalmos			U											
Trichiasis / Distichiasis			G				G							G++
Entropion			G											
Corneal neovascularisation			G				G						G	G
Corneal opacification			G				G						G	G
Corneal infection			G											
Superficial punctate keratopathy			G^				G							
Corneal epithelial defect							G						G	
Loss of Palisades of Vogt							G						G	
Corneal Conjunctivalisation							G						G	
Mucocutaneous junction involvement							G						G	
Meibomian gland involvement							G						G	
Punctal involvement							G						G	

OcMMP, ocular mucous membrane pemphigoid; OcSJS, Stevens-Johnson Syndrome with ocular involvement; CCDs, cicatricial conjunctival diseases; G, graded; U, ungraded (present or absent); M, measured.

**Graded percentage forniceal foreshortening gives the four stages in Mondino system with keratinisation as components of stage 4.*

† Presence or absence of subepithelial fibrosis, inferior forniceal foreshortening, symblepharon, ankyloblepharon (with keratinisation) gives the four stages in Foster system, respectively.

‡ Score based on clinical components with maximum score of 50, and a percentage derived by multiplying by two.

 # Medial canthal keratinization.

^ Fluorescein and Rose Bengal staining graded separately.

§ Staging system created using a combination of Mondino and Foster systems with addition of graded assessment of symblepharon.

‖ Using a fornix depth measurer or fornicometer.

*** Conjunctival measurements using a ruler.*

++ Score based on 13 components of three categories of ocular complications with maximum score of 39 for each eye.

‡‡ Slit beam horizontal and vertical conjunctival measurements.

§§ International panel of experts consensus publication.

**** Based on 12 components of three categories of ocular complications with maximum score of 53 for each eye.*

†† Used in the study but left out of the final tool after analysis because of poor inter and intra-observer correlation.

stages II and III. In stage II, sub-divisions using letters a to d corresponded to the percentage shrinkage of the lower fornix similar to that described by Mondino and Brown: a: ≤ 25%; b: 25–50%; c: 50–75%; d: >75% loss of inferior fornix depth. In stage III, sub-divisions using letters a–d described the percentage of horizontal forniceal involvement by symblephara: a: ≤ 25%; b: 25–50%; c: 50–75%; d: >75% involvement by symblephara. The discrete numbers of countable symblephara are recorded in parentheses after the staging. For example, stage IIaIIIc(3) describes an eye with ≤ 25% inferior forniceal foreshortening with 25–50% horizontal forniceal involvement with three distinct symblephara.

The disadvantage of these methods of assessment is that they are based on clinical judgement of the extent of symblepharon and forniceal shrinkage. Thus, the assessments are largely qualitative and can be subjective. They are also limited to assessing scarring in the lower conjunctival fornix; upper conjunctival forniceal scarring, which can cause significant sight-threatening complications (e.g., upper lid entropion, lagophthalmos), are overlooked in these early methods. Moreover, in severe fibrotic disease, the extent of the fornix and thus the point of conjunctival reflection are often poorly defined. When the lower lid is everted, the forniceal conjunctiva also tends to become corrugated, and the tarsus may buckle. These factors make the assessment of forniceal shrinkage using the methods described by Modino and Brown, Foster, and Tauber technically difficult, as they require a view of the posterior lid surface. Despite their drawbacks, the Tauber and Foster methods have continued to be used by researchers in studies as they are simple enough to allow retrospective gradings from clinical records (6, 24).

Objective Tools to Evaluate Conjunctival Fornices

Recognizing the limitations of these early methods, various groups have subsequently introduced custom-made devices to facilitate the objective measurements of conjunctival fornices (18, 21, 22, 28, 29). Such devices include fornix depth measurers (FDMs), which allow the quantitative measurements of the lower, and in some devices, the upper fornix depths (**Figure 1**).

The first of such FDMs was described by Ivan Schwab et al. in 1992 (18). The authors described a customized metric ruler to objectively measure the inferior fornix depth (18). This ruler was used to monitor patients with drug induced CCDs (18). In this study, 179 glaucoma patients receiving topical glaucoma medications were measured to assess them for drug-induced CCDs; 420 control subjects with no history of ocular diseases were also measured (18). Using two-way analysis of variance (ANOVA), good inter-observer reliability and test-retest reliability were reported (0.901 and 0.945, respectively) (18). This was thus the first description of a validated objective tool to provide a quantitative measure of the inferior conjunctival fornix depth (18). Using measurements obtained from the control subjects, the authors were also able to provide age- and sex-stratified mean fornix depth values (18). Their data showed that there was a progressive shortening of mean fornix depths with advancing age; and that female participants tended to have shorter mean fornix depths, although this difference was less noticeable with advancing age (18). Such normalized data proved to be important in later research studies, allowing for sex- and age-adjustments whenever fornix depths were measured (22, 27).

Subsequently, two separate groups have developed other customized metric rulers to allow measurements of not only the lower, but also upper fornix depths which had previously been neglected as a result of poor access (21, 22). In 2009, Kawakita et al. designed a dull-edge steel rod (15 cm in length; 2 mm diameter) with a millimetric scale at each end (21). In this case series, the authors performed forniceal measurements in five Japanese patients with Stevens-Johnson syndrome and ocular involvement (OcSJS) and 20 healthy participants. This was the first study that provided "normal" mean fornix depth measurements for superior nasal and temporal fornices, inferior nasal and temporal fornices; and medial nasal and temporal fornices. The authors also estimated the overall area of conjunctival fornix to be ∼909.6 mm^2. However, due to the small sample size, stratification of normalized values based on age or sex could not be performed. This tool's inter-observer and test-retest reproducibility were also not reported.

In 2011, a separate group evaluated the upper and lower fornix depths of a heterogenous cohort of 26 patients (51 eyes) and 18 healthy control participants with various causes of CCDs (22). This group used a polymethymethacrylate FDM (22), similar to that described by Schwab et al. (18), but of increased length to allow upper fornix depth measurements. Within this series reported by Williams et al., 17 patients had an identifiable cause of cicatricial disease: 10 with OcMMP, two with OcSJS, and five with other severe dry eye diseases (including three with Sjogren's syndrome). Furthermore, the investigators implemented a correction factor for age by adapting age-specific lower fornix depths data published by Schwab et al. (18). They calculated the percentage loss of lower fornix using the equation: [(fornix depth (FD) age – FDM measurement)/FD age] × 100 = percentage (%) loss of fornix; the "FD age" values were derived from published age-specific lower fornix depths in normal eyes. Reproducibility of upper and lower fornix depth measurements were also established (22). Triplicate measurements of FDM readings of the central lower fornix depths by two examiners showed exact agreement in 86–89% of measurements; 100% of intra-observer measurements were within 1 mm for both examiners. The inter-observer agreement for lower fornix depth measurement was 86%, allowing for ± 1 mm variability. The intra-observer and inter-observer intraclass correlation coefficients (ICC) for lower fornix depth percentage foreshortening were 0.94 (95% CI 0.92–0.95) and 0.93 (95% CI 0.91–0.95), respectively. The investigators showed that upper fornix depth measurements were more variable. Triplicate measurements of FDM readings of the central upper fornix depths by two examiners showed exact agreement in 70–88% of measurements. Between the observers, there were agreements within 1 mm and 2 mm in 71 and 92% of the measurements, respectively. The intra-observer and inter-observer intraclass correlation coefficients for upper fornix depth percentage foreshortening were 0.92 (95% CI 0.89–0.94) and

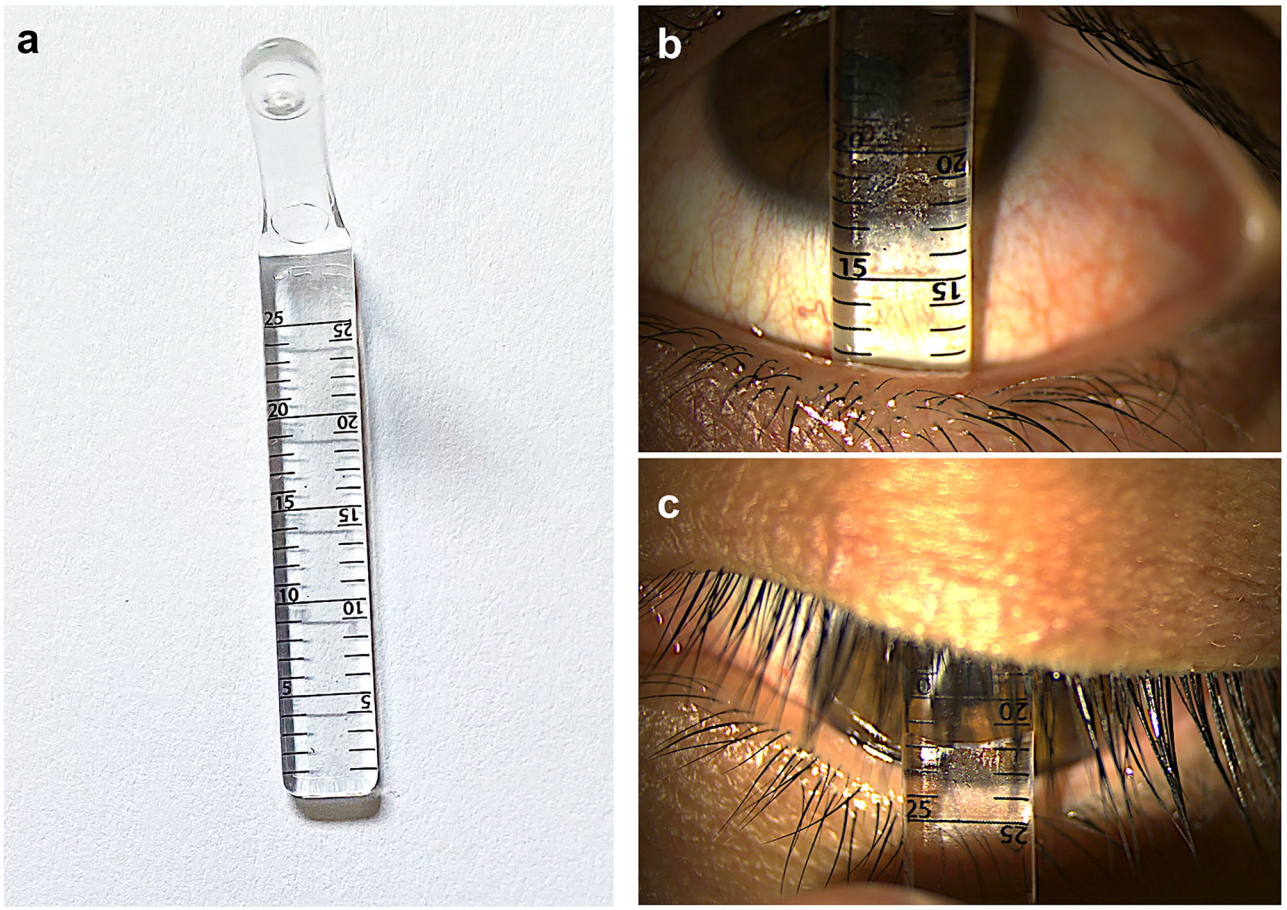

FIGURE 1 | Measuring central conjunctival fornix depths. **(a)** An example of a fornix depth measurer (Scope Ophthalmics Ltd, United Kingdom). Note the millimetric markings in opposite directions to facilitate measurements in both upper and lower fornices; **(b)** to measure the central lower fornix depth, eyes are made to look in up gaze and readings taken at the eyelid margin; **(c)** to measure the central upper fornix depth, eyes are made to look in down gaze.

0.89 (95% CI 0.81–0.93), respectively. This is the first study demonstrating the reproducibility of both upper and lower fornix depth measurements. Subsequent validation studies using a similar FDM was established in healthy eyes of Caucasian and South Asian subjects (28, 29).

In 2004, Rowsey et al. reported a new technique to quantify the degree of conjunctival scarring (19). The authors performed conjunctival stretching measurements in patients with OcMMP. Measurements (in mm) were taken from the lower limbus to the posterior edge of the retracted lower eyelid in three different positions of gaze: 5-o'clock position, 6-o'clock position, and 7-o'clock position. The sum of the three measurements represented the final value. By taking normal conjunctival measurements as 45 mm and the authors calculated percentage fornix foreshortening. They postulated that a shortening in 3 mm of fornix depth indicated disease progression. However, the investigators in this study did not account for the association of conjunctival anatomy to the age, sex, and ethnicity of patients. Furthermore, in this small case series of four patients, validation on reproducibility of measurements was not reported.

More recently, Reeves and associates described an alternative method aimed to quantify both lower vertical forniceal depth and horizontal diseased conjunctiva (23), similar to that described by Rowsey et al. (19). In this system, vertical fornix depth was measured using a slit-lamp, adjusting the slit-beam length to lie between the limbus at 6 o'clock and the start of the fibrosis with the lower lid gently retracted and the patient in upgaze. In their series, authors assumed a normal fornix depth of 10 mm. By subtracting 10 mm from the vertical fornix depth measurement and multiplying by 10, the percentage fornix foreshortening was calculated. For the horizontal conjunctiva affected by scarring, the total conjunctival width was first measured using a standard transparent ruler, along a horizontal line 2 mm above the start of the inferior scarred conjunctiva (if this is present), between the inner aspect of the nasal and lateral edges of the inferior posterior lid margin. The combined width of any symblephara was then subtracted from the total conjunctival horizontal width to give a percentage horizontal foreshortening. Reporting on 44 patients with OcMMP, they showed good levels of inter-observer agreement for both vertical and horizontal measurements (kappa

statistic 0.86 and 0.80, respectively) (23); good correlation was also found between this system and the system described by Rowsey et al. (19). The authors concluded that both systems would give a complete grading of the severity of conjunctival scarring (23).

Nevertheless, limitations to systems described by Rowsey et al. and Reeves et al. exist. Firstly, the upper conjunctival fornix depth, an important measure of cicatrical disease as mentioned above, cannot be quantified using these methods. Secondly, lid laxity, which is common in eyes with OcMMP, can make these methods challenging by limiting sufficient stretch in the eyelid to achieve adequate measurements of the bulbar conjunctiva. Thirdly, unlike fornix depth measurements, data obtained from normal healthy eyes, stratified by age, sex, and ethnicity, is not available for these grading methods. Fourthly, the maximum length of the slit-beam on a standard slit-lamp is 8 mm. As the inferior fornix depths of healthy eyes are often $>$ 10 mm, this limits the utility of the method described by Reeves et al. in quantifying fornix depths. Lastly, measuring only the forniceal depth or horizontal shortening from the bulbar conjunctival surface may not be ideal. Reeves et al. have remarked that the tarsal plate is relatively fixed anatomically and thus forniceal shortening on the posterior lid surface occurs in the conjunctiva below the inferior tarsus. This may not be entirely accurate. As described by Foster et al., subepithelial fibrosis over the tarsal plate is known to be an early clinical feature of CCDs (15). Such scarring changes along the tarsus often results in vertical contractures and shrinking of the tarsal length. This is well-described in CCDs (13). Using a FDM that uses the posterior lid margin as a point of reference allows the examiner to measure forniceal foreshortening below the tarsal plate, in addition to the shortening of the tarsus itself.

Disease Activity, Damage, and Morbidity: More Comprehensive Ocular Surface Disease Scoring Systems (OSDISS)

In 2017, a steering group of international ocular surface diseases experts (OSDISS study group) published a set of core domains for the evaluation of ocular surface diseases (OSDs), through consensus using a modified Delphi technique (13). This document described the recognized clinical descriptors of OSDs and recommended that ocular surface manifestations should be classified into "*disease activity*" and "*damage*" (**Table 2**). "*Disease activity*" are clinical parameters that are the result of active inflammation, which can often be reversed with time or following treatments such as immunomodulation. Ocular surface "*damage*" represents clinical features that are irreversible, defined in the consensus document as persisting for over 6 months. These features result from changes in ocular surface anatomy, physiology, pathology, or function. In CCDs, examples of parameters describing "*damage*" are those related to conjunctival scarring, such as subepithelial fibrosis, forniceal foreshortening, symblepharon, and ankyloblepharon (**Figures 2a–c**) "*Damage*" also represents the longer-term sight-threatening effects or complications of ocular surface inflammation and scarring. These have also been described as "*ocular morbidity*" (27) (**Figures 2d–i**) The evaluation of ocular surface manifestations classed under "*ocular morbidities*" is important in determining the severity of disease, as the presence of these are often associated with poor visual prognosis (13). Some examples of clinical manifestations categorized under "*ocular morbidity*" include punctate epitheliopathy, corneal vascularisation, corneal conjunctivalisation, corneal opacification, and ocular surface keratinisation. In the consensus document, a need for a validated ocular surface disease scoring system (OSDISS) which evaluates both "*disease activity*" and ocular surface "*damage*" was emphasized (13). Such an OSDISS is important in clinical practice for the accurate detection of disease (diagnosis), evaluation of disease severity, prognostication of disease, and the objective monitoring of treatment response. It is also required for the standardization of research data collection, especially when evaluating potential therapies for CCDs.

Studies described in this review have so far been focused on improving the detection and grading conjunctival scarring, caused by various CCDs. Grading systems introduced in these studies focus on one aspect of ocular surface "*damage*," but have largely failed to account for "*disease activity*." These grading systems tend to infer "*disease activity*" and progression by changes in the degree of conjunctival scarring. However, irreversible conjunctival scarring can often take weeks to years to develop, often as a result of uncontrolled inflammation. Thus, tools that can detect active disease and the severity of activity are crucial, to ensure timely control of inflammation and the

TABLE 2 | Categories of ocular surface manifestations in ocular surface disease scoring systems (OSDISS).

Categories in ocular surface disease scoring systems (OSDISS)	Ocular surface manifestations
Disease activity	• Conjunctival hyperaemia • Limbitis
Ocular surface damage: Scarring	• Subepithelial fibrosis • Forniceal shortening • Symblepharon • Ankyloblepharon • Restriction in ocular motility
Ocular surface damage: Morbidity	• Lagophthalmos • Trichiasis/Distichiasis • Entropion • Mucocutaneous junction involvement • Meibomian gland dysfunction • Punctal involvement • Tear deficiency • Punctate epitheliopathy • Corneal epithelial defect • Corneal neovascularisation • Corneal infection • Loss of palisades of Vogt • Corneal opacification • Corneal conjunctivalisation • Conjunctival keratinisation • Corneal keratinisation • Visual acuity

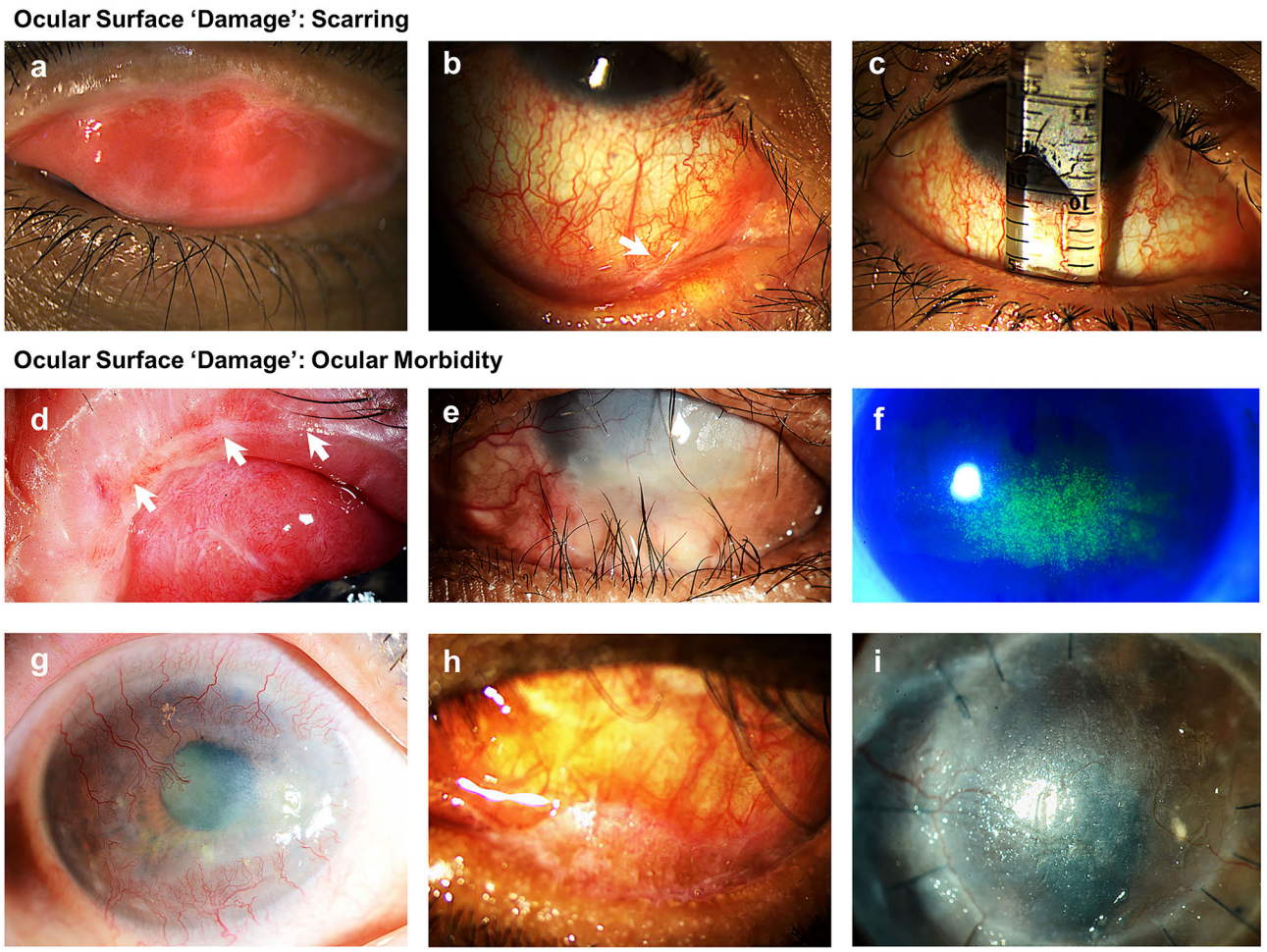

FIGURE 2 | Examples of clinical manifestations of ocular surface "damage" related to scarring and ocular morbidity. **(a)** Subepithelial fibrosis; **(b)** presence of symblepharon; **(c)** conjunctival forniceal foreshortening illustrated using a fornix depth measurer; **(d)** disruption to meibomian glands and mucocutaneous junction; **(e)** trichiatic and distichiatic lashes; **(f)** superficial punctate keratopathy; **(g)** four quadrant central and peripheral corneal vascularization with opacification; **(h)** conjunctival and lid margin keratinization; **(i)** corneal keratinization.

prevention of irreversible ocular surface damage. Moreover, these systems also lack the important assessment of "*ocular morbidity*."

The first documented OSDISS, that included the evaluation of parameters of both "*disease activity*" and ocular surface "*damage*," was introduced by Francis et al. in 1990 (16). Through a case series of 17 patients with OcMMP, the authors used a defined grading schema which comprised 16 components of OSD manifestations. An ungraded absence or presence of conjunctival inflammation was included in the grading schema as an evaluation of "*disease activity*." "*Damage*" in terms of conjunctival scarring was included as graded assessments of subepithelial fibrosis, upper and lower forniceal foreshortening, number of symblephara, and ocular motility. "*Damage*" in terms of *ocular morbidity* was evaluated as assessments in visual acuities (graded), fluorescein staining (graded), Rose Bengal staining (graded), Schirmer's test (graded), trichiasis (graded), entropion (graded), lagophthalmos (ungraded), corneal vascularisation (graded), corneal infection (graded), and medial canthal keratinisation (graded). This system gives a numerical grading score based on clinical components with a maximum score of 50, and a percentage derived by multiplying by two. Although comprehensive, this grading schema was never validated and thus has not been widely adopted by clinicians and researchers.

Munyangango et al. subsequently described a graded method for scoring "*disease activity*" in OcMMP. Each eye is divided into four quadrants and the degree of conjunctival hyperaemia graded on an eight point score (0.5, 1, 1.5, 2, 2.5, 3, 3.5, 4) (24). In this study, grading of conjunctival scarring was based on the system described by Tauber et al. (24). No other parameters of ocular surface "*damage*" or *ocular morbidity* were included (24). This system of conjunctival inflammation grading was later adopted within a systemic MMP scoring system published following consensus of an international panel of experts in bullous diseases (25). However, the recording of ocular surface "*damage*" in this system was ungraded (presence or absence) and poorly defined

as "ocular scarring," with no reference to specific clinical features of conjunctival scarring.

In 2007, Sotozono et al. published a grading system for patients with SJS / TEN (20). Unlike previously described assessment techniques, this system graded the severity of disease based on "*disease activity*" and the effects of cicatrisation (*damage*). It comprised 13 components within three categories of ocular complications. These included eyelid complications (meibomian gland involvement, trichiasis, mucocutaneous junction involvement, punctal involvement), conjunctival complications (hyperaemia and symblepharon formation), and corneal complications (punctate keratopathy, corneal epithelial defect, loss of palisades of Vogt, conjunctivalization, neovascularization, opacification, and keratinization). Each component was graded 0–3, depending on the severity of the complication. Through multivariable regression, the authors showed that their grading of corneal neovascularization, opacification, and keratinization had significant effects on logMAR visual acuities. Despite no data on inter- and intra-observer reproducibility, this system has been widely adopted in OcSJS research (30–32).

The system introduced by Sotozono et al., evaluating the chronic ocular complications of SJS, was more recently modified by Sharma et al. (26). To differentiate the more severe cases from the less severe ones, these authors expanded the grading of each ocular surface manifestation to give a maximum score of 5 (instead of 3). In this system, the authors showed that all 12 components of three categories used for grading, and total severity scores, correlated significantly with the CDVA of patients. Nonetheless, like the system proposed by Francis et al., the examiner using either Sotozono et al.'s or Sharma et al.'s method, needs to assess multiple clinical parameters, many of which are subjective.

To fulfill unmet needs as set out in the 2017 international OSDISS study group consensus (13), our group recently set out to design a concise, validated, semi-quantitative clinical severity assessment tool for CCDs (27). The aim was to create a much simpler grading system, that would still include components that measure inflammation or "*disease activity*" and ocular surface "*damage*" (scarring and ocular morbidity). Clinical manifestations of CCDs to be evaluated were chosen from previously described disease activity and damage indices for OcMMP and OcSJS (13, 16), and the observations of our cross-sectional and longitudinal OcMMP studies (6, 33). The original design of the assessment tool comprised of 12 components in three functional categories: (a) *inflammation grading* (bulbar conjunctival hyperaemia, limbitis), (b) *scarring grading* (subconjunctival fibrosis, limitation in ocular motility, upper and lower fornix symblephara, upper and lower central fornix depth measure), and (c) *ocular morbidity grading* (distichiasis, conjunctival and corneal keratinisation, corneal vascularisation, and corneal opacity). Through a rigorous validation exercise, the assessment tool was subsequently modified to include only components with good inter-observer and intra-observer (test-retest) agreements and components which showed low redundancy. The assessment of redundancy was performed by correlation analyses between each component and the other components, where poor to moderate correlations indicated that one component did not have the potential to adequately predict the presence or severity other components. Examples of components which showed low redundancy included upper and lower symblephara assessments, upper and lower fornix depth measurements, corneal vascularisation, and corneal opacity.

Of the 12 components, seven were found to have moderate to excellent levels of agreement: (a) *inflammation grading* (bulbar conjunctival hyperaemia), (b) *scarring grading* (upper and lower fornix symblephara, upper and lower central fornix depth measure), and (c) *ocular morbidity grading* (corneal vascularisation, corneal opacity). In our proposed clinical assessment tool, each of the seven components within each category have a graded scoring scale. A combined composite score (on a percentage scale out of 100) can then be calculated to provide the user with an overall assessment of disease severity.

Unlike published inflammation scoring schemes which have mostly used subjective assessments of conjunctival injection (20, 34), the method we introduced was guided by comparison to a standard panel of photographs and showed good inter-observer agreement (interclass correlation coefficient, ICC = 0.88, 95% CI 0.84 – 0.90). Good inter- and intra-observer agreements to quantify fornix foreshortening were also achieved with the use of a FDM, similar to that validated in previous studies (22, 28, 29). Furthermore, this is the first scoring tool that apportioned different weightage to certain OSD manifestations within the scoring system. This is considered important in determining disease severity. For example, within the morbidity category, opacities affecting the central cornea are given a proportionally higher weighted score, compared to opacities affecting the peripheral cornea.

Poor levels of agreements were observed in limitation in motility component (scarring category) and thus, this was left out of the final assessment tool. Due to their clinical importance, four components were left in the final tool, despite insufficient statistical data to show reproducibility. However, unlike the seven components that showed adequate levels of agreement, these four components are recorded but not scored and do not contribute to the overall composite disease severity score. These include ocular surface keratinisation (morbidity category), limbitis (inflammation category), distichiasis (scarring category), and subconjunctival fibrosis (scarring category). Although there was inadequate agreement in ocular surface keratinisation, it was retained as it is a known indicator of ocular surface disease severity and poor visual prognosis. Limbitis was absent in the study participants, and thus adequate levels of agreement could not be determined. However, limbitis was left in the final assessment tool as it is an important marker of severe ocular surface inflammation and a feature of poor visual prognosis. Similarly, subconjunctival fibrosis, an important early diagnostic sign of CCDs was found in 98% of participants and thus was left in the final tool. Inadequate levels of agreement could not be determined also for distichiasis; however, this was left in as an important marker of ocular surface fibrosis, especially in OcSJS.

The final tool proposed thus comprised of 11 components:

a) *Inflammation grading*

   i. Bulbar conjunctival hyperaemia (scored and contribute to composite score)
   ii. Limbitis (recorded but not scored)

b) *Scarring grading*

   i. Upper and lower fornix symblephara (scored and contribute to composite score)
   ii. Upper and lower central fornix depth measure (scored and contribute to composite score)
   iii. Subconjunctival fibrosis (recorded but not scored)

c) *Ocular morbidity grading*

   i. Corneal vascularisation (scored and contribute to composite score)
   ii. Corneal opacity (scored and contribute to composite score)
   iii. Distichiasis (recorded but not scored)
   iv. Ocular surface keratinisation (recorded but not scored)

In our final proposed assessment tool for CCD, each category comprises important measures required for clinical evaluation and for clinical trials. This tool can be used in its entirety, to provide an overall disease severity score. Alternatively, the different categories (inflammation, scarring, or morbidity grading) can be used independently.

The scoring system used in our clinical assessment tool has been compared to the system introduced by Sotozono et al., in a cohort of patients with OcSJS. Good correlation and agreement were found between the two grading systems [Pearson r 0.93, $p < 0.001$]. This is despite a significant reduction in the number of components graded, from 13 in the Sotozono et al. grading tool to 7 in our tool. Our validated clinical assessment tool for CCDs, which uses a minimal number of clinical components to evaluate the severity of disease has since been prepared in a form ready for use in clinical practice and clinical trials.

CONCLUSION

This review summarizes the development of the scoring systems available for CCDs. It describes the deficiencies of some of the previous grading tools, which focused mostly on ocular surface scarring caused by CCDs. The importance of scoring systems that make distinctions between disease "*activity*" and "*damage*," is increasingly recognized (13, 35). An overview of such scoring systems has thus been provided in this review, with the benefits and limitations of each system. We hope that this review will serve as a useful guide for ophthalmologists and researchers when choosing an assessment tool for clinical practice or clinical trials.

AUTHOR CONTRIBUTIONS

HO, JD, and JM: conceptualization, writing draft, review, and editing. HO: data curation. HO and JM: funding acquisition. All authors approved the manuscript.

FUNDING

This work has been funded by a Singapore National Eye Centre Health Research Endowment Fund, Singapore (Ref: R1430/13/2017), a SingHealth Foundation Grant, Singapore (Ref: SHF/FG707S/2017), and a SingHealth Duke-NUS Ophthalmology & Visual Sciences Academic Clinical Programme Award (Ref: 05/FY2019/P1/18-A33). None of the funders had any role in the design or conduct of this research. Part of JD's salary was paid by the Moorfields Eye Hospital and the UCL Institute of Ophthalmology National Institute of Research (NIHR) Biomedical Research Centre (BRC).

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Conflict of Interest: The authors declare that the research was conducted in the absence of any commercial or financial relationships that could be construed as a potential conflict of interest.

frontiers in Medicine

MINI REVIEW
published: 27 August 2021
doi: 10.3389/fmed.2021.643955

Clinical Aspects of Stevens-Johnson Syndrome/Toxic Epidermal Necrolysis With Severe Ocular Complications in India

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Stevens-Johnson syndrome/toxic epidermal necrolysis (SJS/TEN) is a spectrum of rare, severe immunological blistering skin reactions which are triggered by medication intake or infections. The acute phase is characterized by necrolysis of the skin and desquamation of mucosa, primarily oral and ocular, with significant mortality rates. The chronic phase is characterized by multi-organ sequelae with increased rates of morbidity and reduced quality of life for patients who have survived the acute phase. Since the primary goal in the acute phase is saving the life of the patient, ocular involvement is often missed and a significant proportion of patients present to an ophthalmologist with the chronic ocular sequelae. In India, chronic ocular sequelae and low vision are observed in two-thirds of patients who present in the chronic phase of SJS/TEN. In the chronic phase of ocular involvement, there are definite windows of opportunity which if targeted with specific interventions such as scleral lenses and mucous membrane grafts can help reduce the incidence of corneal blindness and improve the quality of life for patients with SJS/TEN. Over the last decade, several studies from India have advanced the understanding of the natural course of ocular involvement in SJS/TEN and the outcomes of timely interventions in the chronic phase of the disease. We present an overview of the epidemiology of ocular complications of SJS/TEN in India, the specific challenges faced in the management of ocular complications in the acute stage and recent advances in management of the chronic ocular complications of the disease.

Keywords: Stevens-Johnson syndrome, toxic epidermal necrolysis, corneal blindness, limbal stem cell deficiency, lid margin keratinization, amniotic membrane, mucous membrane grafts

OPEN ACCESS

Edited by:
Mayumi Ueta, Kyoto Prefectural University of Medicine, Japan

Reviewed by:
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Mee Kum Kim, Seoul National University, South Korea

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Specialty section:
This article was submitted to Ophthalmology, a section of the journal Frontiers in Medicine

Received: *19 December 2020*
Accepted: *29 July 2021*
Published: *27 August 2021*

Citation:
Shanbhag SS, Sangwan VS, Singh A, Donthineni PR, Basu S, Srinivasan B, Agarwal S and Iyer G (2021) Clinical Aspects of Stevens-Johnson Syndrome/Toxic Epidermal Necrolysis With Severe Ocular Complications in India. Front. Med. 8:643955. doi: 10.3389/fmed.2021.643955

INTRODUCTION

Corneal blindness and ocular morbidity caused due to the ocular sequelae of SJS/TEN are challenging to address and treat. The ocular involvement of the disease is broadly categorized into an acute phase and a chronic phase. The acute phase usually constitutes the first 2 weeks from the onset of the disease. Each phase has its disease characteristics, presentation features, management options and preventive measures. In lieu of our recent understanding related to several of these

distinct parameters and their pathophysiology, there has been a paradigm shift in management strategies in each phase.

The exact difference in incidence and prevalence of the disease and the severity of its ocular complications/sequelae among various parts of the world is not known. Based on published reports, this seems to be high in India. Few of the largest series of chronic ocular sequelae of SJS and their management are from India highlighting this possibility.

The goal of this review article is therefore to present the Indian perspective of the disease magnitude, clinical features, current management options including recent and ongoing research, and future directives. In addition, challenges unique and specific to the Indian subcontinent, existing lacunae and possible means to overcome these in the future will be highlighted.

DISEASE MAGNITUDE/EPIDEMIOLOGY OF SJS/TEN IN INDIA

The annual incidence of SJS/TEN in India is not known. A systematic review on cutaneous adverse drug reactions (CADRs) in the Indian population calculated an incidence rate of 9.22/1000 cases, out of which SJS/TEN were the most common severe CADRs (6.84%) (1). In a study by Sushma et al., 19.5% of hospitalized patients with severe cutaneous adverse reaction (SCAR) over 9 years were diagnosed with SJS/TEN (2). Although a rare condition, the overall mortality of SJS/TEN in the Indian population is estimated to be 12.94% with 3.92% in SJS cases, 5.26% in SJS-TEN overlap cases and 28.20% in TEN cases, thus signifying the gravity of this disease (3).

Based on published literature from India, the most common etiology for SJS/TEN was drug intake (97.14%) (3). The most common culprit drugs were antibiotics (37.27%), anti-epileptics (35.73%), and non-steroidal anti-inflammatory drugs (NSAIDs - 15.93%) (3). Individual drugs that were identified were carbamazepine (18.25%), phenytoin (13.37%), fluoroquinolones (8.48%), paracetamol (6.17%), and sulfonamides (6.16%). Regional differences were observed, with South Indian studies reporting a higher percentage of cases with the causative factor being fluoroquinolones, while West and North Indian studies reporting a higher percentage of cases with the causative factor being sulfonamides (3).

A systematic review reported that 40.29% patients of acute SJS/TEN in the Indian population had ocular complications in the acute phase, making this one of the most common organ systems affected in the acute phase (3). For the patients who suffer chronic ocular sequelae, the most identified etiology was ingestion of a drug (58–78%), the most common of which were sulfonamide antibiotics (49%), mainly cotrimoxazole (30%) followed by NSAIDs and antiepileptic drugs (4–7).

The largest published studies from India on chronic ocular complications related to SJS/TEN reported that the mean duration from onset of SJS/TEN to presentation to a corneal specialist is ∼3.8–7 years (6–10), with 41–66% patients presenting more than a year after acute SJS/TEN (6, 7). Sixty percent eyes of patients in the chronic phase presented with low vision or blindness (6). Lid abnormalities were observed in 97% eyes, conjunctival complications in 65% eyes, and corneal complications in 85% eyes (6). In a study from India that evaluated pediatric patients with dry eye, 33% eyes were observed to have the etiology of SJS/TEN and 38% of these eyes had severe visual impairment or blindness (11). Another study observed that 23% patients who presented to a tertiary ophthalmological institute with bilateral limbal stem cell deficiency (LSCD) in India had the etiology of SJS/TEN (12).

CLINICAL FEATURES AND CURRENT MANAGEMENT OPTIONS

Acute Phase

Recent published studies have shown that amniotic membrane transplantation (AMT) in the acute phase significantly reduces the incidence of severe chronic ocular complications and subsequent corneal blindness. A randomized controlled trial performed in India which compared the outcomes of AMT with conventional medical therapy in the form of topical steroids, topical antibiotics, topical lubricants clearly showed that AMT in combination with medical therapy prevented chronic ocular sequelae at a follow-up of 6 months (13). In patients that underwent AMT, not a single eye suffered from corneal haze, LSCD, symblepharon, ankyloblepharon, or lid-related complications. However, almost 99% of patients presenting to ophthalmological institutions in the chronic phase after a period of a year or more of acute SJS/TEN had not undergone AMT in the acute phase in India (6, 7).

Chronic Phase

Reduced attention to ocular care in the acute stage either due to lack of accessibility to an ophthalmologist or of awareness has led to a high incidence of chronic ocular complications. Many studies have been published from India on different aspects of the chronic stage sequelae. These study inferences have been highlighted in this section.

Diagnosis of SJS/TEN in the Chronic Phase of Advanced Cicatricial Conjunctivitis

In India, SJS/TEN is the referral diagnosis for most patients with advanced chronic cicatricial conjunctivitis (CCC). Detailed documentation of the drug history and the acute phase of SJS/TEN may not be provided by all patients. Shanbhag et al. recently published a scoring system to ensure correct diagnosis of SJS/TEN in patients who present with advanced CCC (14). Vazirani et al. have used this scoring system in an algorithm to reach a specific diagnosis in eyes with CCC thus helping in appropriate decision-making regarding further medical and surgical interventions in these eyes (15).

Classification of Chronic Sequelae

A classification or a scoring system for involvement of different parts of the ocular surface in these eyes provides a quantitative tool to identify progression of disease and to compare outcomes of various medical and surgical interventions, especially in the chronic phase of SJS/TEN. A scoring system has been proposed by Sharma et al. to reflect the advanced severity of the chronic

ocular surface complications that are commonly seen in India in patients with SJS/TEN (16). Sharma et al. scored 12 ocular surface parameters (6 corneal, 3 conjunctival, and 3 eyelid) ranging from 0 to 5 and demonstrated that there was a co-relation with corrected distance visual acuity.

Ocular Surface Flora and Incidence of Microbial Keratitis in the Chronic Phase

Venugopal et al. prospectively evaluated the conjunctival flora in Indian patients with SJS/TEN and noted that 59% eyes in the SJS/TEN group had positive bacterial cultures from conjunctival swabs as compared to 13% eyes in patients without SJS/TEN (17). The most common isolate was Corynebacteria species in 34% eyes followed by coagulase-negative staphylococci in 29% eyes. In eyes with SJS/TEN that developed microbial keratitis, Bagga et al. noted positive microbiological cultures in 69% eyes with isolated bacterial infections in 60% eyes and polymicrobial infections noted in 38% eyes (18). The most common bacteria isolated were Staphylococcus species (35% eyes). Sharma et al. prospectively studied eyes with microbial keratitis and noted isolated bacterial infections in 63% eyes with polymicrobial infections in 29% eyes (19). Corneal perforation was noted in 31% eyes out of which 70% of eyes required a therapeutic penetrating keratoplasty, thus demonstrating a higher need for surgical interventions in these eyes.

Lacrimal Gland in the Chronic Phase of SJS/TEN

Recent studies from India by Singh et al. have clearly shown that in eyes with severe SJS/TEN with no secretion of aqueous component of tears, the morphology of the acinar structures of the orbital lobe is normal thus establishing the fact that dry eye in SJS/TEN is not secondary to primary involvement of the lacrimal gland (20, 21). This gives more credence to the theory that fibrosis of the superotemporal conjunctiva around the ductules of the lacrimal gland which drain tears onto the ocular surface is the main etiology for aqueous deficiency dry eye in patients with SJS/TEN. The morphological appearance of the lacrimal gland has also been described by Singh et al. in patients with SJS where the gland appears to have a flat contour with subepithelial scarring, sometimes accompanied by symblepharon in the region of the lacrimal gland with engorged conjunctival vessels (22). Singh et al. also described that the amount of ductules actively secreting tears were significantly reduced or absent in eyes with SJS/TEN as compared to normal eyes (23).

Treatment Options

Lid Margin Keratinization

The exact etiopathogenesis for LMK is not yet known, however various pathophysiological mechanisms have been put forth by Singh et al. in a recently published study that described the histopathological features of excised keratinized lid margins (24).

Most corneal complications in SJS/TEN can be attributed to LMK. For the treatment of the lid-related keratopathy (LRK) secondary to LMK, two modalities that have been most effective are prosthetic replacement of ocular surface ecosystem (PROSE) lenses and lid margin mucous membrane grafts (MMG). In addition to preventing keratopathy, PROSE lenses help reduce symptoms due to dry eye and improve vision in patients with corneal scarring (**Figure 1**). MMG harvested from the oral mucosa after excision of keratinized lid margin helps prevent keratopathy (**Figures 2a,b**). The surgical technique for lid margin MMG has been published recently (25).

The first study from India to evaluate the outcomes of MMG in eyes with LRK due to SJS/TEN was published by Iyer et al. in 2010 (8). In this study, 93% eyes had an improved ocular surface and improved BCVA (best corrected visual acuity) over 6 months of follow-up and patients demonstrated significant improvement in comfort. In another retrospective largest interventional study in SJS over 25 years by Iyer et al.; symptomatic improvement was noted in 88% with recurrence of keratinization in 8.4% (10). MMG was found to have a beneficial effect on the ocular surface by reducing the corneal vascularization, haze and punctate keratopathy, thereby aiding in improved vision. A well-performed surgery is a key to a beneficial outcome corroborated by tear cytokine analysis (26). In addition, the role of an altered retinoid metabolism in etiopathogenesis as well as the impact of mucous membrane grafting on it was studied. A corelation pointing toward a possible therapeutic role of topical retinoic acid in a select subgroup of patients was noted (27). Further studies are required to clearly understand the exact role of retinoid metabolism and ocular sequelae of SJS.

Subsequent studies from India by Basu et al. and Shanbhag et al. studied the natural history of LRK due to LMK and noted that definitive therapy in the form of MMG and PROSE lenses significantly improve BCVA and prevent development or progression of LRK when compared to conservative therapy in the form of topical medications (6, 7). A combination of MMG and PROSE lenses helped in maintaining and improving BCVA

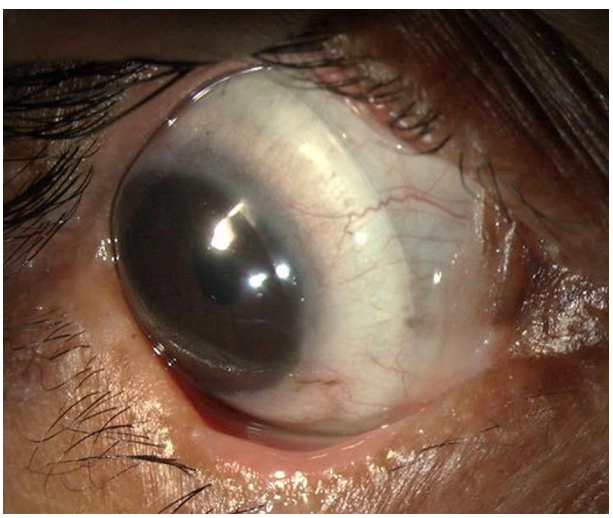

FIGURE 1 | Scleral lenses [prosthetic replacement of ocular surface ecosystem (PROSE) lenses] used for management of severe dry eye in a patient with chronic ocular sequelae post Stevens-Johnson syndrome/toxic epidermal necrolysis.

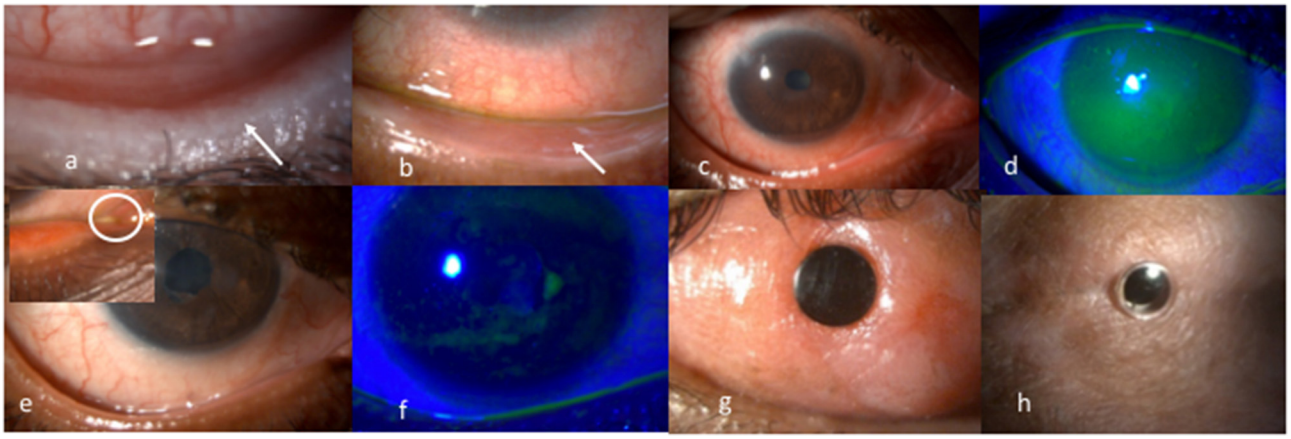

FIGURE 2 | (a) Lower lid margin keratinization causing a sand paper effect on the ocular surface due to blink related microtrauma. **(b)** Post mucous membrane grafting for lid margin keratinization showing a smooth lid margin maintained at years following surgery. **(c,d)** Inflamed ocular surface with diffuse superficial punctate keratopathy on corneal fluorescein staining pre punctal cautery. **(e,f)** Resolution of surface inflammation and punctate keratopathy post punctal cautery improving patient's symptoms of photophobia and foreign body sensation. **(g)** 15 years post modified osteo odonto keratoprosthesis maintaining a best corrected visual acuity of 20/20. **(h)** 5 years post Boston type 2 keratoprosthesis maintaining best achieved corrected visual acuity of 20/30.

in eyes with LRK, with better outcomes in the pediatric age group with MMG while PROSE lenses showed better outcomes in the adult age group while a combination of both showed the best outcomes in both groups regardless of age (7).

Dry Eye

Iyer et al. reported an improvement in 45.8% and stability of surface in 53.6% of the 231 eyes where punctal cautery was done in chronic SJS (10) (**Figures 2c–f**). Outcomes of minor salivary gland transplantation in eyes with SJS/TEN performed in Indian patients have also been encouraging (28).

Fornix Reconstruction and Adnexal Procedures

Fornix reconstruction and symblepharon release using an amniotic membrane (AM), MMG or with COMET (cultivated oral mucosal epithelial transplantation) help address unstable tear film, exposure keratopathy and improved fitting of PROSE lenses in eyes with shortened fornices (9, 10, 29, 30) (**Figures 3a,b**). Outcomes of COMET in eyes with SJS/TEN have been described from two centers in India with both showing improved outcomes and restoration of the anatomy of the ocular surface (31, 32). Successful resolution of recurrent cicatricial entropion due to SJS/TEN was shown by Singh et al. with the use of labial mucosa for spacing the anterior lamella and reconstruction of the lid margin and posterior lamella with minimal recurrence rate at a follow-up period of 16 months (33).

Cataract Surgery in SJS/TEN

Decrease in vision due to cataract or localized corneal opacity can be addressed with cataract extraction and/or an optical iridectomy, respectively. Cataract surgery in SJS/TEN can be challenging in the setting of a poor ocular surface, severe dry eye, corneal scar, and symblepharon. Surface stabilization procedures should be performed before undertaking cataract surgery. Three studies from India have described the outcomes of cataract surgery in patients with SJS/TEN (34–36). Phacoemulsification was the most common surgical procedure performed. Measures such as endo-illuminator use for better visualization and use of viscoelastic on the corneal surface throughout the surgery have been described to improve the outcomes in these eyes.

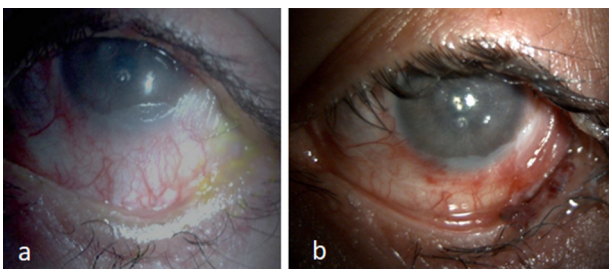

FIGURE 3 | (a) Keratinized surface with shortened fornix. **(b)** Two years following fornix reconstruction with mucous membrane and amniotic membrane graft with relatively moist surface and improvement in corneal luster using PROSE lens.

Keratoprosthesis in SJS/TEN

Keratoprosthesis (kpro) forms the mainstay of treatment in the end-stage of the disease (37) (**Figures 2g,h**). Given the high risk for complications, the Boston Type 1 Kpro is not routinely recommended in moist SJS eyes. The outcomes of different kpro devices in eyes with SJS/TEN such as the modified osteo-odonto keratoprosthesis, the Boston Type 2 Keratoprosthesis, the LVP keratoprosthesis, and the Lux keratoprosthesis have been published from India (38–42). Although the incidence of complications are higher in eyes with SJS/TEN, the outcomes with all the keratoprostheses devices have been shown to be encouraging in patients with end-stage corneal blindness. In the authors' experience, the outcome of any keratoprosthesis is best

when it is performed in an eye that has not undergone prior multiple keratoplasties.

SPECIFIC CHALLENGES

Lack of a registry or database of SJS affected individuals in the country makes it difficult to estimate the incidence and prevalence of the disease. Routine use of over the counter medications and common use of sulphonamide antibiotics for infections in primary health centers could be a factor responsible for increased occurrence of the condition. General practice of deferring seeking immediate medical care in India for a disease condition that simulates chicken pox in the early stage delays presentation to a health care facility. This practice shortens the time in the acute phase to offer treatment and delays initiation of ophthalmic care in the short window period available. Lack of accessibility to an ophthalmologist in a center that provides primary intensive care coupled with the lack of awareness of the role of an ophthalmologist in the acute phase further compromises the ocular care in the acute phase. Furthermore, immediate referral, post the acute phase, to an ophthalmologist to monitor the onset and course of chronic sequelae is not a routinely adopted practice. This further delays the identification and implementation of preventive or treatment strategies early on. Similarly, the delay in referral to a cornea specialist till the occurrence of a manifest significant decrease in visual acuity, by which time the ocular surface is irreversibly affected, closes the doors on availing the windows of opportunities.

ONGOING RESEARCH AND FUTURE DIRECTIVES

Promoting Awareness

The role of an ophthalmologist in the acute phase needs to be emphasized. In addition, the need for and the benefits of AMT in the acute phase, where indicated, has to be impressed upon ophthalmologists. This would help promote bedside consultations from an ophthalmologist as soon as the disease is diagnosed. Likewise, the need for early referral in the chronic phase to cornea specialists, irrespective of visual acuity, has to be asserted. This process of creating and spreading awareness has begun and will continue to gain momentum. India has been in the forefront in advancing research and care in this field through several recently published works of importance. This has helped create a spotlight for the condition amongst ophthalmologists in the country contributing to improved awareness. Additional measures to promote awareness could include interdisciplinary meetings among ophthalmologists, intensivists, pediatricians and dermatologists, alongside specialty fellowships.

Genotyping for Prevention of SJS/TEN

The most sought approach to prevention of SJS would be preemptive HLA (human leukocyte antigen) genotyping before prescription of a drug. Strong associations between drugs and HLA types have been studied, thus making an individual high-risk to develop SJS/TEN if they possess a certain HLA type, and they were to ingest a specific drug (43, 44). If preemptive genotyping is performed to screen the HLA type before prescribing the medication, it may be possible to prevent SJS/TEN. There are studies which have performed HLA genotyping in patients who have developed SJS/TEN to carbamazepine, phenytoin, lamotrigine, levetiracetam, and cold medications in the Indian population (45–53). Significant associations have been noted between SJS/TEN secondary to carbamazepine intake and HLA-B*15:02, HLA-A*31:01, HLA-B*57:01, and HLA-DRB1*07:01 (45, 46, 50, 54). Also, significant associations have been noted between HLA-A*33:03, HLA-B*44:03, and HLA-C*07:01 and patients with SJS/TEN and severe ocular complications secondary to cold medicine (multi-ingredient cold medications and NSAIDs) intake (51, 52). A significant genome-wide association has been noted between SJS/TEN secondary to cold-medicine intake and *IKZF1* SNPs (single nucleotide polymorphisms) in the Indian population with severe mucosal involvement suggesting that IKZF1 might be a potential marker for cold-medicine related SJS/TEN (55). To make preemptive genotyping effective, multicentre studies analyzing drug-HLA associations are required to study the cost-effectiveness. Pre-emptive genotyping for known associations would be the way forward facilitated by curtailed costs to conduct the same.

Monitoring

A national database to monitor adverse drug reactions could advance our knowledge of the exact drugs and the components in these drugs that are responsible for causing SJS/TEN. A registry-based approach to document all cases of SJS/TEN nationally could help in projecting the true incidence rates.

Further Research

The burden of ocular morbidity in the country due to SJS/TEN is huge with most patients presenting with severe ocular surface disorders that need surgical interventions. Several issues related to etiopathogenesis of specific organ/tissue damage in SJS, including lacrimal gland and lid margin remains yet to be explored and understood. This would help further potential therapeutic strategies.

CONCLUSION

The cumulative data from the Indian subcontinent in the field of ocular sequelae of SJS, clinical as well as research oriented, is substantial. Nevertheless, the task ahead to better define several parameters as well as refine our understanding of etiopathogenesis specific to the country, if any, and therefore develop appropriate management strategies, is huge. The authors believe that further studies in the above said directions will help pave the way forward.

AUTHOR CONTRIBUTIONS

SS, VS, AS, PD, SB, BS, SA, and GI: concept and design of the study, drafting the article or revising it critically

for important intellectual content, and final approval of the version to be published. SS, AS, and GI: literature search. All authors contributed to the article and approved the submitted version.

FUNDING

This study was funded by Hyderabad Eye research foundation (HERF) (to SS, PD, SB).

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frontiers in Medicine

MINI REVIEW
published: 17 November 2021
doi: 10.3389/fmed.2021.651247

Pathogenesis of Stevens-Johnson Syndrome/Toxic Epidermal Necrolysis With Severe Ocular Complications

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Stevens-Johnson syndrome (SJS)/toxic epidermal necrolysis (TEN) is an acute inflammatory vesiculobullous reaction of the mucosa of the ocular surface, oral cavity, and genitals, and of the skin. Severe ocular complications (SOC) are observed in about half of SJS/TEN patients diagnosed by dermatologists and in burn units. Ophthalmologists treat SOC, and they tend to encounter the patients not only in the acute stage, but also in the chronic stage. Our investigation of the pathogenesis of SJS/TEN with SOC led us to suspect that abnormal innate mucosal immunity contributes to the ocular surface inflammation seen in SJS/TEN with SOC. We confirmed that cold medicines such as NSAIDs and multi-ingredient cold medications are the main causative drugs for SJS/TEN with SOC. Single nucleotide polymorphism (SNP) association analysis of cold medicine-related SJS/TEN with SOC showed that the Toll-like receptor 3 (*TLR3*)-, the prostaglandin-E receptor 3 (*PTGER3*)-, and the *IKZF1* gene were significantly associated with SNPs and that these genes could regulate mucocutaneous inflammation including that of the ocular surface. We also examined the tear cytokines of SJS/TEN with SOC in the chronic stage and found that IL-8, IL-6, IFN-γ, RANTES, eotaxin, and MIP-1β were significantly upregulated in SJS/TEN with SOC in the chronic stage. Only IP-10 was significantly downregulated in SJS/TEN with SOC in the chronic stage. This mini-review summarizes the pathological mechanisms that we identified as underlying the development of SJS/TEN with SOC.

Keywords: Stevens-Johnson syndrome (SJS), toxic epidermal necrolysis (TEN), severe ocular complications (SOC), cold medicine, *TLR3*, EP3, *IKZF1*

OPEN ACCESS

Edited by:
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Specialty section:
This article was submitted to Ophthalmology, a section of the journal Frontiers in Medicine

Received: *09 January 2021*
Accepted: *25 October 2021*
Published: *17 November 2021*

Citation:
Ueta M (2021) Pathogenesis of Stevens-Johnson Syndrome/Toxic Epidermal Necrolysis With Severe Ocular Complications. Front. Med. 8:651247. doi: 10.3389/fmed.2021.651247

INTRODUCTION

Stevens-Johnson syndrome (SJS) is an acute inflammatory vesiculobullous reaction of the skin, the mucosa of the ocular surface, the oral cavity, and of the genitals; its severe phenotype is called toxic epidermal necrolysis (TEN).

Ophthalmologists tend to encounter the patients in the chronic stage, they can find it difficult to differentiate between SJS and TEN because the vesiculobullous skin lesions present in the acute stage have healed, so they tend to report SJS and TEN with severe ocular complications (SOC) broadly as "ophthalmic SJS" (1).

Approximately half of all SJS/TEN patients diagnosed by dermatologists and in burn units presented with SOC, e.g., severe conjunctivitis with pseudomembrane and ocular surface epithelial defects in the acute stage (2). When ophthalmologists encounter patients in the chronic stage, based on a confirmed history of acute-onset high fever, serious mucocutaneous illness with skin eruptions, and involvement of at least two mucosal sites including the ocular surface and ocular sequelae, e.g., severe dry eye, symblepharon, trichiasis, conjunctival inversion to the cornea, their diagnosis tends to be SJS/TEN (1, 3–6). SJS/TEN patients with severe conjunctivitis, epithelial defects, and pseudomembrane on the ocular surface in the acute stage often suffer serious ocular sequelae such as severe dry eye and vision disturbance that affect their daily life (7).

We reported cold medicines, including multi-ingredient cold medications and NSAIDs, as the main causative drugs of SJS/TEN with SOC (1, 4–6, 8, 9). About 80% of the SJS/TEN with SOC patients treated at the Kyoto Prefectural University of Medicine developed SJS/TEN within several days after taking medicines to combat the common cold (1, 4–6, 8–11).

We also observed that patients with SJS/TEN with SOC presented with opportunistic infection of the ocular surface by bacteria, especially MRSA and MRSE. The MRSA and MRSE detection rate was higher on the ocular surface of patients with SJS/TEN with SOC than in individuals with other devastating ocular surface disorders (12). SJS/TEN with SOC patients presented with persistent inflammation of the ocular surface even in the chronic stage. Their ocular surface inflammation was exacerbated by colonization with MRSA and MRSE, although, under normal conditions, colonization with these bacteria need not elicit ocular surface inflammation (1). Based on these observations we considered the possibility of an association between a disordered mucosal innate immune response and SJS/TEN with SOC. We postulated that a balance between the mucosal innate immunity of the ocular surface and bacterial pathogenicity is important. When host mucosal innate immunity is normal, commensal bacteria are in a symbiotic relationship with the host, however, when the host mucosal innate immunity is compromised, commensal bacteria including MRSA and MRSE can become pathogenic and contribute to the ocular surface inflammation seen in SJS/TEN with SOC (1).

We have been investigating the pathogenesis of ophthalmic SJS for more than 10 years. This mini-review summarizes our research findings on the pathological mechanisms underlying SJS/TEN with SOC.

GENES ASSOCIATED WITH SJS/TEN WITH SOC AND THEIR FUNCTIONS

Although SJS/TEN with SOC can be induced by drugs, not all patients taking these drugs develop SJS/TEN with SOC. Since the incidence of SJS with SOC is very low, we suspected a genetic predisposition (1, 3) and first performed single nucleotide polymorphism (SNP) association analysis using candidate genes associated with innate immunity. We also carried out genome-wide association studies (GWAS) and found several susceptibility genes for SJS/TEN with SOC. Thereupon we subjected some of these susceptibility genes to function analysis using mouse models.

TLR3

TLR3 recognizes double-stranded (ds) RNA, a component of the life-cycle of most viruses and mimics polyI:C. Among toll-like receptors (TLRs) *TLR1—TLR10*, *TLR3* is expressed most intensely on the ocular surface epithelium. Its expression there is stronger than in mononuclear cells and we documented that *TLR3* was able to induce many cytokines and genes on the ocular surface (13–15). SNP association analysis of *TLR3* revealed that in Japan, *TLR3* SNPs were significantly associated with SJS/TEN with SOC (8, 16–18).

Using a murine model of experimental allergic conjunctivitis as a model for ocular surface inflammation, we examined *TLR3* gene function in *TLR3* knock-out (KO)- and *TLR3* transgenic (*TLR3*Tg) mice. We found that ocular surface inflammation was significantly reduced in *TLR3* KO- and significantly increased in *TLR3*Tg mice (19). We also reported that *TLR3* was expressed in the epidermis of the skin and that in a murine model of contact dermatitis, the severity of skin inflammation was significantly lower in *TLR3* KO mice and significantly greater in *TLR3*Tg mice than in wild-type mice (20). Yasuike et al. (21) made the same findings in a murine atopic dermatitis model as we did using a murine model of ocular surface inflammation and contact dermatitis. These findings led us to suspect that *TLR3* was able to positively regulate mucocutaneous inflammation of the skin and ocular surface (22) and might contribute the mucocutaneous inflammation seen in patients with SJS/TEN with SOC (22).

EP3

GWAS and additional analysis revealed that the prostaglandin E receptor 3 (*PTGER3*) gene was significantly associated with CM-SJS/TEN with SOC in Japan and Korea (4, 17, 23).

We performed function analysis of the *PTGER3* gene whose protein is EP3, one of four receptors (EP1, EP2, EP3, and EP4) of prostaglandin E_2. Cold medicine ingredients, e.g., acetaminophen and NSAIDs, e.g., ibuprofen and loxoprofen, suppress the production of prostanoids including PGE_2 (1, 8, 22). PGE_2 acts on EP3 in the ocular surface epithelium and epidermis, and negatively regulates ocular surface- and skin inflammation (24, 25). Kunikata et al. (26) reported that EP3 negatively regulates respiratory tract inflammation. We suggested that the suppression of PGE_2 production by cold medicines might contribute to the pathogenesis and onset of CM-SJS/TEN with SOC (1, 4, 6, 8, 11, 22) because PGE_2 acts on EP3 and negatively regulates mucocutaneous inflammation (24–26).

Our examination of EP3 protein expression on the human ocular surface showed that EP3 protein levels were much lower in the conjunctival epithelium of patients with SJS/TEN with SOC than in the controls, i.e., patients with conjunctival chalasis or chemical burns (27). We postulated that EP3 expression might be strongly down-regulated on the ocular surface of

patients with SJS/TEN with SOC and contribute to ocular surface inflammation in these patients (27).

IKZF1

Using the Affymetrix AXIOM genome-wide ASI 1 array we performed GWAS of samples from 117 Japanese patients with CM-SJS/TEN with SOC and 691 controls (28). The *IKZF1* gene was strongly associated with CM-SJS/TEN with SOC (6) and our meta-analysis of samples from Japanese-, Korean-, Indian-, and Brazilian patients showed a significant genome-wide association between CM-SJS/TEN with SOC and *IKZF1* [rs4917014 (G vs. T), odds ratio (OR) = 0.5, $p = 8.5 \times 10^{-11}$] (6), suggesting that *IKZF1* may be a universal marker for susceptibility to this disease (6).

Function analysis of *IKZF1* SNPs revealed that the ratio of the splicing isoforms *Ik2/Ik1* may be affected by these SNPs, which are significantly associated with susceptibility to CM-SJS/TEN with SOC and that the function of Ikaros, the protein of *IKZF1*, might be enhanced in CM-SJS/TEN with SOC (6). Ikaros, a transcription factor that regulates numerous biological events, has been reported to regulate important cell-fate decisions involved in the development of adaptive immunity (29).

We suspected that the epithelium played a role in the pathobiology of CM-SJS/TEN with SOC (1) because *TLR3* was strongly expressed in ocular surface epithelial cells (13, 14) and keratinocytes (20), and it regulated ocular surface inflammation (19) and dermatitis (20, 21), and because EP3, which negatively regulates mucocutaneous inflammation, was dominantly expressed on the ocular surface epithelium (24), epidermis (25), and the airway epithelium (26).

To address this issue we produced K5-*Ikzf1*-EGFP transgenic mice (*Ikzf1*Tg) by introducing the Ik1 isoform into cells expressing keratin 5, which is expressed in epithelial tissues such as the epidermis and conjunctiva. We found that mucocutaneous inflammation was exacerbated in *Ikzf1*Tg mice; they developed dermatitis and some developed blepharoconjunctivitis. Histological analysis showed not only dermatitis but also tissue inflammation of their tongues, blepharoconjunctiva, and paronychia (30) as did patients with SJS/TEN with SOC in the acute stage of the disease (1) (**Figure 1**).

As our findings suggested that *IKZF1* plays a critical role in maintaining mucocutaneous homeostasis, we proposed that the gene participates in the exacerbation of the mucocutaneous inflammation seen in patients with CM-SJS/TEN with SOC (11, 22, 30).

Gene–Gene Interactions

Considering the contrasting roles of *Ptger3* and *TLR3* in mucocutaneous inflammation, we looked for an unknown functional interaction between EP3, the protein of *Ptger3*, and *TLR3*. We found that EP3 negatively regulated *TLR3*-dependent ocular surface inflammation (8, 11, 17, 22). Ocular surface inflammation in *TLR3*/*Ptger3*-double-KO mice was decreased to a level similar to that in *TLR3*-KO mice and significantly lower than in wild-type mice (17). Moreover, in conjunctival epithelial cells the EP3 agonist suppressed the production and mRNA expression of polyI:C-induced various cytokines such as RANTES, IP-10 (31), and MCP-1 (32), and TSLP (33).

On the other hand, the expression of *IKZF1* mRNA was upregulated by *TLR3* in human epidermal keratinocytes and conjunctival epithelial cells (30), suggesting an interaction between *TLR3* and *IKZF1* (30). Furthermore, since CM-SJS/TEN with SOC developed in individuals who had taken cold medications to combat the common cold due to viral

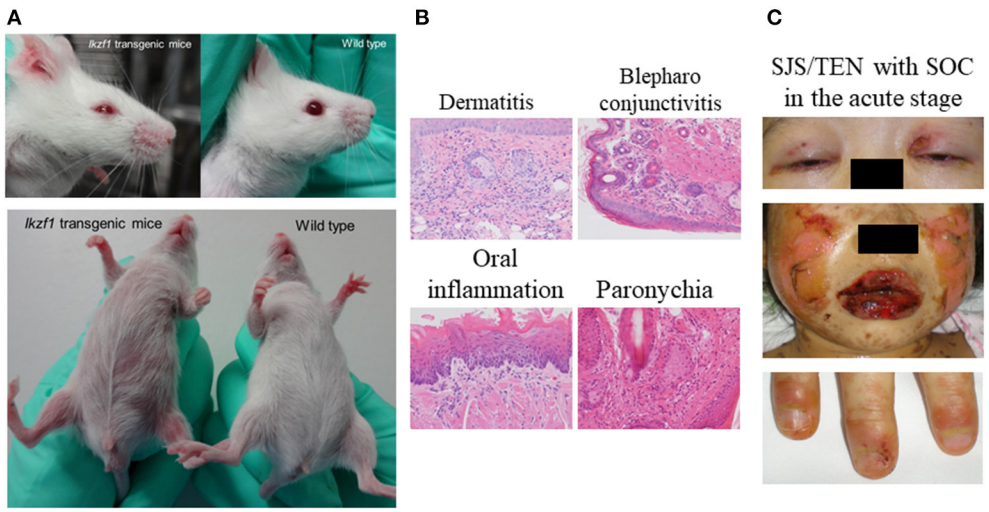

FIGURE 1 | Finding of K5-*Ikzf1*-EGFP transgenic mice (*Ikzf1*Tg). *Ikzf1*Tg mice were introduced the Ik1 isoform into cells expressing keratin 5, which is expressed in epithelial tissues such as the epidermis and conjunctiva. *Ikzf1*Tg mice developed dermatitis and some developed blepharoconjunctivitis **(A)**. Histological analysis showed not only dermatitis but also tissue inflammation of their tongues, blepharoconjunctiva, and paronychia **(B)** as did patients with SJS/TEN with SOC in the acute stage of the disease **(C)**. Reprinted with permission from Ueta et al. (10, 28).

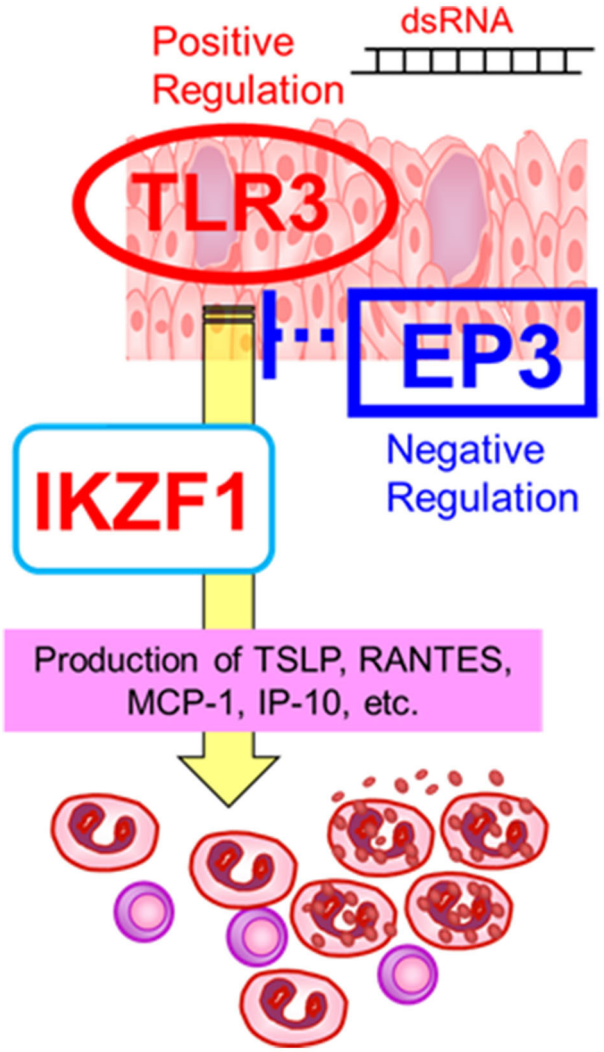

FIGURE 2 | Gene–gene interactions. The susceptibility genes such as *TLR3*, *PTGER3*, and *IKZF1*, might contribute the mucocutaneous inflammation of SJS/TEN with SOC. Reprinted with permission from Ueta et al. (19).

or mycoplasma, we suspect that not only cold medicines and susceptibility genes such as *TLR3*, *PTGER3*, and *IKZF1*, but also some microbial infections with, for example viruses or mycoplasma, are important and necessary to trigger the onset of SJS/TEN with SOC (1, 8, 11) (**Figure 2**).

OTHER STUDIES

We also examined tear cytokines of SJS/TEN with SOC in the chronic stage. IL-8, IL-6, IFN-γ, RANTES, eotaxin, and MIP-1β were significantly upregulated in SJS/TEN with SOC in the chronic stage, while only interferon-γ-inducible protein 10 (IP-10) was significantly downregulated (34). In human corneal and conjunctival epithelial cells, IP-10 is highly induced by the *TLR3* ligand polyI:C (15), possibly as a consequence of abnormal innate immunity that involves the presence of *TLR3* in SJS/TEN with SOC (1, 8, 11).

Moreover, we found that in SJS/TEN patients with SOC, IL-8 was significantly upregulated in eyes with conjunctivalization, neovascularization, or opacification (35). Granzyme B (GrzB) was upregulated in eyes with keratinization, IL-1α in eyes with opacification, and IP-10 was downregulated in eyes with conjunctivalization or neovascularization (all: $p < 0.05$) (35). These observations suggest that IL-8 and IP-10 are involved in conjunctivalization and neovascularization, and that GrzB is involved in keratinization (35).

DISCUSSION

This mini review suggests that SJS/TEN with SOC is pathogenetically related with a disordered innate immune response.

We identified *TLR3*, *PTGER3*, and *IKZF1* as susceptibility genes for SJS/TEN with SOC, demonstrated that they are able to regulate mucocutaneous inflammation, including ocular surface inflammation, and reported functional interactions between *TLR3* and *PTGER3*, or *TLR3* and *IKZF1*.

Since CM-SJS/TEN with SOC is a rare and probably has a complex genetic background, it is reasonable to posit multiplicative gene interactions. Multiple susceptibility genes for CM-SJS/TEN with SOC, including innate immunity-related genes such as *TLR3,* may also be involved in functional networks. The absence of a balance between these genes results in abnormal innate immunity and may trigger the development of mucocutaneous inflammation seen in patients with CM-SJS/TEN with SOC (1, 8, 11).

We reported that 80% of our SJS/TEN with SOC patients developed SJS/TEN within several days after taking cold medicines including multi-ingredient cold medications and non-steroidal anti-inflammatory drugs (NSAIDs) to combat the common cold (1, 4–6), suggesting that cold medicines are major causative drugs for SJS/TEN with SOC. We have also suggested that the onset of CM-SJS/TEN with SOC was associated not only with certain drugs but also with putative microbial infection (1, 8, 11, 22).

Moreover, we also analyzed the possible association between human leukocyte antigen (HLA) genotypes and cold medicine-related SJS/TEN (CM-SJS/TEN) with SOC, and found that in the Japanese it was strongly associated with *HLA-A*02:06* and significantly associated with *HLA-B*44:03* (5). Interestingly, these *HLA* genotypes were not involved in CM-SJS/TEN without SOC (5), suggesting that the genetic predisposition such as the *HLA* genotype might be different in SJS/TEN patients with/without SOC (5). We also found that CM-SJS/TEN with SOC was significantly associated with *HLA-B*44:03* in Indian- and Brazilian-, especially Caucasian Brazilian patients, and *HLA-A*02:06* was associated with CM-SJS/TEN with SOC in Koreans (36).

Based on the totality of the above-cited observations we suggest that in addition to microbial infections and cold medicines, the combination of multiple gene polymorphisms

and their interactions might result in abnormal innate immunity and contribute strongly to the onset of CM-SJS/TEN with SOC (1, 8, 11).

We looked for susceptibility genes for SJS/TEN with SOC in the human genome, and investigated their function in a mouse model of ocular surface inflammation and dermatitis. We demonstrated that *TLR3*, *PTGER3*, and *IKZF1*, susceptibility genes for SJS/TEN with SOC, were able to regulate mucocutaneous inflammation (4, 6, 17, 19–21, 23, 30). Using human samples, we found that EP3 protein levels were much lower in the conjunctival epithelium of patients with SJS/TEN with SOC than in our control subjects (27), and that IP-10, which is greatly induced by the TLR3 ligand on the ocular surface epithelium, was significantly downregulated in the tears of patients with SJS/TEN in the chronic stage (34). These findings on human subjects support our hypothesis that abnormal mucosal innate immunity contributes to the ocular surface inflammation of SJS/TEN with SOC patients (1, 8, 11). Additional studies that focus on the innate immunity of the ocular surface are needed to elucidate the pathogenesis of SJS/TEN with SOC.

AUTHOR CONTRIBUTIONS

MU wrote this mini review article.

FUNDING

This work was supported by grants-in-aid from the Ministry of Education, Culture, Sports, Science, and Technology of the Japanese government, by the JSPS Core-to-Core Program, A. Advanced Research Networks, and partly supported by grants-in-aid for scientific research from the Japanese Ministry of Health, Labor, and Welfare.

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frontiers in Medicine

MINI REVIEW
published: 01 December 2021
doi: 10.3389/fmed.2021.649661

Findings by an International Collaboration on SJS/TEN With Severe Ocular Complications

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Stevens-Johnson Syndrome (SJS) is an acute inflammatory vesiculobullous reaction of the skin and mucosa, e.g., the ocular surface, oral cavity, and genitals. In patients with extensive skin detachment and a poor prognosis, the condition is called toxic epidermal necrolysis (TEN). Not all, but some patients with SJS/TEN manifest severe ocular lesions. Approximately 50% of SJS/TEN patients diagnosed by dermatologists and in burn units suffer from severe ocular complications (SOC) such as severe conjunctivitis with pseudomembrane and ocular surface epithelial defects in the acute stage. In the chronic stage, this results in sequelae such as severe dry eye and visual disturbance. Before 2005, our group of Japanese scientists started focusing on ophthalmic SJS/TEN with SOC. We found that cold medicines were the main causative drugs of SJS/TEN with SOC and that in Japanese patients, *HLA-A*02:06* and *HLA-B*44:03* were significantly associated with cold medicine-related SJS/TEN with SOC (CM-SJS/TEN with SOC). We expanded our studies and joined scientists from Korea, Brazil, India, Taiwan, Thailand, and the United Kingdom in an international collaboration to detect the genetic predisposition for SJS/TEN with SOC. This collaboration suggested that in Japanese patients, cold medicines, including NSAIDs, were the main causative drugs, and that *HLA-A*02:06* was implicated in Japanese and Korean patients and *HLA-B*44:03* in Japanese-, Indian-, and European ancestry Brazilian patients. Our joint findings reveal that there are ethnic differences in the HLA types associated with SJS/TEN with SOC.

Keywords: Stevens-Johnson syndrome (SJS), toxic epidermal necrolysis (TEN), severe ocular complications (SOC), HLA, cold medicine

OPEN ACCESS

Edited by:
Teresa Bellon, University Hospital La Paz Research Institute (IdiPAZ), Spain

Reviewed by:
Maja Mockenhaupt, University of Freiburg Medical Center, Germany
Chia-Yu Chu, National Taiwan University Hospital, Taiwan

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Specialty section:
This article was submitted to Ophthalmology, a section of the journal Frontiers in Medicine

Received: *05 January 2021*
Accepted: *04 November 2021*
Published: *01 December 2021*

Citation:
Ueta M (2021) Findings by an International Collaboration on SJS/TEN With Severe Ocular Complications. Front. Med. 8:649661. doi: 10.3389/fmed.2021.649661

INTRODUCTION

Stevens-Johnson syndrome (SJS) is an acute inflammatory vesiculobullous reaction of the mucosa of the ocular surface, oral cavity, and genitals, and of the skin. In patients with extensive skin detachment and a poor prognosis, the condition is called toxic epidermal necrolysis (TEN). In the acute stage of SJS/TEN, approximately 50% of patients present with severe ocular lesions such as severe conjunctivitis with pseudomembrane and ocular surface epithelial defects (1).

Ophthalmologists encounter patients not only in the acute- but also the chronic stage. Dermatologists, on the other hand, tend to see SJS/TEN patients only in the acute stage, although in some countries such as France and Germany dermatologists also followed up the patients long time. Our ophthalmologic diagnosis of SJS/TEN was based on a confirmed history of acute-onset high fever, serious mucocutaneous illness with skin eruptions, and involvement of at least two mucosal sites, including the ocular surface (2–9). SJS/TEN patients with severe ocular complications (SOC)

in the acute stage often develop sequelae such as vision loss and very severe dry eye that prevent their having a normal life (10).

We defined acute-stage SOC as a condition with severe conjunctivitis with pseudomembrane and epithelial defects on the ocular surface (cornea and/or conjunctiva) (11). Chronic-stage SOC was defined as a condition with sequelae such as severe dry eye, trichiasis, symblepharon, and conjunctival invasion into the cornea (**Figure 1A**) (10). Ophthalmologists tend to diagnose both SJS and TEN with SOC broadly as "ophthalmic SJS" (**Figure 1B**) (4).

Dermatologists and others reported anticonvulsants such as carbamazepine and allopurinol (a uric acid-lowering drug) as being the main SJS/TEN-inciting drugs (12), while Japanese dermatologists reported that NSAIDs and multi-ingredient cold medications were main causative drugs for SJS/TEN (13). HLA analyses have shown that a genetic predisposition plays a role in the response to disease-eliciting drugs. Carbamazepine-induced SJS/TEN manifested a very strong association with the *HLA-B*15:02* allele in Taiwanese Han Chinese patients (14), and the *HLA-A*31:01* allele was strongly associated with carbamazepine-induced SJS/TEN in Japanese- (15) and European patients (16), the HLA-B*57:01 allele was associated with carbamazepine-induced SJS/TEN in European patients (17). Allopurinol-induced SJS/TEN was strongly associated with *HLA-B* 58:01* in Han Chinese- (18), European ancestry- (19), and Japanese patients (20). Interestingly, not all patients with carbamazepine-induced SJS/TEN develop SOC (21). Allopurinol has been reported to elicit SJS/TEN without SOC (22).

We reported that about 80% of SJS/TEN with SOC patients seen at the Kyoto Prefectural University of Medicine developed SJS/TEN within several days after taking cold medicines (we recognized the onset of SJS/TEN when the patients had eruptions.) (8).

These included multi-ingredient cold medications and non-steroidal anti-inflammatory drugs (NSAIDs) (2, 4, 6, 8, 23). Our Brazilian collaborators found that 53% of their SJS/TEN with SOC patients had taken cold medicines (24) as had 69% of Thai patients with SJS/TEN with SOC (25), and 50% of Taiwanese patients (26). Our Korean collaborators suspected that NSAIDs and cold medicines were associated with SOC in their SJS/TEN patients (27). These observations suggest that such medicines are major causative drugs in SJS/TEN with SOC patients of different ethnicities.

This mini-review cites the results of our international collaborative efforts to identify the genetic predisposition for SJS/TEN with SOC.

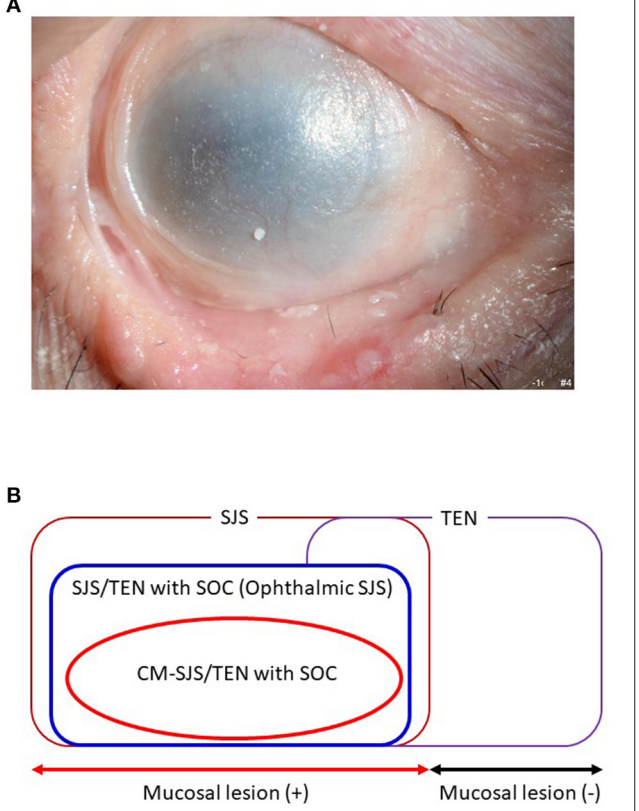

FIGURE 1 | (A) Ocular surface finding of SJS/TEN with SOC. **(B)** Ophthalmic SJS means SJS/TEN with SOC.

HLA TYPES ASSOCIATED WITH SJS/TEN WITH SOC

The extreme rarity of cutaneous and ocular surface reactions to drugs led us to suspect individual susceptibility. Therefore, we entered an international collaboration to analyze the association between HLA genotypes and SJS/TEN with SOC.

Japan

In 2007, our Japanese group first reported the HLA types associated with SJS/TEN with SOC; the ocular disease was strongly associated with *HLA-A*02:06* [40 patients, 113 controls; odds ratio (OR) = 5.1, $p = 0.00003$] (28). Finding that about 80% of our Japanese SJS/TEN with SOC patients developed SJS/TEN after taking cold medicines to combat the common cold (8), we started to focus on cold medicine-related SJS/TEN (CM-SJS/TEN) with SOC. We reported that the ocular disease was strongly associated with *HLA-A*02:06* [151 patients, 639 controls; (OR = 5.6, $p = 2.7 \times 10^{-20}$)] and significantly associated with *HLA-B*44:03* [151 patients, 639 controls; OR = 2.0, $p = 1.3 \times 10^{-3}$] (2). These HLA genotypes were not associated with cold medicine-unrelated, i.e., other medicine-related SJS/TEN with SOC (2). This suggested that the associated HLA genotypes were different and depended on the causative drug(s) (2, 4, 29). Moreover, *HLA-A*02:06* and *HLA-B*44:03* were not associated with CM-SJS/TEN without SOC (2), suggesting that different HLA genotypes were involved in the development of SJS/TEN with- and without SOC (2).

We reported that the main causative drugs for SJS/TEN with SOC in Japanese patients were cold medicines, including multi-ingredient cold medications and NSAIDs taken to combat the common cold. As we also found that acetaminophen, present in various cold medicines, was the most frequently implicated

causative drug (2, 30), we focused on acetaminophen-related SJS/TEN with SOC. Analysis of the involved HLA types revealed that *HLA-A*02:06* was strongly associated with acetaminophen-related SJS/TEN with SOC [80 patients, 113 controls; OR = 5.4, $p = 8.0 \times 10^{-7}$] (30).

Korea

Together with our Korean collaborators we investigated the HLA types (*HLA-A*02:06* and *HLA-B*44:03*) that were associated with CM-SJS/TEN with SOC in Japanese patients. We compared ours with samples from Korean patients and found that in Koreans, CM-SJS/TEN with SOC was also significantly associated with *HLA-A*02:06* (31 patients, 90 controls; OR = 3.0, $p = 0.018$), but not with *HLA-B*44:03* (3).

Our Korean collaborators suspected that NSAIDs and cold medicines were associated with SOC in Korean patients with SJS/TEN (27). They reported that allopurinol-induced SJS/TEN might not elicit serious acute or chronic complications of the ocular surface (22).

They then focused on Korean CM-SJS/TEN with SOC and investigated all of *HLA-class I (HLA-A, HLA-B, HLA-C*). In their patients they identified *HLA-A*02:06* (40 patients, 120 controls; OR = 3.0, $p = 0.0083$) and *HLA-C*03:04* (40 patients, 120 controls; OR = 3.5, $p = 0.010$) as potential positive markers for CM-SJS/TEN with SOC, and *HLA-C*03:03* (40 patients, 120 controls; OR = 0.10, $p = 0.0056$) as a possible indicator of protection against CM-SJS/TEN with SOC in the Korean population (31).

Brazil

Together with our Brazilian collaborators we investigated the HLA types (*HLA-A*02:06 and HLA-B*44:03*) that were associated with Japanese CM-SJS/TEN with SOC. Comparison of our and Brazilian samples revealed that in Brazilian CM-SJS/TEN with SOC, there was a significant association with *HLA-B*44:03* (39 patients, 134 controls; OR = 2.7, $p = 0.024$), but not with *HLA-A*02:06,* a genotype not found in all Brazilian population (3). Interestingly, focused on European ancestry of Brazilians, the association with *HLA-B*44:03* was stronger (15 patients, 62 controls; OR = 6.2, $p = 0.0037$) than in all Brazilians (3).

As the Brazilian collaborators found that 53% of their SJS/TEN with SOC patients had taken cold medicines before disease onset (24), they investigated the associated HLA types of CM-SJS/TEN with SOCs. Their studies suggested *HLA-A*66:01* as a potential marker for CM-SJS/TEN with SOCs in Brazilians (39 patients, 133 controls; OR = 24.0, $p < 0.001$) of both Pardo- (19 patients, 66 controls; OR = 12.2, $p = 0.03$) and European ancestry (16 patients, 61 controls; OR = 21.2, $p = 0.04$) and that *HLA-B*44:03* (16 patients, 61 controls; OR = 5.50, $p = 0.01$) and *HLA-C*12:03* (16 patients, 61 controls; OR = 8.79, $p = 0.008$) might be markers only in individuals of European ancestry. Moreover, they stated that *HLA-A*11:01* (39 patients, 133 controls; OR = 0.074, $p = 0.008$) might be a marker of resistance to CM-SJS/TEN with SOC (24).

Because Dipyrone was broadly used as cold medicine in Brazil, we also focused on dipyrone-related SJS/TEN with SOCs and found that *HLA-B*44:03* (carrier frequency: $p = 0.002$, Pc = 0.02, OR = 8.8; gene frequency: $p = 0.001$, Pc = 0.01, OR = 7.5) and *HLA-DQB1*04:02* (gene frequency: $p = 0.003$, Pc = 0.03, OR = 12.6) were significantly associated with cases of dipyrone-related SJS/TEN with SOCs in the Brazilian population of European ancestry, and that *HLA-C*05:01* (carrier frequency: $p = 0.001$, Pc = 0.01, OR = 9.4; gene frequency: $p = 0.002$, Pc = 0.02, OR = 15.0) was significantly associated with cases of dipyrone-related SJS/TEN with SOCs in the Brazilian population of mixed raced ancestry (32).

India

Together with our Indian collaborators we investigated the HLA types (*HLA-A*02:06 and HLA-B*44:03*) associated with Japanese CM-SJS/TEN with SOC.

In samples from Indian patients with CM-SJS/TEN with SOC there was a significant association with *HLA-B*44:03* (20 patients, 55 controls; OR = 12.3, $p = 1.1 \times 10^{-5}$), but not with *HLA-A*02:06* (3). Although the number of Indian patients was small, the association between Indian CM-SJS/TEN with SOC and *HLA-B*44:03* was strong and significant (3).

According to Kannabiran et al. (33), Indian ophthalmologists found it difficult to obtain a detailed history of disease onset from their SJS/TEN with SOC patients and in many patients they could not identify causative drugs. HLA analysis showed that *HLA-A*33:03* (80 patients, 50 controls; OR = 3.4, $p = 2.7 \times 10^{-3}$), *HLA-B*44:03* (80 patients, 50 controls; OR = 12.2, $p = 7.3 \times 10^{-9}$), and *HLA-C*07:01* (80 patients, 50 controls; OR = 6.5, $p = 4.4 \times 10^{-6}$) were risk alleles. *HLA-B*57:01* (80 patients, 50 controls; OR = 0.05, $p = 3.0 \times 10^{-4}$) and *HLA-C*06:02* (80 patients, 50 controls; OR = 0.1, $p = 4.0 \times 10^{-4}$) were protective alleles in the Indian population. Haplotypes comprised of *HLA-B*44:03* and *HLA-C*07:01* were strongly associated with SJS/TEN with SOC in the Indian population (80 patients, 50 controls; OR = 11.0, $p = 1.1 \times 10^{-7}$) (33).

Thailand

Together with our Thai collaborators we investigated causative drugs in their SJS/TEN with SOC patients and performed HLA analysis using Thai samples. *HLA-A*33:03* (71 patients, 159 controls; OR = 2.6, $p = 0.0028$), *HLA-B*44:03* (71 patients, 159 controls; OR = 6.0, $p < 0.0001$), and *HLA-C*07:01* (71 patients, 159 controls; OR = 4.9, $p < 0.0001$) exhibited a significant associations with SJS/TEN with SOC (25). Among 71 Thai SJS/TEN with SOC patients, 49 (69%) had a history of taking cold medications prior to SJS/TEN onset.

A focus on CM-SJS/TEN with SOC revealed that *HLA-B*44:03* (49 patients, 159 controls; OR = 7.2, $p < 0.0001$) and *HLA-C*07:01* (49 patients, 159 controls; OR = 6.1, $p < 0.0001$) were significantly associated with Thai CM-SJS/TEN with SOC. In 17 of 49 patients with CM-SJS/TEN with SOC (34.7%), a haplotype comprised of *HLA-B*44:03* and *HLA-C*07:01* was present. This was the case in only 11 of 159 controls (6.9 %) (OR = 7.1, $p = 5.5 \times 10^{-6}$), suggesting that the *HLA-B*44:03—HLA-C*07:01* haplotype was a potential risk factor for CM-SJS/TEN with SOC in the Thai population (25).

In Thailand, as in the USA and UK, cold medicines, especially acetaminophen (paracetamol), are widely-used over-the-counter

drugs. Elsewhere we reported that in Japan, acetaminophen is the most frequently included drug in various cold medicines (2, 30). Therefore, we focused on Japanese acetaminophen-related SJS/TEN with SOC and analyzed the HLA types (30). Together with our Thai collaborators we also investigated Thai patients with acetaminophen-related SJS/TEN with SOC and analyzed the HLA types. Jongkhajornpong et al. (34) reported a significant association with *HLA-A*33:03* (20 patients, 60 controls; OR = 5.4, $p = 0.0030$), *HLA-B*44:03* (20 patients, 60 controls; OR = 9.0, $p = 0.0004$), *HLA-C*07:01* (20 patients, 60 controls; OR = 9.3, $p = 0.0002$), and the *HLA-B*44:03—HLA-C*07:01* haplotype (20 patients, 60 controls; OR = 9.0, $p < 0.001$) in Thai patients with acetaminophen-related SJS/TEN with SOC, suggesting that they may have a role in the pathogenesis of SOC in acetaminophen-related SJS/TEN.

Taiwan

Our Taiwanese collaborators found that the main causative drugs in 26 Han Chinese with SJS/TEN with SOC were cold medicines; in 13 of 26 patients with SOC, cold medicines were the causative drugs, in none of 7 patients without SOC they identified cold medications as causative (26). Their findings echoed earlier studies that implicated cold medicines in the development of SOC in 80% of Japanese SJS/TEN patients (2, 35), 53% of Brazilian patients (24), and 69% of Thai patients (25).

Together with our Taiwanese collaborators we performed HLA analysis of SJS/TEN with SOC in the Han Chinese and found that *HLA-A*02:07* (26 patients, 98 controls; OR =3.2, $p = 0.049$) was associated with their development of the disease. Our focus on CM-SJS/TEN with SOC revealed that *HLA-A*02:07* (13 patients, 98 controls; OR = 5.6, $p = 0.016$) was strongly associated with the development of SOC among Han Chinese CM-SJS/TEN patients (26). Single amino acid substitutions in major histocompatibility complex (MHC) class I molecules were found to play a role in distinct peptide repertoires. For example, three *HLA-A2* subtypes, i.e., *HLA-A*02:04*, *HLA-A*02:06*, and *HLA-A*02:07*, differed by only a single amino acid residue substitution; each harbored the *HLA-A*02:01* molecule at the floor of their binding grooves. Allele-specific peptide motifs for each *HLA-A2* subtype differed substantially from the *HLA-A*02:01* motif in the dominant anchor residues (36). Although the carrier- and gene frequency of *HLA-A*02:06* in Japanese patients with CM-SJS/TEN with SOCs was significantly higher than in the control group, the frequency of *HLA-A*02:07* was similar in both groups (2). We found that the expression of *HLA-A*02:07* but not of *HLA-A*02:06* was associated with CM-SJS/TEN with SOC in the Han Chinese patients (26).

No *HLA- B*44:03* expression was detected in Han Chinese SJS/TEN patients or the controls (26), a finding compatible with earlier studies that showed that only 0.41–0.63% of the Taiwanese Han Chinese population harbored *HLA-B*44:03* (37, 38). This observation suggests a genetic diversity in the pathogenesis of SJS among different ethnic groups although, because the number of samples was small, these studies must be expanded to include more samples.

United Kingdom

Our UK collaborators found that 9 of their 28 patients with SJS/TEN with SOC (32%) had taken cold medicines (39). Together with our UK collaborators we analyzed the association of *HLA-A, HLA-B, and HLA-C* alleles with SJS/TEN in 33 patients residing in the UK (28 patients with- and 5 without SOC) and in age-matched controls. There was a statistically significant and novel negative allele association with *HLA-B*07:02* (25 patients, 15 controls; OR = 0.16, $p = 0.012$) and with *HLA-C*07:02* (25 patients, 15 controls; OR = 0.09, $p = 0.030$) in a sub-group of European ancestry SJS/TEN patients (both with and without SOC) but not in their controls. This finding identified these alleles as being protective (39). Interestingly, a focus on European ancestry patients with SJS/TEN with SOC revealed only the association with *HLA-B*07:02* (23 patients, 15 controls; OR = 0.17, $p = 0.027$), but not with *HLA-C*07:02*. When the focus was directed on European ancestry patients with CM-SJS/TEN with SOC, both associations with *HLA-B*07:02* and *HLA-C*07:02* disappeared (39). Thus, although *HLA-B*07:02* was associated with SJS/TEN with SOC in European ancestry, it may not be a biomarker for CM-SJS/TEN with SOC in that population. Because the number of samples was small, these studies must be expanded to include more samples.

DISCUSSION

A summary of our collaborative HLA analyses is shown in **Table 1**. It shows that *HLA-B*44:03* was significantly associated with CM-SJS/TEN with SOC in the Japanese (2), in Brazilians, especially European ancestry Brazilians (3, 24, 32), in Indian patients (3, 33), and in Thais (25, 34). *HLA-A*02:06* was significantly associated with CM-SJS/TEN with SOC in the Japanese (2) and in Koreans (3, 31). Ma et al. (26) suggested that *HLA-A*02:07*, differing by only a single amino acid residue substitution from *HLA-A*02:06,* might be significantly associated with CM-SJS/TEN with SOC in Taiwanese patients.

The acetaminophen-associated HLA type might be a little different between CM-SJS/TEN with SOC in Japanese- (HLA-A*02:06) (30) and Thai patients (*HLA-B*44:03—HLA-C*07:01* haplotype) (34). Moreover, the dipyrone-associated HLA types for CM-SJS/TEN with SOC in the Brazilian population were *HLA-B*44:03* and *HLA-DQB1*04:02* in European ancestry, and *HLA-C*05:01* in mixed raced ancestry (32).

We think that a common function of cold medicines such as acetaminophen, dipyrone, and NSAIDs is highly implicated in the onset of SJS/TEN with SOC (4, 23, 30, 40).

The common function of cold medicines is the suppression of prostaglandin E_2 (PGE_2) production which suppress mucocutaneous inflammation. PGE_2 acts on EP3 (PGE_2 receptor 3) in the epidermis (41) and the mucosal epithelium (42, 43) and negatively regulates mucocutaneous inflammation. We suspect that cold medicines that include acetaminophen and dipyrone could upregulate inflammatory responses by suppressing the production of PGE_2 which suppress mucocutaneous inflammation, that they augment abnormal immune responses,

TABLE 1 | Carrier frequencies of each country.

Country	Ratio of CM-SJS/TEN with SOC /SJS/TEN with SOC	CM-SJS/TEN with SOC				SJS/TEN with SOC				Acetaminophen-SJS/TEN with SOC			
		Number of cases	HLA-A	HLA-B	HLA-C	Number of cases	HLA-A	HLA-B	HLA-C	Number of cases	HLA-A	HLA-B	HLA-C
JAPAN	76.0% (76/100) (4) 68.6% (151/220) (6)	151 cases vs. 639 controls [2014 (6)]	HLA-A*02:06 OR = 5.6 $p = 2.7 \times 10^{-20}$	HLA-B*44:03 OR = 2.0 $p = 1.3 \times 10^{-3}$		40 cases vs. 113 controls [2007 (3)]	HLA-A*02:06 OR = 5.1 $p = 0.00003$ HLA-A*11:01 OR = 0.1 $p = 0.0076$			80 cases vs. 639 controls [2020 (26)]	HLA-A*02:06 OR = 6.0 $p = 4.7 \times 10^{-12}$	HLA-B*13:01 OR = 4.1 $p = 2.0 \times 10^{-3}$ HLA-B*44:03 OR = 2.4 $p = 2.1 \times 10^{-3}$	HLA-C*14:03 OR = 2.3 $p = 3.4 \times 10^{-3}$
KOREA	Not reported [NSAIDs, including cold medicine, might be associated with SOC in Korean patients with SJS/TEN (24)]	40 cases vs. 120 controls (27)	HLA-A*02:06 OR = 3.0 $p = 0.0083$		HLA-C*03:03 OR = 0.10 $p = 0.0056$ HLA-C*03:04 OR = 3.5 $p = 0.010$								
BRAZIL	52.7% (39/74) (22)	74 cases vs. 133 controls (22)	HLA-A*11:01 OR = 0.074 $p = 0.008$ HLA-A*66:01 OR = 24.0 $p < 0.001$	HLA-B*44:03 OR = 2.7 $p = 0.04$	HLA-C*12:03 OR = 5.6 $p = 0.006$								
		19 Pardo cases vs. 66 Pardo controls (22)	HLA-A*66:01 OR = 12.2 $p = 0.03$										
		16 European cases vs. 61 European controls (22)	HLA-A*66:01 OR = 21.2 $p = 0.04$	HLA-B*44:03 OR = 5.5 $p = 0.01$	HLA-C*12:03 OR = 8.8 $p = 0.008$								
INDIA	Unknown because many patients have no detail memories	20 cases vs. 55 controls(ref) (only focused on HLA-A*02:06 and B*44:03) (7)		HLA-B*44:03 OR = 12.3 $p = 1.1 \times 10^{-5}$		80 cases vs. 50 controls (28)	HLA-A*33:03 OR = 3.4 $p = 2.7 \times 10^{-3}$	HLA-B*44:03 OR = 12.2 $p = 7.3 \times 10^{-9}$ HLA-B*57:01 OR = 0.05 $p = 3.0 \times 10^{-4}$	HLA-C*06:02 OR = 0.1 $p = 4.0 \times 10^{-4}$ HLA-C*07:01 OR = 6.5 $p = 4.4 \times 10^{-6}$				
THAILAND	69.0% (49/71) (23)	49 cases vs. 159 controls (23)		HLA-B*44:03 OR = 7.2 $p < 0.0001$	HLA-C*07:01 OR = 6.1 $p < 0.0001$	71 cases vs. 159 controls (23)	HLA-A*33:03 OR = 2.6 $p = 0.0028$	HLA-B*27:04 OR = 0.065 $p = 0.0066$ HLA-B*44:03 OR = 6.0 $p < 0.0001$	HLA-C*07:01 OR = 4.9 $p < 0.0001$ HLA-C*12:02 OR = 0.11 $p = 0.0093$	20 cases vs. 60 controls (29)	HLA-A*33:03 OR = 5.4 $p = 0.0030$	HLA-B*44:03 OR = 9.0 $p = 0.0004$	HLA-C*07:01 OR = 9.3 $p = 0.0002$
TAIWAN	50.0% (13/26) (26)	13 cases vs 98 controls (26)	HLA-A*02:07 OR = 5.6 $p = 0.016$			26 cases vs. 98 controls (26)	HLA-A*02:07 OR = 3.2 $p = 0.049$						
UK (White only)	39.1% (9/23) (39)	9 cases vs 15 controls (39)		(HLA-B*07:02) Not significant $p = 0.23$		23 cases vs. 15 controls (39)		HLA-B*07:02 OR = 0.17 $p = 0.027$					

and that they elicit the induction of SJS/TEN with SOC (4, 23, 30, 40).

Besides HLA types, we investigated other SJS/TEN with SOC susceptibility genes. Our genome-wide association study revealed *IKZF1* to be a susceptibility gene for CM-SJS/TEN with SOC in Japanese-, Korean-, and Indian populations (6). It was also significantly associated with CM-SJS/TEN with SOC in Thai patients (44). Consequently, *IKZF1* may be a universal marker for CM-SJS/TEN with SOC (6, 44). Elsewhere (45) we documented that *IKZF1* regulates mucocutaneous inflammation. We reported that *IKZF1* transgenic mice developed spontaneous mucocutaneous inflammations such as ocular surface- and oral inflammation and dermatitis (45).

In the Japanese population we identified *PTGER3* as a susceptibility gene for CM-SJS/TEN with SOC (8), and we reported that *HLA-A*02:06* and *PTGER3* polymorphisms exerted additive effects in Japanese and Korean patients with CM-SJS/TEN with SOC (OR = 10.8 and 14.2, respectively) (46).

We also suggest that in addition to microbial infections and cold medicines, the combination of multiple gene polymorphisms and their interactions contributes strongly to the onset of CM-SJS/TEN with SOC. Abnormal Innate Immunity might strongly contribute the pathology of SJS/TEN with SOC (4, 23).

Despite the genetic diversity in SJS/TEN with SOC among different ethnic groups, to prevent its onset and to reduce the incidence of blindness due to SJS/TEN, efforts must continue to identify the genetic predisposition for SJS/TEN with SOC.

AUTHOR CONTRIBUTIONS

MU wrote this mini review.

FUNDING

This work was supported by grants-in-aid from the Ministry of Education, Culture, Sports, Science and Technology of the Japanese government, by the JSPS Core-to-Core Program, A. Advanced Research Networks, and partly supported by grants-in-aid for scientific research from the Japanese Ministry of Health, Labor, and Welfare.

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