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Advances in understanding of the pathogenesis and therapeutic implications of drug reaction with eosinophilia and systemic symptoms: an updated review

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Drug reaction with eosinophilia and systemic symptoms or drug-induced hypersensitivity syndrome (DRESS/DIHS) is one type of severe cutaneous adverse reaction (SCAR). It is featured by fever, widespread skin lesions, protracted clinical course, internal organ involvement, and possibly long-term autoimmune sequelae. The presence of high-risk human leukocyte antigen (HLA) alleles, hypersensitivity reaction after culprit drug ingestion, and human herpesvirus reactivation may all contribute to its complex clinical manifestations. Some recent studies focusing on the roles of involved cytokines/chemokines and T cells co-signaling pathways in DRESS/DIHS were conducted. In addition, some predictors of disease severity and prognosis were also reported. In this review, we provided an update on the current understanding of the pathogenesis, potential biomarkers, and the relevant therapeutic rationales of DRESS/DIHS.

KEYWORDS

drug reaction with eosinophilia and systemic symptoms, DIHS, hypersensitivity, eosinophilia, HHV-6

1. Introduction

Drug hypersensitivity reaction are adverse effects that occur when the immune system reacts inappropriately to a medication. These reactions can range from mild to severe and can involve various organs and tissues, with the skin being the most commonly affected. These reactions can be categorized into two primary types: immediate drug hypersensitivity

reactions and delayed drug hypersensitivity reactions (1, 2). Immediate hypersensitivity reactions occur within hours of drug exposure and are typically mediated by Immunoglobulin E (IgE) antibodies. These reactions can manifest as urticaria (hives), angioedema (swelling of the deeper layers of the skin), bronchospasm, or anaphylaxis. Delayed hypersensitivity reactions, on the other hand, occur days to weeks after drug exposure and are usually mediated by T cells. These reactions can present as various skin manifestations, including maculopapular eruptions, or severe cutaneous adverse reactions (SCARs), such as Stevens–Johnson syndrome and toxic epidermal necrolysis (SJS/TEN), acute generalized exanthematous pustulosis, and drug reaction with eosinophilia and systemic symptoms (DRESS). These severe reactions can cause systemic involvements and can be fatal (1, 2). DRESS syndrome is one of the life-threatening drug-induced SCARs. It is characterized by distinctive cutaneous manifestations, internal organ involvement, hematologic abnormalities, and probably long-term autoimmune sequelae (3). Typically, the symptoms develop 2 weeks to 3 months after taking the causative drugs. Patients may present with extensive erythema, facial edema, lymphadenopathy, and high-grade fever (4). Various degrees of internal organ involvement including hepatitis, nephritis, interstitial pneumonia, and myocarditis may occur. Marked elevated levels of blood eosinophils and the presence of atypical lymphocytes are hallmarks of hematologic manifestations.

Historically, similar manifestations were described as a variety of entities according to the causative drugs, like phenytoin hypersensitivity (5), dapsone hypersensitivity (or sulfone syndrome) (6), and allopurinol hypersensitivity syndrome (7). The term "DRESS" was first introduced by Bocquet et al. to make the description of this syndrome more consistent and unambiguous (8). Instead, another term "drug-induced hypersensitivity syndrome (DIHS)" is more widely used by Japanese experts (9). The diagnostic criteria of DRESS defined by the Registry of Severe Cutaneous Adverse Reactions (RegiSCAR) group and the criteria of DIHS are similar except for the inclusion of the status of Human herpesvirus 6 (HHV-6) reactivation in the diagnostic criteria of DIHS (10, 11). Current consensus denotes that these two terms (DRESS and DIHS) are likely within the same disease spectrum, and the diagnosis of DIHS may represent a more severe phenotype (10). In this review, we aimed to summarize the updated understanding of the pathogenesis and biomarkers of DRESS/DIHS as well as the relevant therapeutic implications.

2. Pathogenesis in drug reaction with eosinophilia and systemic symptoms

DRESS is considered a T cell-mediated delayed-type hypersensitivity reaction in the Gell and Coombs classification (12). Traditionally, DRESS is classified as a type IVb reaction that corresponds with $CD8^+$ and $CD4^+$ T cells responses underlying the production of interferon-γ (IFN-γ), interleukin (IL)-4, IL-5, and IL-13, resulting in eosinophilia. Currently, there are several proposed pathomechanisms majorly involved in DRESS. DRESS is a drug hypersensitivity reaction due to specific culprit drugs induced immune response in genetically susceptible patients, and HHV reactivation may synergistically contribute to its pathogenesis. The diverse manifestations of DRESS/DIHS may result from the complex interplay between the drug-specific and the antiviral immune responses (Figure 1).

2.1. Genetic susceptibility

Human leukocyte antigen (HLA) molecules have an essential role in the immune reaction. They specifically present antigens to the T cell receptors (TCRs) (13). Antigen-specific T cells are then selected and the following immune responses are initiated (13). The HLA genes are located at the major histocompatibility complex (MHC) region on chromosome 6p21.3 and are the most polymorphic genes in the human genome (14, 15). Many pharmacogenetic studies have been conducted to investigate the association between HLA alleles and the specific drug-induced DRESS/DIHS. Until now, a variety of risky HLA alleles have been reported. These associated HLA alleles are usually drug- and ethnic-specific (see Table 1). The results suggest these "risky" HLA molecules may preferentially present specific drug antigens to specific TCRs and initiate adverse immune responses. Therefore, people with risky HLA alleles are more susceptible to specific drug hypersensitivity reactions. According to the different prevalence of specific risk alleles in different ethnicities, pre-prescription screening tests were recommended by some organizations for populations at risk (68). The preemptive strategies have demonstrated some success in lowering the incidence of SCARs (69).

2.2. Models of drug recognition by drug-specific T cells

Traditionally, it was commonly believed that T cells typically recognized peptides with at least 8–9 amino acids (MHC class I) and 12–15 amino acids (MHC class II) presented by antigen-presenting cells (APCs) (70). In drug hypersensitivity, several models were proposed for recognition of the small drug compounds by T cells with subsequent initiation of immune response. Currently, three main models were widely discussed (Figure 2): the hapten/pro-hapten model, the pharmacological interactions model (p-i concept), and the altered peptide repertoire model (71). In the hapten/pro-hapten model, the drug (hapten) or its reactive metabolites (pro-hapten after processing) would covalently bind to a larger protein or peptide. This formation of a hapten-protein/peptide complex called "haptenation" make this complex recognizable to the T cell receptor and gains the ability to activate the downstream immune response (71). The theory was best demonstrated in cases of penicillin-induced cutaneous adverse reactions (72). In the p-i concept, by contrast, the causative drugs may noncovalently and directly bind to the immune receptors like TCR or specific HLA molecules. The binding of these drugs is sufficient to stimulate the signaling transmission through the TCR without the need for a classic antigen-processing pathway (73). This concept was demonstrated and introduced by delicate studies conducted by Pichler's group (74–76) and supported by the study conducted by Wei et al. (77) in the field of SCAR. In the study conducted by Wei et al. (77), the carbamazepine can directly interact with the HLA-B*15:02 molecule, be presented to APCs, and initiate immune responses (77). No intracellular antigen processing was involved in the HLA presentation of carbamazepine (77). Similar interaction was also seen in the hypersensitivity reaction induced by dapsone (78). The concept of the altered peptide repertoire model was

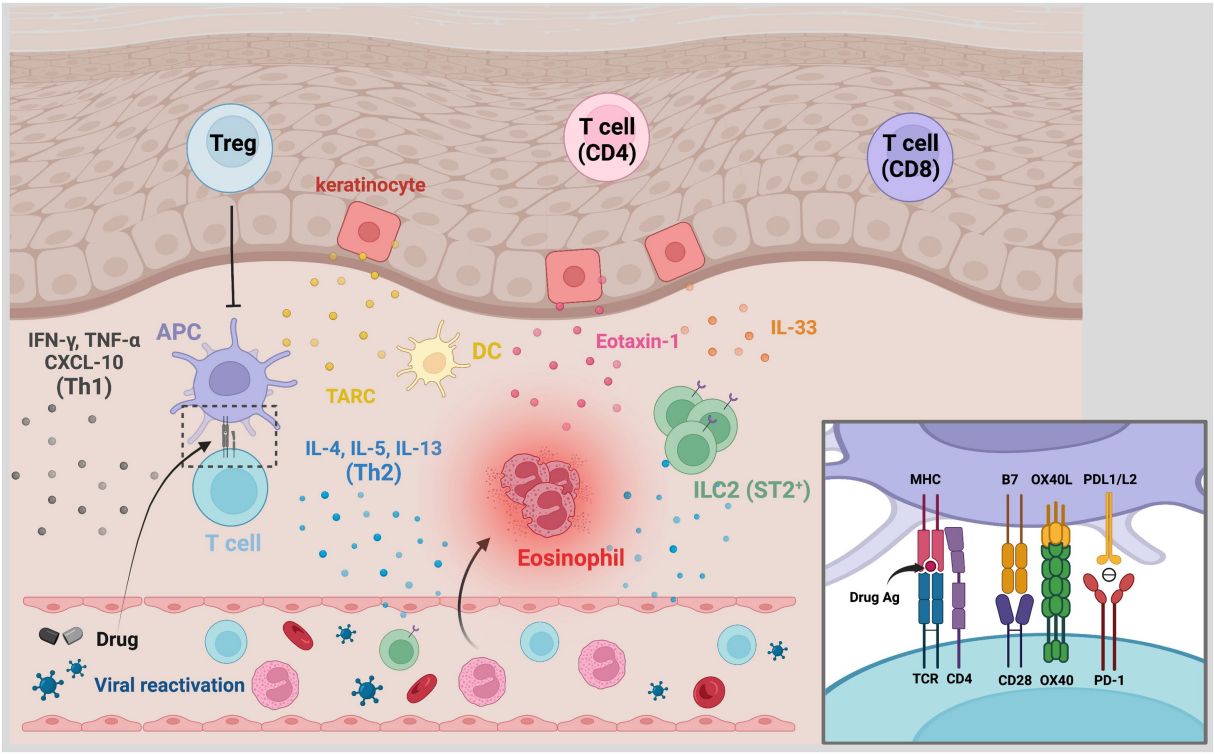

FIGURE 1
Pathogenesis of DRESS/DIHS. The affected skin is rich in $CD4^+$ and $CD8^+$ T cells, regulatory T cells (Tregs), plasma dendritic cells, and type 2 innate lymphoid cells (ILC2). TARC secreted by keratinocytes and DCs would recruit type 2 T helper (Th2) cells to the skin. Through antigen presentation, drug-specific T cells are activated and produced Th2-associated cytokines including IL-4, IL-5, and IL-13. Increased IL-33 levels, which may be secreted by keratinocytes and macrophages, activate ILC2 via its receptor ST2 and promote the production of Th2-associated cytokines. The IL-5, eotaxin-1, and TARC synergistically promote the local accumulation of harmful eosinophils. Th1-associated cytokines and chemokines like IFN-γ, TNF-α, and C-X-C motif chemokine 10 (CXCL-10) have also overexpressed in some cases. Viral reactivation is another characteristic hallmark in DRESS/DIHS. The inset shows the involved signals of antigen presentation. Traditionally, the specific antigen presented by the MHC molecule is recognized by antigen-specific TCR with the aid of B7-CD28 costimulation. The costimulatory interaction between OX40L and OX40, which is presented by activated T cells, may prevent T cells from being inhibited by Tregs. The binding of PD-1 and PDL1/L2 otherwise transmit signals to inhibit T cell proliferation and cytokines production. A compromised inhibitory mechanism of Tregs and PD-1/PDL1/L2 axes can lead to the promotion of these hypersensitivity reactions. CXCL-10, C-X-C motif chemokine 10; DC, dendritic cell; DRESS/DIHS, drug reaction with eosinophilia and systemic symptoms/drug-induced hypersensitivity syndrome; IFN-γ, interferon-γ; ILC2, type 2 innate lymphoid cells; PD-1, programmed cell death protein-1; PD-L1, programmed death ligand 1; TARC, thymus activation-regulated chemokine; TNF-α, tumor necrosis factor-α; Treg, regulatory T cell.

demonstrated in the case of abacavir hypersensitivity syndrome in HLA-B*57:01-positive individuals (79–81). Abacavir binds noncovalently to the antigen-binding groove of HLA-B*57:01, which causes the conformational changes of the binding groove and alters the repertoire of endogenous peptides presented by HLA-B*57:01. Therefore, previously tolerated self-peptides become recognizable and may elicit hypersensitivity reactions. However, interestingly, these models may not be mutually exclusive in drug hypersensitivity reactions. For example, the hapten/pro-hapten theory and p-i concept had both been proposed in sulfamethoxazole-induced hypersensitivity reactions (82, 83). Different antigen-presenting mechanisms may be involved in different cases, further investigation may be needed to elucidate the actual mechanism in different drugs-induced DRESS/DIHS.

2.3. Costimulatory/coinhibitory signaling pathways

For T cell activation to be initiated, two signals are required: the interaction of TCR MHC/TCR interaction (signal 1), and simultaneous costimulatory signals (signal 2) provided by a set of costimulatory molecules. The interaction between CD28 presented on T cells and the CD80/CD86 expressed on the surface of APCs is the prototype for this crucial signaling pathway. Asides from the CD28-CD80/CD86, there are several costimulatory and coinhibitory signaling molecules playing potentially important roles in the pathogenesis of DRESS/DIHS, such as OX40/OX40L, PD-1/PD-L1, and CTLA-4/CD80/CD86 axis (84).

2.3.1. OX40 (CD134) and OX40L

OX40, also known as CD134, is a member of the tumor necrosis factor (TNF) receptor superfamily. Unlike other molecules in the TNF receptor superfamily, the OX40 was not expressed by naïve T cells but transiently expressed by antigen-activated T cells. The ligand for OX40 (OX40L) is expressed broadly by professional APCs, vascular endothelial cells, activated natural killer (NK) cells, and the responding CD4 T cells (85). At least two mechanisms of OX40-OX40L interaction were suggested including (1) promoting the expansion and survival of effector T cells and the generation of memory T cells, and (2) disrupting T-cell tolerance by antagonizing

TABLE 1 HLA alleles with risks in drug hypersensitivities in different populations.

	HLA allele	Phenotype	Ethnicity
Aromatic anticonvulsants			
All[†]	B*08:01, B*13:01, B*56:02	DRESS	Thai (16)
Carbamazepine	A*31:01	DRESS/SJS/TEN	Northern European (17), Japanese (18), Korean (19)
		DRESS	Han Chinese (20, 21), European (20, 22), Spanish (23)
	A*31, Cw*04	DRESS	Iranian (24)
	B*15:11[‡]	MPE/DRESS/SJS	Han Chinese (25)
Phenytoin	B*13:01	DRESS	Thai (26)
	B*51:01	DRESS	Thai (27), Thai children (28)
	B*15:13	DRESS/SJS/TEN	Malaysian (29)
	B*56:02/04	DRESS	Thai (26)
	CYP2C19*3	DRESS	Thai (26)
	CYP2C9*3	DRESS/SJS/TEN	Han Chinese, Japanese, Malaysian (30)
	A*24:02	DRESS	Spanish (23)
	C*14:02	DRESS	Thai children (28)
Lamotrigine	A*24:02	DRESS	Spanish (23)
	A*31:01	DRESS/SJS/TEN	Korean (31)
	A*68:01	HSS[§]/SJS/TEN	European (32)
Allopurinol	B*58:01	HSS[§] DRESS/SJS/TEN	Han Chinese (33), Thai (34), Japanese (35), Korean (36)
	A*24:02, DRB1*13:02[††]	DRESS	Korean (37)
Antiretroviral drugs			
Abacavir	B*57:01	HSS[§]	Americans (38, 39), Australians (40), Whites and Hispanics (41), Indian children (42)
Nevirapine	DRB1*01:01	HSS[§]	Australian (43)
	B*35:05	HSS[§]	Thai (44)
	B*14:02, Cw*08:01, Cw*08:02	HSS[§]	Sardinian (45), Japanese (46)
	C*04:01	DRESS/SJS/TEN	Malawian (47)
	Cw*04	HSS[§]	Han Chinese (48)
Raltegravir	B*53:01	DRESS	African (49, 50)
Antibiotics and anti-inflammatory drugs			
Dapsone	B*13:01	HSS[§]	Han Chinese (51), Indonesian (52), Korean (53)
		DRESS	Han Chinese (54, 55), Malaysian (55), Thai (54)
Co-trimoxazole	B*13:01	DRESS/SJS/TEN	Han Chinese (56), Malaysian (56), Thai (56–58)
Salazosulfapyridine	B*13:01	DRESS	Han Chinese (59)
Sulfonamide	A*11:01	DRESS/SJS/TEN	Japanese (60)
Piperacillin/tazobactam	B62	DRESS	United Kingdom (61)
Vancomycin	A*32:01	DRESS	European Americans (62), Spanish (63), Han Chinese (64)
	B*07:05	DRESS	Han Chinese (64)
	B*40:06	DRESS	Han Chinese (64)
	B*67:01	DRESS	Han Chinese (64)
Others			
Benznidazole	A*68	MPE/DRESS	Latin American (65)
	A*11:01	MPE/DRESS	Latin American (65)
	A*29:02	MPE/DRESS	Latin American (65)
Azathioprine	C*06:02	HSS[§]	Australian (66)
IL-1/IL-6 inhibitors	DRB1*15	DRESS	European (67)

[¶]The risk alleles both for MPE, DRESS, and SJS/TEN are listed but risk alleles only for SJS/TEN are not listed in this table.
[§]Hypersensitivity syndrome (HSS) is a historical term that may not fulfill the current diagnostic criteria of DRESS but have similar clinical manifestations in common.
[†]Include phenytoin, carbamazepine, lamotrigine, phenobarbital, and oxcarbazepine.
[‡]Only limited cases are reported (1 in SJS, 2 in DRESS, and 1 in MPE).
[††]This study investigated Korean patient who are HLA-B*58:01 (+) carriers. The frequency of A*24:02/DRB1*13:02 was significantly higher in the B*58:01 (+) DRESS group than in the B*58:01 (+) tolerant controls.DRESS, drug reaction with eosinophilia and systemic symptoms; HSS, hypersensitivity syndrome; MPE, maculopapular exanthema; SJS, Stevens-Johnson syndrome; TEN, toxic epidermal necrolysis.

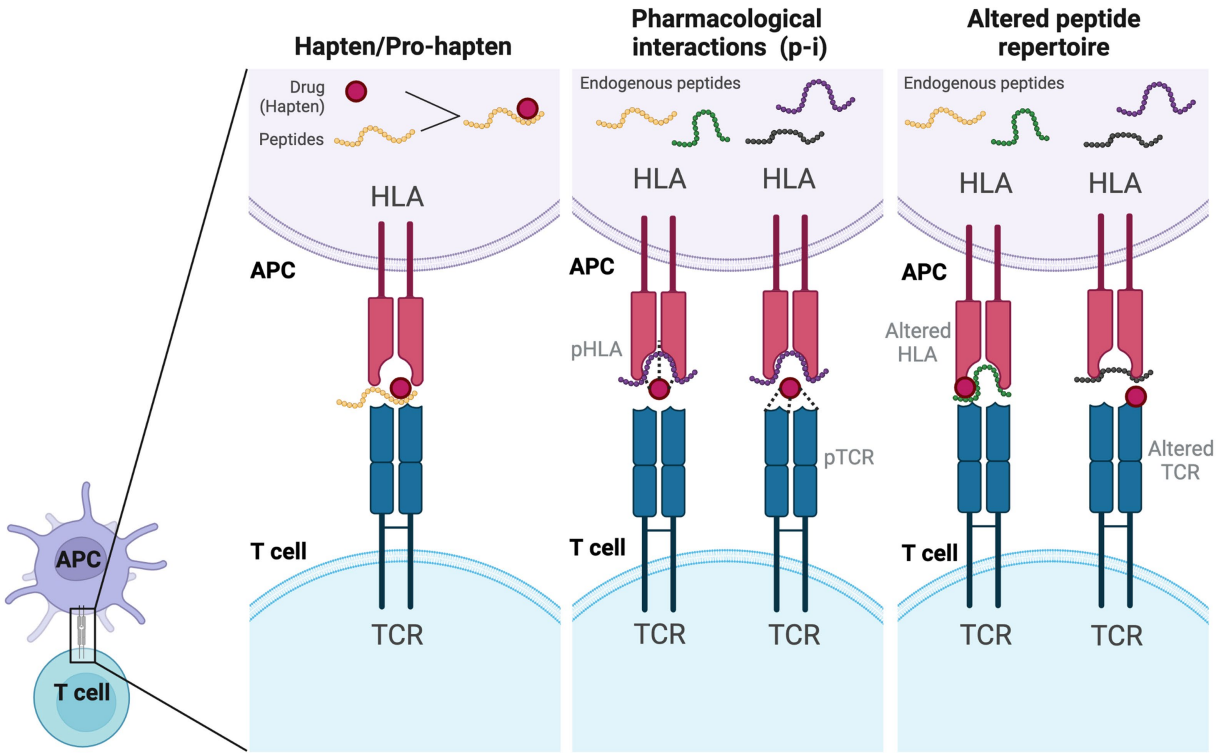

FIGURE 2
Models of antigen presentation and T-cell activation by drugs. In the hapten/pro-hapten model, the drug (hapten) covalently binds to a larger self-peptide and forms a neoantigen which could be presented by specific HLA alleles and recognized by the specific T cell receptor. In the p-i model, the drug would bind to the HLA or TCR noncovalently, which is a processing-independent interaction and can stimulate T cell activation directly. In the altered self-peptide repertoire model, the drug may bind to either the HLA (altered HLA) or TCR (altered TCR), leading to a conformational change and altering the repertoire of self-peptides presented to T cells. APC, antigen-presenting cell; HLA, human leukocyte antigen; TCR, T cell receptor.

Treg-mediated suppression (85). The pathogenic role of OX40-OX40L interaction has been demonstrated in various immune diseases and cancers (86, 87).

Beyond the above-mentioned role in T cell activation, recent studies further delineated another role of OX40 in DRESS/DIHS. Miyagawa et al. found both the OX40-expressing CD4+ T cells and the OX40L-positive cells (in peripheral blood mononuclear cells, PBMCs) were upregulated in DRESS/DIHS in the acute stage compared with other drug eruptions (88, 89). HHV-6 reactivation is regarded to be one of the key contributors to the development of DRESS/DIHS. To be noticed, OX40 was previously identified as a specific receptor that helps the entry of HHV-6 to T cells (90). Recent studies demonstrated that the levels of serum soluble OX40 (sOX40), which may be produced by OX40 shedding and/or alternative splicing, were also increased in the serum of DRESS/DIHS patients, and were correlated with the peak level of HHV-6 viral loads (91). Moreover, the increased percentage of OX40 expression and level of sOX40 were both correlated with the serum levels of TARC/CCL17, a Th2-associated chemokine that is associated with disease severity in patients of DRESS/DIHS (92). In another study, Lee et al. demonstrated increased OX40-expressing CD4+ T cells in the lesional skin in DRESS/DIHS, and the frequency of OX40+ CD4 T cells was also correlated with the DRESS/DIHS severity score (93). These advanced investigations suggest that OX40/OX40L axis plays essential roles not only in T cell activation and Treg regulation but also in the HHV-6 replication and initiation of DRESS/DIHS.

2.3.2. Programmed death (PD)-1/programmed death-ligand-1/(PD-L1) and cytotoxic T-lymphocyte–associated antigen (CTLA)-4

PD-1, PD-L1, and CTLA-4 are well-known coinhibitory molecules since the concept of immune checkpoint blockade emerged as a promising strategy to defeat cancers. Many monoclonal antibodies targeting these molecules or their ligands were approved and have had a large success in cancer treatment (94).

PD-1 is a checkpoint receptor primarily found on activated CD4+ T cells, activated CD8+ T cells, and peripheral B cells (95). Its ligand PD-L1 is expressed on T cells, B cells, macrophages, and dendritic cells (DCs) while another ligand PD-L2 is expressed primarily on APCs (95). Ligation of PD-1/PD-L initiates immunosuppressive signals and inhibits the T cells proliferation, cytokine production, and cytotoxicity of T cells (95, 96). CTLA-4, a structural homolog of CD28, is expressed on CD4+ T cells and CD8+ T cells and would competitively bind to the same ligands of CD80/CD86 on APCs (87). The binding of CTLA-4 transmits an inhibitory signal to negatively regulate the T cell's response (97).

There have been several case reports of immune checkpoint inhibitors induced DRESS/DIHS, showing the potential involvement of these coinhibitory molecules in the pathogenesis of DRESS/DIHS. Two cases developed DRESS/DIHS after using nivolumab, one is for metastatic renal cell carcinoma and another one is for gastric carcinoma (98, 99). For treating metastatic melanoma, two cases developed DRESS/DIHS after using ipilimumab alone or the

combined use of ipilimumab plus nivolumab (100, 101). In addition, an increased incidence of hypersensitivity reaction was also observed when patients received sulfasalazine with concurrent immune checkpoint inhibitors (102). This phenomenon suggests that the immune regulatory pathway acts as another factor in determining drug susceptibility (103, 104). Hammond et al. also provided some evidence that checkpoint inhibition may reduce the threshold for drug-specific T-cell priming, which explain the tendency of drug hypersensitivity in these population (105). The exact roles of these coinhibitory molecules in the development of DRESS/DIHS are still under-investigated, and further studies are warranted.

2.4. Involved cytokines and chemokines

Different types of cytokines and chemokines are involved in the pathogenesis of DRESS/DIHS (summarized in Table 2). DRESS/DIHS is classically considered a Th2-driven reaction with hallmarks of activated lymphocytes and eosinophilia. Th2-associated cytokines such as interleukin (IL)-4, IL-5, and IL-13 were secreted by activated Th2 cells and have a crucial impact on the development of DRESS/DIHS (118, 119). Increased levels of IL-5 were found in the plasma of hypersensitivity syndrome and associated with the generation of eosinophilia in these patients. IL-5 is not only a primary growth factor for eosinophils but also a Th2 chemokine, which plays a key role in promoting the differentiation, survival, and migration of eosinophils (120). Eotaxin-1, a chemokine also known as cysteine cysteine ligand 11 (CCL11), was also identified to be able to regulate eosinophils recruitment and activation synergistically with IL-5 (121). Circulating IL-4- and IL-13-producing CD4 + T cells were significantly higher in patients with DRESS (119). Of note, IL-13-producing T cells were significantly dominant skin-homing CLA+ cells, and the proportions of circulating IL-13-producing cells were correlated with serum thymus activation-regulated chemokine (TARC) levels.

TARC, known as CC chemokine ligand 17 (CCL17), was found to be increased in the serum in DRESS/DIHS patients (92, 116). TARC was produced mainly by DCs, Langerhans cells, and keratinocytes (122). Its main ligand, CC chemokine receptor type 4 (CCR4), is expressed predominantly by Th2-type T cells (122, 123). The TARC/CCL17 can serve as a recruiter for CCR4+ Th2 cells to the inflamed tissue and enhance the type 2 immune responses (122, 123). In DRESS/DIHS, the increased level of serum TARC/CCL17 was found, which is correlated with the blood eosinophil count (124). Moreover, the higher level of TARC/CCL17 in DRESS/DIHS patients at the acute stage was also correlated with the disease activity, and it may predict the presence of HHV-6 reactivation (92, 116).

In addition, IL-33, a member of the IL-1 cytokine superfamily, also activates immune cells and promotes Th2-associated cytokines production *via* selectively binding to its receptor ST2 (125). Recently, an increased number of type 2 innate lymphoid cells (ILC2s) expressing ST2 were identified in the skin and blood in patients with DRESS/DIHS at the acute stage and these patients presented with increased serum soluble ST2 levels (114). The study suggests the IL-33/ ST2 pathway and ILC2s are involved in the pathogenesis of DRESS/DIHS and more studies may be warranted to confirm this relationship.

Nevertheless, the different types of immune reactions may not be exclusive. In addition to interleukin (IL)-4, 5, and 13, which are predominant cytokines involved in Th2 response, tumor necrosis factor (TNF)-α and interferon (IFN)-γ (typically for Th1 response) are also found to be overexpressed in DRESS/DIHS in some studies (109, 112, 126) and the elevated levels of TNF-α and IL-6 preceded the HHV-6 infection (112). TNF-α and IFN-γ were primarily produced by the expanded population of activated CD8+ T cells (110). Paradoxically, in patients with DRESS/DIHS and HHV-6 reactivation, TNF-α and IFN-γ levels were lower during an early stage (127). Moreover, overexpression of granulysin, granzyme B, and soluble Fas ligand (sFasL) in the skin lesions and increased levels of them in the serum were also noticed in DRESS/DIHS (106–108). The elevated levels of sFasL and granzyme B were also found to be correlated with the elevation of liver enzymes (108). Granulysin and granzyme B are two cytotoxic molecules that were regarded as key mediators in the SJS/TEN (128, 129). sFasL were found elevated in SJS/TEN and could be an indicator for early diagnosis of SJS/TEN (130). These findings suggest that these cytotoxic proteins may also play important roles in the pathogenesis of cutaneous and liver manifestations in DRESS/DIHS. Recently, interferon-γ-induced protein (IP)-10/CXCL10, which is a major chemokine involved in the Th1 cell priming and differentiation, has also been reported to be associated with the development of long-term sequelae in DIHS/DRESS and DRESS with HHV-6 reactivation (127, 131). The detailed role of these Th1 cytokines in DRESS/DIHS is not clear, and further research is warranted for clarifying their function.

In another study including an analysis of 40 DRESS/DIHS patients, overexpression of IL-17 and IL-17E was demonstrated (110). In previous mice models, IL-17E could regulate Th2 immune response and result in an elevated level of eosinophils, IL-4, IL-5, eotaxin, and immunoglobulin E (132). These results suggest IL-17E may also play some role in amplifying the immune response in DRESS/DIHS. Other cytokines such as IL-2 and IL-15 were also found elevated in the PBMC and serum in DRESS/DIHS patients, respectively (109–111, 113). The IL-2 was crucial for the proliferation and activation of T cells, and the elevation of IL-15 seemed to be associated with the development of CMV reactivation in DRESS/DIHS (113, 133).

2.5. Herpesvirus reactivation and antiviral responses

Association between the reactivation of latent viruses of the HHV family and DRESS/DIHS has been well studied. The most well-known scenario is HHV-6 reactivation, which can be found in 43–100% of patients with DRESS/DIHS and was included in the diagnostic criteria for DIHS (127, 134, 135). The presence of HHV-6 reactivation may represent a more severe phenotype (135, 136). Other members of the HHV family like EBV, CMV, and HHV-7 were also reported to be involved in the pathogenesis of DRESS/DIHS (110, 137).

HHV-6 infects T cells and establishes life-long latency in humans (138). One study demonstrated that the HHV-6-positive monomyeloid precursors ($CD11b^{+}CD13^{+}CD14^{-}CD16^{high}$) would be recruited to the lesional skin in the acute stage of DRESS/DIHS (139). The responsible chemoattractant may be high-mobility group box (HMGB)-1, which is a member of the damage-associated molecular pattern molecule (DAMP) family (139). The HMGB-1 level has been found to increase in the blood and skin in patients with DRESS/DIHS (139). Subsequently, the recruited monomyeloid precursors may potentiate the transmission

TABLE 2 Cytokines, chemokines, and cytotoxic molecules involved in DRESS/DIHS.

Molecules	Secreted cells	Function in ADRs	Clinical significance	Tissue with high expression	References
Granulysin	$CD8^+$ T cells NK cells	Induce cell apoptosis	-	Skin, serum	(106, 107)
Granzyme B	$CD8^+$ T cells NK cells	Induce cell apoptosis	Correlated with liver function impairment	Skin, serum	(108)
IFN-γ	Th1 cells $CD8^+$ T cells NK cells	Induces MHC II molecules on monocytes and keratinocytes Stimulate IgG and IgM Inhibit Th2 immune response Activate macrophages and NK cells	Higher levels in patients with severe visceral involvement	PBMC	(109–111)
IL-2	Activated T lymphocytes	Stimulate T-cell activation and regulate T-cell functions Activate NK cells	Higher levels in patients with severe visceral involvement	PBMC	(109–111)
IL-4	Th2 cells Mast cell NK cells Keratinocytes	Decrease the production of Th1 cells The proliferation of activated B-cell and mature T-cell Switch antibody class to IgE Upregulate MHC II expression	-	PBMC	(109)
IL-5	Th2 cell Mast cells	Promote the formation and differentiation of eosinophil Work with IL-3 and GM-CSF synergistically	-	PBMC	(109, 111)
IL-6	Monocytes/ macrophages $CD4^+$ T cells Keratinocytes	Activation, growth, and differentiation of T cells Maturation of B cells and production of antibody Induces acute-phase protein production	Indicator of HHV-6 reactivation	Serum	(112)
IL-13	Th2 cells Mast cells Keratinocytes	Inhibits macrophage activation Activate B cells, induces IgE antibody Decreases pro-inflammatory cytokines in keratinocytes and endothelial cells	-	PBMC	(109, 111)
IL-15	Monocyte/ macrophages Dendritic cells Epithelial cells	Activation and proliferation of T and NK cell B-cell growth and differentiation Maturation of dendritic cells.	Predict the development of CMV reactivation	Serum	(113)
IL-17	Th17 cells	Activates macrophages, fibroblasts, keratinocytes, and endothelial cell Mediate proinflammatory responses	-	PBMC	(110)
IL-33	Epithelial cells Fibroblasts Endothelial cells	Induce the Th2 immune response through its receptor ST2 triggered by infections or allergens	Its "decoy" receptor sST2 was elevated in the acute stage and correlated with disease activity	Skin, serum[¶]	(114)
IP-10/CXCL10	Monocytes Endothelial cells Fibroblasts	Th1 cell priming and differentiation Chemoattraction for monocytes/macrophages, T cells, NK cells, and dendritic cells	Indicator of HHV-6 reactivation Predict the development of long-term sequelae	Skin, plasma	(115)
Soluble Fas ligand	$CD8^+$ T cells Keratinocytes	Induce cell apoptosis	Correlated with liver function impairment	Skin, serum	(108)
TARC/CCL17	Keratinocytes Dendritic cells Endothelial cells	Th2 cell chemokine and ligand for CCR4 Eosinophil chemoattractant	Correlated disease activity Indicator of HHV-6 reactivation	Skin, serum	(92, 116, 117)

(Continued)

TABLE 2 (Continued)

Molecules	Secreted cells	Function in ADRs	Clinical significance	Tissue with high expression	References
TNF-α	Monocytes/ Macrophages $CD4^+$ and $CD8^+$ T cells Keratinocytes	Regulate keratinocyte apoptosis Activates vascular endothelium Activates macrophages and stimulates nitric oxide production Induces fever and septic shock	Indicator of HHV-6 reactivation Higher levels in patients with severe visceral involvement	Skin, serum, PBMC	(108, 110, 112)

[¶]Increased level in serum of steroid-delayed responders.
ADRs, adverse drug reactions; CMV, cytomegalovirus; GM-CSF, granulocyte/macrophage colony-stimulating factor; HHV-6, human herpesvirus-6; IFN-γ, interferon-γ; IL, interleukin; IP-10, interferon-γ-induced protein-10; MHC, major histocompatibility complex; NK cell, natural killer cell; PBMC, peripheral blood mononuclear cell; TARC, thymus activation-regulated chemokine; TNF-α, tumor necrosis factor-α.

of HHV-6 to the skin-resident CD4+ T cells (139). The HHV-6 infection of the CD4+ T cells subset serves as an indispensable step for the replication and activation of the virus (138, 139). In the acute stage of DRESS/DIHS, higher expression of OX40 (CD134), an entry receptor of HHV-6 as aforementioned, by activated CD4+ T cells has also been found (88). Hence, these studies suggested that the skin might be the primary site where HHV-6 reactivation starts (88, 139).

There have been several proposed mechanisms eliciting HHV-6 reactivation during the development of DRESS/DIHS. One possible theory is the direct effect of culprit drugs or their metabolites on viral reactivation. In one *in vitro* study conducted by Mardivirin et al., HHV-6 replication was increased by amoxicillin in the MT4 cell line (140). Similar effects were observed in other *in vitro* studies of valproic acid, which enhanced both HHV-6 and CMV replications (141, 142). Another theory proposed is related to the alterations of cellular and cytokine profiles in the early stage of DRESS/DIHS. In the early stage, the numbers of B cells and serum gammaglobulin reduced and Treg cells expanded (143–146). Serum levels of pro-inflammatory cytokines and chemokines such as TNF-α, IFN-γ, IL-1, IL-2, and IL-6 have been found lower in DRESS/DIHS patients with HHV-6 reactivation than the patients without (127). In addition, the plasmacytoid dendritic cells (pDCs), which produced type 1 interferon (IFN-α/β) upon activation to help neighboring cells resist viral infection, have also been found to have decreased levels in the circulation in patients with DRESS/DIHS around the time of viral reactivation (147–150). These relatively immunocompromised conditions were supposed to be related to the viral reactivation in DRESS/DIHS. On the contrary, the number of pDCs increased in the dermis of lesional skin, suggesting that pDCs may be recruited from circulation to skin during HHV-6 reactivation and enhance antiviral response nearby (147). In addition, the levels of TARC/CCL17 are also significantly elevated at an acute stage in DRESS/DIHS, and their levels are even higher in patients with the presence of HHV-6 reactivation (116, 117). As aforementioned, TARC/CCL17 would recruit CCR4+ Th2 cells and promote subsequent Th2 responses (122, 123).

Recently, Pichler et al. postulated another theory called the "virus-release hypothesis" (151). In this hypothesis (Figure 3), DRESS/DIHS caused by intense drug-induced p-i stimulation would activate polyclonal cytotoxic T lymphocytes (151, 152). Within these p-i-activated T cells, there are also herpes virus-specific cytotoxic T cells. The virus-specific T cells kill the herpes virus-infected cells and lead to the release of intracellular herpes viruses. Therefore, blood viremia could be detected with or without symptoms of viral reactivation. This hypothesis can be supported by the previous study results, which denoted the possibility of simultaneously increased serum viral loads of different herpes viruses like HHV-6, CMV, and EBV (153). Most patients with viremia do not present with associated symptoms. However, patients with CMV reactivation are more commonly related to poor prognosis and complications (113, 151). Nevertheless, whether the herpes virus reactivation or viremia is a causative or reactive factor in the pathogenesis of DRESS/DIHS is still in debate. More studies are warranted to uncover this mysterious veil.

2.6. The COVID-19 era

The COVID-19 pandemic has adversely affected our healthcare system across different countries and has a large impact on dermatology practice (154, 155). Different kinds of dermatoses development after the prolonged use of self-protect equipment, COVID-19 infection, and administration of COVID-19 vaccines were frequently reported (155). Drug hypersensitivity reactions like maculopapular drug rashes, have been reported associated with COVID-19 infection (151, 156). There were several supporting evidence for the potential pathomechanism including an increased SARS-CoV-2 spike protein receptor (angiotensin-converting enzyme 2) expressed by keratinocytes, and SARS-CoV-2 RNA isolated from the skin of COVID-19 infected patients (156). The use of systemic treatment for these immune-mediated dermatological disorders could be more complex (157). Moreover, DRESS/DIHS and other SCARs were reported potentially to be induced by the COVID-19 vaccinations (158–160). Schroeder et al. reported a definite case of DRESS/DIHS after the administration of second dose of Pfizer/BioNtech COVID-19 vaccine (160). The authors hypothesized that the reaction of skin and internal organs may be caused by the inefficient detoxification of the vaccine and accumulation of the reactive metabolites (160). However, the exact immune mechanism and causal relationship between COVID-19 vaccines and SCARs are hard to ascertained. More research is warranted to delineate the pathogenesis of COVID-19 vaccines on SCARs.

3. Prognosis and potential biomarkers

DRESS/DIHS presents with diverse clinical manifestations and has potential life-threatening risks (3, 68, 161). Risk stratification and biomarker monitoring of these patients are important for guiding management strategy.

Clinically, the outcomes of patients may differ due to the different causative drugs. For example, anticonvulsants and

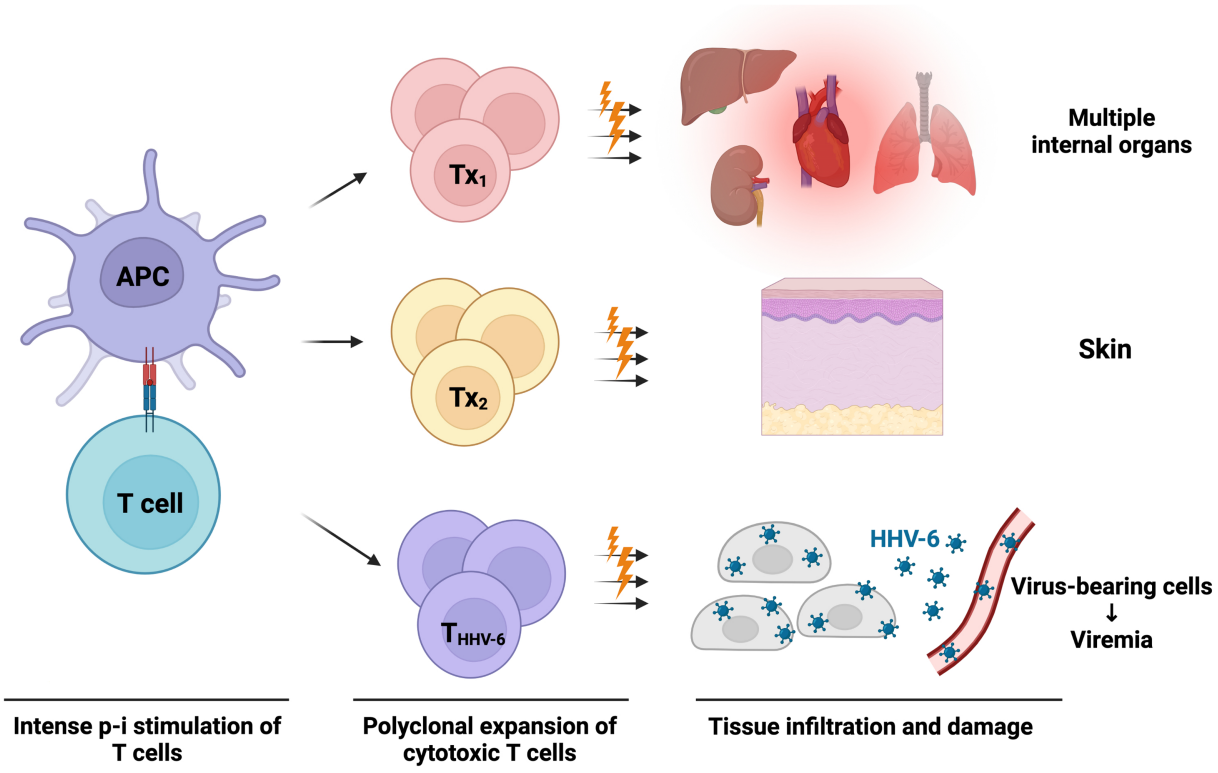

FIGURE 3
The virus-release hypothesis proposed by Pichler et al. (151) The massive p-i stimulation in DRESS/DIHS can lead to strong polyclonal T-cell expansion and activation. These p-i activated T cells are composed of cytotoxic T cells targeted at various internal organs, skin, and even virus peptide-specific T cells (may be reactive against HHV-6, CMV, EBV, etc.). These cytotoxic T cells attack organs, skin, and herpes peptide-expressing cells, causing acute symptoms of DRESS/DIHS and subsequent release of the prefabricated viruses. Therefore, viremia of various herpes viruses may be detected at a later stage. APC, antigen-presenting cell; CMV, cytomegalovirus; DRESS/DIHS, drug reaction with eosinophilia and systemic symptoms/drug-induced hypersensitivity syndrome; EBV, Epstein–Barr virus; HHV-6, human herpesvirus-6; T_{HHV-6}, HHV-6 specific cytotoxic T cell; T_x, drug-stimulated T cells against various tissue.

allopurinol were reported to be associated with a poorer prognosis compared with other culprit drugs like antibiotics (162, 163). Dermatological features with the presence of facial edema (164), laboratory examinations with higher lymphocyte count (165), severe liver injury (165), and the presence of HHV reactivation (166) were also linked to a worse prognosis or more severe disease. In addition, tachycardia, leukocytosis, tachypnea, coagulopathy, gastrointestinal bleeding, and systemic inflammatory response syndrome were associated with poor outcomes in DRESS patients (167). Recently, there were two scoring systems proposed to assess the disease severity and predict outcomes. One scoring system proposed by Mizukawa et al. composed of multiple clinical and laboratory data, including age, duration of drug exposure, allopurinol exposure, pulsed steroid use, the extent of skin involvement, fever, appetite loss, renal dysfunction, liver dysfunction and elevated CRP (168). The patients with a total score ≥ 4 represent severe cases with a predilection for later development of CMV diseases and complications (168). The other risk prediction model developed by Sharma et al. included 6 variables (age, sex, rash morphology, facial edema, medication class, and antinuclear antibody positivity) that were associated with the risk of the recurrence of DRESS syndrome (169). However, these models are derived from relatively small numbers of cases and the generalizability to other populations needs further validation.

Aside from these clinical features, some biomarkers were mentioned in studies to provide diagnostic and prognostic clues. Serum TARC/CCL17, soluble ST2, and sOX40 levels were all elevated at the acute stage in patients with DRESS/DIHS (91, 114, 116, 124, 170). The serum TARC/CCL17 levels were correlated with other indicators of systemic inflammation, and the soluble ST2 levels were correlated with IL-33 and alanine aminotransferase levels (114, 170). These are potential biomarkers of early identification and disease severity stratification in DRESS/DIHS. In addition, the elevated levels of serum TNF-α, TARC/CCL17, and sOX40 were also possible indicators of HHV-6 reactivation in DRESS/DIHS (117, 170, 171). Developing a scoring system using the above distinct clinical presentations and potential biomarkers may be a promising strategy for risk stratification and better outcome prediction. However, the availability of measuring these biomarkers may limit the application, especially in resource-poor healthcare facilities.

4. Treatments

Since DRESS/DIHS is a relatively rare disease, no prospective randomized control trials have yet been performed to evaluate the efficacy and safety of each treatment modality. The clinical phenotype

is heterogenous, and the management approach should be optimized according to the severity and the extent of organ involvement. Currently, there is still no international consensus or guideline on the use of immunomodulant in the treatment of DRESS/DIHS. Recently, there is a guideline for the diagnosis, management, treatment, and prevention of DRESS syndrome conducted by Spanish specialists and experts (68). The Spanish guideline made a comprehensive summary of current management considerations and provided a consensus-based stepwise management algorithm (68).

In general, the gold standard for treatment is causative drug identification and withdrawal with supportive care. Closely monitoring and assessing clinical symptoms, laboratory data, and imaging results are crucial. Multidisciplinary team care and timely consultation with other specialists are also important, especially while severe organ involvement. Systemic corticosteroids usually remain the first line of treatment, though the efficacy and risk profile of this treatment is difficult to be investigated in randomized controlled trials (68). A moderate-to-high dose (0.5–1 mg/kg/day of prednisolone equivalent dose) may be used to achieve improvement of the clinical symptoms and laboratory parameters (68, 172, 173). If the patients presented with more extensive organ involvement, a higher dose of corticosteroids may be applied. Initiation of systemic corticosteroids is recommended as first line therapy in patients with severe organ injury, such as nephritis (174), hepatitis (175), and pneumonitis if there are no contraindications (68). For patients present with more extensive organ involvement, initiating a higher dose of corticosteroids may be warranted (68). However, some disadvantages of systemic corticosteroids were reported including disease flare-ups during tapering (172), increased risk of opportunistic infection (162), and viral reactivations of HHV-6 and CMV (134). Therefore, the benefits and harms should be balanced while applying systemic corticosteroids for patients with DRESS/DIHS. For patients with a mild form of DRESS/DIHS without severe organ involvement, some authors advocate for using topical high-potency corticosteroids alone because of a lower complication rate compared with patients using systemic corticosteroids (162, 176, 177).

Other therapeutic agents have also been reported, though the evidence is mainly from small case series or case reports (see Table 3; Supplementary Table S1). Cyclosporin is another frequently reported potential therapeutic agent. Successful responses in treating patients with DRESS/DIHS have been observed in some case reports (178–181). A recent case–control study involving 26 patients (5 using cyclosporin and 21 using systemic corticosteroids) with DRESS/DIHS demonstrated cyclosporin is an effective treatment with good tolerability in patients contraindicated with systemic corticosteroids usage (183). Another study conducted by our team previously involving 8 DRESS/DIHS patients showed cyclosporin may be an effective and safe alternative treatment as a steroid-sparing agent for recalcitrant corticosteroid-dependent DRESS (182). Therefore, as per the Spanish guideline (68), cyclosporin can be considered as a second-line therapy for patients with poor control with corticosteroids or as a first-line therapy if the systemic corticosteroids are contraindicated. The recommended doses of cyclosporin use are still undetermined, but 3–5 mg/kg/day for a short course (7-day) with subsequent tapering may be considered according to current evidence. An open-labeled randomized clinical trial to compare the efficacy between high-dose cyclosporin (5 mg/kg/day) and pulse systemic corticosteroids in DRESS/DIHS is recently under enrolling (NCT04988256). More evidence of the efficacy and safety of cyclosporin may be established in the future.

For intravenous immunoglobulin therapy (IVIG), inconsistent treatment results were reported in different studies (184–190). Successfully treated cases were reported from case reports and case series with variable doses and duration (0.2 to 2 g/kg/day for 2 to 5 days) as monotherapy, salvage therapy, or combined therapy with systemic corticosteroids. However, in a relatively large prospective study involving six patients, the author did not support the IVIGs as monotherapy for DRESS/DIHS because of severe adverse events and the absence of beneficial effects (191). Mycophenolate mofetil, cyclophosphamide, rituximab, and plasmapheresis are other potential modalities for management, but the evidence of their effect is primarily from case reports (192–197). These agents may be considered when the patients are refractory to the above therapies. Antiviral agents like ganciclovir and valganciclovir can be considered add-on therapies if viral reactivations with suspected of contributing to severe complications (e.g., encephalitis, hemophagocytosis, or severe erosive colitis) (68).

Target-specific biologic agents have emerged and shown promise in treating a variety of autoimmune and inflammatory diseases. Since IL-5 is one of the key pathogenic cytokines in DRESS/DIHS, IL-5/IL-5 receptor (IL-5R) blockade has been reported to be a potential strategy in the management of recalcitrant DRESS/DIHS (198). There are currently three available humanized monoclonal antibodies for IL-5/IL-5R blockade. Mepolizumab and reslizumab, directly target the IL-5 and inhibit IL-5 signaling; while benralizumab targets the α subunit of the IL-5R. Until now, 15 cases had been reported. Mepolizumab was used in seven cases (198–202), benralizumab in eight cases (198, 202–205), and reslizumab in one case of DRESS/DIHS (206). In cases using mepolizumab or reslizumab, multiple injections for 3 months may be needed to reach complete remission because relapses are common after administration (198–201, 206). Only one case demonstrated obvious clinical improvement after single dose of mepolizumab (202). By contrast, in cases using benralizumab, one subcutaneous injection at a dose of 30 mg may be sufficient in most patients (198, 203–205). However, the effectiveness of these agents for DRESS/DIHS was established based on a small number of cases.

Another signaling pathway-targeted therapy also provides a promising future for treating patients with DRESS/DIHS. By using high-output single-cell transcriptomic analysis, the Janus kinase-signal transducer and activator of transcription (JAK–STAT) signaling pathway showed significantly upregulated in a patient with DRESS/DIHS refractory to high dose corticosteroid, mycophenolate mofetil, and cyclosporine (207). A pan-JAK inhibitor with tofacitinib (up to 10 mg per day) was then administered according to the identified JAK3 and STAT1 signatures, and the disease was getting controlled well after tofacitinib treatment (207). The JAK–STAT pathway is responsible for the upstream signal for many cytokines including IL-4 (JAK1, JAK23, TYK2), IL-5 (JAK1, JAK2), and IL-13 (JAK1, TYK2), which were involved in the pathogenesis of DRESS/DIHS (210). There were another two case reports demonstrating the effectiveness of tofacitinib in treating life-threatening DRESS/DIHS complicated with myocarditis (208, 209). Although disease relapse was noticed when tofacitinib was suddenly stopped in these cases, symptoms would improve rapidly after tofacitinib was reintroduced. Long-term use and slow tapering of tofacitinib may be needed.

TABLE 3 Summary of current alternative therapeutic options and evidence other than systemic corticosteroids.

Treatment	Mechanism	Clinical indication	Reported dose[¶]	Evidence (study design)
Topical corticosteroids alone	Inhibitory effects on a broad range of immune responses	Non-severe DRESS (absence of life-threatening organ involvement)	Potent or very potent TCS (betamethasone or clobetasol) 1–2 times/day	Case series (162, 176, 177)
Cyclosporin	Calcineurin inhibitor: inhibition of production and release of IL-2 and downstream activation of resting T-lymphocytes.	1. First-line therapy in early DRESS or patients contraindicated to corticosteroid 2. Second-line therapy in corticosteroid-refractory or recurrent relapsing DRESS	3–5 mg/kg/day for 3–7 days (first-line therapy) or longer A lower dose (1–3 mg/kg/day) has also been reported	Case reports (178–180) Case series (181, 182) Retrospective case–control study (183)
IVIG	1. Replacement therapy for harmful autoantibodies 2. Provides passive immunity by increasing the antibody titer with antigen–antibody reaction potential	1. Monotherapy in patients contraindicated to corticosteroids 2. Add-on therapy as salvage therapy or steroid-sparing agent	0.2–2 g/kg/day for 2–5 days or monthly for 8 months as a steroid-sparing agent	Case reports (184–188) Case series (one prospective study) (189–191)
Cyclophosphamide	Alkylating agent: prevents cell division by cross-linking DNA strands and decreasing DNA synthesis	DRESS with severe internal organ (renal) involvement	750 mg/m^2 once and relayed by oral cyclophosphamide (100 mg/day) for 6 months	Case reports (192, 193)
Plasmapheresis	Rapid removal of disease-causing autoantibodies or cells	Recurrent, relapsing, or corticosteroid-refractory DRESS with life-threatening organ involvement	4 sessions	Case reports (194–196)
Mycophenolate mofetil	IMPDH inhibitor which inhibits *de novo* guanosine nucleotide synthesis and blocks DNA synthesis	Corticosteroid-refractory DRESS with severe myocarditis (one fatal outcome)	Not specified in studies	Case reports (194, 197)
Mepolizumab	Anti-IL-5 monoclonal antibody	Recurrent, relapsing, or corticosteroid-refractory DRESS	100–300 mg monthly with single or multiple doses	Case reports (198–202)
Benralizumab	Anti-IL-5 receptor monoclonal antibody	Recurrent, relapsing, or corticosteroid-refractory DRESS	30 mg once or monthly	Case reports (198, 202–205)
Reslizumab	Anti-IL-5 monoclonal antibody	For continued use of the culprit drug	100 mg once followed by 200 mg once	Case report (only one case) (206)
Tofacitinib	Pan-JAK inhibitor	Recurrent, relapsing, life-threatening, or corticosteroid-refractory DRESS	5–10 mg/day for more than 1–10 months[§]	Case reports (207–209)

[¶]Summary of doses that had been reported in the literature.
[§]Higher dose (10 mg twice daily) was also reported in one case. Relapse of the symptoms was also reported in one patient taking tofacitinib for more than 10 months.DRESS, drug reaction with eosinophilia and systemic symptoms; IL, interleukin; IMPDH, inosine monophosphate dehydrogenase; IVIG, intravenous immunoglobulin; JAK, Janus kinase; TCS, topical corticosteroids.

Moreover, OX40-OX40L and TARC/CCL17-CCR4 interaction pathways may also be potential targets for treating DRESS/DIHS. The therapeutic application of the available biologics of anti-OX40 and anti-OX40L antibodies, such as rocatinlimab and amlitelimab, has been under investigation for many immune diseases and cancers as well as Th2 dominant atopic dermatitis (87, 211). Mogamulizumab, a humanized anti-CCR4 monoclonal antibody targeting TARC/CCL17-CCR4 axis, was also applied for treating refractory or relapsed adult T cell leukemia/lymphoma and cutaneous T cell lymphoma (212). The potential therapeutic effects of these novel drugs on drug hypersensitivity reactions still need further investigation.

5. Conclusion

DRESS/DIHS is a rare but severe adverse drug reaction with distinct clinical features and complicated pathomechanisms. Genetic polymorphism, specific signaling pathways in T cell activation, cytokines and chemokines production, and HHV reactivation are involved in the pathogenesis of DRESS/DIHS. Some scoring systems and potential biomarkers are proposed, but not widely applied in clinical practice yet. Systemic corticosteroids are still the first line of DRESS/DIHS management, and other steroid-sparing immunomodulators may be promising treatment modalities, especially for refractory cases and those contraindicated to corticosteroids. More research is required to clarify the pathogenesis and determine the advantages and risks of the newly developed treatment modalities.

Author contributions

C-BC, W-KH, and C-CL: conceptualization. C-BC and W-KH: methodology and investigation. C-BC and W-HC: resources,

supervision, and project administration. C-BC, W-KH, C-CL, and C-WW: writing—original draft preparation. C-BC, W-KH, C-WW, C-CL, S-IH, and W-HC: writing—review and editing. C-BC, C-CL, and S-IH: visualization. All authors contributed to the article and approved the submitted version.

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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.

Publisher's note

Supplementary material

The Supplementary material for this article can be found online at: https://www.frontiersin.org/articles/10.3389/fmed.2023.1187937/full#supplementary-material

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