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Insights in pediatric rheumatology: 2021

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Table of contents

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CASE REPORT
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Multicentric Carpo-Tarsal Osteolysis Syndrome Mimicking Juvenile Idiopathic Arthritis: Two Case Reports and Review of the Literature

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Multicentric carpo-tarsal osteolysis syndrome (MCTO) is a rare skeletal disorder commonly caused by MAF bZIP transcription factor B (*MAFB*) mutation. Clinically, it is characterized by aggressive osteolysis, which mainly affects the carpal tarsal bones, and is frequently associated with progressive nephropathy. Since the painful swelling and motion limitation on the wrists and/or ankles of MCTO mimics those of juvenile idiopathic arthritis (JIA), very often, MCTO is misdiagnosed as JIA. Here, we report two MCTO patients initially diagnosed with JIA but showed no response to treatment: P1, with a medical history of more than 10 years, was presented with a typical triad of arthritis-osteolysis-nephropathy; while P2 showed oligoarthritis. Gene tests were then taken and revealed a novel mutation, p.P63Q, and a previously reported conversion, p.S54L, in the *MAFB* gene. We also summarized the clinical and genetic features of a cohort containing 49 genetically confirmed MCTO patients. All 51 gene-confirmed MCTO cases (49 identified from the literature plus two patients identified herein) developed the disease during childhood. The median delay in diagnosis was 3.83 years (0–35 years). All cases presented bony lesions, and two-thirds had secondary renal lesions (32/48; three unknown), half of which (16/32) progressed into renal failure. Almost two-thirds (34/51), 75% (38/51), and 71% (36/51) of patients had no record of eye problems, facial abnormalities, and other manifestations. Most were misdiagnosed as JIA but didn't respond to treatment. Based on our experience, we suggest that clinicians should comprehensively evaluate the involvement of multiple systems in JIA patients, especially the kidney and eyes. And for JIA patients who underwent more than 3-month treatment with Bio-DMARD, genetic tests are recommended when they show little/no clinical and imaging changes, their high disease activity remains, and their disease activity remission is <50%, especially when combined with a triad of arthritis-osteolysis-nephropathy.

Keywords: multicentric carpo-tarsal osteolysis syndrome, MAFB protein, juvenile idiopathic arthritis, genetic testing, Denosumab

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INTRODUCTION

Multicentric carpo-tarsal osteolysis syndrome (MCTO, OMIM#166300) is a rare skeletal disorder characterized by early childhood onset of aggressive osteolysis, which significantly affects the carpal and tarsal bones, as well as other large joints such as the elbow and knee joints (1). Patients with MCTO often develop progressive nephropathy, leading to renal failure; they might also display subtle facial features, including a triangular shape, micrognathia, and exophthalmos (1). Most cases are sporadic, although familial cases have been reported.

MCTO is often misdiagnosed as juvenile idiopathic arthritis (JIA), especially as oligoarthritis because the painful swelling and motion limitation on the wrists and/or ankles of MCTO mimics those of JIA. However, they can be differentiated by clinical, laboratory, radiological, and genetic criteria (2). In contrast to JIA, MCTO has other clinical manifestations such as renal, ocular, and facial abnormalities. Apart from the triad of arthritis-osteolysis-nephropathy, joint involvement in MCTO patients usually begins from the wrist or ankle, which is rarely seen in oligoarticular JIA. In MCTO, reduction and eventually absence of pain, as well as the relief of wrist motions restriction is striking as time goes on. Typical osteolysis changes and complete bone loss can be found in MCTO patients, although laboratory investigations do not show signs of inflammation. In addition, MCTO patients can develop into family clusters.

Here, we report two Chinese boys of similar age but showing entirely different characteristics regarding the onset and progression of MCTO. Both were misdiagnosed with JIA and responded poorly to JIA treatment. Genetic test eventually confirmed the diagnosis of MCTO. We also reviewed the genetic and clinical manifestations of a larger cohort of MCTO patients reported in the literature to better understand this disease and help clinicians diagnose earlier, facilitating the treatment and management of the disorder.

CASE REPORTS

Patient 1 was a 12-year-old boy born to healthy unrelated parents with no family history of any skeletal lesions or nephropathy. His first rheumatologic symptoms (a painful, swollen right wrist, and limited passive and active flexion and extension of the right wrist) appeared at 2 years and 4 months old. His right 2^{nd}-5^{th} proximal interphalangeal joints (PIPs) gradually became swollen and painful 6 months later. After excluding other known conditions, he was suspected of having oligoarticular JIA since <4 joints were involved during the first 6 months according to International League of Associations for Rheumatology (ILAR) classification criteria (3), and treated for 1 year with leflunomide (LEF) and diclofenac sodium. Although treatment relieved the swelling and pain in the wrist, significant restriction on the joint motion remained. Clinicians at another hospital added methotrexate (MTX) to the protocol, which continued for 3 years. Until he grew up to 7 years old, when he recovered from joint symptoms, his parents quitted the treatment concerning the side effects of the medication.

Between the ages of 7 and 11, the joint swelling or pain was absent, and no imaging examination or urine tests were performed. However, at 11 years old, his right elbow, right wrist, and right 2^{nd}-5^{th} PIPs showed mild swelling and became painful over a few days to a week. A few months later, a stiff right elbow, with limited range of motion (both active and passive) and a flexion deformity, was noted. Magnetic resonance imaging (MRI) of the elbows was performed at 11 years and 8 months old, which showed an abnormal patchy signal in the right humeral olecranon fossa, joint cavity effusion, and synovial thickening. No X-ray of the wrists or other joints was taken because they were asymptomatic. He restarted JIA treatment with MTX, naproxen, and a tumor necrosis factor-α (TNFα) receptor inhibitor (etanercept, given for 3 months). However, there was no improvement in the lesions or subjective symptoms. A second MRI of the right elbow and wrist 7 months later revealed progression of the previous bone lesion, with joint deformation, damage to the articular surface (cartilage and bone), and synovitis. The carpal bones in the right wrist were missing. The left hand was not evaluated. Treatment was changed to MTX, sulfasalazine (SSZ), and diclofenac sodium for another 3 months, but with no symptomatic improvement.

The patient visited our hospital at 12.5 years old (**Figure 1A**). Although his parents were of average height, that of the patient was between the 10–25^{th} percentile (150 cm), and his weight was below the 3^{rd} percentile (30 kg). Physical examination revealed subtle facial abnormalities (protruding forehead and micrognathia), but no clinical evidence of an abnormality in the temporomandibular joints (**Figure 1B**). Respiratory, cardiovascular, and abdominal examinations were normal, and his cognitive function was appropriate for his age. He had marked angular malformation of the right elbow and ulnar deviation of both hands, which was more pronounced on the right (**Figures 1C,D**). Both wrist joints and bilateral 1^{st}-5^{th} PIPs were swollen and painful, but his shoulders, hips, knees, and spine were not affected.

Laboratory tests revealed normal antinuclear antibody, rheumatoid factor (RF), anti-citrullinated protein antibody levels, erythrocyte sedimentation rate (ESR) and C-reactive protein (CRP); elevated IL-6 (482.59 pg/ml, normal range: 0–16.6pg/ml) and TNF-α (12.45 pg/ml, normal range: 0–5.2pg/ml). Radiographs of the hands (**Figure 2A**) revealed osteoporosis and absence of most of the carpal bones; all PIPs and the metacarpophalangeal joints of the right hand were narrowed to some degree, and the second metacarpophalangeal joints of the right hand were deformed. The proximal part of the bilateral metacarpal was tapering. X-ray of the elbows (**Figures 2B,C**) revealed deformation of the distal right humerus and proximal ulnar and radius. Destruction of the ossification center, narrowing of the right elbow joint space, and swelling of the soft tissue around the right elbow joint was noted. The lower extremities were not affected, radiographs of both feet were normal (not shown).

Renal involvement began at 2 years old, when proteinuria (0.06 g/day), with normal renal function and normal blood pressure, was noted. The proteinuria resolved without treatment over the next 4 years of follow-up. During hospitalization

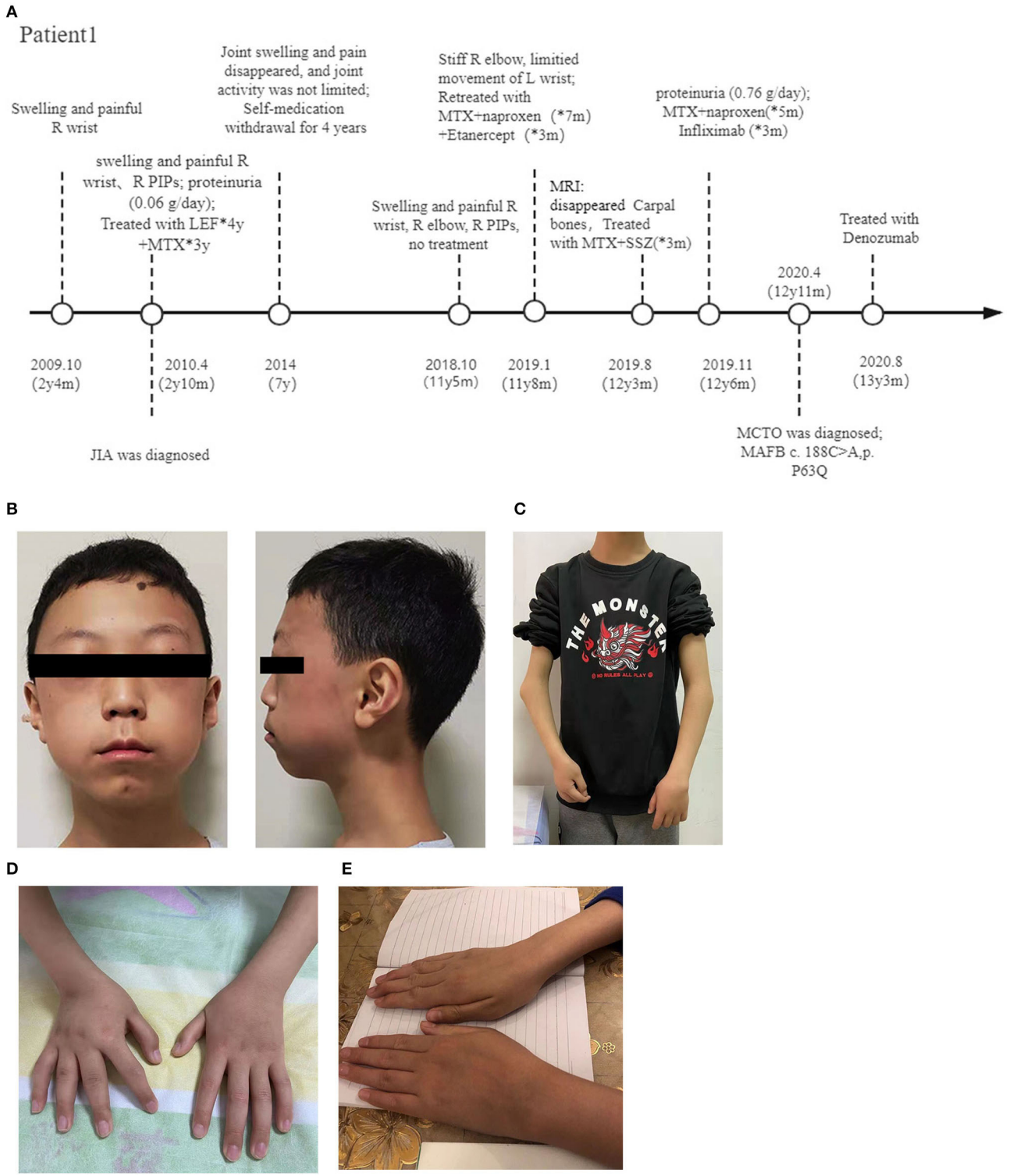

FIGURE 1 | Photographs of the patients. **(A)** Diagram of the disease progression of patient 1. **(B)** Anteroposterior view of patient 1 at 12 years old, showing a triangular face, micrognathia, and a protruding forehead. View of the same patient showing elbow deformities and a short forearm **(C)**, and ulnar deviation of both wrists **(D)**. **(E)** Swollen left wrist of patient 2. R, right; y, year; m, month; PIP, proximal interphalangeal; MTX, Methotrexate; LEF, Leflunomide; SSZ, Sulfasalazine; MCTO, Multicentric carpo-tarsal osteolysis syndrome; MAFB, MAF bZIP transcription factor B.

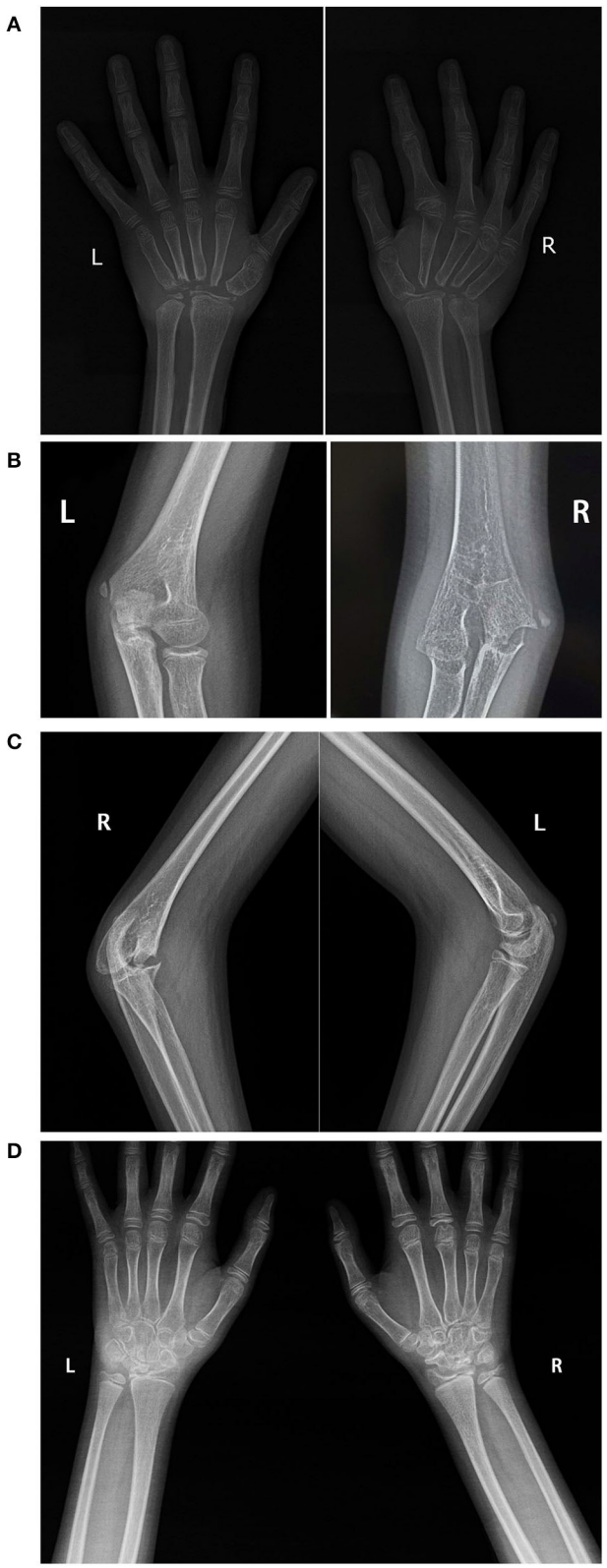

FIGURE 2 | Radiological findings. X-ray of the hands of patient 1 **(A)**, taken at 12 years old, showing severe erosion of the carpal bones and the proximal

(Continued)

FIGURE 2 | metacarpal bones. X-ray of the elbows of patient 1 **(B,C)**, showing deformation of the distal right humerus and proximal ulnar and radius; destruction of the ossification center, narrowing of the space in the right elbow joint, and swelling of the soft tissue around the right elbow joint. X-ray of the wrist of patient 2 **(D)** showing abnormal bilateral carpal bone morphology, especially the proximal row of carpal bones.

(at the age of 12.5 years), proteinuria (0.76 g/day) was detected incidentally during a routine checkup; therefore, to assess renal involvement, we examined blood pressure, serum creatinine, albumin, and total cholesterol levels, all of which were normal. Renal ultrasound revealed compression of the left renal vein. Captopril was used to reduce urinary protein levels.

After being discharged from the hospital, he was treated as extended oligoarthritis, and his disease activity was assessed by clinical Juvenile Arthritis Disease Activity Score (cJDAS) 27 monthly, which was constantly high (identified by cJDAS > 4) (4). Even after 3 months of TNFα receptor inhibitor (infliximab) treatment, fewsignificant changes in clinical manifestations and imaging were seen, and his disease activity remission was <50% (cJDAS $= 32$ and 30, before and after infliximab treatment). Therefore, we considered his treatment was invalid and suggested he do a genetic test. The trio whole-exome sequencing (WES) results revealed a *de novo* heterozygous missense mutation at NM_005461: c.188 C > A (NP_005452.2: p. P63G) (**Supplementary Figure 1A**, **Table 1**). Comparative genomics analysis revealed conservation of proline 63 in the transactivation domain of MAF bZIP transcription factor B (*MAFB*) (**Supplementary Figures 1C,D**). According to American College of Medical Genetics and Genomics (ACMG) guidelines (5), this mutation is pathogenic (the revised ACMG criteria include PS2 + PM1 + PM2 + PM5 + PP3). The gene test results coupled with the typical clinical manifestations finally led to a diagnosis of MCTO. He was then treated with Denosumab (a single dose of 60 mg) at 13 years and 3 months old; 1 month later, his joint pain almost disappeared. He then received another two doses of Denosumab (60 mg per month, every 2 months). At the last follow-up (aged 13 years and 7 months) he had developed proteinuria (1.0 g/day), but renal function was normal. Swelling and pain in all affected joints were relieved significantly, and the rate of joint destruction had slowed (as assessed by MRI).

Patient 2, a previously healthy male, developed swelling and pain in both wrists, along with limited movement at 11 years and 9 months old. 1 month later, he was hospitalized. Physical examination revealed that his height was in the 50–75th percentile (155 cm), and his weight was in the 10–25th percentile (35 kg). He had no facial dysmorphisms, and examination of his heart, lungs, abdomen, and neurological system was unremarkable. Swelling and tenderness were present in the wrist joints, particularly the left wrist (**Figure 1E**), and dorsiflexion of the 4th metacarpophalangeal joints of both hands was limited.

Radiography of the wrists revealed abnormal morphology of the carpal bones on both sides, especially the proximal

carpal bones. Destruction of the joints in the right wrist was more severe than that in the left (**Figure 2D**). Laboratory tests including ESR, CRP level, RF, and anti-citrullinated protein antibody levels, HLA-B27 status, urine tests, and renal function were normal. Bone mineral density tests suggested a reduction in bone mass. He was diagnosed with oligoarticular JIA and treated with naproxen, MTX, and calcium. However, there was no symptomatic improvement, so he received a 3-month course of the TNFα receptor inhibitor adalimumab at 11 years and 11 months old. But it did not work either. Therefore, a genetic test was suggested. Meanwhile, he received two doses of the TNFα receptor inhibitor (infliximab), whereupon the pain, and swelling in the wrists were relieved, but the range of motion (active and passive) in the wrist joints worsened.

The gene test results revealed a *de novo* heterozygous mutation, NM_005461:c.161C > T (NP_005452.2: p. S54L), in *MAFB* (**Supplementary Figure 1B**, **Table 1**). This mutation was in the highly conserved transactivation domain (**Supplementary Figures 1C,D**), which is reported to be pathogenic. And it confirmed a diagnosis of MCTO. At the last follow-up, he was aged 12 years and 5 months, and treatment with Denosumab was under consideration.

TABLE 1 | Clinical and genetic characteristics of the two MCTO patients.

Characteristics	Patient 1	Patient 2
Gender	Male	Male
Age at onset of bone lesions	2 years 4 months	11 years and 9 months
Age at MCTO diagnosis	12 years	12 years and 3 months
Diagnostic delay	10 years	6 months
Age at onset of renal lesions	2 years	-
Age at onset of renal failure	–	–
Family history	–	–
Bone lesions	+	+
Joints (except wrists and ankles) affected	+	–
Renal lesions	+	–
Renal failure	–	–
Eye problems	–	–
Facial abnormality	+	–
Other manifestations	–	–
Treatment NSAIDs	+	+
DMARDs	MTX, LEF, SSZ	MTX
TNFα inhibitors	Etanercept, Infliximab	Infliximab, Adalimumab
Denosumab	+	–
ACEI	+	–
Calcium supplements	+	+
MAFB variants	c.188 C > A, p. P63G	c.161C > T, p. S54L
Inherited derivation	*de novo*	*de novo*

MCTO, Multicentric carpo-tarsal osteolysis syndrome; NSAIDs, Non-steroidal anti-inflammatory drugs; DMARDs, Disease-modifying antirheumatic drugs; MAFB, MAF bZIP transcription factor B; MTX, Methotrexate; LEF, Leflunomide; SSZ, Sulfasalazine; TNF α, Tumor necrosis factor-α; ACEI, Angiotensin-Converting Enzyme Inhibitors.

DISCUSSION

MCTO is a rare skeletal disease. Although it has been described over the years, definitive diagnosis and proper management remain a challenge. In this study, we reported two MCTO cases previously misdiagnosed as JIA and responded poorly to JIA treatment. And eventually, we identified them as MCTO caused by *MAFB* mutation using high-throughput sequencing.

Here, we also reviewed 49 cases of MCTO harboring specific genetic mutations in *MAFB* (6–21) since 2012, when Zankl et al. (6) first reported that a mutation in *MAFB* was responsible for MCTO. The *MAFB* mutations and clinical presentations are listed in **Supplementary Tables 1**, **2**, together with the two new patients reported herein (making $n = 51$ patients in total). We also compared the major clinical features of the Chinese patients with other cohorts (**Table 2**).

Most patients (46/51, 90%) were from countries other than China. Approximately one-third (16/49, two unknown) had a positive family history. The disease occurrence did not associate with gender since the male: female ratio was 18:15 (18 unknown). All patients developed the disease during childhood with a median onset age of bone lesions at 2 years (0–12 years). By contrast, the median diagnosis age of MCTO was 11 years (1.5–38 years), and the median diagnostic delay was 3.83 years (0–35 years). The median onset age of renal lesions was 5.83 years (1.17–29 years), while that of renal failure was 14.5 years (5–42 years), and the median time of progression from lesion identification to renal failure was 3 years (0–13 years).

Almost all patients have a delayed diagnosis, which varies from 2 months to 35 years. There are several reasons for the diagnostic delay: First, the previous diagnosis was based mainly on typical clinical manifestations such as osteolysis and renal involvement; however, it may take years for these to develop, which can lead to delay. Second, although the bony and renal lesions are the most prominent features, JIA patients with eye problems, facial abnormalities, and other manifestations are more likely to be suspected of having other diseases. However, nearly two-thirds (34/51), 74% (38/51), and 70% (36/51) of MCTO patients had no record of eye, facial, and other manifestations, suggesting a lack of awareness among clinicians about the disease. Ignorance of these clinical manifestations may prevent early diagnosis and treatment. Therefore, we suggest that clinicians comprehensively evaluate the involvement of multiple systems in patients with bony lesions, especially the kidney and eyes, and conduct long-term follow-up. Based on our experience, it is recommended to conduct genetic tests for JIA patients who underwent more than 3-month treatment with Bio-DMARD when they show little/no clinical and imaging changes, high disease activity remains, their disease activity remission is <50%, and especially when combined with a triad of arthritis-osteolysis-nephropathy.

MAFB, which is expressed widely by pancreatic α cells, renal podocytes, epidermal keratinocytes, hair follicles, and hematopoietic stem cells, functions during embryonic urethral formation (22–27). Thus, MAFB protein regulates various developmental processes, including osteoclastogenesis and renal development (23, 28), and possibly the development of

TABLE 2 | Comparison of the major clinical features between Chinese patients with those in other cohorts.

Characteristics	Total ($n = 51$)	*n*	Chinese ($n = 5$)	*n*	Western ($n = 46$)	*n*
Gender ratio (male:female)	18:15	33	3:2	5	15:13	28
Age at onset of bone lesions (years)	2 (0–12)	29	2 (0.5–11.75)	5	2 (0–12)	24
Age at MCTO diagnosis (years)	11 (1.5–38)	31	12.1 (1.9–16)	5	9.25 (1.5–38)	26
Diagnostic delay (years)	3.83(0–35)	27	8 (0.35–10.7)	5	3.79 (0–35)	22
Age at onset of renal lesions (years)	5.83 (1.17–29)	21	5 (2–12)	3	6.415 (1.17–29)	18
Age at onset of renal failure (years)	14.5 (5–42)	12	10	1	17 (5–42)	11
Time to progress to renal failure (years)	3 (0–13)	10	5	1	1 (0–13)	9
Family history (%)	33 (16/49)	49	0 (0/5)	5	36 (16/44)	44
Bone lesions (%)	100 (51/51)	51	100 (5/5)	5	100 (46/46)	46
Joints except wrists and ankles affected (%)	97 (30/31)	31	80 (4/5)	5	100 (26/26)	26
Renal lesions (%)	67 (32/48)	48	60 (3/5)	5	67 (29/43)	43
Renal failure (%)	50 (16/32)	32	33 (1/3)	3	52 (15/29)	29
Eye problems (%)	29 (5/17)	17	0 (0/5)	5	42 (5/12)	12
Facial abnormality (%)	85 (11/13)	13	60 (3/5)	5	100 (8/8)	8
Other manifestations (%)	80 (12/15)	15	40 (2/5)	5	100 (10/10)	10

other organs and systems. The clinical manifestations vary among patients.

All 51 patients had wrist/ankle involvement, although 97% (30/31, 20 unknown) reported involvement of other joints, mostly the elbow, knee, and hip joints, and four patients had scoliosis (**Supplementary Table 2**). Two-thirds (32/48, 3 unknown) of patients had renal lesions, and half of these (16/32) progressed into renal failure. Renal biopsies obtained from four patients with early renal involvement (biopsy was performed at 3, 4, 13, and 14 years old, respectively) revealed focal segmental glomerular sclerosis (FSGS) (10, 18, 19) (**Supplementary Table 2**). Overall, 29% (5/17) of patients had eye problems, with corneal opacity as the primary manifestation. Almost 85% (11/13) of probands had subtle craniofacial abnormalities, including triangular faces, micrognathia, maxillary hypoplasia, and consequent exophthalmos (22). In addition, 80% (12/15) of probands had other clinical manifestations, such as multiple organ and tissue involvement, including the respiratory system, the cardiovascular system, the nervous system, the circulatory system, the immune system, and the skin (**Supplementary Table 1**). However, these symptoms were usually sporadic and not observed repeatedly in our patients or other reported cases. Of note, nearly two-thirds (34/51), 75% (38/51), and 71% (36/51) of patients had no record of eye, facial, and other manifestations, respectively, which may have contributed to the delay in diagnosis.

There are differences with respect to the organs affected, the onset of disease, rate of disease progression, and disease severity. The mechanism underlying this heterogeneity is unknown. We were interested to find out whether the genotype may contribute to these differences. Therefore, we examined the relationship between gene mutations and clinical manifestations. All 51 cases harbored *MAFB* gene mutations, including two cases in which *MAFB* conversion was not described in detail (10, 16); thus, mutations in only 49 patients are listed in **Supplementary Table 1**. All mutations were missense and lay within a short region of the amino-terminal transcriptional activation domain (amino acids 54–71, see **Supplementary Table 2**, **Supplementary Figure 2**). We carefully compared the genotypes and clinical phenotypes of all patients but found no clear links. However, we found that the same *MAFB* mutation, p.S69L, may have varying clinical manifestations (14, 19). In addition, some patients with severe renal or skeletal changes may harbor mutations at different genetic loci. The relationship between genotype and phenotype needs more case observations and follow-up as well as in-depth study of the associated mechanism(s).

Currently, there are no recognized effective treatment options for bone lesions and nephropathy associated with MCTO. Treatment with NSAIDs, traditional disease-modifying antirheumatic drugs (DMARDs, e.g., MTX and LEF), glucocorticoids, and diphosphonates (e.g., alendronate and pamidronate) are ineffective against pain or osteolysis. Bio-DMARDs (e.g., etanercept, infliximab, adalimumab, tocilizumab, and abatacept) are not reported to slow down osteolysis progression appreciably, although etanercept, infliximab, and tocilizumab are reported to relieve pain (7, 16). Other drug treatments, such as calcium supplements, should be taken with caution since one patient developed a hypercalcemia-induced convulsive episode during treatment (21). For patients with severe bone damage, surgical treatment is necessary. Indeed, 12% (6/51) of patients underwent surgery for functional correction and it helped improve their day-to-day "function (7, 10, 17, 19). Of note, two patients treated with Denosumab, an anti-RANKL antibody showed fair improvement with not only less pain, but also a marginal slowdown in the rate of osteolysis in one patient, and partial improvement on the MRI 9 months later in the other patient (18, 29). RANKL-induced osteoclastogenesis is negatively regulated by MAFB, which is encoded by the *MAFB* gene, thus reducing MAFB expression can increase

osteoclastogenesis (28). According to molecular pathogenesis and case reports, Denosumab might be the most promising drug to treat bony lesions. P1 received three doses of Denosumab (60 mg) over 4 months, and he seemed to respond well: joint swelling and pain, as well as inflammation, as assessed by MRI, were reduced. However, at present, there is no consensus about the dosage, the interval of use, or the mechanism of the action on Denosumab. Therefore, further studies are needed.

Regarding nephropathy, traditional oral steroids and/or other immunosuppressive drugs had no effect, although there was an exceptional case in which treatment with cyclosporine A was successful (30). For patients with proteinuria only, angiotensin-converting enzyme inhibitors (ACEI) can be used, although nearly half of patients progress into renal failure. Dialysis and kidney transplants will be needed.

To investigate whether patients of different ethnicities have different presentations, we compared Chinese patients' clinical manifestations and genetic information with those of other cohorts (**Table 2**). We found no differences in the gender ratio, onset age of bone and kidney lesions, and bone and renal involvement incidence. All Chinese MCTO patients were sporadic cases without a family history, and none had eye problems. In the observed cases, the proportion with kidney involvement, abnormal facial features, and other manifestations seems lower in Chinese patients than in non-Chinese patients. However, the age of MCTO diagnosis is higher, and the diagnostic delay is more prolonged in Chinese patients. Only one Chinese patient developed renal failure. Overall, there is insufficient data to say whether there are ethnic differences.

CONCLUSIONS

MCTO is a rare skeletal disorder and is often misdiagnosed as JIA. Here, we report two newly diagnosed Chinese MCTO patients. The results emphasized the importance of genetic tests and systemic reviews for JIA patients who show insufficient responses to treatment.

DATA AVAILABILITY STATEMENT

The datasets presented in this article are not readily available due to patient ethical concerns. Requests to access the datasets should be directed to the corresponding author.

ETHICS STATEMENT

The studies involving human participants were reviewed and approved by the Ethics Committee of Children's Hospital of Chongqing Medical University (2020-244-1). Written informed consent was obtained from the individual(s), and minor(s)' legal guardian/next of kin, for the publication of any potentially identifiable images or data included in this article.

AUTHOR CONTRIBUTIONS

JW: patient management, data collection, and manuscript writing. LW: manuscript review and data analysis. YX: data analysis. ZZ: manuscript review and interpretation. YA, XY, and YZ: patient management and data analysis. XT: manuscript review, data analysis, and interpretation. All the authors read and approved the final version of the manuscript.

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SUPPLEMENTARY MATERIAL

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CASE REPORT
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Stercoral Colitis in a Patient With Pediatric-Onset Systemic Lupus Erythematosus: Case Analysis and Review of the Literature

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Systemic lupus erythematosus (SLE) is an autoantibody-related disease that affects multiple organs. Stercoral colitis (SC) is a rare type of inflammatory colitis with a high mortality rate. Here, we report the first case of pediatric-onset lupus in a case complicated by stercoral colitis. We also conducted a literature review of patients with SC under 30 years old to provide useful clues for rapid diagnosis at a young age. A 28-year-old female with a history of lupus and neuropsychiatric SLE was admitted with severe abdominal pain. She was found to have stercoral colitis during surgery. Two years later, the patient underwent Hartman's operation due to ischemia of the colon. In addition, 10 patients younger than 30 years old with a diagnosis of SC were analyzed based on clinical presentation, physical examination, laboratory exam, imaging and treatment. All cases had a favorable outcome without mortality. Stercoral colitis is a rare but lethal complication, emphasizing the importance of a multidisciplinary approach. Differential diagnosis should include stercoral colitis for patients with SLE developing unexplained sharp abdominal pain.

Keywords: pediatric-onset systemic lupus erythematosus, stercoral colitis, stercoral perforation, case report, neuropsychiatric SLE (NPSLE)

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INTRODUCTION

Systemic lupus erythematosus (SLE) is an autoantibody-related disease that affects multiple organs. In addition, some SLE patients have gastrointestinal presentations or complications, including 6% of those with chronic constipation (1). Such involvement may be due to lupus enteritis, lupus mesenteric vasculitis, inflammatory bowel disease or adverse reactions of drugs used to treat SLE (2). Furthermore, patients with pediatric-onset lupus, accounting for 15–20% of lupus cases, have severe presentations, with 19% having gastrointestinal manifestations (3, 4).

Stercoral colitis is a rare type of inflammatory colitis with a high mortality rate ranging from 32 to 57%; it occurs mainly in elderly individuals with a history of chronic constipation, and it presents in a moribund state (5). Chronic constipation may lead to fecaloma formation in the large bowel and cause an increase in intraluminal pressure, eventually inducing bowel wall necrosis and perforation, known as stercoral perforation.

Most patients are diagnosed during emergency laparotomy or post-mortem (6).

To our knowledge, this is the first reported pediatric-onset lupus case complicated by stercoral colitis. The importance of the possibility of the occurrence of this disease in patients with SLE should be highlighted, even in young adults and especially in those with early childhood-onset disease. Moreover, due to the high mortality rate of stercoral colitis, awareness is promptly required for immediate diagnosis and treatment.

CASE PRESENTATION

A 28-year-old female was diagnosed with pediatric-onset lupus at the age of 8, with initial presentations of fever, malar rash, arthritis, positive antinuclear antibodies (ANAs), and elevated anti-dsDNA antibodies. In addition, she had episodes of neuropsychiatric SLE (NPSLE) at the ages of 19, 22, and 24, with seizures, cranial neuropathies of the facial nerve and transverse myelitis with neurogenic bladder, respectively, and treated with one dose of 0.5 g/m^2 intravenous cyclophosphamide pulse therapy. Furthermore, she experienced a brain abscess at the age of 25 years. After the above presentations, she regained clear consciousness without cognitive dysfunction or neurologic deficits. Daily medication was maintained with 5 mg prednisolone (i.e., cumulative dose of ∼144 g) and 100 mg azathioprine daily, with regular follow-up at our pediatric rheumatology clinic.

Later, she presented to our emergency department with severe abdominal pain and fever for 1 day. She had a history of chronic constipation and urinary tract infection for 2 weeks before admission, and her last bowel movement was 3 days prior. On arrival, she showed tachycardia (123 beats per min) and a body temperature of 38°C but no hypertension or hypotension (121/70 mmHg). Physical examination revealed a distended abdomen, severe tenderness in the lower abdomen, positive peritoneal signs, rebounding pain and decreased bowel sounds; rectal examination was not performed. Blood laboratory tests showed elevated inflammation markers, a C-reactive protein (CRP) level of 77.35 mg/L, a white blood cell count of 7,900/μL, and normal platelet count, serum creatinine, electrolyte and liver function test results. There were no obvious symptoms of lupus attacks, such as discoid rash, oral ulcer or arthralgia. SLE activity remained stable. C3 and C4 levels were 63.4 and 19.1 mg/dL, respectively, and her anti-dsDNA antibody level was 382.0 U/mL, lower than those over the previous 6 months. Disease activity, as quantified by the SLEDAI-2K score (7), was calculated to be 6, which indicated that a lupus flare was unlikely.

The initial plain abdominal radiograph in **Figure 1** shows a non-specific intestinal gas distribution without abnormal calcification or pneumoperitoneum. Ultrasound examination revealed a dilated colon, accompanied by air-fluid levels and ascites with a large amount of residual urine. A Foley catheter was inserted, but her abdominal pain did not improve. As peritonitis was suspected, she was given 1,000 g ceftriaxone and 500 mg metronidazole. However, at 6 hour after admission, the abdominal pain worsened, and repeated blood tests revealed the progression of inflammatory markers, with a CRP level of 197 mg/L. A subsequent computed tomography (CT) scan indicated a large number of fecal impactions and colon dilations, along with colon wall thickening and pneumatosis coli, as depicted in **Figure 2**. Laparoscopic exploration indicated poor perfusion of the upper rectum with pericolonic fibrin and turbid ascites in the pelvic cavity, but no perforation was found. Rigid sigmoidoscopy showed ischemia of the rectal mucosa. The ischemic rectum was removed, and primary anastomosis of the descending colon and rectum was performed, with a diverting loop transverse colostomy over the right quadrant of the abdomen (**Figure 3**). The pathology illustrated in **Figure 3** showed focal ischemic changes, severe mucosal damage and focal transmural necrosis of the large intestine, which were evidence for diagnosis. All cultures were negative, and the patient was discharged at 46 days after surgery. However, 2 years later, the patient experienced abdominal pain and shock, and CT revealed inferior mesenteric artery occlusion and ischemia of the descending sigmoid colon. During the second operation, we observed ischemic colitis with gangrene changes, and the Hartmann procedure was performed. The patient recovered smoothly under our outpatient follow-up.

LITERATURE REVIEW-BASED CASE SERIES

Medical records, including clinical records, physical examination results, laboratory results and imaging series, were reviewed by Lin LL and Gau CC of Taiwan's tertiary center. This study was approved by the Ethics Committee on Human Studies at Chang Gung Memorial Hospital in Taiwan, R.O.C. (IRB 201601678A3C501). Informed consent was obtained from the patient. We report this case according to CARE (for Case Reports) guidelines (8).

In a review of the literature by Lin LL and Gau CC, clinical manifestations, imaging findings, management strategies and outcomes were analyzed. We used the Medline subheading keywords "systemic lupus erythematosus (SLE)," "stercoral colitis," and "stercoral perforation" to search for studies in PubMed published between 1965 and August 2020 in English. Relevant articles and additional references were found by checking the citations in the articles retrieved.

To date, fewer than 200 cases of stercoral colitis or stercoral perforation have been reported, and only 10 patients [3 males (9–11) and 7 females (12–17)] younger than 30 years old are reported in PubMed. The analysis of patients aged 2–28 years old is shown in **Table 1**. Except for the present patient, all of the young adult or adolescent patients experienced psychiatric problems or were under substance use. According to the presentations, most patients (8 of 10) complained of abdominal pain, but only 40% had fever. According to physical examinations, signs of peritonitis were detected only in six cases (cases 1, 3, 5, 8,

Abbreviations: ANAs, antinuclear antibodies; CRP, C-reactive protein; CT, computed tomography; NSAIDs, non-steroidal anti-inflammatory drugs; NPSLE, neuropsychiatric SLE; SC, stercoral colitis; SLE, systemic lupus erythematosus; WBC, white blood cell.

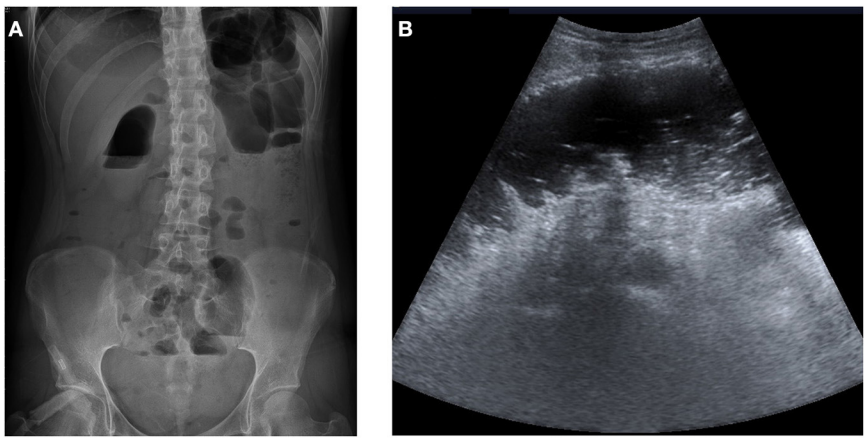

FIGURE 1 | (A) The initial abdominal plain film showed non-specific bowel gas distribution without abnormal calcification or free air. **(B)** Ultrasonography of the abdomen revealed colon dilatation with air-fluid levels and ascites.

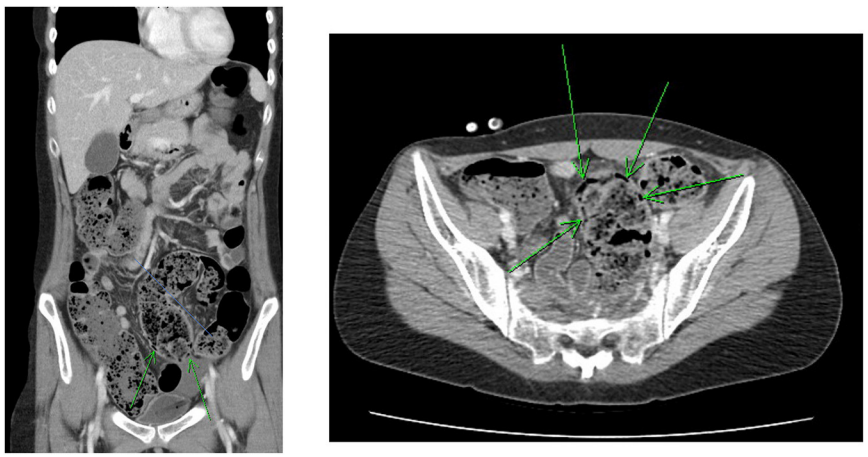

FIGURE 2 | Abdominal CT revealed much fecal impaction and colon dilatation along with colon wall thickening and pneumatosis intestinalis (arrow).

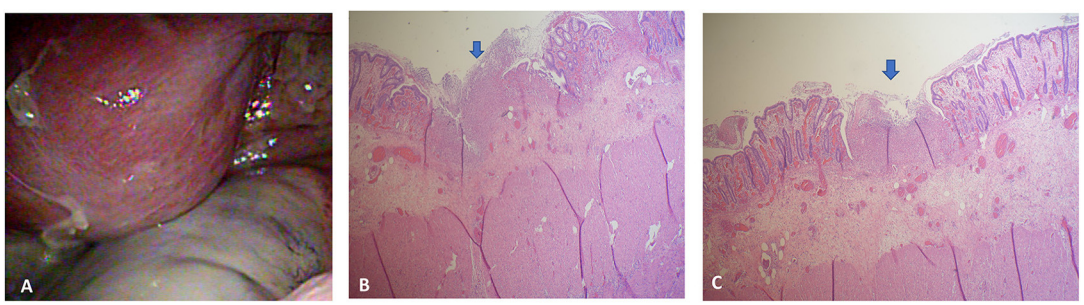

FIGURE 3 | (A) Exploratory laparoscopy revealed poor perfusion of the upper rectum with pericolonic fibrin and turbid ascites in the pelvic cavity. **(B)** The section showed ischemic change, intensive mucosal injury, and focal transmural necrosis of the large intestine (arrow). **(C)** The specimen showed focal ischemic change and transmural necrosis of the large intestine.

9, and 10). Laboratory testing showed obvious inflammatory processes in 6 patients, with 2 having metabolic acidosis and one patient both anemia and acute kidney injury. According to the indications of Kumar et al. (18), 7 cases showed diagnostic signs of stercoral perforation and CT features of fecal protrusion through the colonic wall; extraluminal air was found in half of the cases. Seven of the patients underwent surgery, and all of them were alive.

TABLE 1 | Comparison of our patient with published data on stercoral colitis or perforation at young ages.

Case	Patient	Past history	Presentation	Vital sign	Physical finding	Laboratory	Image	Operation	Course
Our case (Case 1)	28 yo female	Lupus, NPSLE, brain abscess	Severe abdominal pain with fever for 3 day	BT 38°C HR 123 bpm BP 121/70 mmHg	**Abdomen** tenderness, peritoneal sign	inflammatory process	**X-ray**: non-remarkable **CT**: fecal impaction and colon dilatation with pneumatosis	Diverting loop transverse colostomy	Discharge at 46 days post-operatively Reoperation 2 years later
Hussain et al. (13) (Case 2)	28 yo female	Opioids for chronic pain	Diffuse, chronic abdominal pain, nausea, anorexia, and the complete inability to defecate for 6 weeks	Normal	**Abdomen** soft, diffusely tenderness, hypoactive bowel sound without peritoneal sign **Rectal exam**: hard mass	Unremarkable	**CT**: gastric distension and a moderate to large amount of colonic stool	No	Endoscopic decompaction and discharge
Brown et al. (12) (Case 3)	27 yo female	3-year heroin use and depression medication	1-week abdominal pain and 12-hour vomiting	HR 160 bpm RR 30/min SpO2 100% BP 90/60 mmHg	**Abdomen** distended and peritonitic	Metabolic acidosis, AKI, inflammatory process, anemia	**X-ray**: no subdiaphragmatic air **CT:** portal venous gas and free intraperitoneal fluid and gas and massive fecal distension	Hartmann's procedure perforation in the sigmoid colon	Discharged at 4 weeks post-operatively
Canders el al. (9) (Case 4)	26 yo male	Anxiety around using the restroom	Cramping abdominal pain in the lower quadrants and shortness of breath	BT 38.3°C HR 120 bpm RR 16/min SpO2 96% BP 109/81 mmHg	**Abdomen** distended and non-tender, with stool palpable in the left lower quadrant and normal bowel sounds **Rectal exam** Hard stool	Normal	**X-ray**: dilated colon with severe fecal impaction without pneumoperitoneum. **CT**: fecal impaction with bowel ischemia	No	Intravenous fluids, oral laxatives, and water enemas. Discharged on hospital day 8
Lundy and Gadacz (10) (Case 5)	25 yo male	Chronic constipation Narcotics	Severe, diffuse abdominal pain that began 3 h	Tachycardic, diaphoretic, and tachypneic	**Abdomen** rigidity with involuntary guarding.	N/A	N/A	A resection of distended sigmoid and rectum	An uneventful recovery and discharged
McHugh et al. (14) (Case 6)	17 yo female	Chronic constipation Eating disorder	24-h history of left-sided abdominal pain	HR 140 bpm BP 100/77 mmHg	**Abdomen** distended and tender across her lower abdomen without guarding or rebound **Rectal exam**: feces in the rectum	Anemia Inflammatory process	**X-ray**: severe fecal throughout the large intestine, without free air **CT**: colonic perforation, with sigmoid colon dilated to 11 cm	Total colectomy with end ileostomy Perforation at the sigmoid colon without fecaloma	Repeated laparotomy
Proulx and Glass (15) (Case 7)	9 yo female	Chronic constipation	Nausea, vomiting, and diarrhea for several hours	BT 97.2°F (36.2°C) HR 154 bpm RR 22 bpm SpO_2 95% BP 70/50 mm Hg SpO_2 95%	**Abdomen** palpable suprapubic mass, mild generalized tenderness without peritoneal sign **Rectal exam** normal tone with a large stool mass	Leukocytosis Metabolic acidosis	**CT** large stool burden in the rectum, comprising a mass of ∼7 cm	No	Fluid supplement, manual decompaction, antibiotics, anorectal irrigation every 6 h. Discharged on hospital day 8
Park et al. (11) (Case 8)	6 yo male	Ehlers-Danlos Syndrome	Abdominal pain for 4 days without nausea, vomiting, or fever	Tachycardic Normotensive	**Abdomen** tenderness to percussion, pain with movement, and voluntary guarding	Normal	**X-ray**: unremarkable **CT**: free fluid with peripheral edema below the kidneys	Loop colostomy perforation on the lateral mesenteric border of descending colon	Discharged on day 11 post-operatively However, reoperation at 14 months later

(Continued)

TABLE 1 | Continued

Case	Patient	Past history	Presentation	Vital sign	Physical finding	Laboratory	Image	Operation	Course
Huang et al. (17) (Case 9)	4 yo female	Chronic constipation	Sudden and severe abdominal pain	Fever	**Abdomen** diffuse peritonitis	Leukocytosis	**X-ray**: Subdiaphragmatic air	Segmental colectomy Perforation at antimesocolic site over mid-sigmoid Colon	No complication
Al Omran et al. (16) (Case 10)	2 yo female	Overdose of Ibuprofen	a 3-day history of cough, fever and general aches	BT 39.1°C HR 155 bpm RR 50/min BP 90/34 mmHg	**Abdomen**: distended, with guarding and rebound tenderness	Leukocytosis	**Coronal anteroposterior CT:** free air and abundant fecal in the pelvis **Contrast-enhanced axial CT:** portal and retroperitoneal air	Double-barrel colostomy Perforation on the antimesenteric side of the sigmoid colon	Discharged a week after surgery

NPSLE, neuropsychiatric systemic lupus erythematosus; yo, year-old; HR, heart rate; RR, respiratory rate; SpO_2, saturation oxygen; BP, blood pressure; AKI, acute kidney injury; N/A, not applicable; BT, body temperature.

DISCUSSION

Stercoral perforation is a rare but fatal complication of constipation and fecal impaction. Before our patient, fewer than 200 cases have been reported since the first report in 1894 (19). Maurer et al. asserted that 1.2% of all emergency colorectal procedures and 3.2% of all colonic perforations involve stercoral perforation (6). In a retrospective study, stercoral perforation occurred in 81% of patients, especially with relation to a long-term history of chronic constipation with a median age of 62 (19). In general, patients taking medication such as non-steroidal anti-inflammatory drugs (NSAIDs) have a higher risk of stercoral perforation (20, 21) due to the propensity of these drugs to travel slowly and transiently through the bowel.

By exploring the published English literature (PubMed search from 1965 through August 2020), we found only two cases of stercoral colitis in patients with SLE (22, 23). In one case report, a 45-year-old woman with SLE presented with epigastric pain for 12 hours, and the author believed that the cause of stercoral perforation was related to NSAIDs (22). Another case report involved a 44-year-old SLE woman presenting with stercoral perforation due to long-term steroid use (23). Our patient is the first pediatric-onset (onset age at the 8) lupus case complicated by stercoral colitis without a disease flare or NSAID medication use. Although there is a reports that ischemia colitis is associated with antiphospholipid syndrome (24), but reviewing her 20-year history of lupus, no antiphospholipid antibodies were found. In addition, it is reported that some anticonvulsants can induce stercoral colitis (25), but only one short-term benzodiazepines was used 9 year ago to control a seizure. Importantly, we mainly considered the four neurological events (seizure, cranial neuropathy, transverse myelitis, and brain abscess) lead to impaired nerve innervation and cause neurogenic bladder and chronic constipation, which resulted in this catastrophic stercoral colitis. The sigmoid colon and rectum, especially the rectosigmoid junction, are the most vulnerable parts of the colon for stercoral colitis development. An insufficient blood supply at the rectosigmoid junction is specifically defined as Sudeck's point with insufficient or absent anastomosis between the superior rectal artery and inferior mesenteric artery branch at the watershed area (17, 26). Although her lupus condition was stable, bowel inflammation may also have contributed to poor tissue recovery in this insufficient blood supply area and the need for a second operation. In terms of the multiple manifestations of lupus, a correct diagnosis is difficult in this population.

Various causes of abdominal pain in lupus may indicate misdiagnosis, such as lupus enteritis, primary peritonitis and chronic lupus peritonitis (27, 28). Lupus enteritis, including mesenteric arteritis or vasculitis, gastrointestinal vasculitis and intestinal vasculitis, is a rare but life-threatening complication of SLE. Furthermore, postprandial abdominal pain can be insidious due to chronic mesenteric ischemia (27). Primary peritonitis secondary to SLE can develop rapidly, but the simultaneous use of immunosuppressive agents might mask the symptoms. In view of the aforementioned challenges of misleading diagnosis,

stercoral colitis is easily overlooked, but prompt treatment is required due to its rapid progression.

According to Maurer et al.'s definition (6), there are three diagnostic criteria: (1) a round or ovoid colonic perforation more than 1 cm in diameter on the antimesenteric side; (2) fecalomas observed in the colon, protruding through the perforation site or lying within the abdominal cavity; and (3) pressure necrosis or ulceration with chronic inflammatory reactions around the perforation site. In addition, it has been reported that the mortality rate is 32–60%, regardless of age (5). In our analysis, all patients met the diagnostic criteria, were still alive and had been discharged from the hospital; thus, a young age may result in favorable outcomes.

Early diagnosis of stercoral colitis remains a dilemma. According to a previous review, not all cases involve fever, peritoneal signs, elevation of inflammatory markers, metabolic acidosis, or electrolyte imbalance (16, 29). In addition, urinary retention, incontinence or frequency may be early signs of fecal obstruction (30). A tubular mass may be palpable in the lower left quadrant because the fecal-filled rectosigmoid and rectal exam can reveal feces located at the sigmoid colon and obstruction (31, 32). One of the patients in our review was at the age of two and unable to express abdominal discomfort; therefore, diagnosis may be difficult to confirm. Our lupus patient had urinary retention, which should be one of the early signs of chronic constipation. Our review is also in line with previous research showing that peritoneal signs and inflammation laboratory data were observed in only 60% of cases.

Although previous experts have mentioned that pain during an upright abdominal X-ray examination can provide clues about stercoral colitis or perforation, including colonic swelling at the impaction site, calcified fecaloma, or free air, fecal matter may obscure these findings (6, 33). The pivotal diagnostic role of CT radiologic investigation includes a large fecaloma with distention >6 cm of the affected colon, wall thickening >3 mm of the affected colon, pericolonic fat stranding, mucosal discontinuity, free fluid, pericolonic abscess and extraluminal gas bubbles (18, 33–35). However, in our review of patients at a young age, plain abdominal X-ray did not reveal remarkable findings for most patients, with only half displaying perforation on CT images.

According to Wu et al.'s research, 52% of patients can be treated non-operatively through an intestinal regimen (36). However, if peritonitis occurs, emergency laparotomy should be performed to rule out situations that may be related to stercoral perforation. Stercoral colitis can be diagnosed through pathology and intraoperatively (6). The usual surgery is Hartmann's procedure, which removes possible lesions (37). Intraoperative colonoscopy should be applied to determine the presence of additional stercoral ulcers, and a specimen of the altered or dilated colon should be taken to prevent recurrence of stercoral perforation (17). Additionally, pathology can reveal mucosal hemorrhage, submucosal congestion, and sharp demarcation without undermining the ulcer margins and transmural necrosis on the perforated side (29, 36). In our young age case analysis, 30% of patients received conservative treatment with good prognosis but two cases need re-operation. One was our patient and the other was a patient with Ehlers-Danlos syndrome, a connective tissue disease, and both underlying diseases may cause poor wound healing.

CONCLUSION

It is important to identify SLE patients with severe abdominal pain who may be at risk of stercoral colitis or perforation. Stercoral colitis is a rare yet lethal complication that can occur in patients as young as 28 years old, and differential diagnosis should highlight the importance of a multidisciplinary approach. In addition to appendicitis, peritonitis, or vasculitis, differential diagnosis should include stercoral colitis for patients with SLE who develop unexplained sharp abdominal pain.

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.

ETHICS STATEMENT

The studies involving human participants were reviewed and approved by Ethics Committee on Human Studies at Chang Gung Memorial Hospital in Taiwan, R.O.C. (IRB 201800989A3). Written informed consent to participate in this study was provided by the participants' legal guardian/next of kin.

AUTHOR CONTRIBUTIONS

C-CG and L-LL carried out the case analysis, participated in the sequence alignment, and drafted the manuscript. C-YW and J-LH participated in the design of the study and performed the statistical analysis. J-LH conceived of the study and participated in its design. All authors contributed to the article and approved the submitted version.

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BRIEF RESEARCH REPORT
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Hip Involvement in Juvenile Idiopathic Arthritis: A Roadmap From Arthritis to Total Hip Arthroplasty or How Can We Prevent Hip Damage?

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Objectives: To describe the clinical characteristics of hip involvement in juvenile idiopathic arthritis (JIA) from arthritis to hip osteoarthritis (HOA) and total hip arthroplasty (THA).

Study Design: Seven hundred fifty-three patients aged 2–17 years with JIA were included in the study. The comparison analysis was performed between the following subgroups: (i) JIA without hip involvement ($n = 600$; 79.7%) vs. JIA with hip involvement without HOA ($n = 105$; 13.9%), (ii) JIA with hip involvement with HOA, but without THA ($n = 32$; 4.3%) and JIA with hip involvement with HOA and with THA ($n = 16$; 2.1%). Clinical, laboratory characteristics and treatment regimens compared.

Results: Hip involvement was present in 20.3% of patients. HOA was present in 6.4% (12*1,000 patient-years) of the entire JIA group and 31.4% of patients with hip involvement. Sixteen patients (2.1%; 4.0*1,000 patient-years) required THA. The following factors were associated with HOA: sJIA (OR = 3.6, $p = 0.008$; HR = 3.0, $p = 0.002$), delayed remission (OR = 4.2, $p = 0.004$; HR = 1.4, $p = 0.538$), delay in biologic therapy initiation (OR = 7.5, $p = 0.00001$; HR = 6.7, $p = 0.002$), alkaline phosphatase <165 U\l (OR = 4.1, $p = 0.0003$; HR = 5.2, $p = 0.000004$), treatment with corticosteroids (CS) (OR = 2.6, $p = 0.008$; HR = 1.2, $p = 0.670$), cumulative corticosteroids >2,700 mg (OR = 4.3, $p = 0.032$; HR = 1.4, $p = 0.527$). The following factors were associated with THA: delay in biologic treatment initiation (OR = 1.04, $p = 0.0001$; HR = 9.1, $p = 0.034$), delayed hip involvement (OR = 5.2, $p = 0.002$; HR = 3.0, $p = 0.044$), and methylprednisolone pulse therapy (OR = 10.8, $p = 0.0000001$; HR = 5.6, $p = 0.002$).

Conclusion: Both sJIA and systemic CS, impaired calcium-phosphorus metabolism, and delayed hip arthritis are associated with HOA development in JIA. HOA is considered to be a severe adverse event of CS treatment, especially delayed hip involvement.

Keywords: juvenile idiopathic arthritis, hip osteoarthritis, total hip arthroplasty, corticosteroids, avascular osteonecrosis of the femoral head

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INTRODUCTION

Juvenile idiopathic arthritis (JIA) encompasses seven different subtypes according to International League Against Rheumatism (ILAR) classification, but in real clinical practice, it is often divided into systemic and non-systemic groups, which differ in clinical features and treatment approach (1, 2). Many delayed complications, i.e., linear growth retardation, osteoporosis, and severe functional disability due to secondary structural changes in the adjacent bone and osteoarthritis formation (3, 4), are associated with the chronic course of the disease and inadequate therapy. Hip joint is one of the most frequently damaged joints in JIA, manifested in pain, severe walk disturbances, and total hip arthroplasty (THA) is required even in childhood in case of end-stage hip osteoarthritis (HOA) (5). There is little data on specific predictors of HOA development in different JIA subtypes. The introduction of steroid-sparing agents, such as methotrexate and biologics, into treatment regimens, dramatically influenced the course and outcomes of the disease. However, structural changes of joints, primarily in the hip, do still occur despite our current therapies (6). Nowadays, most JIA patients undergoing THA have shifted to an older age group (7, 8). Known HOA risk factors are not specific: early onset of the disease, early radiological hip changes, and higher baseline activity and inflammation. Chronic immune-related joint inflammation and corticosteroid usage are tightly connected with the risk of avascular necrosis (AVN) (9). Corticosteroids are considered the leading risk factor of AVN in adults, but there are few data in children. The association of AVN development with corticosteroid dosing was described well in juvenile systemic lupus erythematosus (SLE) and oncohematological disorders (10, 11). Anecdotally, hip osteoarthritis due to AVN is studied better in SLE than in JIA, although JIA is the more common. It is worth noting that both AVN and end-stage HOA are treated by total joint replacement, which is still a challenge in pediatric practice. Our study aimed to describe the clinical characteristics of hip involvement in juvenile idiopathic arthritis (JIA) from arthritis to hip osteoarthritis (HOA) and total hip arthroplasty (THA).

METHODS

Ethical Expertise

Written consent was obtained according to the declaration of Helsinki. The local Ethical Committee of Saint Petersburg State Pediatric Medical University (protocol number 11/10 from 23.11.2020) approved this retrospective study's protocol.

Study Design and Patient Selection

Seven hundred fifty-three patients with JIA aged 2–17 years were included in a retrospective single-center study between January 2007 and December 2016. Diagnosis of JIA and JIA subtypes was made according to ILAR criteria (1). Inclusion criteria: (i) all subtypes of JIA according to ILAR criteria; (ii) at least two evaluations in our center; (iii) data about disease onset and course if the patient had an initial observation in another center; (iv) data about at least 2 year-course was available. Exclusion criteria: (i) the presence of overlap immune-mediated diseases (inflammatory bowel disease, chronic non-bacterial osteomyelitis), (ii) a history of non-inflammatory hip pathology (congenital dislocation of the hip, dysplastic osteoarthritis, acetabular dysplasia, post-traumatic changes).

Patients were divided into four categories (**Figure 1**), according to the stage of hip involvement: (i) patients who underwent THA due to HOA ($n = 16$), (ii) patients with HOA without indications for THA ($n = 32$), (iii) patients with hip arthritis (HA) without femoral head structural changes ($n = 105$), and (iv) patients without hip arthritis ($n = 600$). Diagnosis of HOA was established according to Dale radiographic JIA classification for interpretation of hip radiograms: grade 0 (normal joints), grade 1 (juxta-articular osteoporosis and/or periarticular soft tissue swelling), grade 2 (growth disturbance), grade 3 (growth abnormality and marginal bony erosions), grade 4 (deformation and severe erosions), and grade 5 (gross destruction and deformation) (12). Hip arthritis (HA) was diagnosed based on synovial inflammation with or without joint effusion on magnetic resonance imaging (MRI) or/and ultrasound examination *without specific radiological changes on X-ray (Dale classification grades 0–2)*. Hip osteoarthritis was diagnosed beginning with grade 3 by Dale classification if such signs as erosions, deformation, flattening of the femoral head, joint space narrowing, and sclerosis in the joint-forming bones were detected by radiological examination. MRI or computer tomography (CT) examination was performed for each patient with HOA. Every patient with hip involvement had at least two radiological examinations. All x-rays, CT scans, and MRIs were reassessed by an experienced pediatric rheumatologist (MK) and orthopedic surgeon (SK) with 30+ years of experience in THA. All doubtful cases, were excluded from the study ($n = 354$). Data of the WOMAC scale, Oxford hip score, hip pain severity, inability to walk, and patients' and parental consent were the indications for THA. In patients with THA, a histological examination was performed.

Data Collection: We Evaluated

Demographic characteristics: gender, onset age, JIA category, type of hip involvement, the time before HOA and THA, number of patients with delayed hip involvement. Delayed hip involvement means the absence of hip involvement in the first 6 months since the JIA onset.

Laboratory activity at the last visit (hemoglobin, WBC, platelets, ESR, and CRP levels) were included in the analysis.

Bone metabolism (calcium, inorganic phosphate, alkaline phosphatase, parathyroid hormone, and 25OHD levels) in the same time points as a laboratory activity.

Treatment regimens, cumulative corticosteroid doses, the route of administration, biologic and non-biologic DMARDs.

Achievement of inactive disease and significant flare (lead to change treatment).

Statistical Analysis

Sample size was not calculated initially. Statistical analysis was performed with the software STATISTICA, version 10.0

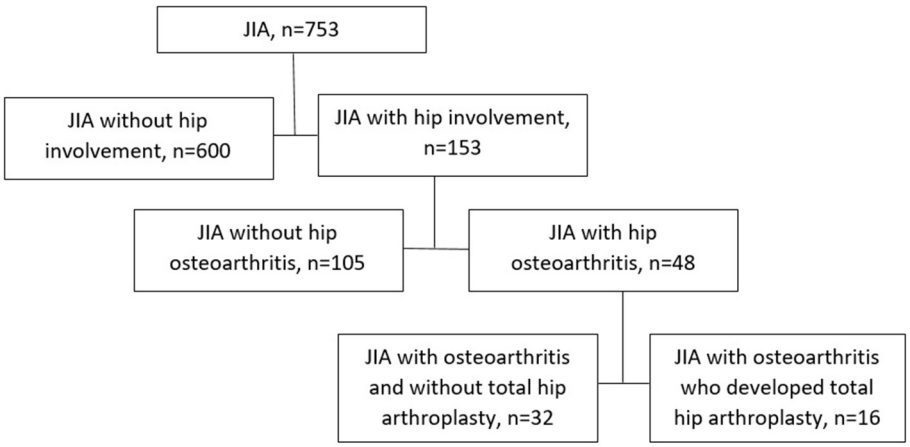

FIGURE 1 | The distribution of the enrolled patients, according to the stage of hip involvement.

(StatSoft Inc., USA). All continuous variables were checked by the Kolmogorov-Smirnov test, with no normal distribution identified. The quantitative variables were median (Me) and percentiles (25; 75) for continuous variables and absolute frequencies and percentages for categorical variables. Pearson's $\chi 2$ test or the Fisher's exact test in the expected frequencies <5 was used to compare the categorical variables. Two quantitative variables were compared using the Mann-Whitney test and Kruskal-Wallis Anova test if the number of variables was more than two. The ability of each variable to discriminate HOA from hip arthritis without structural changes was evaluated with sensitivity and specificity analysis, AUC-ROC (area under the receiver operating characteristic curve) with 95% confidence interval (CI), calculating odds ratio (OR) for the detection the best cut-offs of continuous variables. The higher values of OR of variables interfere with the better discriminatory ability. We used the "best" threshold for our data's ROC curve analysis because it provides the most appropriate mean between sensitivity and specificity. Survival analysis in each group, with HOA as the event of interest, was conducted through the Kaplan-Meier method. The log-rank test compared survival curves. Factors significantly associated with the time of HOAonset or achievement of the remission was then tested in a Cox proportional hazards regression model, calculating the Hazard-ratio (HR) with a 95% confidence interval (95%CI). $P < 0.05$ was considered statistically significant.

RESULTS

Any type of hip involvement (hip arthritis, hip osteoarthritis, and total hip arthroplasty due to hip osteoarthritis) was found in 153 (20.3%) patients with JIA. Hip arthritis was detected more frequently in ERA (37.6%), systemic arthritis (32.6%), polyarthritis (19.2%), and rarely in psoriatic arthritis (10%), and oligoarthritis (4.2%). Hip osteoarthritis (with and without THA) developed in 48 (6.4%) of JIA patients, and it amounted to 31.4% of patients with hip involvement. Bilateral hip involvement was in 22 (45.8%) of HOA patients, in total 70/96 (72.9%) of hips were involvement. HOA frequently occurred in patients with systemic arthritis and ERA compared to polyarthritis and psoriatic arthritis. No cases of hip osteoarthritis in oligoarthritis were observed. The third of the patients (51/153; 33%) had no hip arthritis at onset and developed it later. These patients had more frequent corticosteroid administration (39.2%) than patients with hip arthritis at the JIA onset (21.2%), $p = 0.023$. The time between JIA onset and HOA development ranged from systemic arthritis (4.5 years) to ERA (5.5 years) and polyarthritis (6.5 years) patients. Sixteen patients (2.1%, 4.0*1000PY) required THA: systemic arthritis (8.6%), polyarthritis (3%), and ERA (1.6%) through a similar time in ERA and sJIA (7 years) and through 11 years in polyarthritis. The time between HOA and THA was similar in all JIA categories, the shortest being in ERA (0.8 years) and the longest in sJIA (2.1 years). The distribution of different types of hip involvement is presented in **Table 1** and **Figure 2A**. Significant differences in the cumulative probability of HOA development (**Figure 2B**) and THA (**Figure 2C**) were observed in different JIA categories. The probability of the development of HOA ranged from psoriatic arthritis (minimal) to polyarthritis, ERA, and sJIA (maximum), but the probability of THA ranged from ERA (minimum) to polyarthritis and sJIA (maximum).

Patients with any hip involvement had later JIA onset age, longer JIA course, higher laboratory inflammatory activity (CRP and ESR levels, anemia, leuko-, and thrombocytosis), a higher number of clinically active joints, high distribution of HLA B27, and more often belonged to the ERA JIA category. The highest proportion of the patients with bilateral hip involvement was observed in patients whom THA was undergone and the lowest in the patients with hip arthritis (**Table 2**). Patients with hip involvement had cervical spine involvement and arthritis of the upper body, higher frequency of all types of corticosteroids usage: systemic oral, pulse therapy and hip intra-articular as well as higher corticosteroid cumulative doses, high frequency of biologics, more extended period before achievement of remission

TABLE 1 | Hip involvement in children with JIA categories.

Features of hip involvement, *n* (%)	Total (*n* = 753)	OA (*n* = 204)	PA (*n* = 265)	PsA (*n* = 40)	ERA (*n* = 186)	sJIA (*n* = 58)	*p*
Female, *n* (%)	458 (60.8)	136 (66.7)	195 (73.6)	18 (45.0)	71 (38.2)	37 (63.8)	0.0000001
The age of inclusion in the study, years, Me [25–75%]	12.3 (7.9–16.5)	10.4 (6.3–14.3)	11.4 (7.1–16.2)	15.8 (10.6–17.6)	15.2 (12.1–17.6)	10.4 (6.7–14.7)	0.00001
Intact hip, *n* (%)	600 (79.7)	195 (95.6)	214 (80.7)	36 (90.0)	116 (62.4)	39 (67.2)	0.0000001
Any hip involvement, *n* (%)	153 (20.3)	9 (4.4)	51 (19.2)	4 (10.0)	70 (37.6)	19 (32.8)	0.0000001
Hip arthritis, *n* (%)	105/153* (68.6)	9 (4.4)	38 (14.3)	2 (5.0)	48 (25.8)	8 (13.8)	0.0000001
All HOA, *n* (%)	48/153*(31.4)	0 (0.0)	13 (4.9)	2 (5.0)	22 (11.8)	11 (19.0)	0.0000001
Frequency of HOA,*1000 PY	12	0	8.6	10.6	20.3	37.1	0.0000001
HOA w/o THA, *n* (%)	32/153* (20.9)	0 (0.0)	5 (1.9)	2 (5.0)	19 (10.2)	6 (10.3)	0.0000001
HOA with THA, *n* (%)	16/153* (10.4)	0 (0.0)	8 (3)	0 (0.0)	3 (1.6)	5 (8.6)	0.0000001
HOA with THA, *1000PY	4.0	0	5.3	0	2.8	16.9	0.0000001
THA of HOA (%)	33.3	na	61.5	na	13.6	45.5	0.0000001
Time to HOA, years, Me [25–75%]	5.0 (2.4–9.4)	na	6.5 (4.4–13)	2.5 (1.8–3.2)	5.5 (1.5–9.0)	4,5 (3.9–5.7)	0.649
The time between JIA onset and THA, years, Me [25–75%]	7.8 (4.6–12.9)	na	11.2 (4.4–14.1)	na	7.1 (5.0–11.0)	7.4 (4.3–8.2)	0.905
The time between HOA and THA, years, Me [25–75%]	1.4 (0.6–2.3)	na	1.4 (1.0–3.2)	na	0.8 (0.5–1.8)	2.1 (0.4–2.5)	0.970

** Calculated to patients who had hip involvement (n = 153), CS, corticosteroids; ERA, enthesitis-related arthritis; HOA, hip osteoarthritis; JIA, juvenile idiopathic arthritis; na, not applicable; OA, oligoarthritis; PA, polyarthritis; PsA, psoriatic arthritis; PY, patient-years; sJIA, systemic JIA; THA, total hip arthroplasty.*

and lower probability of remission [Log Rank test, $p = 0.00006$, HR = 1.6 (95%CI: 1.2; 2.0), $p = 0.0003$, **Table 2**; **Figure 2D**]. No significant differences in total and ionized calcium and 25OHD levels between patients with different types of hip involvement were observed, but in logistic regression analysis, Ca < 2.42 mmol/l was associated with HOA: OR = 4.2 (95%CI: 1.7; 10.2), $p = 0.0006$, RR = 3.1 (95%CI: 1.3; 7.4), $p = 0.012$. Alkaline phosphatase levels were lower in THA 165 (121; 412) U/l and HOA groups 123 (79; 182) U/l, compared to patients with hip arthritis 207 (143; 352) U/l and with no hip involvement 225 (147; 390) U/l ($p = 0.001$). Subsequent analysis was done with four different types of hip involvement (**Table 2**).

HOA was associated with more frequent corticosteroids usage (oral and pulse-therapy), delayed hip involvement, lower levels of alkaline phosphatase, and decreased probability of remission, compared to patients with hip arthritis without structural changes [LogRank test $p = 0.00002$; HR = 1.7 (95%CI: 1.1; 2.8) $p = 0.028$; **Figure 2E**]. Patients with HOA frequently required biologic administration due to the severity of the JIA (**Table 3**).

Bilateral THA was undergone in 4 (25%) and unilateral in 12 (75%) of patients, in total 20 (62.5%) of hips were replaced. Patients who underwent THA also had increased inflammation, more active joints, treatment with methylprednisolone pulse-therapy, decreased probability of achievement of remission, and delay in biologic therapy initiation [Log Rank test $p = 0.0003$, HR = 2.2 (95%CI: 1.2; 5.0), $p = 0.012$, **Table 2**; **Figure 2F**]. Factors associated with THA were: delay in biologic therapy initiation, delayed hip involvement, and methylprednisolone pulse therapy (**Table 3**).

DISCUSSION

JIA is a chronic immune-mediated joint disease of childhood. There are no specific predictors for the long-term outcome for every subtype, only the general ones: early onset age of the disease, initial high activity, and female gender, which are considered unfavorable prognostic markers (13, 14). A research group from Canada created an alternative view of ILAR classification that highlighted hip involvement as a predictor of poor outcomes (15).

Our results support these findings. Patients with hip involvement had lower chances for remission and a longer time before it, their disease activity was higher, requiring corticosteroid therapy and more biologics compared to others. Hip involvement often occurred in systemic, enthesitis-related and polyarticular JIA categories with the highest rate of HOA and THA development. Shorter time of HOA development, delayed hip involvement, need of corticosteroids, and uncontrolled inflammation were hallmarks of HOA in sJIA, whereas male gender, older age, HLA B27-positivity, spine involvement, hip arthritis in the onset together with the shortest time between HOA and THA were markers of HOA in ERA. The main predictors of HOA and THA in JIA children were uncontrolled inflammation, higher total dose of corticosteroids and delayed initiation of biologic treatment. So, we have a chance to prevent HOA and THA by correction of the above mentioned HOA and THA predictors.

In the literature, hip arthritis occurred in 20–50% of patients with non-systemic JIA and 20–73% of patients with sJIA (15), and we noted the same rate in our study: 19.3 and 32.8%, respectively. If sJIA occurs before 10 years, it has a higher hip

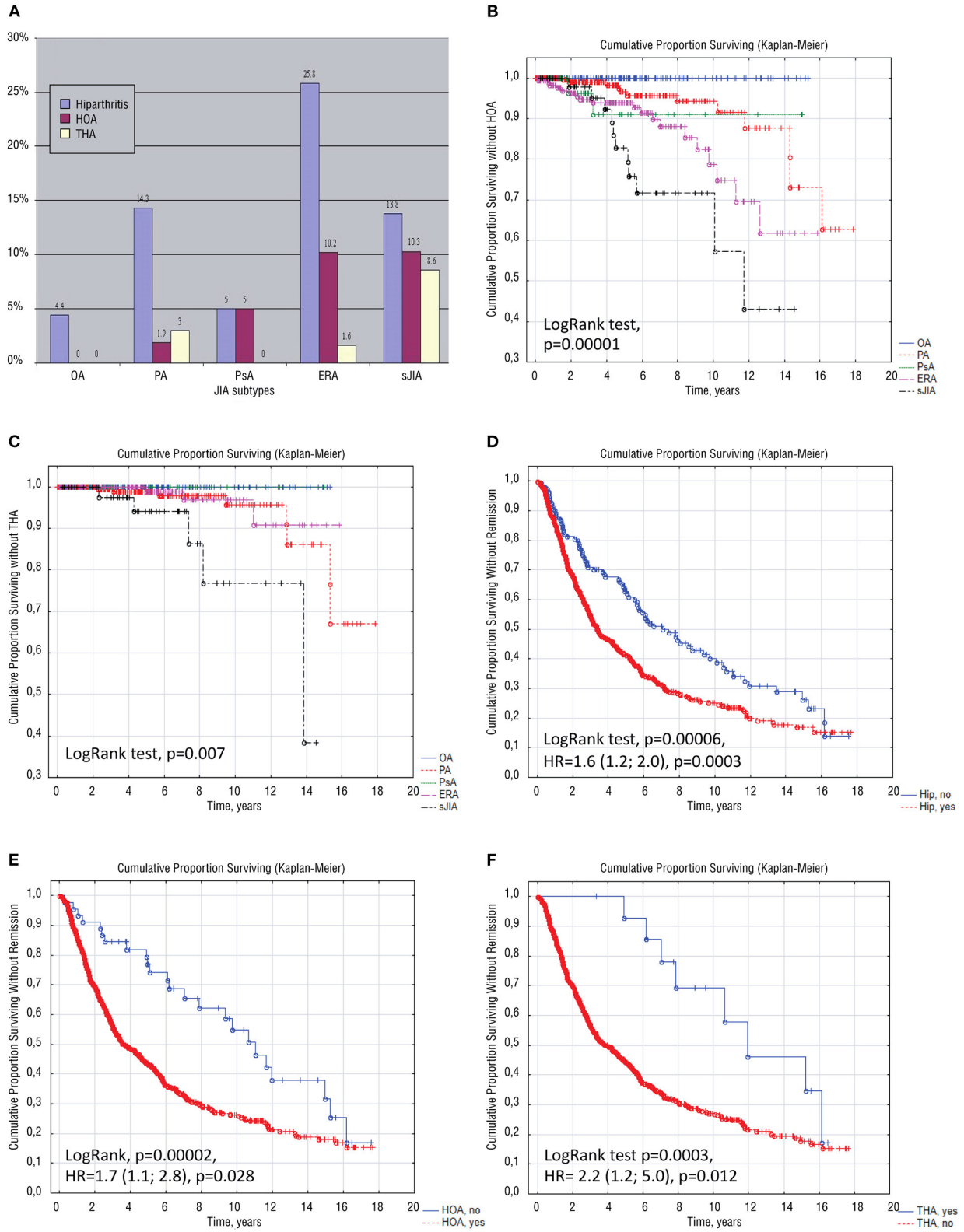

FIGURE 2 | Multiple schemes are depicting the distribution of different types of hip involvement in children with JIA categories **(A)**, the cumulative probability of surviving without hip osteoarthritis **(B)** and without total hip arthroplasty **(C)** in children with distinct JIA categories; Cumulative probability of achievement of remission in JIA depending on the hip involvement **(D)**, on the development of hip osteoarthritis **(E)** and depending on total hip arthroplasty **(F)**. ERA, enthesitis-related arthritis; HOA, hip osteoarthritis; HR, hazard ratio; JIA, juvenile idiopathic arthritis; OA, oligoarthritis; PA, polyarthritis; PsA, psoriatic arthritis; sJIA, systemic JIA; THA, total hip arthroplasty.

TABLE 2 | The features of juvenile idiopathic arthritis in different types of hip involvement.

JIA features	THA ($n = 16$)	HOA ($n = 32$)	Hip arthritis ($n = 105$)	All hip involvement ($n = 153$)	No hip arthritis ($n = 600$)	Total, $n = 753$	p_1	p_2
Females, *n* (%)	9 (56.3)	19 (59.4)	50 (47.6)	78 (51)	379 (63.2)	457 (60.7)	0.006	0.266
Europeans, *n* (%)	14 (87.5)	26 (81.3)	88 (83.8)	128 (83.7)	536 (89.5)	664 (88.3)	0.045	0.221
Onset age, years, Me [25–75%]	8.0 (3.5–11)	8.3 (4.3–13)	7.4 (4.0–11.5)	7.6 (4.0–11.6)	5.5 (2.8–10.1)	6.0 (3.0–10.4)	0.00017	0.0004
JIA duration, years, Me [25–75%]	8.5 (6.5–3.2)	5.4 (2.8–11.0)	6.2 (3.7–9.5)	6.4 (3.4–10.3)	3.7 (1.5–6.8)	4.3 (1.9–7.5)	0.0000001	0.0001
JIA subtypes								
Oligoarthritis, *n* (%)	0 (0)	0 (0)	9 (4.4)	9 (5.9)	195 (95.6)	204 (27.1)	0.0000001	0.0000001
Polyarthritis, *n* (%)	8 (50)	5 (15.6)	38 (14.3)	51 (33.3)	214 (80.7)	265 (35.2)		
Psoriatic, *n* (%)	0 (0)	2 (6.2)	2 (5)	4 (2.6)	36 (90)	40 (5.3)		
ERA, *n* (%)	3 (18.7)	19 (59.4)	48 (25.8)	70 (45.7)	116 (62.4)	186 (24.7)		
sJIA, *n* (%)	5 (31.2)	6 (18.7)	8 (13.8)	19 (12.4)	39 (67.2)	58 (7.7)		
Laboratory								
ANA, *n* (%)	3/8 (37.5)	5/16 (31.3)	23/59 (39.0)	31/83 (37.3)	181/377 (48)	212/460 (46.1)	0.008	0.173
HLAB27, *n* (%)	3/6 (50)	9/19 (47.4)	22/50 (44.0)	34/75 (45.3)	66/233 (28.3)	100/308 (32.5)	0.004	0.0007
Active joints, n	22 (9; 53)	9 (5; 16)	9 (5; 18)	10 (5; 20)	5 (3; 10)	6 (3; 12)	0.0000001	0.00001
Hip arthritis at onset, *n* (%)	5 (31.3)	12/29 (41.4)	52/90 (57.8)	69 (45.1)	na	69/153 (45.1)	na	0.07*
Bilateral involvement, *n* (%)	13 (81.3)	18 (56.3)	44 (44.5)	75 (49.0)	na	75 (10.0)	na	0.009*
Number involved hips, *n* (%)	29/32 (90.6)	50/64 (78.1)	149/210 (71.0)	228/306 (74.5)	na	228/1506 (15.1)	na	0.013*
Treatment								
Intra-articular CS, *n* (%)	6 (37.5)	5 (15.6)	27 (25.7)	38 (24.8)	276 (46)	314 (41.7)	0.000002	0.00002
Hip CS injection, *n* (%)	0 (0)	2 (6.3)	5 (4.8)	7 (4.6)	na	7/153 (4.6)	na	0.0000001*
Oral CS, *n* (%)	9 (56.2)	12 (37.5)	24 (22.9)	45 (29.4)	107 (17.9)	152 (20.2)	0.002	0.00009
Pulse-therapy CS, *n* (%)	11 (68.8)	10 (31.2)	25 (23.8)	46 (30.1)	89 (14.8)	135 (17.9)	0.00001	0.0000001
Any CS, *n* (%)	15 (93.8)	16 (50)	53 (50.5)	84 (54.9)	361 (60.2)	445 (59.1)	0.37	0.006
Cumulative CS, grams, Me [25–75%]	5.0 (3.0–14.0)	4.5 (0.5–2.0)	3.0 (1.3–6.0)	3.5 (1.5–7.8)	1.5 (1.0–3.8)	2.7 (1.0–5.0)	0.003	0.0014
Methotrexate, *n* (%)	14 (87.5)	26 (81.3)	77/95 (73.3)	117 (76.5)	456 (76.0)	573 (76.1)	0.372	0.438
Biologic, *n* (%)	15 (93.8)	28 (87.5)	56 (53.3)	99 (64.7)	252 (42.0)	351 (46.6)	0.000001	0.0000001
Time to biologic, years Me [25%;75%]	7.5 (4.4–11.4)	4.0 (1.9–8.6)	4.9 (2.2–7.6)	4.8 (2.3–8.4)	4.1 (1.7–7.7)	4.2 (1.9–7.8)	0.09	0.128
Outcomes								
Remission, *n* (%)	8 (50.0)	16 (50.0)	63 (60.0)	87 (56.9)	398 (66.3)	485 (64.4)	0,029	0.102
Time to remission, years Me [25%;75%]	9.3 (6.6–15.4)	5.6 (3.3–11.4)	4.8 (1.5–8.0)	5.6 (2.4–9.5)	2.9 (1.4–5.9)	3.2 (1.5–6.6)	0.000001	0.00001
Flare, *n* (%)	0 (0)	0 (0)	13 (12.4)	13 (8.5)	124 (20.7)	137 (18.2)	0.002	0.016

*p_1, comparison of all patients with all types of hip involvement ($n = 153$) with no hip involvement ($n = 600$); p_2, comparison between four groups: THA ($n = 16$), HOA ($n = 32$); HA ($n = 105$) and no HA ($n = 600$); *p-value calculated for three groups: THA, HOA, HA. CS, corticosteroids; ERA, enthesitis-related arthritis; HA, hip arthritis; HOA, hip osteoarthritis; JIA, juvenile idiopathic arthritis; Me, median; THA, total hip arthroplasty.*

TABLE 3 | Factors, associated with hip osteoarthritis and total hip arthroplasty.

Factors, associated with HOA	OR (95% CI)	*p*	HR (95% CI)	*p*
Systemic JIA, yes	3.6 (1.4; 9.8)	0.008	3.0 (1.5; 6.0)	0.002
Delayed remission (>5 years), yes	4.2 (1.5; 11.6)	0.004	1.4 (0.5; 3.8)	0.538
Delay in biologic treatment initiation, yes	7.5 (2.8; 20.5)	0.00001	6.7 (2.0; 25.0)	0.002
Alkaline phosphatase < 165 U/l, yes	4.1 (1.9; 8.8)	0.0003	5.2 (2.6; 11.1)	0.000004
Oral corticosteroids, yes	2.6 (1.3; 5.5)	0.008	1.2 (0.6; 2.1)	0.670
Methylprednisolone pulse-therapy, yes	2.5 (1.2; 5.1)	0.013	1.5 (0.8; 2.7)	0.239
Delayed hip involvement, yes	4.6 (2.2; 9.6)	0.00003	2.4 (1.3; 4.4)	0.005
Cumulative corticosteroids >2,700 mg	4.3 (1.1; 17.1)	0.032	1.4 (0.5; 4.3)	0.527
Factors, associated with THA				
Delay in biologic treatment initiation	1.04 (2.4; 136.2)	0.0001	9.1 (1.2; 71.4)	0,034
Methylprednisolone pulse-therapy	10.8 (3.7; 31.7)	0.0000001	5.6 (1.9; 16.7)	0.002
Delayed hip involvement	5.2 (1.7; 15.8)	0.002	3.0 (1.03; s9.1)	0.044

CI, confidence interval; JIA, juvenile idiopathic arthritis; HR, hazard ratio; HOA, hip osteoarthritis; OR, odds ratio; THA, total hip arthroplasty.

damage rate (15.1%) than in patients who develop sJIA after 10 years (7.1%) (3, 16). If sJIA started before 6 years, it had more frequent radiographic changes than the older group (17). In our cohort, opposite data was observed: patients older than 7.5 years had a higher probability of HOA [HR = 6.0 (95%CI: 2.7; 13.5), $p = 0.00001$ for the whole cohort, and OR = 5.8 (95%CI: 1.4; 24.0), $p = 0.009$ for sJIA]. The long study period included patients from the "pre-biologic era" (before the 2010 year), which might influence our results, e.g., higher onset age, compared to previous studies. Hip involvement is often bilateral and delayed in the literature-on average, hip arthritis develops 2 years after the disease starts, and HOA develops 6 years later with typical radiological changes (18, 19). The time gap between JIA onset and HOA development in our group was similar (an average of 5 years) but depended on the JIA category. The known risk factors of HOA in sJIA are early onset age of the disease, persistent inflammation, generalized lymphadenopathy, polyarthritis, and thrombocytosis over 600 $\times$ 10^9/l (20, 21). In our study, the main predictors of HOA were systemic corticosteroids, systemic arthritis, delayed remission, and delay in biologic treatment initiation, together with decreased bone metabolism and delayed hip involvement is mentioned as having an ischemic pathway of hip damage. In sJIA subgroup the main predictors in the multiple regression analysis were onset age ($p = 0.049$) and corticosteroids >2,700 mg ($p = 0.008$) and white blood cell number ($p = 0.024$) and in non-systemic forms of JIA–corticosteroids >2,700 mg ($p = 0.012$), alkaline phosphates ($p = 0.013$) and calcium level ($p = 0.026$). Delayed hip involvement was associated with high disease activity and poor prognosis. Such patients received more steroids in the "pre-biologic era," which was one of the predictors of subsequent femoral head avascular necrosis. Differences in bone metabolism were associated predominantly with systemic corticosteroids, especially decreased alkaline phosphatase activity. No differences in 25OHD might be explained by a more thorough control of vitamin D supplementation for children treated with systemic steroids, glucocorticoid-induced osteoporosis, and HOA formation.

Hip avascular necrosis (AVN) can be either idiopathic or a complication of the various illnesses (22). It is caused by a depressed blood supply in the bones due to various reasons. Predominantly it occurs in overloaded parts of the skeleton: femoral head, knee, and tarsus (23). Mostly, it is a problem of adult patients but occurs during childhood too. The pathway of corticosteroid-induced AVN is not fully understood. Vasculopathy, hypercoagulation, and overweight are discussed (24). The most sensitive childhood period is the time of growth plate closure because of significantly reducing blood supply and risk of ischemia. Our study noted that patients with sJIA developed HOA earlier than patients with other JIA subtypes, and it was associated with an aggressive course and prolonged corticosteroid treatment, with earlier disease onset and higher inflammatory activity. Patients with polyarticular subtype had the highest corticosteroid use and THA level within nsJIA. Patients with sJIA received more systemic steroids than other JIA categories, in which intra-articular steroids were more frequent. Different pathological mechanisms in systemic and non-systemic patients lead to HOA: side effects of systemic corticosteroids in sJIA lead to AVN and inflammation (osteitis) in ERA patients. Fast progression to HOA in sJIA leads to THA in childhood, and ERA progression is usually slower. Systemic arthritis, corticosteroids, delayed remission, related to delayed biologic administration in "pre-biologic era." Control of inflammation, steroid avoidance, and "on time" biologic administration highlights their role in preventing HOA and THA.

Nowadays, THA is the sole therapeutic option for HOA and AVN. Indications for THA were fourth and fifth Dale scale grades and included severe persistent pain and inability to walk (5). It is still challenging because of the patient's young age, systemic disease, medications, multiple affected joints, bone loss, continuous growth, risk of perioperative infections, and absence of data regarding implant use and revision terms (25). The most prevalent diagnosis for THA in adulthood is primary osteoarthritis (66.1%), dysplastic hip (9.8%), osteonecrosis (9.8%), post-Perthes changes (2.5%), rheumatoid arthritis (1.9%),

and other reasons, including outcomes of JIA (0.2%) (26). Fortunately, THA frequency in JIA patients, especially during childhood, decreased and shifted to an elderly group due to early diagnosis, biologic therapy, and corticosteroid avoidance (9, 27). Despite the expanding access to biologic therapy, unfortunately, many patients continue to receive corticosteroids. Long-term corticosteroid treatment, together with chronic inflammation, may lead to pathological bone and joint changes that mainly occur before growth is complete (5). Even at low doses, long-term corticosteroid therapy is associated with AVN risk in the general population, without nosology correlation (22). It was highlighted that 10 mg prednisolone daily was associated with a 6.7% increase in AVN rate. The cumulative boundary dose is 2,000 mg, and the high-risk dose is more than 10,000 mg (23). In our study, it was 2,700 mg-an independent risk factor of HOA development. The high risk of AVN development varies from 3 months to 1 year after corticosteroid therapy (10). It is interesting to note that if THA in JIA has occurred, the survival of the prosthesis is significantly poorer in patients receiving corticosteroids than those who had methotrexate (28). There are practically no recent investigations about corticosteroids and HOA correlation in JIA patients with biologic treatment.

The main limitations of the study are related to its retrospective nature. Authors could not influence steroid administration, dosage, and duration, as well as time to biologic administration. The extended study period included two subgroup patients: (i) ∼before 2011 (no access to biologics and corticosteroid prevalence) and (ii) since 2011 (better access to biologics and fewer corticosteroids usage). A relatively high proportion of patients with THA in childhood might be considered a tail-effect of the first subgroup and access to THA. The absence of an extended follow-up observation period blinds the actual scope of the problem in adults with JIA. More patients with JIA will develop hip osteoarthritis and will have THA in the future, and the whole population with aging. In our study, the diagnosis of HOA was established according to Dale's radiographic JIA classification, but it was initially created for the knee and was not validated for the hip joint, so some misinterpretations were possible. The lowest age of the study inclusion in sJIA might underestimate the actual magnitude of the problem.

CONCLUSION

Systemic JIA is a significant factor associated with HOA along with systemic corticosteroids and impaired calcium-phosphorus metabolism, as well as persistent inflammation, non-achievement of remission, and delay in biologic treatment initiation. The delayed hip involvement in systemic JIA allows considering HOA as a severe adverse event of corticosteroid therapy and a complication of sJIA itself. Strict monitoring of the systemic corticosteroids administration and disease control in JIA in general and in the systemic JIA, in particular, is required. It is necessary to avoid systemic corticosteroids in patients with non-systemic JIA and switch to biologic therapy as soon as possible, especially in corticosteroid-dependent or refractory patients. Corticosteroid administration should be limited to life-threatening conditions and must be tapered rapidly with early biologic intervention in sJIA. It is recommended to consider calcium-phosphorus metabolism, check vitamin D plasma level and prescribe therapeutic doses of vitamin D in patients treated with corticosteroids. Further investigation is required to clarify the mechanisms of HOA in JIA patients.

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 Ethical Committee of Saint Petersburg State Pediatric Medical University (protocol number 11/10 from 23.11.2020). Written informed consent to participate in this study was provided by the participants' legal guardian/next of kin.

AUTHOR CONTRIBUTIONS

LS and MK contributed to the conception and design of the study. LS, IA, RR, NL, SK, and MK organized the database and contributed equally to all of the following aspects of the manuscript: conception, acquisition of data, drafting, and revising the article. LS and MK performed the statistical analysis and wrote the first draft of the manuscript. IA, RR, NL, and SK wrote sections of the manuscript. All authors contributed to manuscript revision, read, and approved the submitted version.

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Tocilizumab in Systemic Juvenile Idiopathic Arthritis: Response Differs by Disease Duration at Medication Initiation and by Phenotype of Disease

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Objective: We performed a single-center retrospective study to determine the different efficacy of tocilizumab (TCZ) in the early and late stages and in three phenotypic subgroups (monocyclic, polycyclic, and persistent) of systemic juvenile idiopathic arthritis (sJIA).

Methods: Clinical and serological parameters of 77 sJIA patients treated by TCZ were collected from November 1, 2013 to May 1, 2019. Patients were grouped based on the duration group A $<$ 6 months ($n = 41$) and group B $>$ 6 months ($n = 36$) and divided into three phenotypes: monocyclic ($n = 12$), polycyclic ($n = 14$), and persistent ($n = 51$) course.

Results: At baseline, group A had pronounced ESR, fever less active arthritis than group B ($p < 0.05$). After 12 weeks of therapy, TCZ alleviated fever, ESR, CRP, and systemic-onset juvenile arthritis disease activity score-27 (sJADAS27) in both group A and group B ($p>0.05$), while the efficacy of TCZ in relieving active arthritis in group A was better than that in group B ($p<0.05$). After 1 year of TCZ therapy, it showed that patients with monocyclic phenotype had the highest clinical response rate (91.7%, odds ratio = 0, 95% CI: 24–24, $p = 0.00$), followed by the polycyclic (28.6%, odds ratio = 2.1, 95% CI: 10.5–18.8, $p = 0.00$) and the persistent course (9.8%, odds ratio = 1.2, 95% CI: 9.5–13.8, $p = 0.00$).

Conclusion: TCZ can quickly relieve fever and inflammation, especially when patients have less active arthritis with shorter disease duration. The long-term efficacy of TCZ is related to the phenotypes, among which the monocyclic is the best, and the persistent is the worst.

Keywords: systemic juvenile idiopathic arthritis, tocilizumab, clinical trial, pediatric, treatment

INTRODUCTION

Systemic juvenile idiopathic arthritis (sJIA) is a systemic inflammatory disease clinically characterized by fever, lymphadenopathy, arthritis, rash, and serositis. sJIA is the most serious subtype of juvenile idiopathic arthritis (1) and accounts for 30% to 40% of all JIA in Asia (2). A significant number of patients develop severe disease and treatment-related complications such as persistent arthritis, growth delay, and osteoporosis. Serious complications which are potentially fatal including macrophage activation syndrome (MAS) occur in 10% to 15% of children with sJIA (3–5). sJIA is divided into three phenotypes: monocyclic, polycyclic, and persistent course (6, 7).

The etiology of sJIA is not fully understood; proinflammatory cytokines including interleukin (IL)-6, IL-1, and IL-18 play an important role in the pathogenesis of the disease. IL-6 mediates systemic inflammation in sJIA, leading to joint synovial hyperplasia and joint destruction (8–10). Blockade of IL-6 represents the main mechanism of sJIA treatment and prevention of potential complications (11).

In 2011, the United States and Europe successively approved tocilizumab, a humanized monoclonal antibody TCZ against the IL-6 receptor for treating children with sJIA. Due to the heterogeneity of sJIA, the clinical response of patients treated with TCZ is different; hence, it is needed to better characterize the profile of patients with sJIA who are more likely to respond to IL-6 blockade. Pacharapakornpong et al. (12) found that in the early TCZ treatment (<6 months), sJIA patients had a higher remission rate than late TCZ treatment (>6 months). In this study, we performed a single-center retrospective study to determine the different efficacy of TCZ in the early and late stages and in three phenotypic subgroups (monocyclic, polycyclic, and persistent) of sJIA. The safety profile and therapeutic effect of TCZ were observed and analyzed to provide a clinical basis for the treatment of children with sJIA.

MATERIALS AND METHODS

Study Design and Population

We conducted a single-center retrospective study including patients with sJIA meeting the 2011 American College of Rheumatology designation criteria (13), who were starting TCZ in the Department of Rheumatology and Immunology, Chongqing Medical University, from November 1, 2013 to May 1, 2019. Patients with other rheumatic, infectious, neoplastic, and autoinflammatory diseases were excluded. Patients treated with other biological agents (e.g., infliximab and etanercept) in the previous 3 months were allowed. The enrolled patients who were in the active stage of the disease were allowed non-Steroidal anti-inflammatory drugs (NSAIDs), glucocorticoids, and disease-modifying antirheumatic drugs (DMARDs) (e.g., MTX, thalidomide, hydroxychloroquine, and leflunomide), among which the glucocorticoid dose was standardized to $\leq$1 mg/kg/day.

TCZ was given at a dosage of 8–12 mg/kg (12 mg/kg for body weight $<$ 30 kg, 8 mg/kg for body weight $\geq$ 30 kg) with a slow intravenous infusion every 2 weeks. After 12 weeks, TCZ was given every 4 weeks and every 6 weeks after an initial 24 weeks of treatment. All children received TCZ at least six times. This study is in line with the ethical standards set by the Chinese Medical Ethics Committee, and the subject's guardians provided informed consent.

Assessment and Outcomes

(1) The temperature, the presence of skin rash, arthritis severity, and liver and spleen lymph nodes of sJIA patients were measured before TCZ treatment, and after 2, 12, 24, and 52 weeks.

(2) Laboratory indexes of white blood cell, hemoglobin, platelet, alanine aminotransferase, aspartate aminotransferase, erythrocyte sedimentation rate (ESR), and C-reactive protein (CRP) were recorded during the TCZ treatment follow-up.

(3) The systemic-onset juvenile arthritis disease activity score-27 (14) (sJADAS-27) scoring system was used to evaluate the efficacy of TCZ treatment during the follow-up. The sJADAS-27 score includes five aspects: a physician's assessment of disease activity, parent and child's assessment of disease activity, the number of active joints, ESR, and clinical manifestations. The sum of the following five scores determines the sJADAS27 score. Assessment of disease severity: doctors, parents, and children used a 10-cm intuitive visual analog scale to evaluate disease activity, with a total score of 10 points (0 points for disease-free activity and 10 points for maximum disease activity) for the doctor score and 10 points for the parent and children score. The number of active joints: each active joint scores 1 point. Arthritis activity refers to swelling joint and limitations of joint movement due to pain or tenderness. ESR: standardized to 0 to 10 points using the formula (ESR-20)/10 (if ESR $<$ 20 mm/h, it is converted to 0, and if ESR $\geq$ 120 mm/h it is converted to 10). Clinical aspects: fever, 37–38°C scores 1 point, 38–39°C scores 2 points, 39–40°C scores 3 points, $>$40°C, 4 points; rash scores 1 point; lymphadenopathy, liver and/or spleen swelling, serositis, anemia, hemoglobin $<$ 90 g/l, platelets $>$ 600 $\times$ 10^9/l, and/or ferritin $>$ 500 ng/ml score 1 point each. The evaluation of joints under the sJADAS27 score includes 27 joints: one cervical joint, two elbow joints, two wrist joints, six first to third metacarpophalangeal joints, 10 proximal interphalangeal joints, two hip joints, two knee joints, and two ankle joints.

(4) Based on Wallace criteria (15), therefore, no clinical activity is defined as no joint with active disease, no fever, rash, serositis, hepatosplenomegaly, or systemic lymphadenopathy caused by sJIA, no active uveitis, normal ESR/CRP level (ESR $<$ 20 mm/H, CRP $<$ 8 mg/l, a high ESR/CRP level not caused by sJIA is acceptable); the best possible score of disease activity is reported by a physician global assessment (such as a score of 0 on the visual analog scale); and the duration of morning stiffness is $<$ 15 min. Clinical remission is defined as no clinically active disease for $\geq$ 6 months. A period of active disease is defined as one or more of the following: $>$1 active joint; abnormal ESR/CRP levels; a score of 0–10 on the visual analog scale; overall disease activity defined by a physician global assessment score $>$ 0; parent and child health overall status score $\geq$ 0.

(5) Monocyclic: disease activity followed by a long period of remission lasting for 2 years. Polycyclic: alternating periods

TABLE 1 | Baseline characteristics of patients with systemic juvenile idiopathic arthritis.

	Group A ($n = 41$)	Group B ($n = 36$)	p-value
Male (%)	26 (63.4)	26 (72.2)	0.410
Age at diagnosis (years)	6.8(1.25–12)	5.8(2.25–13.75)	0.582
Disease duration before tocilizumab treatment (months)	0.8(0–6)	24.2(6–84)	0.000*
Number of patients who previously received DMARDs (%)	22 (53.7)	29 (80.6)	0.013*
Number of patients who previously received glucocorticoids (%)	27 (65.9)	25 (69.4)	0.737

*Data are presented as median and IQR, and number and percentages. n, number of patients; DMARDs, disease-modifying antirheumatic drugs; *p < 0.05.*

of disease activity and remission, manifesting as recurrent attacks. Persistent course: fever and active arthritis lasting for more than 3 months, accompanied by a significant increase in inflammatory indicators such as ESR and CRP (6, 7).

Statistical Analysis

Statistical analysis was conducted using SPSS23.0 statistical software. The Shapiro–Wilk's test was used for checking the normality in the distribution of numeric variables. The statistical description is presented as mean and standard deviation for quantitative data conforming to the normal distribution, medians and interquartile range (IQR) for continuous variables, and number and percentages for categorical variables. Comparison between groups was analyzed by χ^2 test, repeated measurement analysis of variance (ANOVA), and rank-sum test. Comparison of prognosis among groups was analyzed by survival analysis. p-value < 0.05 was considered statistically significant.

RESULTS

Short-Term Efficacy of TCZ

A total of 77 sJIA patients (52 males and 25 females) with a median age of 6.3 years (2.5 ∼ 12 years) and a median disease duration of 11 months (0 ∼ 52 months) were enrolled at baseline. Patients were grouped based on the duration (before TCZ treatment): group A ≤ 6 months ($n = 41$) and group B > 6 months ($n = 36$) (**Table 1**).

At baseline, group A had pronounced ESR, fever, and less active arthritis compared to group B ($p < 0.05$). There were 40 (40/41) patients with fever in group A, 29 (29/36) in group B (**Table 2**). Active arthritis was mainly in the knees, ankles, wrists, and hips in both groups A and B. After 2 weeks of TCZ treatment, fever, active arthritis, sJADAS-27 score, white blood cell counts, ESR, and CRP levels had significantly relieved ($p < 0.05$) in both group A and group B. After the 12 week treatment, the effect of TCZ in relieving active arthritis in group A was better than in group B ($p < 0.05$). There was no difference between group A and group B in relieving fever, sJADAS-27 score, white blood cell count, ESR, and CRP (each $p > 0.05$), as shown in **Table 2**.

Long-Term Efficacy of TCZ

The treatment duration of TCZ in group A was 9.5 months (IQR 3–36) and 11.7 months (IQR 3–24) in group B. All patients were followed up for at least 24 months.

At the 1 year follow-up, there was no significant difference in the proportion of patients who achieved clinical remission, no clinical activity, and clinical activity period in both group A and group B ($p > 0.05$). Three clinical phenotypes were defined as follows: monocyclic ($n = 12$), polycyclic ($n = 14$), and persistent ($n = 51$) course. A comparison of the efficacy of TCZ in patients with three phenotypes revealed significant differences in the outcome; it showed that patients with monocyclic phenotype had the highest clinical response (with no clinical manifestation and normalized inflammation parameter) rate (91.7%, odds ratio = 0, 95% CI: 24–24, $p = 0.00$), followed by the polycyclic (28.6%, odds ratio =2.1, 95% CI: 10.5–18.8, $p = 0.00$) and the persistent course (9.8%, odds ratio =1.2, 95% CI: 9.5–13.8, $p = 0.00$) (**Figure 1**).

A comparison of prognosis among groups was analyzed by survival analysis. All the patients were followed up for 24 months. In the initial stage of TCZ treatment, the three phenotypes of patients had good clinical responses. As time went by, the clinical response of a single course was better than polycyclic and persistent course.

ADVERSE EVENTS

This study represented 67.5 years of TCZ exposure in 77 sJIA patients; adverse events occurred in 21 patients (**Table 3**). Leukopenia was observed in seven patients, including one leukopenia induced by streptococcal infection, two infusion reactions characterized by fever and cold chills, and facial blushing, which occurred during the second infusion of TCZ. This was relieved by discontinuing the infusion and intravenous dexamethasone treatment and did not reoccur during later TCZ infusions. One infusion reaction occurred during the sixth TCZ infusion, presented as fever, chills, and cyanosis, and was also relieved by discontinuing the infusion and intravenous dexamethasone treatment. For this patient, TCZ treatment was terminated. Two patients experienced MAS, one at 3 months and the other at 6 months of tocilizumab treatment. Two patients had continuous active disease during tocilizumab treatment, and MAS was improved after comprehensive treatment instead of TCZ.

DISCUSSION

The treatment of sJIA usually requires NSAIDs, DMARDs, and glucocorticoids (6). It is necessary to use biological agents when it is refractory to glucocorticoids and DMARDs (10, 16). The pathophysiological basis of sJIA is the activation of pro-inflammatory cytokines, especially IL-1β and IL-6 (17, 18). Currently, there are two main biological treatment strategies for sJIA: IL-1 and IL-6 biologic blockade (19, 20). However, in China, IL-1 blockers are still unavailable so that IL-6 blockers are the main biologic treatment for sJIA.

TABLE 2 | Changes in clinical parameters after tocilizumab treatment in children with systemic juvenile idiopathic arthritis.

	Group	Baseline	Week 2	Week 4	Week 12	F	*p*-value
Fever	A	40/41[1]	2/41[a]	4/41	6/41	0.759	0.386
	B	29/36	9/36[a]	5/36	4/36		
Number of active arthritis episodes	A	3.2 ± 3.0[1]	1.1 ± 1.9[a]	0.5 ± 1.0[b]	0.7 ± 1.6	6.395	0.014*
	B	4.4 ± 3.7	2.4 ± 2.4[a]	1.7 ± 2.0[b]	1.1 ± 1.9[c]		
sJADAS-27 score	A	21.7 ± 4.2	6.0 ± 4.9[a]	4.8 ± 5.3	4.9 ± 6.1	3.298	0.73
	B	21.8 ± 5.8	10.4 ± 7.0[a]	7.4 ± 6.4[b]	5.2 ± 5.2[c]		
WBC ($\times 10^9$/L)	A	19.9 ± 10.0	14.6 ± 9.0[a]	13.2 ± 9.1	12.7 ± 10.5	3.652	0.06
	B	15.6 ± 7.1	11.8 ± 5.6[a]	10.2 ± 4.2[b]	10.7 ± 8.0		
ESR (mm/H)	A	91.5 ± 30.6[1]	18.4 ± 20.1[a]	22.3 ± 36.9	26.2 ± 40.0	2.652	0.108
	B	76.8 ± 28.0	21.1 ± 21.8[a]	15.4 ± 23.5	13.3 ± 22.8		
CRP (mg/L)	A	78.4 ± 42.3	13.1 ± 13.1[a]	22.1 ± 32.5	19.1 ± 24.3	0.152	0.698
	B	89.7 ± 33.7	17.8 ± 23.9[a]	14.0 ± 17.6[b]	17.8 ± 28.5		

*Data are presented as mean ± standard deviation, and number and percentages. [1]Comparison between group A and group B at baseline, $p < 0.05$: [a]compared with baseline, $p<0.05$; [b]compared with 2 weeks of treatment, $p < 0.05$; [c]compared with 4 weeks of treatment, $p < 0.05$. *Comparison of the effect of tocilizumab (12 weeks of treatment) in group A and group B, $p < 0.05$. CRP, C-reactive protein; ESR, erythrocyte sedimentation rate; WBC, white blood cell count.*

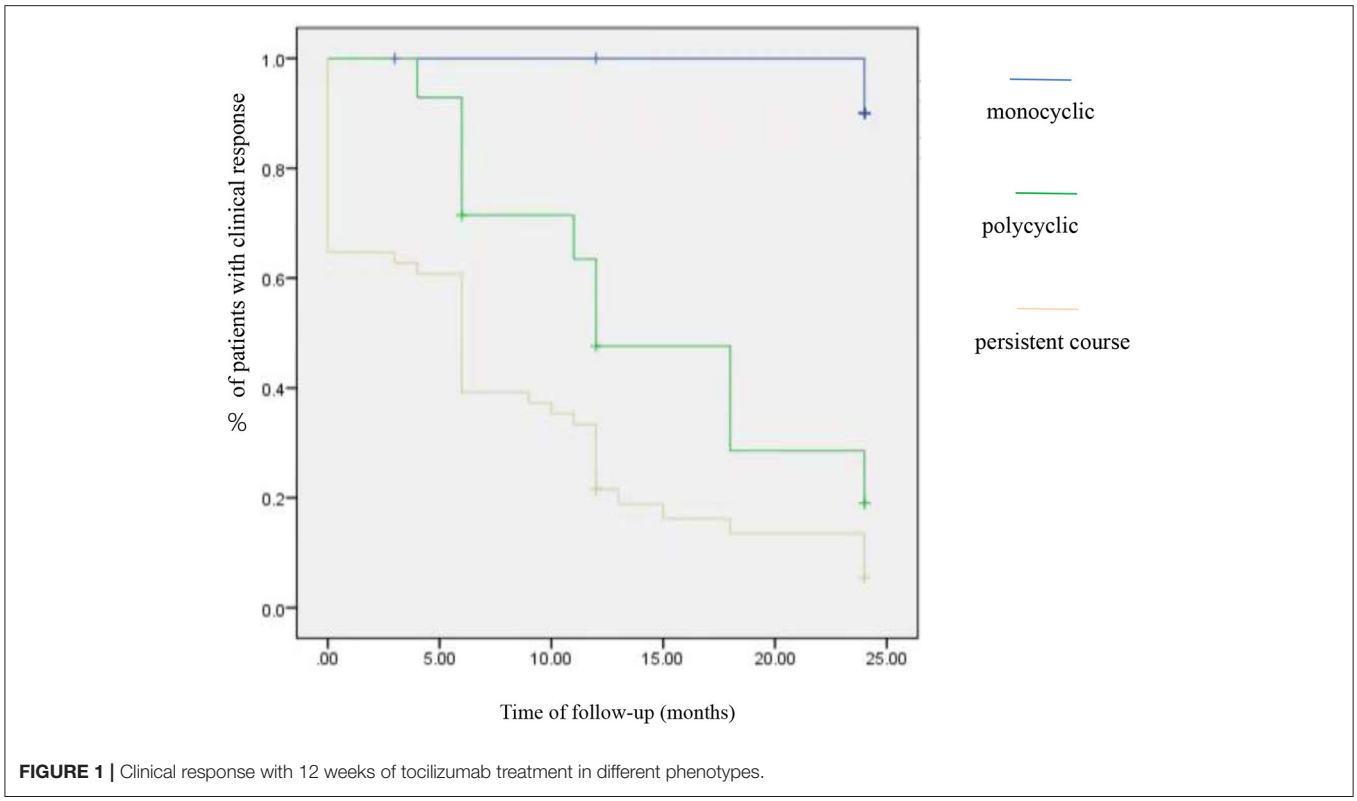

FIGURE 1 | Clinical response with 12 weeks of tocilizumab treatment in different phenotypes.

In our study, we found that fever, active arthritis, sJADAS-27 score, white blood cell count, ESR, and CRP can be relieved after 2 weeks of TCZ treatment. TCZ has significant short-term efficacy for sJIA. Furthermore, we observed sJIA patients with TCZ administration in early stage and found that it had better remission of active arthritis than those administrated in the late stage after 12 weeks of treatment. TCZ can quickly relieve fever and inflammation (indicated by decreased CRP and ESR) (21–24), especially for patients showing less active arthritis in the early stage. Doaa et al. (25) identified that younger patients with shorter disease duration and greater systemic manifestations showed more favorable outcomes by TCZ therapy. These observations are consistent with the window of opportunity hypothesis, which suggests that IL-6 blockade may be more effective in early sJIA, when the disease is characterized by more prominent systemic presentation and less active arthritis (26). Likewise, Alexeeva et al. (27) found that only earlier age

TABLE 3 | Adverse events in patients receiving tocilizumab.

Adverse event	Number
Leukopenia	7
Elevated transaminases	5
Infusion reaction	3
Pneumonia, pulmonary consolidation	2
Septicemia	1
Streptococcal infection	1
Macrophage activation syndrome	2

at initiation of TCZ therapy was a statistically significant factor associated with reaching the best response to therapy in polyarticular JIA.

The course of sJIA varies and is divided into three phenotypes (7). In this study, sJIA was classified as monocyclic (n = 12, 15.6%), polycyclic (n = 14, 18.2%), and persistent course (n = 51, 66.2%). Bielak et al. (28) defined three phenotypes of sJIA: monocyclic, polycyclic, and polyarticular disease, which occurs as arthritis flares in >4 joints. Systemic inflammation, such as fever, elevated CRP, and ESR, is not more prominent in patients with multi-joint sJIA than single-joint sJIA, and systemic inflammation gradually evolves into an autoimmune disease phenotype (24, 29). The heterogeneity of sJIA contributes to the differences. Bielak et al. found that polycyclic and monocyclic sJIA responded better to tocilizumab than polyarticular sJIA. In our study, the clinical response was worst in patients with persistent course and the best in monocyclic. A previous study indicated that IL-1 inhibitors may be useful if patients do not respond to TCZ. sJIA with persistent course often show polyarticular JIA, and in these patients, TCZ is effective for fever and inflammation, but not for polyarthritis. Therefore, sJIA with persistent course who do not respond to TCZ may need an IL-1 antagonist or a TNF-a monoclonal antibody (30). To obtain optimal therapeutic responses, it is necessary to predict the disease phenotype of sJIA at an early stage. Singh-Grewal et al. (7) proposed that the clinical features observed at 3 months (the presence of active arthritis and fever) and 6 months (elevated ESR > 26 mm/H requiring corticosteroid treatment) are accurate predictors of a patient's disease course. This information helps identify patient's risk of developing into persistent disease and having a higher likelihood of a poor functional outcome, which need timely therapeutic intervention to prevent from joint damage and disability. Therefore, early TCZ treatment is recommended for such patients with early predictions that may be persistent courses.

The most common adverse effect observed in our study was granulocytopenia, which was mild and not accompanied by severe infection. Clinical remission was achieved in six of the seven cases, suggesting that patients who develop granulocytopenia after TCZ treatment may have a greater chance to obtain clinical remission. Neutropenia associated with sJIA is dependent on IL-6 levels, and leukocytopenia and granulocytopenia may be used as biomarkers of susceptibility to treatment with IL-6 monoclonal antibodies (31). There were two cases of MAS, which was not unexpected given that previous studies report that 20% to 25% of patients with sJIA treated with biological agents develop MAS (32). Current research suggests that TCZ does not prevent the occurrence of MAS, and indeed in some patients, TCZ may even trigger this reaction. The specific cause and mechanism are unclear. It is possible that when a patient experiences an obvious episode of active sJIA, TCZ antagonizes IL-6 which could trigger a negative feedback loop, therefore causing amplified and excessive inflammation and inducing MAS. Therefore, the timing of TCZ treatment is a critical factor.

LIMITATION POINTS IN THIS STUDY

In this study, glucocorticoids were standardized to ≤1 mg/kg/day to avoid the effect of high doses, but almost 60%–70% patients enrolled were taken at baseline. In addition, we did not study the beneficial effects of TCZ on glucocorticoid reduction and catch-up growth. Moreover, due to economic conditions, TCZ was not added every 2 weeks strictly, which could have a partial impact on the research results. It was a single-center retrospective study with low number of patients enrolled, so prospective cohort studies and further multicenter clinical studies are needed to shed additional light on this matter and ultimately improve the care of patients with sJIA.

CONCLUSION

We demonstrated that TCZ can quickly relieve fever and inflammation, especially when patients have less active arthritis with shorter disease duration. The long-term efficacy of TCZ is related to the phenotype; therefore, it is necessary to predict the disease phenotype of sJIA at an early stage. These findings may help to define the profile of patients with sJIA who are more likely to benefit from TCZ.

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 authors.

ETHICS STATEMENT

Written informed consent was obtained from the minor(s)' legal guardian/next of kin for the publication of any potentially identifiable images or data included in this article.

AUTHOR CONTRIBUTIONS

XY analyzed the data and wrote the paper. WT and ZZ collected and analyzed the data. YZ and CL collected the patients. XT

ideated the study and revised the paper. All authors approved the final version of the manuscript.

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BRIEF RESEARCH REPORT
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The Safety and Efficacy of Tofacitinib in 24 Cases of Pediatric Rheumatic Diseases: Single Centre Experience

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JAK-inhibitors are small molecules blocking the JAK-STAT pathway that have proven effective in the treatment of different immune-mediated diseases in adults and juvenile idiopathic arthritis (JIA).

Aim of Study: To evaluate the safety and efficacy of tofacitinib in children with different rheumatic diseases.

Material and Methods: We extracted information from 24 children with the following diagnosis: JIA ($n = 15$), undifferentiated systemic autoinflammatory diseases (SAIDs) ($n = 7$), and juvenile dermatomyositis (JDM) ($n = 2$) who have been treated with tofacitinib for a period of longer than 6 months. The treatment outcomes were classified according to the opinion of the attending physicians as having a complete response (CR), i.e., the absence of disease activity, or a partial response (PR)—a significant improvement of symptoms and disease activity, or no response (NR)—no changes in disease activity.

Results: CR was achieved in 10/24 patients; 7/15 among JIA patients, 1/2 among JDM patients, 4/7 among SAID patients, and PR in 5/15 of JIA, 1/2 of JDM, and 3/7 of SAID patients. Three non-responders with JIA discontinued tofacitinib. Corticosteroids were successfully tapered off in 11/14 patients and discontinued in 2/14 patients. Four patients had side effects not requiring treatment discontinuation: liver enzyme elevation ($n = 2$), hypercholesterolemia ($n = 1$), lymphadenitis ($n = 1$).

Conclusion: JAK-inhibitors are effective new therapies for the treatment of multiple immune-mediated diseases. Our experience has shown the best results in patients with JIA and JIA-associated alopecia, and type I interferonopathies. More data from randomized controlled clinical trials are needed to use JAK-inhibitors safely in pediatric rheumatic diseases.

Keywords: juvenile idiopathic arthritis, juvenile dermatomyositis, tofacitinib, JAK-inhibitors, interferonopathy, interferon type-I, alopecia

INTRODUCTION

A JAK-STAT signaling pathway is involved in the regulation of cell proliferation and differentiation, apoptosis, and immune signaling (1). Dysregulation in the JAK-STAT pathway has been implicated in the pathogenesis of a number of diseases: infections and sepsis, chronic arthritis, inflammatory bowel disease, multiple sclerosis, tumors, and others (2, 3). Therapies targeting the JAK-STAT pathway have been promising in the treatment of various immunological and inflammatory conditions (3). The success of the use of kinases-blockers in oncology (4) has paved the way for the use of JAK-inhibitors in rheumatic diseases, especially in rheumatoid arthritis: ruxolitinib (5), tofacitinib (6) and baricitinib (7). Food and Drug Administration (FDA) has approved tofacitinib for the treatment of rheumatoid arthritis (8), psoriatic arthritis, ulcerative colitis, and since 2020 for polyarticular juvenile idiopathic arthritis[1] There are data from RCT in JIA available (9). Clinical trials of JAK-inhibitors for systemic lupus erythematosus, dermatomyositis, alopecia areata, atopic dermatitis, Crohn's disease, and uveitis are still ongoing (10). The indications of JAK-inhibitors for pediatric rheumatic diseases other than juvenile idiopathic arthritis, the optimal dosage, and safety have not been fully evaluated and recommendations are still pending.

PATIENTS AND METHODS

Ethics

The Ethic Committee of Saint-Petersburg Sate Pediatric Medical University approved the study (protocol # 1/3 or 11.01.2021). Written consent of legal representatives for inclusion of the data and using of the pictures was obtained.

Attending physicians who participated in patients' treatment and evaluations are all pediatric rheumatologists with over 10 years of experience in this field.

Patient Recruitment

The clinical and laboratory data from 24 children, who had been treated with tofacitinib for longer than 6 months were included in this retrospective case series study. Patients were divided into three groups: juvenile idiopathic arthritis (JIA), juvenile dermatomyositis (JDM), and undifferentiated systemic autoinflammatory diseases (SAIDs). Indications for tofacitinib were persistently high disease activity despite the treatment with corticosteroids and/or biologics treatment in most cases. In JIA patients the disease activity was assessed with calculation of JADAS-71 (11). Whole exome sequence (WES) and an interferon signature score were performed in 14/24 children (all children with systemic autoinflammatory disease ($n = 7$), children with JDM ($n = 2$) and sJIA ($n = 4$), and one with polyarticular JIA (multiple autoimmune features). An IFN-signature was measured by real-time PCR quantitation of five IFN I-regulated transcripts (*IFI44, IFI44L, IFIT3, LY6E, MX1*); median expression of ≥ 2 units was considered as a threshold. The treatment outcome was classified according to the opinion of the attending physicians as having a complete response (CR) i.e., the absence of disease activity (for JIA as defined by Wallace criteria) (12), or a partial response (PR)—a significant improvement of symptoms and disease activity (at least 50% improvement in active joints, ESR (erythrocyte sedimentation rate), CRP (C-reactive protein), VAS (visual analog scale) for JIA; improvement in muscle strength, skin rashes, and normalization of the muscle enzymes, ESR, CRP for JDM; a decrease in the number, duration and intensity of fever and rash episodes, improvement of CRP, ESR at least on 50%), or no response (NR)—no changes in disease activity.

Statistics

Statistical analysis was performed with the software STATISTICA, version 10.0 (StatSoft Inc., USA). All continuous variables were checked by the Kolmogorov-Smirnov test, with no normal distribution identified. Continuous variables are presented as median and interquartile ranges (IQRs). Categorical variables are presented as proportions. Missing data were not imputed or included in the analyses. A comparison of two dependent quantitative variables was carried out using the Wilcoxon test. $P < 0.05$ was considered statistically significant.

RESULTS

The safety and efficacy of treatment with tofacitinib were analyzed in three separate groups: JIA, JDM and SAIDs.

Juvenile Idiopathic Arthritis

The main indications for tofacitinib were inefficacy of previous biologic treatment (etanercept, adalimumab, abatacept, tocilizumab, canakinumab), presence of alopecia, and a strong desire of parents and patients to treat alopecia due to psychosocial distress. The data about baseline characteristics on 15 patients with JIA and changes in their disease activity during tofacitinib treatment are shown in **Tables 1**, **2**.

Patient Characteristics

Patients had moderate-severe JIA; the JADAS-71 ranged from 4.5 to 27.7, most of the patients had JADAS-711 > 0 (63.6%). The number of preceding biologics were: four biologics in 3 patients (20%), three biologics in 8 (53.3%), two biologics in 1 (6.7%), one biologic in 2 (13.3%) **Table 2**. Two patients were receiving a combination of tofacitinib and methotrexate. Corticosteroid dose was successfully tapered. Four patients received a combined treatment of tofacitinib with biologics: two sJIA with canakinumab and two patients (one systemic and one polyarticular) with tocilizumab. In patient 1 and patient 13, the previous treatment with tocilizumab and tofacitinib alone was ineffective, and after adding tofacitinib to tocilizumab, patients had a better outcome compared to the previous treatment arms. After achieving the remission in patient 13, the interval between tocilizumab was extended to 6 weeks, and tofacitinib dose decreased from 10 mg two times a day (BID) to 5 mg BID. In two sJIA patients (patient 14 and patient 15) tofacitinib was added to canakinumab due to the relapse of macrophage activation syndrome and the inability to taper corticosteroids.

[1]https://www.accessdata.fda.gov/drugsatfda_docs/label/2020/203214s026lbl.pdf

TABLE 1 | JIA patients: baseline characteristics and clinical course.

JIA baseline characteristics	Results		
Sex: girls/boys, n (%)	12 (80) / 3 (20)		
JIA onset age, years, median (IQR)	4.0 (2.9; 7.1).		
Uveitis, n (%)	2 (13.3)		
Rheumatoid factor positivity, n (%)	2 (13.3)		
Disease duration, years, median (IQR)	6.8 (3.7; 11.8)		
Time to tofacitinib, years, median (IQR)	6.0 (1.9; 10.2)		
Age of tofacitinib initiation, years, median (IQR)	12.0 (8.5; 14.5)		
Duration of tofacitinib treatment, years, median (IQR)	1.9 (0.8; 3.2)		
JIA characteristics	Before tofacitinib	Last visit	*p*
Active joints, median (IQR)	3.0 (1.0; 8.0)	0.0 (0.0; 4.0)	0.013
CRP, mg/l, median (IQR)	0.0 (0.0; 6.2)	0.0 (0.0; 0.0)	0.069
ESR, mm/h, median (IQR)	2.0 (0.0; 1.0)	1.0 (0.0; 0.0)	0.069
PGA-VAS, cm, median (IQR)	4.6 (4.1; 5.2)	1.3 (0.0; 3.9)	0.008
VAS physician, cm, median (IQR)	3.1 (1.8; 3.2)	0.5 (0.0; 2.1)	0.003
JADAS-71	15.0 (8.2; 17.2)	1.3 (0.0; 8.3)	0.003
Corticosteroid treatment, n (%)	5 (33)	4 (26.7)	0.109
Corticosteroids, mg/kg, median (IQR)	0.25 (0.11; 0.5)	0.05 (0.00; 0.35)	0.003

JIA, juvenile idiopathic arthritis; cm, centimeters, CRP, C-reactive protein; ESR, erythrocyte sedimentation rate; IQR, interquartile range; Me, median, PGA-VAS, patient global assessment visual analog scale; JADAS-71, juvenile arthritis disease activity score.

In all sJIA patients, clinical whole exome sequencing (WES) did not revealed known gene variants associated with auto-inflammatory conditions.

Treatment Outcomes

Seven patients (46.7%) achieved complete response (remission according to Wallace criteria), 5 patients (33.3%) had improvement (PR), and 3 (20%) patients were non-responders (NR), and tofacitinib was subsequently discontinued. Twelve patients have continued on tofacitinib. Patient 7 had a partial response, and tofacitinib was switched for an IL-17 inhibitor secukinumab.

Juvenile Idiopathic Arthritis With Total Alopecia

We identified three JIA patients with total alopecia. All patients had autoimmune thyroiditis; however, thyroxine replacement therapy did not influence alopecia, neither did the long-term use of topical corticosteroids.

Patient JIA2 has had severe RF (+) polyarthritis, alopecia subtotalis (**Figure 1A**), a single uveitis episode, autoimmune thyroiditis, and interstitial lung disease (**Figure 1B**). Her RF was more than 7,700 IU/ml (n.v. <20 IU/ml). She did not achieve remission on etanercept, adalimumab, abatacept, tocilizumab and required treatment with corticosteroids. Her alopecia was steroid-dependent. After the tofacitinib treatment with 1.25 mg of prednisolone every other day her arthritis has been under control. She has had a complete resolution of lung disease (**Figure 1C**) on a chest CT scan, and she has had remarkable hair growth (**Figure 1D**). Clinical exome sequencing detected one rare variant of unknown clinical significance (VUS) *IL1RN:* NM_173841: c.10G>C; p.A4P and a likely benign variant in the *MEFV* gene*: NM_000243.3:* c.1105C>T; p.P369S.

Patient JIA4 has had RF-negative polyarthritis since the age of 4 years and developed alopecia areata at the age of 13 following 5 years of treatment with etanercept and methotrexate. She did not respond to scalp steroid injection, she had persistent arthritis, and tofacitinib was initiated after excluding lupus-like syndrome. She required an increased dose of tofacitinib from 5 mg two times every day (BID) to 5 mg three times every day (TID).

Patient JIA10 had oligoarthritis and alopecia areata since the age of 4 years. After 4 years of remission and methotrexate discontinuation, she presented with arthritis flare, developed alopecia totalis, and autoimmune thyroiditis, and both conditions were steroid-dependent (**Figure 1E**). Treatment with tofacitinib 5 mg BID was started to limit her alopecia and arthritis with complete resolution of both conditions (**Figure 1F**).

Juvenile Dermatomyositis

In this cohort of patients, we identified only two cases with juvenile dermatomyositis (JDM). Patient JDM1 is an 8-year-old girl who presented with severe muscle (CMAS=10) and skin involvement. She was treated with methylprednisolone pulse therapy, intravenous immunoglobulin, prednisone 2mg/kg, and methotrexate 15 mg/m^2/week. Her muscle strength has completely recovered in 3 months, but her skin rash deteriorated on steroid tapering. Mycophenolic acid, followed by methotrexate and topical agents were used without efficacy. Interstitial lung disease was diagnosed on CT 2 years after the disease onset (**Figure 1G**). Tofacitinib was initiated 2 years after the disease onset. Her facial erythema improved however, Gottrone's papules did not disappear. Ground glass opacities disappeared (**Figure 1H**). Therapy with tofacitinib allowed for tapering prednisone to 0.1 mg/kg. Her IFN-scores before tofacitinib and one year after the treatment were 33.75 U and 10.25 U (nv <2 U), respectively. Whole exome sequence detected a non-sense variant in the Leukocyte Tyrosine Kinase (*LTK)* gene: NM_002344.6: c.1393_1394del; p.P465* (rs780209477) inherited from her asymptomatic father, and VUS in the *IL21R* gene NM_181078.3: c.128A>C; p.H43P (rs757749249) inherited from her asymptomatic mother. Also, a rare VUS in *PTPN5:* NM_032781: c.1216G>A; p.E406K (rs139371305) was identified.

Patient JDM2 is a 6-year-old girl who has had JDM for 2 years presenting with muscle weakness, heliotrope rash, Gottron papules, livedo reticularis, and necrotizing skin changes above the knees, elbows, clavicula and in bilateral axillae (**Figures 1I,J**). Tofacitinib was initiated after one year from the disease onset with complete resolution of all symptoms (**Figures 1K,L**). Her IFN-scores before and 6 months after the treatment with tofacitinib were 10.8 U and 1.2 U (nv < 2 U), respectively. Clinical exome sequence revealed a rare VUS in the *NLRP12* gene: NM_144687:c.154G>A; p.G52S (rs369053968).

TABLE 2 | Treatment modalities in patients with juvenile idiopathic arthritis.

#	Sex/age of TOF initiation (years)	JIA subtype	Previous treatment	Current treatment	TOF dosage, mg/kg	TOF duration, mo	Efficacy
1	F/14	Poly	MTX, ETA, TCZ, ADA	TOF, TCZ	0.27	22	PR
2	F/9	Poly (RF+) alopecia	CS, ETA, ABC, TCZ, ADA	ICS, TOF	0.3	37	CR
3	F/14	Poly	MTX, ABC, ETA	TOF	0.25	38	CR
4	F/16	Poly alopecia	MTX, ETA	TOF	0.15	31	CR
5	F/17	Poly	MTX, INX, ETA, ADA, TCZ	TOF	0.2	24	PR
6	F/14	ERA	MTX, ETA, ADA, TOF	SEC	0.25	21	PR
7	F/17	Poly	MTX, ADA, TCZ, ETA	TOF	0.15	39	CR
8	M/8	Poly	MTX, ADA, TCZ, TOF	GOL	0.25	6	NR
9	F/10	Poly (RF+)	MTX, CsA, TCZ, ETA, ABC	TOF	0,4	8	CR
10	F/11	Oligo alopecia	ICS, MTX	TOF	0.25	8	CR
11	F/8	Poly	ETA, TCZ, ADA	MTX, TOF	0.5	11	PR
12	F/15	Systemic	hCS, MTX, TCZ, CAN, ETA, TOF	ICS, RTX	0.5	38	NR
13	M/10	Systemic	hCS, TCZ, ABC, CAN, ETA	TOF, TCZ	0.4	23	PR
14	F/12	Systemic	hCS, MTX, CsA, ANA, TCZ, CAN	TOF, CAN	0.25	10	CR
15	M/4	Systemic	hCS, CAN, TOC	ICS, TOF,CAN	0.5	6	PR

ABC, abatacept, ADA, adalimumab, ANA, anakinra, CR, complete response, CS, glucocorticosteroids (h-high dose, l-low dose), ERA, enthesitis-related arthritis, ETA, etanercept, GOL, golimumab, INX, infliximab, JIA, juvenile idiopathic arthritis, MTX, methotrexate, NR, no response, poly, polyarthritis, PR, partial response, RF, rheumatoid factor, RTX, rituximab, SEC, Secucinumab, TCZ, tocilizumab, TOF, tofacitinib.

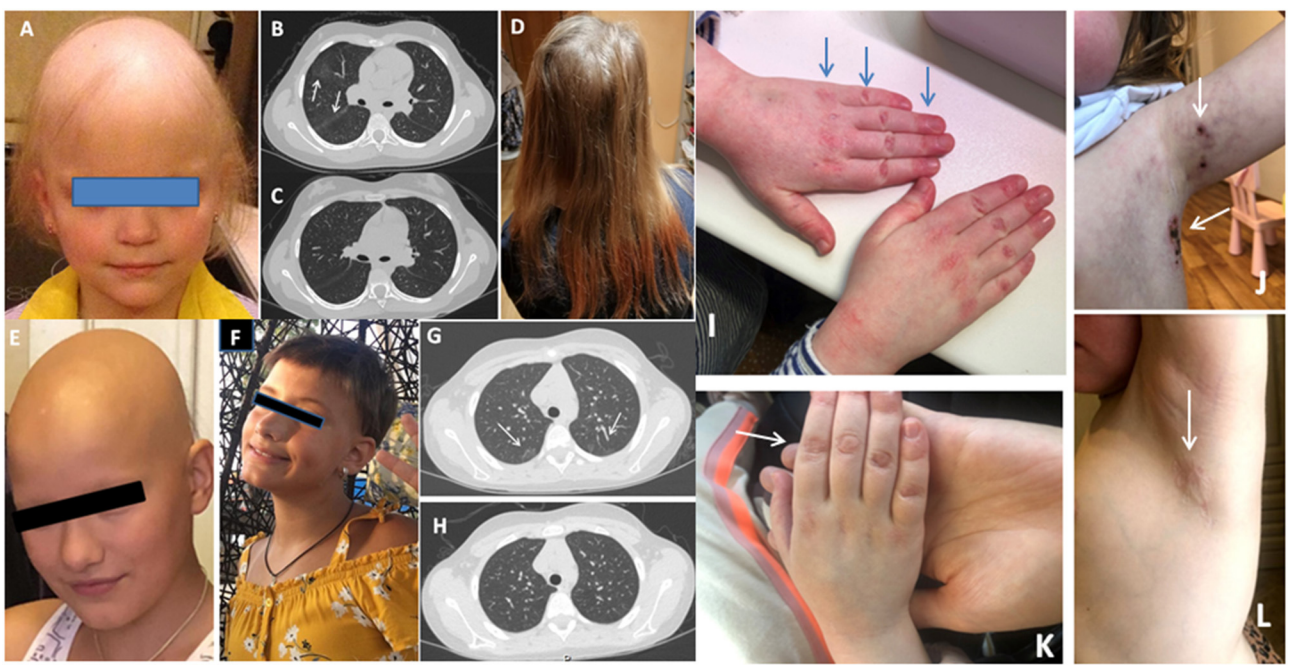

FIGURE 1 | (A) Alopecia in JIA2 patient (before tofacitinib); **(B)** Chest CT from patient JIA2 (interstitial thickness and ground-glass opacities - arrows); **(C)** Chest CT from patient JIA2 following 3 years of tofacitinib therapy (resolution of interstitial thickness and ground glass opacities); **(D)** Hair growth in JIA2 patient (3years on tofacitinib); **(E)** Alopecia in patient JIA10 before tofacitinib treatment and after 6 months of treatment **(F)**; **(G)** Ground-glass opacities in patient JDM1 before tofacitinib (arrows) and 2 years on tofacitinib **(H)**; **(I)** The hands with Gottron papules before tofacitinib treatment in JDM2 patient and the left axillary area (arrows) with necrotizing changes **(J)**; **(K)** the right hand 16 weeks after tofacitinib treatment and the left axillary area **(L)** after 6 months of tofacitinib treatment of the same patient.

No variants in interferon-pathway related genes were identified. In both cases, tofacitinib allowed for tapering steroids and improved the disease's course.

Systemic Autoinflammatory Diseases

Tofacitinib was prescribed to patients with autoinflammatory diseases in the following cases: i) patient has a genetically

TABLE 3 | The clinical characteristics and genetic findings in patients with SAIDs.

#	Sex/age of TOF onset	Symptoms	Previous treatment	Current treatment	Duration	Efficacy	Rare DNA variants
1	F/13	Severe inflammation, aortitis, colitis (Crohn's like), phlebitis	INX, TCZ, ADA	CS (0.1 mg/kg), TOF (0.5 mg/kg)	12	CR	*NOD2*;NM_022162: c.2578G>A; p.Ala860Thr; *NOD2*;NM_022162: c.2722G>C; p.Gly908Arg
2	F/7	Skin rash, recurrent inflammation, failure to thrive	CAN, TCZ	CS (0.1 mg/kg); TOF (0.5 mg/kg); CAN	38	PR (Episodes of fever)	None detected
3	F/15	CANDLE-like interferonopathy	ETA, RTX, CAN	CS (0.15 mg/kg); TOF (0.5 mg/kg)	43	CR	*PSMD5;* NM_005047.3: A splice-region variant
4	F/17	Systemic inflammation, nodular erythema, panniculitis, sialadenitis, hepatitis, headaches, growth failure. High IFN-score before tofacitinib initiation	AZA, MMF	CS (0.15 mg/kg); TOF (0.5 mg/kg)	10	PR; PR (Fever on prednisone tapering)	*IFIH1;*NM_022168: c.2035_2036del; p.Leu679Ilefs*3 and c.1795delG; p.Val599FLeufs*10
5	F/12	Systemic inflammation, scleroderma/lupus like skin disease, pancytopenia, arthritis	TCZ	CS (0.1 mg/kg); TOF (0.5 mg/kg	21	PR	*STAT3;*NM_139276.2: c.1343A>C; p.Gln448Pro
6	F/9	Systemic inflammation, distal necrosis of finger, livedo, erythema, arthritis	CYC, ETA	CS (0.05 mg/kg); TOF (0.5 mg/kg)	19	CR	None detected
7	F/17	Systemic inflammation, panniculitis, polyneuropathy	hCS, CsA, ETA, IVIG	TCZ, TOF (0.3 mg/kg)	6	PR	*IFIHI;*NM_022168: c.1558A>G; p.Thr520Ala

confirmed interferonopathy or disease likely mediated by STAT-pathway; ii) patient has clinical features of interferonopathy without genetic confirmation (early disease onset, recurrent fever, skin rash, lipoatrophy, neuropathy); iii) previous treatment with other biologics failed, and a literature search suggested the possibility of successful use of JAK-inhibitors. Patients' characteristics are shown in **Table 3**.

Patient SAID1 is a 13-year-old girl from consanguineous marriage (second cousins). She initially presented with features suggestive of Crohn's disease and was successfully treated with corticosteroids, azathioprine, and mesalamine. After 1½ years, she suddenly developed fever, high inflammatory markers, and intensive lumbar pain. CT-angiography revealed severe aortitis, and she was diagnosed with Takayasu arteritis. Increased doses of corticosteroids and infliximab (10 mg/kg) improved her systemic inflammation, but after tapering of steroids to 1 mg/kg, the signs of disease re-appeared. Furthermore, the patient developed claudication and multiple phlebitis, she tested positive for the HLAB51 allele, and Bechet's disease was considered in differential diagnosis, although she did not have oral or genital ulcers. We started adalimumab in the induction regimen, but this treatment failed as well as therapy with tocilizumab followed by canakinumab. Whole-exome sequence revealed two rare variants in *NOD2*, one of which has been associated with susceptibility Crohn's disease (**Table 3**). The patient responded well only to an increased dose of tofacitinib (10 mg BID), while the initial dose5—mg BID was partially effective.

Patient SAID2 presented with clinical features (fever, extensive panniculitis, and severe systemic inflammation) suggesting an interferonopathy, at the age of 6 months. She presented at our clinic at the age 6 years with severe growth delay, failure to thrive, and signs of steroid toxicity (she received high doses of steroids throughout her life). Initial treatment was with canakinumab that was gradually increased from 4 mg/kg to 12 mg/kg (150 mg per injection every 4 weeks) with partial response; however, it allowed tapering methylprednisolone to 2–4 mg/day. Overall, this therapy did not suppress her disease activity. Initially, tofacitinib was not available but after 2 years and exacerbation of her symptoms on canakinumab, we added tofacitinib. The patient still had an active disease on 5 mg BID, while her symptoms were ameliorated on 5 mg TID without need to increase steroids. Her clinical WES did not reveal any pathogenic or likely pathogenic variants.

Patient SAID3 had a classical feature of interferonopathy, a CANDLE-like phenotype, with early disease onset, failure to thrive, recurrent fever, short stature, peripheral lipoatrophy, hepatomegaly, erythematosus, livedoid and nodular skin rash with ≪punched scars≫ formation, and necrotizing vasculitis. Before tofacitinib, she failed therapy with etanercept, rituximab, and canakinumab. She developed ischemic lesions with gangrene, severe Cushing's syndrome, dysmorphic features, panniculitis, and hepatosplenomegaly. On tofacitinib, she has had impressive clinical improvement, corticosteroids were tapered off to 0.15 mg/kg, and she additionally received IVIG for control of vasculitis. Her disease flared following COVID-19 infection. We increased the dose of tofacitinib from 5 mg BID to 10 mg BID with monthly IVIG. Her WES identified a novel putative splice site variant in the *PSMD5* gene that warrants further

investigation. PSMD5 is a non-ATPase regulatory subunit that promotes 26S proteasome assembly (13).

Patient SAID4 had clinical features suggestive of interferonopathy: fever, inflammation, panniculitis, sialadenitis, nodular rash, hepatitis, migraine headaches, and growth failure. Her IFN-score was 11.25 U (nv <2 U) before tofacitinib initiation. Her previous treatment with corticosteroids and azathioprine or mycophenolate mofetil was ineffective, and she required high doses of corticosteroids. Treatment with tofacitinib for 3 months only partially controlled her disease (no fever flares, and rash) and allowed tapering corticosteroids to 0.15 mg/kg. Unfortunately, following tapering, her disease flared with highly increased CRP. Her IFN-score was still high at 6 months after the tofacitinib initiation (IFN-score 11.3). She was found to be a carrier for compound-heterozygous loss of function mutations in the *IFIH1* gene, encoding a cytoplasmic viral RNA receptor MDA5 that activates type I interferon signaling. The presence of both variants has been confirmed by Sanger sequencing. Pathogenic variants in this gene have been associated with Aicardi-Goutières syndrome-7 (AGS7) (14).

Patient SAID5 (female, 12 years) presented with scleroderma/lupus like disease (facial features, skin thickness), accompanied with fever, livedoid rash, impressive lymphadenopathy, pleuritis, pancytopenia, increased CRP>200 mg/l (nv<5). Initial treatment with steroids and tocilizumab was partially effective. Following a switch to tofacitinib, her disease was under control, and corticosteroids were given at a minimal dose, 0.1 mg/kg. Tofacitinib was used initially in the doses of 5 mg BID, but her dose was increased to 15 mg/day due to persistent moderate activity, which led to control of her disease activity. She was found to carry a novel VUS variant in *STAT3* NM_139276.2: c.1343A>C; p.Q448P. Heterozygous pathogenic variants in this gene have been associated with hyper IgE syndrome, however this patient did not present with immunodeficiency or eczema.

Patient SAID6 (female, 9 years) presented with features of polyarteritis nodosa (PAN): systemic inflammation, distal tip fingers and tongue necrosis, livedoid rash, erythema nodosum, and arthritis. She was treated with prolonged course of high dose steroids and cyclophosphamide at her local hospital. Deficiency of adenosine deaminase 2 (DADA2) was suspected and she was treated with etanercept for 6 months without efficacy. DADA2 was ruled out as her ADA2 enzymatic level was normal and clinical exome sequencing revealed no ADA2 pathogenic variants. She remained steroid-dependent and switching etanercept to tofacitinib led to complete control of her disease, and corticosteroids were discontinued.

Patient SAID7 is a 16-year-old-girl. She had fever, pancytopenia, petechial rash, hepatomegaly, edema of the lower extremities and systemic inflammation: CRP 201 mg/l, (n.v.<5), ferritin 300,000 ng/ml, (n.v. 13-150), ALT 80 U/l, (n.v. 55) and AST 324 U/l, (n.v. 34). Hematological malignances and autoimmune disorders were ruled out. She was initially treated with pulse methylprednisolone, cyclosporine A in her local hospital. She developed panniculitis nodules in the back, the abdomen and the lower extremities with muscle weakness. Pancytopenia, inflammation had recurred. Biopsy of nodules reveled adipocytes and xanthoma cells and infiltrating lymphocytes. The exudate of nodules contained neutrophils and was sterile. The further treatment with cyclosporine A and etanercept resolved fever and decreased the size and number panniculitis nodules, but cytopenia persisted. Her IFN-score was mildly elevated −5.5 U (nv < 2). Cyclosporine A was stopped. Tofacitinib was started with panniculitis and rash resolving. Due to pancytopenia etanercept was switched for tocilizumab, and 6 months of combined treatment with tofacitinib and tocilizumab resolved all clinical and laboratory manifestations. A rare heterozygous variant in the *IFIH1* gene was identified NM_022168: c.1558A>G; p.T520A (rs145641024), however, current prediction algorithms disagree on the potential impact of this variant on the protein function, and thus this variant is defined as VUS.

Overall Efficacy and Corticosteroid Tapering

Complete response was achieved in 10/24 (41.7%) patients; 5/12 (41.7%) among JIA patients, 1/2 (50%) among JDM patients, 4/7 (57.1%) among SAID patients. Partial response was achieved in 5/15 of JIA (33.3), 1/2 of JDM (50%) and 3/7 (42.9%) of SAID patients. There were three non-responders, both diagnosed with JIA.

During the observation period corticosteroids were successfully tapered in 11/14 (78.6%) patients and median dose of corticosteroids was reduced from 0.25 (0.2; 0.5) to 0.1 (0.05; 0.125) mg/kg (p=0.005) and discontinued in 2/14 (14.3%) patients, who received steroids before tofacitinib.

The median tofacitinib dose in JIA patients was 0.25 (0.2; 0.4) mg/kg, which was lower than in patients with primary interferonopathies (AID and JDM) −0.5 (0.5; 0.5) mg/kg (p=0.003).

Safety

Four patients had side effects not requiring treatment discontinuation: liver enzymes elevation ($n = 2$), hypercholesterolemia ($n = 1$), lymphadenitis ($n = 1$). None has had severe infections, including no cases of new VZV infection were observed during the observation period.

DISCUSSION

JAK-inhibitors are new targeted small molecule based-therapies in pediatric rheumatology. They have shown efficacy in adult rheumatic conditions and are included in clinical guidelines of rheumatoid arthritis (15), psoriatic arthritis (16), ankylosing spondylitis (17). Currently, the experience of JAK-inhibitors in the pediatric population is scarce and limited to a single randomized placebo-controlled study in JIA and several studies in small groups of patients with immune-mediated diseases (18, 19). The largest randomized, double-blind, placebo-controlled withdrawal study of tofacitinib in JIA showed that patients with polyarticular course of JIA treated with tofacitinib have significantly lower rate of disease flare at 44 weeks compared to placebo-group (29% vs 52.9%, p=0.0031). JIA ACR30/50/70 response rates were higher in tofacitinib group (70.8% vs 47.1%,

p=0.003; 66.7% vs 47.1%, p=0.017; 54.2% vs 37.1%, p=0.039) (20). In our group, 5/11 patients with non-systemic JIA had a complete response with 100% improvement in JADAS-71, while only 1 patient with ERA did not respond to tofacitinib and required a change in treatment. The remaining 5/11 patients had a partial response with a median improvement of JADAS-71 at 43.3%. Despite the ongoing disease activity, the treatment with tofacitinib was continued due to improved arthritis course and quality of life and lack of other options for disease control. JAK-inhibitors are recommended in patients with rheumatoid arthritis who don't respond to methotrexate (15, 21), but the place of JAK-inhibitors in the management of JIA has not been yet defined.

Adult-onset Still's disease (AOSD) and systemic JIA (sJIA) are two autoinflammatory diseases with similar clinical presentation and treatment strategies. Interleukin-1 and interleukin-6 cytokines contribute to disease pathogeneses, and anti-IL1 and anti-IL-6 biologics have comparable efficacy in the treatment of these patients (22). JAK-inhibitors block signal transduction downstream of many cytokine receptors, so theoretically they might be more efficacious to control sJIA than classical biologics, especially in the resistant cases (3). Seven of 14 patients (50%) with AOSD achieved complete remission in a Chinese single-center study, whereas partial response was noticed in 6 patients. Four patients discontinued treatment due to partial response or non-response and side effects (23). We have found in the literature only 2 cases of systemic JIA that were treated with JAK-inhibitors. The first is a 13-year-old girl with refractory steroid-dependent disease and six-month treatment with tofacitinib led to the resolution of systemic and articular symptoms and allowed for discontinuation of corticosteroid therapy (24). The second is a 6-year-old girl with fever, polyarthritis and rash who received ruxolitinib for 23 months. Previously, she did not respond to treatment with anakinra, tocilizumab, canakinumab, and infliximab. The efficacy was assessed as partial response, and corticosteroids were reduced from 3 mg/kg to 1 mg/kg on ruxolitinib treatment (25). In this report, we describe our experience with four patients with systemic JIA. Only in 1 case was this treatment ineffective, despite increasing doses up to 10 mg BID, neither this patient responded to previous treatments with multiple biologics. The remaining three patients were receiving combination treatments with biologics (2 patients – tocilizumab and 1 patient canakinumab) showed good clinical and laboratory control of the disease activity. Despite the possibility to block several cytokines, these two patients required combination treatment of tofacitinib with biologics.

The prevalence of alopecia in JIA is scarce. In the Italian cohort of 79 JIA patients one patient (1.3%) had alopecia (26), while in 3,510 patients with alopecia areata JIA was registered in 0.14% of cases (27). Several publications support the evidence of the efficacy of JAK-inhibitors in alopecia treatment. Ying-Xiu Dai et al., reported three cases of alopecia in children successfully treated with tofacitinib (28). In another study, more than 6 months of treatment with tofacitinib improved SALT (Severity of Alopecia Tool) in 9/11 of patients (29). Topical JAK-inhibitors might be another treatment option for alopecia areata. Half of six children with alopecia areata had hair overgrowth on topical JAK-inhibitors treatment (30). In our study, all three patients with JIA and alopecia had impressive hair growth and complete response to therapy regarding their arthritis.

The role of the IFN-I pathway has been reported in the pathogenesis of dermatomyositis. Overexpression of IFN-stimulated genes has been found in the muscle, skin and blood of patients with dermatomyositis. IFN-signature is considered as possible disease activity biomarker and flare predictor (31). Ding and colleges reported successful management of 24/25 children refractory JDM with JAK-inhibitors (18 patients were treated with ruxolitinib and seven patients with tofacitinib). Complete skin rash resolution was achieved in 67% cases, 28% of patients discontinued steroids, and 7/10 patients with decreased muscle strength had improved CMAS score (18). The prospective, open-label clinical trial of tofacitinib in 10 adults with refractory dermatomyositis demonstrated efficacy of JAK-inhibitors in all patients (32).

In our study, two patients with JDM had elevated IFN-score before tofacitinib. Patient JDM1 had a partial skin response without normalization of her IFN-score. Patient JDM2 had complete muscle and skin response with normalization of IFN-score level. The role of IFN-score and JAK-inhibitors in the management of JDM has not been defined, and further investigations are required.

Type I interferonopathy comprises autoinflammatory syndromes characterized by activation of type I interferon signaling. To date, there are more than 20 monogenic types of interferonopathies (33). Clinical classification criteria have been recently developed for interferonopathies, helping to select candidates for genetic testing (34). Baricitinib has been studied in patients with CANDLE ($n = 10$), SAVI ($n = 4$), and undifferentiated interferonopathy ($n = 4$). The remission was achieved in half the patients with CANDLE, but primary response measured by disease-specific daily score and corticosteroid response was reached in 12/18 and 10/14 of patients (19). The efficacy of baricitinib has been demonstrated in a case report of CANDLE syndrome (35) and several cases of SAVI, however to a lesser degree (36, 37). In case series including patients with Aicardi-Goutieres syndrome, which carry mutations in the *IFIH1* gene, the efficacy of JAK-inhibitors in ameliorating skin and systemic manifestations have been reported (38, 39).

The last review of P.G. Gomez-Arias and colleagues, including 24 patients with type I interferonopathies showed that JAK-inhibitors improved clinical symptoms and decreased the number of flares and inflammatory markers (40). Besides, an open-label study of baricitinib (LY3009104) in adult and pediatric Japanese participants with NNS/CANDLE, SAVI, and AGS is ongoing[2].

Adverse events were observed in 153/225 (68%) children with JIA receiving tofacitinib, while serious adverse events were registered in seven patients. Discontinuations due to adverse events required 26 patients to discontinue this treatment in 26 (11.6%) (9).

Short half-life (3 hours) of JAK inhibitors compared to biologics with a longer half-life time, might be an additional

[2]https://clinicaltrials.gov/ct2/show/NCT04517253

benefit for children in preventing susceptibility to infections. In case of infection, the discontinuation of tofacitinib leads to rapid wash-out of medication from the blood (41). Other benefits for children who are destined for life-long therapies, include the lack of immunogenicity and oral administration (9, 42). We have to note about potential significant risks of using JAK inhibitors in combination with biologics and about the potential risks of using tofacitinib dose greater than 5mg two times a day.

CONCLUSION

JAK-inhibitors are effective new therapies for the treatment of multiple immune-mediated diseases. Our experience has shown the best outcomes in patients with JIA and JIA-associated alopecia, and type I interferonopathies, compared to JDM, although we had observed only two patients diagnosed with JDM. More data from systematic real world studies are needed to assess the use of JAK-inhibitors safely in pediatric rheumatic diseases.

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.

ETHICS STATEMENT

The study involving human participants was reviewed and approved by the Ethic Committee of Saint-Petersburg State Pediatric Medical University (protocol # 1/3 from 11.01.2021). Written informed consent to participate in this study was provided by the participants' legal guardian/next of kin. Written informed consent was obtained from the minor(s)' legal guardian/next of kin for the publication of any potentially identifiable images or data included in this article.

AUTHOR CONTRIBUTIONS

MK, RR, ES, and IA designed the study and wrote the manuscript. MK, RR, ES, EI, EG, TG, MK, LS, TL, RM, AK, AT, VM, MD, OK, and VC collected and analyzed data. All authors contributed to manuscript revision, read, and approved the submitted version.

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Is Anti-NXP2 Autoantibody a Risk Factor for Calcinosis and Poor Outcome in Juvenile Dermatomyositis Patients? Case Series

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Juvenile dermatomyositis (JDM) has a wide spectrum of clinical presentations. In the last decade, several myositis-specific antibodies have been identified in patients with JDM and connected with specific organ involvement or specific clinical picture. It has been published that the presence of anti-NXP2 autoantibodies presents a risk for calcinosis in patients with JDM. We aimed to investigate the prevalence of calcinosis and response to the treatment in JDM patients with anti-NXP2. In a retrospective, multinational, multicenter study, data on 26 JDM (19 F, 7 M) patients with positive anti-NXP2 were collected. The mean age at disease presentation was 6.5 years (SD 3.7), the median diagnosis delay was 4 months (range 0.5–27 months). Patients were divided into two groups (A and B) based on the presence of calcinosis, which occurred in 42% of anti-NXP2 positive JDM patients (group A). Four patients already had calcinosis at presentation, one developed calcinosis after 4 months, and 6 developed calcinosis later in the disease course (median 2 years, range 0.8–7.8). The differences in laboratory results were not statistically significant between the groups. The mean age at disease presentation (5.2/7.5 years) trended toward being younger in group A. Children with calcinosis were treated with several combinations of drugs. In four cases, rituximab and, in one case, anti-TNF alpha agents were used successfully. Disease outcome (by evaluation of the treating physician) was excellent in four, good in two, stable in two, and poor in three patients. None of the patients from group B had a poor disease outcome. In conclusion, JDM patients with anti-NXP2 are prone to develop calcinosis, especially if they present with the disease early, before 5 years of age. The development

of calcinosis is associated with worse disease outcomes. The combination of several immunomodulatory drugs and biologic drugs can stop calcinosis progression; however, there are no evidence-based therapies for treating calcinosis in JDM patients.

Keywords: juvenile dermatomyositis, anti-NXP2 autoantibodies, disease outcome, treatment, risk factors

INTRODUCTION

Juvenile dermatomyositis (JDM) has a spectrum of clinical presentations, from mild forms of myositis and skin changes with a monocyclic course to very severe forms with vital organ involvement and late complications, including calcinosis and lipodystrophy (1). In the last decade, there has been a development in the determination of myositis specific autoantibodies (MSA) connected with distinct clinical phenotypes of JDM (2). Among different MSA, anti-NXP2 and anti-PM/Scl are most commonly associated with calcinosis in JDM and the adult form of dermatomyositis. In recently published studies, TIF1γ and MDA5 MSA were also risk factors for calcinosis (3, 4). Calcinosis is one of the major complications of JDM and is found in 20–40% of patients (5, 6). It has been published that young age at disease presentation, regardless of MSA, presents a risk for calcinosis in patients with JDM (7). On the contrary, study in 78 patients showed that younger patients had fewer typical findings at diagnosis and a milder disease course with shorter use of corticosteroids and immunosuppression. MSA were not analyzed in this study (8). However, the presence of anti-NXP2 increases the risk of calcinosis across all ages (7). MSA are also associated with disease severity, worse functional status, and persistent disease activity (9).

The study aimed to collect data on JDM patients with positive anti-NXP2 and analyze the risk for calcinosis, response to treatment, and outcome in the group of patients with calcinosis.

METHODS

Study Design and Study Population

The study design was a retrospective multinational, multicenter study on patients with JDM with positive anti-NXP2. The main objective was to study if anti-NXP2 is connected with calcinosis in patients with JDM and the most effective treatment approach in JDM patients with calcinosis.

Data Collection

We contacted pediatric rheumatology centers through international online pediatric rheumatology forums and personal contacts. Nine centers responded (4 from Europe, 4 from USA and 1 from India). Seven centers participated in a study (3 from Europe, 3 from USA and 1 from India). They included all their patients with andi-NXP2.

Patients' data were collected in a shared excel table. Data on gender, race, age at disease onset and age at disease diagnosis, age at inclusion to the study, clinical picture (skin changes, myositis, arthritis, pulmonary and gastrointestinal involvement), muscle function tests, laboratory results, data on treatment and outcome of disease were collected. Laboratory investigations were performed in each participating centre.

Statistical Analysis

The statistical analysis was performed with IBM SPSS (software version 22), using Student's two-tailed *t*-test (equal variances assumed; Levene's test for equality of variances) for continuous variables (independent samples *t*-test for comparison of two groups and paired-samples *t*-test for comparison of variables before and after treatment) and Fischer's exact test for categorical variables. Statistical significance was set at $p < 0.05$.

Parents of included patients signed informed consent and/or Institutional Review Board (IRB) approval was obtained where needed.

RESULTS

The patient's characteristics are presented in **Table 1**.

We collected 26 patients (19 F, 7 M) with JDM and positive anti-NXP2. Fourteen patients were caucasion, eight Asian, three African-American and one Hispanic ethnicity. The mean age at disease presentation was 6.5 years (SD 3.7), the median diagnosis delay was 4 months (range 0.5–27 months). Patients were divided into two groups (A and B) based on the presence of calcinosis. In the disease course, 11 patients (42%), 10 female and 1 male, developed calcinosis (group A). Four patients already had calcinosis at presentation, one developed calcinosis after 4 months, and six developed calcinosis later in the disease course (median 2 years, range 0.8–7.8). Four patients developed lipodystrophy in group A (1 in group B). In group A, three patients developed skin ulcerations (1 in group B), two patients had polyarthritis (1 in group B), two patients had gut involvement (1 in group B), and one patient had lung involvement (2 in group B).

The mean age at disease presentation (5.2/7.5 years) and mean CK level (1,548.6/1,811.6 U/L) trended toward lower levels in group A. The platelet count (306.5/258.4 10^9/L), and mean values of AST (111.4/103.8 U/L), ALT (72.2/50.8 U/L), LDH (1,048.3/808 IU/L), and IgG (11.8/9.9 g/L) trended toward higher levels in in group A. However, the differences were not statistically significant. ANA antibodies were positive in 9/11 in group A and 12/15 in group B. Beside anti-NXP2 other MSA were also found. One patient in group A was positive for anti-MDA5, another patient in group A and in one patient in group B were positive for anti- PM/Scl-100 and one patient in group B was positive for anti-Mi-2beta and anti- SRP. The data on muscle strength measurement (MMT/CMAS) were available only in a few patients.

Treatments used for patients with calcinosis included methotrexate and glucocorticosteroids (GCS) (all patients),

TABLE 1 | Clinical and laboratory characteristics of 26 JDM patients with anti-NXP2 autoantibodies: *p* values comparing Group A and B were non-significant for all variables.

	All	Group A	Group B
Number of patients	26 (19F/7M)	11 (10F/1M)	15 (9F/6M)
Ethnicity	14c, 8as, 3aa, 1h	5c, 4as, 2aa	9c, 4as, 1aa, 1h
Mean age at disease presentation (y)	6.5 (SD 3.7)	5.2 (SD 2.9)	7.5 (SD 3.8)
Age at study inclusion (y)	11.1 (SD 4.6)	11.5 (SD 4.2)	10.8 (SD 4.8)
Median diagnosis delay (mo)	4 (range 0.5–27)	4 (range 0.5–24)	3.6 (range 0.5–27)
Myositis (%)	25 (96)	11 (100)	14 (93)
Gottron's papule (%)	25 (96)	11 (100)	14 (93)
Typical rash (%)	25 (96)	11 (100)	14 (93)
Lipodystrophy (%)	5 (19)	4 (36)	1 (6)
Skin ulcerations (%)	4 (15)	3 (27)	1 (6)
Polyarthritis (%)	3 (11)	2 (18)	1 (6)
Gut involvement (%)	3 (11)	2 (18)	1 (6)
Lung involvement (%)	3 (11)	1 (9)	2 (13)
ESR (mean, mm)	16.9 (SD 12.1)	13.8 (SD 8.9)	19.3 (SD 13.8)
Platelet count (mean,10^9/L)	281 (SD 91.7)	306.5 (SD 85.8)	258.4 (SD 94.7)
CK (mean, U/L)	1,700.3 (SD 2,508)	1,548.6 (SD 2,397.7)	1,811.6 (SD 2,664.9)
AST (mean, U/L)	107.2 (SD 99.4)	111.4 (SD 111.3)	103.8 (SD 93.1)
ALT (mean, U/L)	59.4 (SD 65.2)	72.2 (SD 87.5)	50.8 (SD 46.6)
LDH (mean, U/L)	909.7 (SD 863.2)	1,048.3 (SD 1,037.3)	808.0 (SD 732.1)
IgG (mean, g/L)	10.8 (SD 3.9)	11.8 (SD 3.7)	9.9 (SD 4.1)
ANA (number of positive patients)	21 (80%)	9 (81%)	12 (80%)
MDA-5	1	1	0
PM-SCL100	2	1	1
Mi-2beta	1	0	1
SRP	1	0	1

Group A—patients with calcinosis, Group B—patients without calcinosis.
F, female; M, male; y, year; mo, month; c, Caucasian; as, Asian; aa, African-American; h, Hispanic.

hydroxychloroquine (9), IVIG (7), cyclosporine (4), bisphosphonate (4), MMF (5), rituximab (4), cyclophosphamide (1), abatacept (1) and TNFα blocker (1).

Disease outcome (by evaluation of the treating physician) was excellent in 4, good in 2, stable in 2, and poor in 3 patients. None of the patients from group B had a poor disease outcome. Patients with excellent disease outcomes from group A were treated with GCS and methotrexate (4), hydroxychloroquine (3), IVIG (1), and cyclosporine (1). Out of two patients who had good outcomes, one was treated additionally with MMF, bisphosphonates, and rituximab, and the second was treated with cyclophosphamide and rituximab. One patient with calcinosis at the presentation (age 4 years) was also treated with anti-TNFα therapy, which stopped progression and partially dissolved the calcinosis. After 2 years of anti-TNFα therapy, the calcinosis started to progress, and the treatment was changed to MMF and rituximab, which stopped the progression of calcinosis.

Muscle enzymes and other laboratory parameters were significantly improved in all patients following treatment at the end of observation period (mean observation time 4.2 years) in a whole group of patients. There were no significant differences between the patients with or without calcinosis (**Table 2**). The data for comparison were available for majority of patients (AST 22/26, ALT 21/26, LDH 20/26, CK 22/26). Results of muscle-functional testing were available for only a few patients, so a statistical analysis was not possible.

TABLE 2 | Laboratory results for AST, ALT, LDH and CK before and after treatment in 26 JDM patients with anti-NXP2 autoantibodies.

	Before treatment (mean)	After treatment* (mean)	*p*
AST (mean, U/L)	112.2	33.9	0.003
ALT (mean, U/L)	64.1	29.3	0.045
LDH (mean U/L)	901.7	314.9	0.011
CK (mean (U/L)	1,845.3	194.6	0.006

**At data collection; mean observation time before, at diagnosis, and after treatment is 4.2 years.*
Normal values: AST < 37, ALT < 35, LDH < 245, CK < 185 U/L.

The clinical characteristics, treatment and outcome of patients with calcinosis are presented in **Table 3**.

DISCUSSION

In this study we collected data about the subgroup of JDM patients with anti-NXP2 autoantibodies. To the best of our

TABLE 3 | Clinical characteristics of calcinosis, treatment and outcome of patients with calcinosis.

	Age*/Sex	Time of onset/Description of calcinosis	Therapy	Outcome**
Patient 1	4/F	At disease presentation/2 solitary small nodules- left cubital fossa with lipodystrophy and one in calf muscles, relapses and progression of small nodules at 6 and 9 years after disease onset-arms, neck, legs; severe calcinosis on right side of the neck with lipodystrophy	Pulse MP, Mtx, CsA, HCQ, MMF, pamidronate, IVIG, anti-TNF alpha, rituximab	Stable
Patient 2	8/F	At disease presentation/solitary nodule on thigh, later progressed into diffuse "calcinosis universalis"—multitude of tiny nodules in the subcutis of upper and lower extremities, genital area, elbow extensor surfaces, 1 at the volar surface of the right forearm with exulceration	Pulse MP, Mtx, HCQ, MMF, pamidronate, IVIG, rituximab	Good
Patient 3	2/F	After 4 years and 10 months of disease duration/very discrete, only on tip of 5th finger of the right hand	Pulse MP, Mtx	Excellent
Patient 4	10/F	After 1 year disease duration/dorsum of right thigh, left distal arm (near cubital fossa)	Pulse MP, Mtx, HCQ, IVIG	Excellent
Patient 5	2.4/F	After 10 months of disease duration/ureteral wall (bilaterally, with ureteral stenosis) and left elbow	Pulse MP, Mtx, CsA, HCQ, IVIG	Good
Patient 6	8.7/F	After 2 years of disease duration/lateral part of left thigh and right gluteal region	Pulse MP, Mtx, CsA, CYC, HCQ, rituximab	Excellent
Patient 7	3.7/M	After 7 years and 10 months of disease duration/small nodules on knuckles	Pulse MP, Mtx, HCQ	Excellent
Patient 8	4.2/F	after 2 years and 2 months of disease duration/right gluteal region, left side neck, left scapular region and left elbow	Oral GCS, Mtx, HCQ, MMF, pamidronate	Stable
Patient 9	3.2/F	After 4 months of disease duration/vulvar region, right eyelid, left popliteal region along the tendons, right sacral region, left Achiles tendon, b/l gluteal region, left scapula, superficial plaque like/nodular—along thigh and shin (b/l), left lateral malleoli No new lesions when on IVIG and Pamidronate infusions, new lesions on stopping IVIG and Pamidronate infusions	Oral GSC, Mtx, CsA, MMF, pamidronate, IVIG	Poor
Patient 10	2/F	At disease presentation/upper and lower legs bilaterally, buttocks and upper arms	Pulse MP, Mtx, HCQ, IVIG	Poor
Patient 11	9.5/F	At disease presentation/first as nodules, later became extensive sheets with oozing skin breaches; arms, legs, trunk	Pulse MP, Mtx, HCQ, MMF, IVIG, rituximab, orencia	Poor

M, male; F, female; MP, methylprednisolone; GCS, glucocorticosteroids; mtx, methotrexate; CsA, cyclosporine; HCQ, hydroxychloroquine; MMF, mofetil mycophenolate; IVIG, intravenous immunoglobulins; CYC, cyclophoyphamide.

**Age at disease onset, **Evaluation by the treating rheumatologist, Kendall and CMA available only in few patients.*

knowledge, we present the largest group of JDM patients with anti-NXP2. In the studies published so far, these patients present about 16–20% of all patients with JDM and develop calcinosis in about 40–50% (3, 4). In the published literature, the risk of calcinosis is estimated to be about 25–30% in JDM patients (10, 11). In our study, 42% of JDM patients with anti-NXP2 developed calcinosis. They trended toward being younger at disease presentation than patients with anti-NPX2 that did not develop calcinosis (5.4/7.6 years); however, the difference was not statistically significant, but the case series is small. The mean age at disease presentation for the whole group of anti-NXP2 positive patients was 6.8 years. In a study of the UK JDM cohort in which histological heterogeneity in 101 patients with juvenile idiopathic inflammatory myopathy was studied, the mean age at disease presentation was similar to our cohort-−6.1 years. In this study, 15 patients (16.7%) were positive for anti-NXP2. On muscle biopsy, there was no specific pattern for the subgroup of patients with anti-NXP2 (12). In two other recently published studies on JDM, the mean age at presentation was higher. In the German cohort, the mean age at disease onset was 7 years, and in the Turkish study, 8.1 years (3, 4). In a German cohort, 21% of patients with anti-NXP2 were younger than 5 years of age, and it was found that patients with anti-NXP2 showed the lowest mean ever-recorded CMAS of all MSA subgroups, and almost half of them had CK levels elevated more than triple that of the normal range (4). In our cohort, 11/26 (42%) patients were younger than 5 years of age at disease onset, and in a subgroup of patients that had or developed calcinosis, 7/11 (63%) were younger than 5 years of age. So it can be assumed that the presence of anti-NXP2 in a young patient is a risk factor for worse disease course and worse outcomes. Importantly, delay in diagnosis, as an important determinant of calcinosis development, was not significantly higher in patients with calcinosis. CMAS and Kendall scores were available in only a few cases in our cohort. Many times these tests were not applicable due to the low age at disease onset. In a group with calcinosis, the Kendall test and CMAS test were available before and after treatment (8 years follow up) for only one patient who was 8 years old at disease onset (Kendall 51/71, CMAS 30/49). CK levels in our cohort of patients with calcinosis were triple that of normal range in 5/11 (45%) and 7/15 (46%) among patients without calcinosis. We did not find any significant laboratory characteristics that would discriminate among patients who had or developed calcinosis and those who did not.

The limitation of our case series study is the small number of patients and the lack of JDM patient groups without anti-NXP autoantibodies for comparison. In studies published so far, other MSA were also connected with calcinosis. In a recently published study including 58 JDM patients, 46 patients were tested for MSA; 34 (76%) had autoantibodies (3). The most commonly found autoantibodies were anti-NXP2 in 10 patients (21%), five patients (50%) developed calcinosis. MDA5 autoantibodies were found in 4 patients; 3 patients (75%) developed calcinosis. TIF1γ antibodies were found in 8 patients, four patients (50%) developed calcinosis. Among other patients with other antibodies, only 25% of patients developed calcinosis, and 25% of patients without antibodies developed calcinosis. None of the patients with Mi-2 antibodies developed calcinosis in the long-term follow-up. In a recently published German cohort, 27% of patients had calcinosis (4). Among them, 5/14 (36%) were positive for anti-NXP2, and 5/12 (42%) were positive for antiTIF1γ. So it seems that besides anti-NXP2 other autoantibodies, mainly TIF1γ, could also be connected with calcinosis.

In our cohort, patients were treated with several non-biological and biological DMARDs. We evaluated treatment by comparing the laboratory results of AST, ALT, LDH, and CK before and after treatment (mean observation time was 4.2 years). The mean values of all the parameters, as mentioned earlier, were significantly lower after treatment. However, we could not prove statistically significant differences between values before and after treatment in both subgroups of patients, with calcinosis and without calcinosis, most probably due to small numbers available for analysis. Laboratory results and muscle-function tests were not available in all patients, which is a significant limitation to our study.

A recently published study showed a significant difference in the choice of medications between pediatric rheumatologists (13). However, despite that, a high proportion of patients had the inactive disease at 2 years and had a low frequency of damage. A combination of several drugs can probably stop the progression of the disease. Although the data are very limited in our case series and the outcome of the disease was only evaluated qualitatively by the treating pediatric rheumatologist, it seemed that the most successful drug, in combination with other conventional drugs, was rituximab which was helpful in 4 difficult cases with the progression of calcinosis. Similar reports on successful treatment were also published by other authors (14–16). Recently, advances in the understanding of the immunopathology and genetics in JDM may help to specify new treatment approaches, especially when conventional therapy is not successful. An upregulated type 1 interferon signature is strongly associated with JDM, which could present the possibility for the treatment of most severe cases with JAK inhibitors (17, 18). However, the safety and efficacy of this therapy still need to be studied in clinical trials.

CONCLUSION

In our case series study, 42% of JDM patients with positive anti-NXP2 presented with calcinosis or developed calcinosis during the disease course. Patients with calcinosis trended toward being younger at disease presentation and had a more severe disease course and worse outcome than patients who did not develop calcinosis despite anti-NXP. More than 60% of children who developed calcinosis in disease course were younger than 5 years of age at disease onset. There were no other significant demographical or laboratory signs that would predict the disease course and outcome. So far, there is no evidence-based treatment for calcinosis in JDM; however, the combination of several immunomodulatory and biological drugs may successfully stop the progression of calcinosis. In our study, rituximab was successfully used in stopping the progression of calcinosis in four cases.

Knowing the MSA profile in a patient with JDM is important for treatment decisions early in disease course and can contribute to more aggressive treatment in young patients with anti-NXP2.

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 Slovenian National Medical Ethics Committee. Written informed consent to participate in this study was provided by the participants' legal guardian/next of kin. Written informed consent was obtained from the minor(s)' legal guardian/next of kin for the publication of any potentially identifiable images or data included in this article.

AUTHOR CONTRIBUTIONS

NT and AP drafted the article. All authors contributed patients and participated in the proces of creating the final version of the article.

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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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REVIEW
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New Insights and Challenges Associated With IgA Vasculitis and IgA Vasculitis With Nephritis—Is It Time to Change the Paradigm of the Most Common Systemic Vasculitis in Childhood?

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What are the challenges ahead and how have we responded so far when it comes to the non-granulomatous systemic vasculitis, characterized mainly by deposits of IgA immune complexes in the endothelium of small blood vessels—IgA vasculitis (IgAV)? That is the question to which we tried to answer. We summarized existing knowledge about epidemiology, pathogenesis, genetics, diagnostic tests and therapy in this somewhat neglected entity in pediatric rheumatology. Since etiopathogenesis of IgA vasculitis is complex, with factors other than galactose-deficient IgA_1-containing immune complexes also being important, and may involve numerous interactions between environmental and genetic factors, genomics alone cannot explain the entirety of the risk for the disease. The incidence of IgAV and nephritis varies worldwide and may be a consequence of overlapping genetic and environmental factors. In addition to the role of the HLA class II genes, some studies have pointed to the importance of non-HLA genes, and modern geostatistical research has also indicated a geospatial risk distribution, which may suggest the strong influence of different environmental factors such as climate, pathogen load, and dietary factors. The application of modern geostatistical methods until recently was completely unknown in the study of this disease, but thanks to the latest results it has been shown that they can help us a lot in understanding epidemiology and serve as a guide in generating new hypotheses considering possible environmental risk factors and identification of potential genetic or epigenetic diversity. There is increasing evidence that an integrative approach should be included in the understanding of IgA vasculitis, in terms of the integration of genomics, proteomics, transcriptomics, and epigenetics. This approach could result in the discovery of new pathways important for finding biomarkers that could stratify patients according to the risk of complications, without an invasive kidney biopsy which is still the gold standard to confirm a diagnosis of nephritis, even if biopsy findings interpretation is not uniform in clinical practice. Ultimately, this will allow the development of new therapeutic approaches, especially important in the treatment of nephritis, for which there is still no standardized treatment.

Keywords: IgA vasculitis, IgA vasculitis nephritis, epidemiology, pathogenesis, clinical presentations, diagnostics, disease activity, treatment

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INTRODUCTION

IgA vasculitis (IgAV) is a non-granulomatous systemic vasculitis, histologically characterized by infiltration of the walls of the blood vessels, mainly arterioles, capillaries and venules, by neutrophils with deposits of immune complexes containing predominantly IgA (1–4). The endothelium of small blood vessels in the skin, synovial membrane, gut, and kidneys is usually involved (2).

Even though IgAV is the most common form of vasculitis in childhood (5), it is somewhat neglected in pediatric rheumatology, as it is mostly perceived as a self-limited disease lasting up to 4 weeks, with care for these patients scattered between nephrologists, rheumatologists, dermatologists, and gastroenterologists (6).

It is important to keep in mind that despite the favorable prognosis for most pediatric patients, various acute and chronic complications are possible (7, 8). Among the acute complications of IgAV, the most frequent are those related to the gastrointestinal system, including bleeding, intussusception, and bowel perforation as the most serious ones (9). The most important chronic complication and the main cause of morbidity and mortality among children suffering from IgAV is the renal aspect of the disease (IgAV nephritis, IgAVN), which therefore represents the main prognostic factor (8). IgAVN occurs in 20–60% of children suffering from IgAV, and among them chronic renal failure has been reported in 1–15% (10–14).

We will try to show how new insights has been gained regarding this disease, including epidemiology, pathogenesis, genetics, diagnostic trials, and therapy, as well as to point out the fact that many questions and dilemmas concerning IgAV remain unanswered.

NEW INSIGHTS IN THE EPIDEMIOLOGY OF IgAV

It is known that the incidence of IgAV varies worldwide ranging from 3 to 55.9 cases per 100,000 children (**Figure 1**), while the prevalence varies between 6.1 and 20.4 per 100,000 children (2, 15–17). The fact that IgAV is not equally present in different parts of the world is also well-known, since it has the highest occurrence in East Asians, intermediate in Europeans, and the lowest in individuals of African ancestry (2, 15). Nevertheless, only recently a study on spatial variability of the incidence of IgAV and IgAVN using modern geostatistical methods has been performed (18). This research is important for several reasons. First, there is a lack of application of geostatistical methods in the field of pediatric rheumatology at all. Most of the previous work explores potential risk factors using observational studies with classical statistical techniques resulting in reduction of information which may be used to deepen the knowledge of potential risk factors involved in the pathomechanism of disease, in this case IgAV. In other words, the geospatial analysis may provide useful information of genetic, socio-economic, and environmental risk factors while simultaneously taking into account their spatial diversity, which can be applied not only in the case of IgAV and IgAVN but also in many other diseases. Second, it was demonstrated that both IgAV and IgAVN may not be randomly distributed in space, but clustered, similar to some other non-communicable diseases, such as inflammatory polyarthritis, heart diseases, and diabetes (18–21).

FIGURE 1 | Distribution of incidence of IgAV around the world.

The IgAV and IgAVN hotspots clusters appear where genetic and environmental factors overlap substantially. It can be speculated whether genetic or environmental factors are dominant in the example of IgAV and IgAVN clustering in Croatia (18, 22). Since IgAVN showed linear clustering in the eastern part of Croatia, which follows the course of the Drava and Danube rivers, in the vicinity of areas of Balkan endemic nephropathy, known to occur primarily due to environmental factors (aristolochic acid) (23), the question arises as to whether the same is true for IgAVN. If this proves correct, it would be contrary to geospatial distribution of IgA nephropathy that is predominantly associated with genetic factors—different variants of innate immunity genes as well as of genes important for defense against parasitic infections (24). That would be another important difference between IgAVN and IgA nephropathy, for which it is still debated whether they are different diseases or just two variants of the same disease (25).

NEW INSIGHTS IN THE PATHOGENESIS OF IgAV

The complexity of the etiopathogenesis of IgAV is reflected in the interaction of genetic and environmental factors, with special emphasis on infections (16, 26). The genetic background is indisputable; this is supported by the fact that the incidence and geospatial distribution of IgAV and IgAVN differ around the world and between the different ethnicities (2), that the incidence of IgAV sometimes has a tendency for familial aggregation (27–29), and, finally, that genome-wide association studies (GWAS) point to the significance of common gene variants in the pathogenesis of this disorder (30, 31).

The results of the GWAS to date classify IgAV as a prototype of a disease related to human leucocyte antigen (HLA) class II loci. A first GWAS pointed to the significance of the polymorphisms in the *HLA-DQA1* and *DQB1* intergenic zone and at the *HLA-DRB1*11* and *DRB1*13* loci (30), while a more recent one showed that haplotype *DQA1*01:01/DQB1*05:01/DRB1*01:01* was associated with susceptibility to IgAV but not with other autoimmune diseases (31). GWAS of IgAV have not detected potential susceptibility loci to IgAV outside HLA class II genes, but since there are no large GWAS for pediatric IgAV and IgAVN, and existing studies are underpowered to detect smaller allelic effects outside of the HLA region, it is possible that variants in various non-HLA genes associated with immune and inflammatory response escaped statistical detection and these are variants that previous studies have shown to be implicated in the etiopathogenesis of IgAV (32). The most important non-HLA genes linked with IgAV susceptibility include cytokines genes (*ILRN*2*, *IL18*, and *TGFB1*), chemokines genes (*MCP1*), adhesion molecules genes (*SELP*), renin-angiotensin system (*RAS*) genes (*Agt, ACE*), and others (*C1GALT1*, *NOS2A*, *eNOS*, *PON1*, and *MEFV*) (32). For example, genetic variants located at the interleukin (*IL*) 18 locus could be associated with a higher risk of developing IgAVN (33), while carriage of interleukin-1 receptor antagonist polymorphism 2 (*ILRN*2*) may be related to severe renal involvement and renal sequelae in patients with IgAV (34). Even though the results of these studies deliver more insight into the various molecular pathways, they are not sufficiently large, and the potential association with IgAV is not as strong as it is the case with HLA genes.

These genetic variants may be responsible for regional and ethnic differences observed in IgAV. Thus, for example, the pathogenic variants in the Mediterranean fever (*MEFV*) gene might predispose to IgAV in patients with familial Mediterranean fever (FMF) and may be associated with different clinical presentation of IgAV in countries where FMF is common (35, 36). In these patients, there might be an increased risk of gastrointestinal complications and IgA deposits on biopsy specimens might be less frequently found, so the diagnosis of IgAV should not be excluded based on absent IgA deposits on skin biopsy in case of clinical presentation suggestive of IgAV (37).

It was shown that epigenetic changes, that regulate gene activity and expression, are involved in pathogenesis of IgAV (38). Luo et al. demonstrated increased global histone H3 acetylation and H3K4 methylation levels in the peripheral blood mononuclear cells of patients with IgAVN compared to healthy controls and patients with IgAV without renal involvement. Furthermore, the authors showed positive correlation of H3 acetylation and H3K4 methylation levels with disease severity. They hypothesized that abnormal levels of histone modifying enzymes can lead to changes in chromatin structure, resulting in increased gene transcription, such as the IL-4 promoter. Another important finding in this study was that in patients with IgAV, the balance between type 1 helper cells (Th1) and type 2 helper cells (Th2) cytokines is disturbed by increasing the level of Th2 specific cytokines (IL-4, IL-6, and IL-13) and decreasing the level of Th1 specific cytokines (IL-2 and IFN-γ) (38).

Recently, a gene which encodes a histone demethylase involved in the epigenetic control of gene expression (*KDM4C*) has been implicated in the genetic predisposition of IgAV, highlighting the relevance of the epigenetic mechanisms in the development of this disease (39).

Multi-hit pathogenesis models for IgAV and IgAVN have been described lately (40, 41) (**Figure 2**). It seems that the aberrantly glycosylated IgA1 plays a key role in the pathogenesis of IgAV, especially in patients who develop IgAVN. IgA_1 from most patients with IgAV lack galactose residues [galactose deficient IgA_1 (Gd-IgA_1)] (42). It is hypothesized that in the Golgi apparatus of IgA_1-producing immune cells aberrant glycosylation occurs due to decreased galactosyltransferase activity and that genetic predisposition and/or mucosal infection and concomitant IL-6 production cause aberrant glycosylation by altering the glycosylation machinery (43). Two potential genetic loci have been identified in a GWAS in adult patients with IgA nephropathy and increased serum levels of Gd-IgA_1 (44). These loci, *C1GALT1* and *C1GALT1C1*, are inherited in an autosomal dominant manner and may be responsible for aberrant glycosylation in IgAV, and not only in patients with IgA nephropathy. IgA and IgG antibodies may recognize Gd-IgA_1 as an autoantigen, which leads to the formation of polymeric immune complexes (Gd-IgA_1-IgA, Gd-IgA_1-IgG, and Gd-IgA_1-sCD89, where sCD89 is soluble IgA Fc alpha receptor). It is possible that these circulating immune complexes accumulate in the blood, resulting in their deposition on the endothelium of small blood vessels in the skin, gut, and kidneys. It was shown that serum levels of Gd-IgA_1 are higher in IgAVN patients compared to IgAV patients without nephritis (45). Some of these Gd-IgA_1-IgG complexes may deposit in the kidneys, resulting in mesangial cell activation, release of inflammatory mediators, and glomerular injury in patients who develop IgAVN (41).

However, some authors proposed a second multi-hit hypothesis to explain the systemic symptoms of IgAV and IgAVN (40). This model is based on assumption that infection with microorganisms that have similar antigenic structures as components of human vessel walls could lead to the production of cross-reactive anti-endothelial cell antibodies (IgA_1-AECA) under specific genetic influences. These antibodies may further induce the production of interleukin-8, which is a potent chemoattractant for neutrophils. After activation, neutrophils may cause damage of vascular endothelial cells.

In the context of the new insights, and related to the coronavirus disease 2019 (COVID-19) pandemic, it should be noted that there are several case reports describing patients with IgAV following COVID-19, and some of them were children (46–48). It is not yet known how the severe acute respiratory syndrome coronavirus 2 (SARS-CoV-2) virus is involved in the pathogenesis of IgAV, whether it is a classical infectious trigger such as the previously described bacteria and viruses or because of its ability to elicit a cytokine response it may be directly involved in the pathogenesis of the disease.

None of the proposed models of IgAV pathogenesis described can explain the fact that in <10% of IgAV patients Gd-IgA_1 in serum or in biopsy specimens is not elevated, nor can they explain the observation that the disease occurs only in some people with

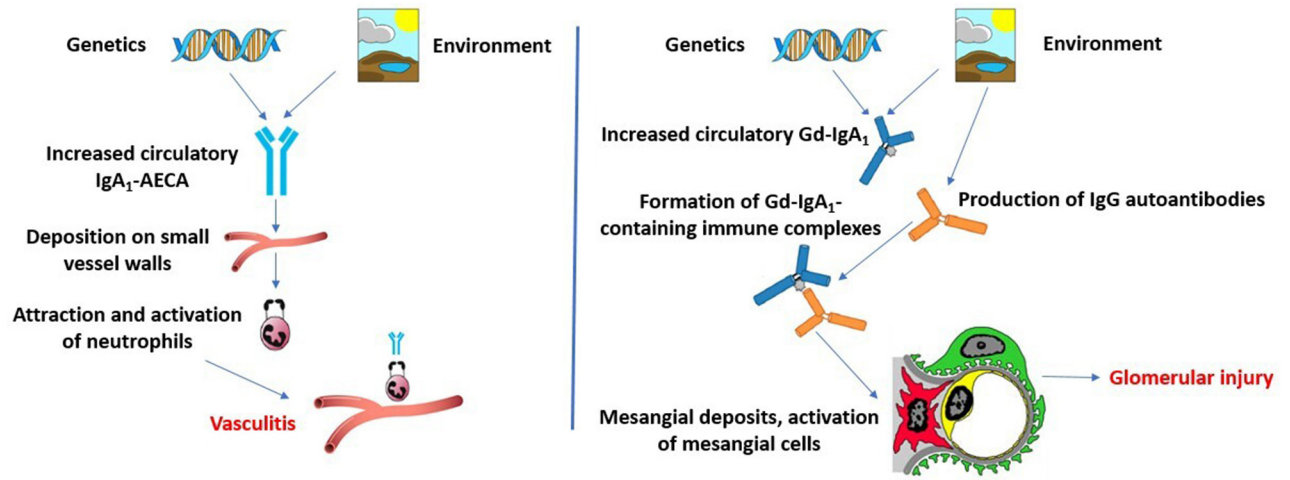

FIGURE 2 | Two multi-hit pathogenesis models for IgAV and IgAVN. Modified according to Heineke et al. (40) and Hastings et al. (41).

IgA_1 glycosylation defect, while in others with elevated Gd-IgA_1 the disease does not occur (49, 50).

NEW INSIGHTS IN THE CLINICAL PRESENTATIONS OF IgAV

The most common and characteristic signs of the disease are skin manifestations in the form of non-thrombocytopenic purpura or petechiae with lower limb predominance. They are present in all patients and are mandatory classification criterion according to the European League Against Rheumatism (EULAR), Pediatric Rheumatology International Trials Organization (PRINTO) and Pediatric Rheumatology European Society (PRES) classification criteria endorsed in Ankara in 2008 (2). A possible diagnostic algorithm of the disease is shown in **Figure 3**.

Nonetheless, atypical distributions are also possible, affecting the head and neck area, involving the upper extremities more than lower extremities, sparing of the lower extremities, or with diffusely distributed lesions (51). Furthermore, hemorrhagic bullae, ulcerations and necrotic lesions can be seen in the most severe cases. Recently, several papers have been published on severe skin changes in patients with IgAV, questioning whether these changes are associated with more severe disease, persistent sequelae, and discussing how to treat patients with such manifestations (52–54). The results of these studies are not uniform, and according to some authors the presence of ulcerations and necroses, persistent purpura ($\geq$1 month) and older age were significant predictors of IgAVN. Also, with increasing severity and duration of cutaneous manifestations in IgAV the risk of developing IgAVN may increase, with a greater likelihood to need aggressive treatment (50). However, others did not notice such associations (52, 53). All the studies conducted so far have in common that they included a very small number of IgAV patients with the most severe cutaneous manifestations, so it is necessary to wait for further results to reach conclusions that will include a larger number of patients.

The second most common feature is represented by musculoskeletal manifestations, in that up to 70–90% of patients with IgAV will have arthralgia or arthritis (51). According to a Korean nationwide population-based study, younger children are more at risk of developing arthritis, and children younger than 7 years of age had frequent joint symptoms (17). In children with IgAV arthritis is non-deforming and heals without chronic damage within a few weeks (51). It is interesting to note that in some studies it was observed that joint involvement and subcutaneous edema in the extremities were less frequent in patients with severe gastrointestinal involvement, thus arthralgia could be a negative predictive factor for severe gastrointestinal involvement in patients with IgAV (55).

More than 50% of children with IgAV may develop gastrointestinal manifestations, and in about 10–20% of patients with gastrointestinal involvement serious complications such as intussusception, bowel perforation, and massive bleeding may occur (9). There are conflicting results from literature regarding the possible association of gastrointestinal symptoms in IgAV and IgAVN. A meta-analysis from 2016 showed that gastrointestinal symptoms were strongly related to renal involvement (56), and several other studies have shown similar results (57–59). Patients in whom IgAV has started with gastrointestinal symptoms and older children with severe gastrointestinal symptoms (severe abdominal pain, intussusception, hematochezia, and/or massive gastrointestinal bleeding) may be a high-risk group for developing IgAVN (59). However, other studies have not confirmed this association (60–62).

Finding associations of individual clinical elements with the prognosis of IgAV and renal involvement would be very important since it would help to identify high risk group of patients that should be follow-up closely and at shorter intervals to detect renal involvement.

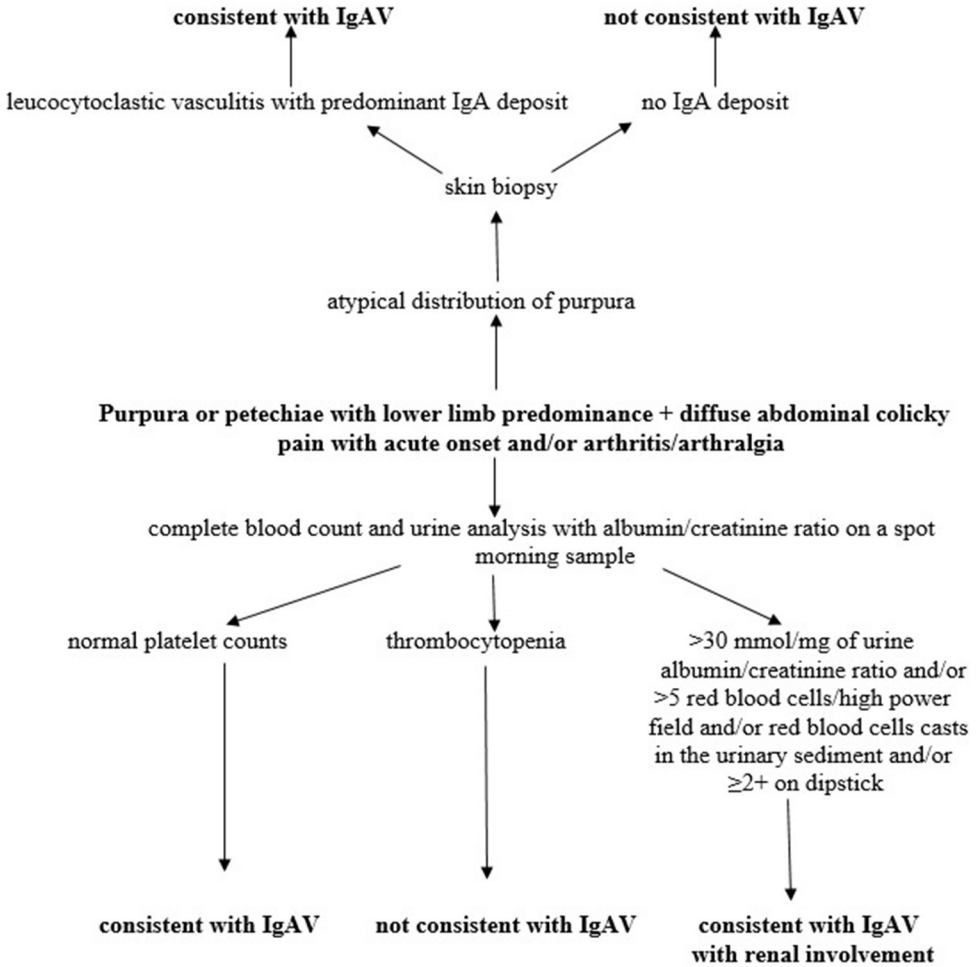

FIGURE 3 | Diagnostic algorithm of IgAV. Modified according to Ozen et al. (2).

NEW INSIGHTS IN THE DIAGNOSTICS OF IgAV, WITH SPECIAL EMPHASIS ON THE ROLE OF BIOMARKERS AND KIDNEY BIOPSY

Renal involvement in IgAV ranges from urinary abnormalities (including hematuria or/and proteinuria) through nephritic and nephrotic syndrome to chronic renal failure. IgAVN is typically mild and most commonly manifest only with pathological urine findings. Chronic renal failure has been reported in 1–15% of children with IgAVN, and in the vast majority of cases it is diagnosed within 6 months of disease onset (11–14).

Current problems related to the diagnosis of renal disease in IgAV can be divided into two groups. On one hand, kidney biopsy is still the gold standard for the diagnosis of IgAVN, but the big problem is the uneven interpretation of the results since several histological classifications are used in the analysis of renal biopsy findings in IgAVN, but it remains unknown which one has the strongest association with the severity and outcome (6). Another problem is that there are currently no biomarkers in routine clinical use for IgAV and IgAVN which can stratify patients with respect to the risk of developing kidney disease progression and contribute to the earlier diagnosis of renal involvement (41).

The most commonly used histological classification is that of the International Study of Kidney Disease in Children (ISKDC) (63, 64). The advantage of this classification is that it is relatively simple and widespread in use, so it is known around the world (6). The most important limitation is that it is grounded mostly on the state of glomeruli, therefore only reflecting active inflammation and neglecting vascular and tubulointerstitial changes. The Oxford classification is increasingly used, and was revised in 2017 (65). Crescents, the lesions on renal biopsy that have long been considered the most important outcome indicators of IgAVN, were not included in the first version of the classification. Although this histological classification is more complex and some studies have shown its potential for use in IgAVN, caution is needed. Indeed, the working group of Oxford classification does not recommend its use in IgAVN since cases of

patients with this condition were not included in the validation cohort, and recent study suggests that the Oxford classification could not be fully validated in IgAVN (65, 66). A finnish group published the modified semi-quantitative classification in 2017 (67). It is the most complicated, but the first to take into account the chronicity components. Although the first results are promising, a study of a longer number of patients is needed to properly validate the classification.

Since renal biopsy is an invasive procedure, and it is still unclear what is the prognostic value of individual histological elements, there is a need for less invasive procedures in diagnostics. Measurement of biomarkers in urine has many advantages: the sample is relatively easy to collect, without using invasive procedures; urine reflects changes in renal parenchyma, unlike blood that is in contact with a number of organs and organ systems. In addition, the number of different core proteins in the urine is lower than in blood (68, 69). Despite the many potential biomarkers that are emerging, the most consistent finding in patients with IgAV remains an increased serum level of Gd-IgA_1 (70). Among urinary biomarkers, IgA and IgM performed best in the study conducted by Pillebout et al. (45). Recent systematic review of urine biomarkers in children with IgAVN showed that the most promising urinary biomarkers in predicting nephritis were kidney injury molecule-1 (KIM-1), monocyte chemotactic protein-1 (MCP-1), N-acetyl-β-glucosaminidase (NAG), and angiotensinogen (AGT) (71). However, none of them proved yet to be an established marker of disease. Further studies are needed to verify whether preclinical markers are superior to the currently usd ones (24-h urinary protein values, urinary protein:creatinine ratio and urinary albumin concentration).

The application of metabolomics has proven to be a promising approach (72). Metabolome is a product of proteome and is considered to be closer to the phenotype in comparison with genome, and proteome. Studies regarding metabolomics in IgAV are scarse. Demir et al. found that DHAP (18:0), prostaglandin D2/I2, porphobilinogen, 5-methyltetrahydrofolic acid, and N-Acetyl-4-O-acetylneuraminic acid/N-Acetyl-7-O-acetylneuraminic acid may serve as biomarkers for predicting kidney disease but studies with larger number of IgAV patients are necessary for validation of these findings (72).

NEW INSIGHTS IN THE ASSESSMENT OF DISEASE ACTIVITY AND DAMAGE IN IgAV

Data regarding vasculitis activity and damage assessment in children with IgAV are limited. Since these are key components of outcome measures in patients with vasculitis for both clinical trials and for observing individual patient disease course, it is important to validate the available assessment tools adapted for the pediatric population (73). For determining disease activity and degree of kidney damage in patients with IgAV/IgAVN two clinical questionares can be used: the Pediatric Vasculitis Activity Score (PVAS) and Pediatric Vasculitis Damage Index (PVDI), respectively (73). PVAS includes 64 clinical features (symptoms or signs of disease) that are divided into nine organ systems; the assessment of new or worsening items in the last 4 weeks, but not for more than 3 months, is recorded. The total number of points represents the activity of the disease and ranges from 0 to 63 points. PVDI includes 72 clinical variables divided into nine organ systems, as well as an "other" section. The duration of symptoms or signs lasting at least 3 months, occurring at any time since the disease onset, is defined as damage.

NEW INSIGHTS IN THE TREATMENT OF IgAV

During the self-limited nature of the disease, in the vast majority of children with IgAV specific treatment is not required. Regarding patients with severe skin manifestations, due to the lack of studies with large number of participants the optimal way of treatment is not known, although most are treated with systemic glucocorticoids, sometimes in combination with dapsone or azathioprine (52, 53). Musculoskeletal manifestations are usually treated with rest and analgesia, while other treatment options are rarely necessary. A different situation occurs in children with severe gastrointestinal manifestations, renal involvement or those with other complications such as neurological, lung or multiple organ involvement. Recently, the European initiative SHARE (Single Hub and Access point for pediatric Rheumatology in Europe) developed consensus-based recommendations for diagnosis and treatment of IgAV (74). It is important to emphasize that these recommendations are not intended for pediatric rheumatologists and nephrologists, but for general pediatricians and physicians who have little or no experience with severe IgAV and IgAVN patients.

In children with severe abdominal pain or gastrointestinal hemorrhage, glucocorticoids should be considered: oral or pulsed glucocorticoids if oral route is not tolerated or they have failed to respond. Mycophenolate mofetil, cyclophosphamide, intravenous immunoglobulin, rituximab, methotrexate, colchicine, and hydroxychloroquine may be considered as second-line treatments (51). Other supportive treatment, such as, nasogastric decompression, parenteral nutrition, and antibiotics may be required.

According to the SHARE management algorithm, IgAVN is divided into three categories, taking into account proteinuria, estimated glomerular filtration rate and percentage of crescents on renal biopsy (74). Children without proteinuria or renal dysfunction usually do not need any specific therapeutic intervention. In patients with mild forms of IgAVN, defined as $\leq$2.5 g/day of proteinuria in 24 h urine collection with normal estimated glomerular filtration rate, first-line therapy consists of oral glucocorticoids, and in the case of persistence of proteinuria, second-line drugs may be used (e.g., azathioprine, mycophenolate mofetil, or glucocorticoid pulses). Glucocorticoids, usually parenterally and in pulsed doses, are the first choice in the treatment of moderate IgAVN, defined as <50% crescents on renal biopsy and impaired estimated glomerular filtration rate (<80 ml/min/1.73 m^2) or severe persistent proteinuria (>2.5 g/day of proteinuria in 24 h urine collection for more than 4 weeks). In the absence of response, second-line drugs are added: azathioprine, mycophenolate

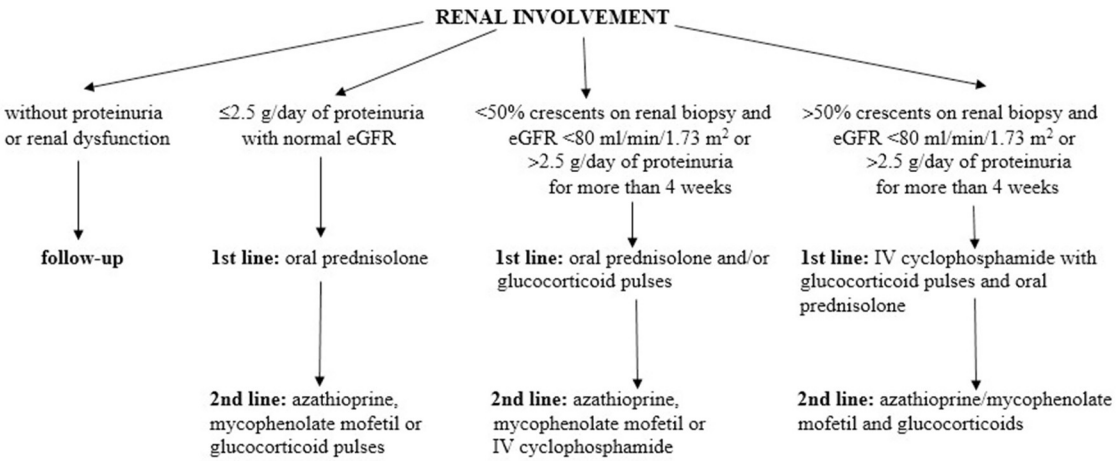

FIGURE 4 | The SHARE recommendations for IgAVN treatment. Modified according to Ozen et al. (74).

mofetil, or cyclophosphamide parenterally. Treatment of the most severe forms of IgAVN consists of two phases: the first one is induction using pulsed doses of glucocorticoids in combination with intravenous cyclophosphamide pulses, and the second phase is maintenance therapy with lower doses of glucocorticoids in combination with immunomodulators: azathioprine or mycophenolate mofetil. To prevent or limit secondary glomerular damage in patients with IgAVN who have persistent proteinuria (lasting more than 3 months), angiotensin converting enzyme inhibitors or angiotensin receptor blockers are recommended. The SHARE recommendations for IgAVN treatment are summarized in **Figure 4**.

For unresponsive cases there is an option of plasma exchange that showed efficacy in one study while there is not enough evidence regarding the use of rituximab (although it has been described in case reports and case series) or intravenous immunoglobulins (51, 75).

In addition to the SHARE recommendations, there is also the Kidney Disease: Improving Global Outcomes (KDIGO) practice guideline on glomerulonephritis, which in one chapter provide recommendations for the treatment of IgAVN in children and adults (76). Angiotensin converting enzyme inhibitors or angiotensin receptor blockers are suggested for children with persistent proteinuria 0.5–1 g/day per 1.73 m^2, while for those with proteinuria >1 g/day per 1.73 m^2, after a trial of angiotensin converting enzyme inhibitors or angiotensin receptor blockers, a 6-month course of glucocorticoid therapy should be considered. Children with crescentic IgAVN with nephrotic syndrome and/or deteriorating kidney function should be treated with glucocorticoids and cyclophosphamide according to KDIGO practice guideline.

The biggest problem in treating children with IgAV is the lack of high-level evidence and randomized controlled trials (74).

When it comes to new therapeutic options, there is room for improvement. Since the most important chronic complication of the disease is IgAVN, and according to some hypotheses the pathogenesis of IgAVN could be closely related to the pathogenesis of IgA nephropathy (40, 41, 43), new targeted therapies being investigated in IgA nephropathy could soon be extended to IgAVN. Examples of such therapeutic options include budesonide, which can target Peyer's patches in the ileum where the production of Gd-IgA1 is thought to originate (77); bortezomib, a proteasome inhibitor which is a plasma cell depleting agent (it affects production of IgG autoantibodies) (78); complement inhibitors such as APL-2, CCX168, LNP023, and OMS721 (79); or the spleen tyrosine kinase inhibitors (80). Currently, precision medicine has not found its place in the treatment of vasculitis (81).

NEW INSIGHTS IN THE FOLLOW-UP OF PATIENTS WITH IgAV

It is proposed to follow-up patients with IgAV for at least 6–12 months even if the initial blood pressure measurements and urinalysis are normal (74), measuring regularly blood pressure and performing urinalyses to detect presence of haematuria, and quantification of albuminuria and/or proteinuria. Bearing in mind that recently published research has indicated that a certain group of patients (such as older children with the onset of gastrointestinal symptoms before other IgAV symptoms and severe GI form of IgAV, as well as those who develop ulcerations and necroses and persistent purpura) may be at higher risk for the later development of nephritis, the question arises whether some children should be monitored longer than recommended (54, 59).

The question of how long to follow-up children who have developed IgAVN and entered disease remission is still unanswered. During 23 years of follow-up, it was shown that up to 44% of patients with severe IgAVN at onset and up to 13% with mild IgAVN at onset developed reduced renal function and/or hypertension (12). Another study indicated that 70% of pregnancies in women with IgAVN with onset in childhood

were complicated by hypertension and/or proteinuria (82). These data call for caution and emphasize the need for long-term observation even in patients who went into remission.

CONCLUSION

In this review, we describe how new insights have been gained regarding this disease, which will necessarily require a paradigm shift if we want to make further progress in terms of developing a non-invasive diagnosis of nephritis (which is the most common chronic complication of the disease), as well as its treatment (the main problem being the lack of high-level evidence based on randomized controlled trials). The incidence of IgAV and IgAVN varies worldwide and may be a consequence of overlapping genetic and environmental factors. Besides HLA class II genes, various non-HLA genes may also have significance in its etiopathogenesis. Factors other than Gd-IgA_1-containing immune complexes may also be important in a multi-hit pathogenesis of this disease. Renal biopsy is still the gold standard for the diagnosis of IgAVN, but in interpretating the histologic findings it should be taken into account that tubulointerstitial changes could be very important as predictors of poor outcome, so other histologic classifications than ISKDC, such as the revised Oxford classification (MEST-C score) may be considered. The most consistent biomarker in patients with IgAV is represented by increased serum levels of Gd-IgA1, while non-invasive confirmation of nephritis is still pending. In the absence of high-level evidence concerning treatment based on randomized controlled trials, SHARE recommendations have been developed. Patients with IgAV, and especially with IgAVN, should be followed-up for long-term, even when the remission of the disease is established, because of possible complications.

AUTHOR CONTRIBUTIONS

MJ and MS reviewed the literature and wrote much of the manuscript. TG and RC reviewed the literature and wrote parts of the manuscript, planned and oversaw the entire review, and contributed to all aspects of the manuscript. All authors contributed to the article, approved the submitted version, and agree to be accountable for the content of the work.

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REVIEW
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An Update on Childhood-Onset Takayasu Arteritis

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Takayasu Arteritis (TAK) is a rare large vessel vasculitis affecting the aorta and its major branches. The heterogeneous and often severe clinical manifestations result from systemic and local inflammation as well as end-organ ischemia. Disease flares are common and contribute to accrued damage over time with significant morbidity and mortality. Newer understanding of the pathogenesis in TAK has paved the way for the use of pathway targeting agents such as tumor necrosis factor (TNF)α- or interleuking (IL)-6-inhibitors with improved disease control. Nevertheless, long-term data are lacking, particularly in children; prognosis often remains guarded and the disease burden high. This article aims at providing a comprehensive review of childhood-onset TAK with a focus on recent publications.

Keywords: Takayasu Arteritis, large vessel vasculitis, childhood vasculitis, pediatrics, review

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INTRODUCTION

Takayasu Arteritis (TAK) is the most common large vessel vasculitis in children. It is characterized by granulomatous inflammation of the aorta, its major branches and the pulmonary arteries that may result in segmental stenosis, occlusion, dilatation and/or aneurysms. Systemic inflammation, local inflammatory processes and organ dysfunction secondary to ischemia lead to a highly variable clinical presentation and significant morbidity if untreated. Therapy is often extrapolated from adult studies given the very low prevalence of the disease in children. Better understanding of pathophysiologic mechanisms has resulted in the use of cytokine targeting therapies. Although early recognition and therapy seem to improve outcome in childhood-onset TAK, long-term follow-up data are lacking and prognosis remains guarded. This article reviews recent publications on epidemiology, pathogenesis, clinical presentation, laboratory biomarkers, imaging, treatment, and outcomes with a focus on the pediatric literature.

EPIDEMIOLOGY

The incidence and prevalence of TAK are much higher in adults compared to children. A recent systematic review and meta-analysis found an incidence rate of 1.11 per million person-years (95% CI 0.70, 1.76) with considerable variation across different populations (1). Indeed, the described incidence rates of TAK range from 0.3 to 3.3 per million per year and the prevalence from 0.9 to 360 cases per million depending on the population and geographic region studied, with higher rates observed particularly in Asia (2).

Epidemiological data in childhood-onset TAK are scarce. The annual incidence rate reported in a Swedish study was 0.4 (95% CI 0, 1.1) per million for childhood-onset TAK (3). The prevalence estimated from a National Health Insurance database in South Korea varied between 0.04 (95% CI 0.00, 0.08) for children 0 to 4 years old and 0.63 (95% CI 0.36, 0.91) per 100,000 for those 15–19 years old, with an increase of the age-standardized prevalence of TAK over the years (4).

Takayasu Arteritis most commonly affects young women with a peak incidence between 20 and 40 years of age. It is unknown why TAK occurs predominantly in women. In children, female preponderance is lower than in adult-onset TAK and estimated around 2.5:1–3:1 (5). Mean age at disease onset in the pediatric population is 12 years, but TAK has been described across all ages and even in infants (6–9).

PATHOGENESIS

While there are still major gaps in our understanding, the etiology of TAK has begun to be elucidated. Current knowledge of pathophysiology is mostly extrapolated from adult studies and animal models of large vessel vasculitis (10). Both, the innate and adaptive immune systems have been implicated in the pathophysiology of TAK (11). Histologically, the inflammatory process usually predominates in the adventitia and the outer part of the media, but may affect all three blood vessel layers. The consequences are vessel wall damage with laminar necrosis and elastic fiber fragmentation, and eventually fibrosis and arterial remodeling (12). Inflammatory cell infiltrates of the arterial wall consist of macrophages and lymphoid cells (αß CD4+ and CD8+ cells, γδ T-cells, natural killer cells, and B cells) (13).

Multiple proinflammatory cytokines have been implicated in the pathogenesis of TAK (14). Increased levels of tumor necrosis factor (TNF)α, interferon (IFN)α, IFNγ, interleukin (IL)-6, IL-8, IL-12, IL-17, and IL-18 have been observed in the peripheral blood of patients with TAK compared to healthy controls. Serum IL-6 and IL-18 levels have been shown to correlate with disease activity (15–18). Novel insights in disease pathways and identification of key pro-inflammatory cytokines have led to the use of cytokine targeting agents such as TNFα- or IL- 6-, and more recently janus kinase (JAK)-inhibitors.

T cells, and particularly Th1 and Th17 responses seem to play an important role in driving the systemic and vascular manifestations in TAK, as demonstrated by increased expression of Th1 and Th17-related cytokines in patients with TAK that correlate with disease activity (17).

Furthermore, recent data indicate the implication of the mammalian target of rapamycin (mTOR) pathway in T cell activation and the development of vascular lesions in TAK. mTOR is a kinase that drives different signaling pathways to regulate cell differentiation, proliferation and metabolism (19), as well as vascular remodeling (20, 21). In addition, mTOR Complex 1 (mTORC1) has been involved in the differentiation of Th1 and Th17 cells (22). In patients with TAK, mTORC1 pathway is hyperactivated in CD4+ T cells and correlates with disease progression (23). This hyperactivity of mTORC1 has been identified as a critical mechanism underlying the altered differentiation of Th1 and Th17 cells (23). *In vitro* and mouse model studies show, that blockade of mTORC1 by sirolimus, a specific mTOR inhibitor, or by genetic knockdown, successfully suppresses the hyperactivation of the mTOR pathway, altered differentiation of CD4+ T cells and arterial inflammation (23, 24). Thus, targeting the mTORC1 pathway may represent an interesting novel therapeutic strategy in patients with TAK (25).

Growing evidence supports the crucial role of the Janus Kinase/Signal Transducers and Activators of Transcription (JAK-STAT) signaling pathway in the pathophysiology of TAK. This was first shown in a large vessel vasculitis mouse-model, in which the JAK1/3 inhibitor tofacitinib significantly reduced vessel wall infiltrates and expression of IFNγ, IL-17, and IL-21, and further diminished angiogenesis and hyperplasia of the intima (26). Using transcriptome analysis, Régnier et al. found an important enrichment for pathways linked to IFN, and especially type I IFN in patients with TAK (27). The upregulation of type I specific IFN gene signature was confirmed in patients with TAK compared to healthy controls, and treatment with either ruxolitinib, a JAK1/2 inhibitor, or tofacitinib reduced T cell activation and restored T cell homeostasis *in vitro* (27). The same group has recently established a specific follicular helper T cell signature that characterizes TAK and highlighted the cooperation of follicular helper T cells and B cells through the JAK/STAT pathway in patients with TAK, further supporting the use of JAK-inhibitors as promising treatment strategy (28). In summary, cytokine signaling dependent on JAK/STAT is critically important in TAK and opens new therapeutic avenues, and studies are currently underway.

The involvement of humoral immune mechanisms has previously been demonstrated by the presence of circulating anti-endothelial cell antibodies (29), autoantibody-producing B cells in inflammatory vascular lesions (30), and increased numbers of plasmablasts in patients with TAK, which correlate with disease activity (31). More recently, the identification of two major endothelial autoantigens, both negative regulators of endothelial activation, and their corresponding autoantibodies further highlighted the involvement of the adaptive immune system in the pathophysiology of TAK (32). These findings supported the use of anti B cell agents in TAK (33).

Furthermore, a complex genetic predisposition may contribute, at least in parts, to the pathogenesis of TAK. Multiple susceptibility loci, including both HLA class I and II, have been identified in various studies, but only HLA-B*52 has been associated with TAK beyond ethnicity (11, 34). Genome-wide association studies established non-HLA susceptibility loci such as *IL12B, IL6, RPS9/LILRB3*, and *FCGR2A/FCGR3A,* which represent potential targets in pathophysiology and treatment of TAK (35).

More recently, monogenic causes including mutations in *NOD2, STAT1* gain-of-function, and *XIAP* have been described in association with TAK (36–39). Clinical features associated with monogenic causes of TAK are early-onset of symptoms, associated other inflammatory and autoimmune diseases such as inflammatory bowel disease or thyroid disorder, and/or features reminding of primary immunodeficiency.

Finally, triggers of the immune response, such as the involvement of Mycobacterium tuberculosis has been suggested for a long time. Although high prevalence of tuberculosis has been described in patients with TAK (i.e., detection of active tuberculosis in up to 18% of patients with TAK, presence of mycobacterium tuberculosis DNA in aortic tissue in up to 70% of cases), particularly in regions with a high prevalence of tuberculosis infection, there is not enough evidence to establish a causal relationship (40). A possible cross-reaction between mycobacterial and arterial antigens is matter of ongoing discussion.

To summarize, almost all arms of the immune response, from cellular components of both the innate and adaptive immune systems to downstream humoral mediators and their signaling components, have been implicated in the pathogenesis of TAK, pointing to the complexity of the immune reaction. It remains to be elucidated, what is causation and what association.

DIAGNOSIS

The diagnosis of childhood-onset TAK is based on clinical criteria and angiographic abnormalities, and is supported by laboratory findings. It requires a high index of suspicion, especially in children, because (1) onset is often insidious with non-specific symptoms mimicking many inflammatory conditions, (2) the clinical presentation greatly varies due to variable localization and extent of the vessels involved, and (3) the occurrence is rare.

Different sets of classification criteria have been proposed for childhood-onset TAK. The initial 1990 American College of Rheumatology (ACR) classification criteria for TAK were based on data from adult patients with TAK (41). In 2005, the vasculitis working group of the European League against Rheumatism/Pediatric Rheumatology European Society (EULAR/PReS) proposed new classification criteria for childhood-onset TAK (42). These were subsequently endorsed by EULAR, the Pediatric Rheumatology International Trial Organization (PRINTO), and PReS (EULAR/PRINTO/PReS) (43). They optimized the 1990 ACR classification criteria by including the mandatory criterion of angiographic abnormalities (not only conventional angiography, but also more recent imaging modalities such as CT or MRI), as well as the extra criteria arterial hypertension and elevated acute phase reactants. The latter was added to help differentiate TAK from non-inflammatory conditions [e.g., fibromuscular dysplasia (FMD)]. The EULAR/PRINTO/PReS classification criteria for childhood-onset TAK, presented in **Table 1**, have a sensitivity and specificity of 100 and 99.9%, respectively (43). Of note, these are classification criteria, that are not required to be met to make a diagnosis of TAK and initiate treatment.

CLINICAL PRESENTATION

Disease often presents with non-specific constitutional symptoms, including fever and systemic inflammation (pre-pulseless stage), and evolves to vascular symptoms attributable to occlusive arteritis. Up to 25% of children are diagnosed during the late inactive, "burnt-out" phase of the disease, where symptoms result from irreversible vascular damage rather than active vasculitis lesions (44–46). TAK may be associated with other inflammatory diseases, such as inflammatory bowel disease, spondyloarthritis or sarcoidosis (47–50). A child with TAK, pyoderma gangrenosum and chronic recurrent multifocal osteomyelitis has also been described (51).

In children, the aorta (arch, thoracic or abdominal) is most commonly affected, followed by the renal, subclavian, carotid, and splanchnic arteries (5, 52; **Figure 1**). Stenotic lesions predominate, but occlusion, concentric vessel wall thickening and aneurysms may also be observed. Lesions are characteristically located close to the origin of the aortic branches, with an often segmental and patchy distribution (53).

Table 2 summarizes childhood-onset TAK cohorts published during the last decade (6, 7, 44–46, 52, 54–62). Children may present with non-specific symptoms such as fever, dyspnea, headaches, weight loss or abdominal pain. Unlike adults, musculoskeletal symptoms including arthritis are infrequent (5), although they are more commonly described in pediatric TAK cohorts from South America (54, 56, 63). Cutaneous involvement (erythema nodosum, pyoderma gangrenosum) (51, 64) and ocular disease such as retinal vasculitis (47, 65) are rare in children. Presentation may be dramatic and life-threatening when acute hypertensive crisis, heart failure or arterial dissection develop (66–69).

Organ-specific manifestations result from ischemia secondary to vascular stenosis. Arterial hypertension is the main presenting feature (56–100% of children depending on ethnicity, with higher prevalence in Asians) and is primarily related to renal artery stenosis and subsequent renovascular hypertension (44, 58). Arterial hypertension and other clinical signs of hypoperfusion such as blood pressure discrepancy between limbs, decreased peripheral pulses and bruits over large arteries are found in over 60% of children at diagnosis and highlight the necessity of a rigorous physical exam, especially in a child with unexplained systemic inflammation. Claudication of extremities, secondary to decreased blood supply, is reported in a third of children at presentation. Abdominal pain, often related to vasculitis of the abdominal aorta or the mesenteric arteries may occur. Prevalence of cardiovascular complications such as cardiomyopathy, ischemic heart disease, heart failure and valvular disease is estimated between 5 and 27% (6, 45), but coronary artery involvement is reported in only about 11% of children with TAK (44). Neurologic involvement including headache, dizziness, seizures, transitory ischemic attacks, and stroke may be observed. In adults, stroke is more often ischemic than hemorrhagic. While ischemic strokes are more commonly a consequence of steno-occlusive lesions in the carotid and vertebrobasilar vessels, hemorrhagic strokes usually occur as a result of steno-occlusive lesions in the abdominal aorta and renal arteries (70).

More recently, several groups have been directly comparing pediatric and adult TAK cohorts (5, 52, 54, 60–62).

TABLE 1 | EULAR/PRINTO/PReS classification criteria for childhood-onset TAK.

Criterion	Glossary
Angiographic abnormality (mandatory criterion)	Angiography (conventional, CT, or MRI) of the aorta or its main branches and pulmonary arteries showing aneurysm/dilatation, narrowing, occlusion, or thickened arterial wall not due to fibromuscular dysplasia, or similar causes; changes usually focal or segmental
1. Pulse deficit or claudication	Lost/decreased/unequal peripheral artery pulse(s)
	Claudication: focal muscle pain induced by physical activity
2. Blood pressure (BP) discrepancy	Discrepancy of four limb systolic BP > 10 mm Hg difference in any limb
3. Bruits	Audible murmurs or palpable thrills over large arteries
4. Hypertension	Systolic/diastolic BP greater than 95th centile for height
5. Acute phase reactant	Erythrocyte sedimentation rate > 20 mm per first hour or CRP any value above normal (according to the local laboratory)

CT, computer tomography; CRP, C-reactive protein; EULAR, European League Against Rheumatism; MRI, magnetic resonance imaging; PRES, Pediatric Rheumatology European Society; PRINTO, Pediatric Rheumatology International Trials Organization.

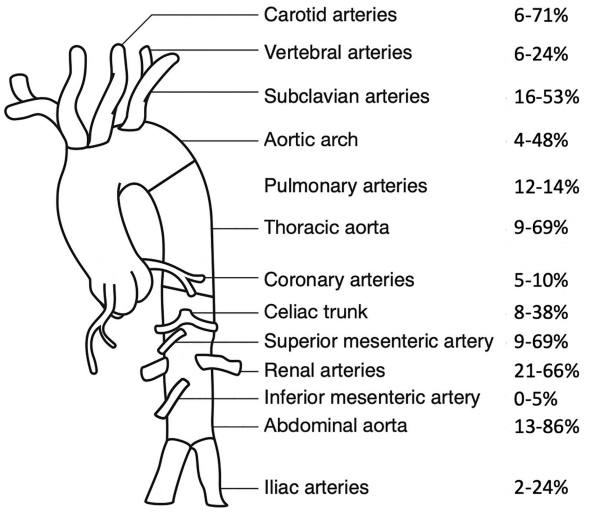

FIGURE 1 | Frequency of arterial involvement at presentation, modified according to Aeschlimann et al. (44). Frequencies of arterial involvement in pediatric Takayasu Arteritis are reported as percentages, paired vessels are presented as one combined value. Data are extracted from Refs. (6, 7, 44, 46, 52, 54, 55, 62).

Childhood-onset TAK has a lower female predominance (5, 52, 54) and a shorter diagnostic delay, possibly due to a more pro-inflammatory presentation (5, 62). Children have more commonly arterial hypertension, less claudication of the upper extremities, and less carotidynia. This reflects the vascular disease pattern, which more often affects the aorta and the infra-diaphragmatic renal and mesenteric arteries in children, but more frequently the aortic arch in adults (5, 52, 61, 62). Higher disease activity scores such as the Indian TAK Clinical Activity Score (ITAS 2010) at diagnosis have been reported in the pediatric compared to the adult population, but this does not seem to be associated with accrued damage over time (52, 54, 62).

Duration of symptoms before treatment initiation has been positively associated with disease extent and damage (52). Disease course is most commonly relapsing-remitting, especially when untreated, but monophasic evolution may be observed.

LABORATORY FEATURES AND SEROLOGICAL BIOMARKERS

Although various biomarkers have been explored for monitoring disease activity in TAK, none has yet been identified for reliable use in clinical practice. In children, elevation of acute phase reactants such as C-reactive protein (CRP) and erythrocyte sedimentation rate (ESR) is commonly observed (45, 55), but their sensitivity to reflect disease activity is uncertain, and they also lack specificity (71). In addition, they rapidly normalize and are masked under IL-6 blockade, adding further challenges to disease activity assessment in tocilizumab-treated patients (72). Anemia and thrombocytosis may be associated with chronic inflammation, particularly in children.

Among inflammatory molecules, IL-6, a pro-inflammatory cytokine that drives CRP synthesis and thrombocytosis and increases ESR seems promising as a biomarker and a treatment target. In tocilizumab-treated patients with TAK, longitudinal IL-6 monitoring might be useful for assessing disease activity and for detecting infections. While infections seem to trigger a significant, but short-term peak in serum IL-6, persistent IL-6 elevation may indicate subclinical disease activity or relapse (73, 74).

Further, IL-6 independent inflammatory biomarkers, such as S100 proteins or pentraxin-3 are being investigated (75). Pentraxin-3, for example, an acute phase protein synthetized locally at sites of inflammation, has been reported to correlate with disease activity in adults with TAK and may help to predict subclinical vascular inflammation (76). As mentioned previously, anti-endothelial antibodies have recently been identified in patients with TAK (32), but like many other serological biomarkers, they have limited availability and are not used in clinical practice; as a result, their clinical value yet remains to be defined. Studies searching for novel laboratory biomarkers are ongoing.

IMAGING

Vascular imaging aims at depicting morphologic anomalies of the aorta and its branches suggestive of arteritis, and at

TABLE 2 | Demographic and clinical characteristics of pediatric TAK cohorts, modified according to Aeschlimann et al. (135).

Autor (REF)	Zhu (59)	Jales-Neto (54)	Szugye (6)	Goel (55)	Clemente (56)	Misra (57)	Elefthe riou (45)	Feng (58)	Aeschlimann (44)	Sahin (7)	Fan (46)	Lei (60)	Danda (52)	Bolek (61)	Karabacak (62)	Summary	Brunner (136)
Country	China	Brazil	United States	India	Brazil	India	United Kingdom	China	Canada	Turkey	China	China	India	Turkey	Turkey		
Year of publication	2010	2010	2014	2014	2016	2015	2015	2017	2017	2019	2019	2020	2021	2021	2021	2010–2021	2010
Patients (*n*)	14	17	21	40	71	29	11	11	27	16	101	9	119	25	24	535	241
Sex F:M	3.7:1	1.8:1	2.5:1	1.9:1	2.6:1	1.9:1	1.8:1	1.8:1	2.9:1	3:1	3.2:1	8:1	2.4:1	3.2:1	7:1	3.2:1	3.0:1
Age at onset, mean (range), years	10.2 (7–16)	16* (1–18)	11.5 (0.1–17)	12.5* (1–16)	9.2 ± 4.2 SD	13* (IQR 11–15)	11.8 (1–17)	9.4 (1–14)	12.4* (IQR 9.1–14.4) at dx	12.1* (0.5–16.1)	14* (IQR 12–16)	14.3	14* (IQR 11–15)	12.8	14* (IQR 9–14)	12.7	10 (1–18)
General features, *n* (%)																	
Fever	4 (29)	7 (41)	3 (14)	18 (45)	NR[d]	16 (55)	4 (36)	5 (45)	5 (19)	7 (44)	13 (13)	4 (44)	35 (29)	NR	6 (25)	127/439 (29)	47/160 (29)
Weight loss	5 (36)	10 (59)	10 (48)	2 (5)	NR[d]	7 (24)[e]	4 (36)	NR	8 (30)	3 (19)	4 (4)	4 (44)	12 (10)	NR	10 (42)	79/428 (18)	44/199 (22)
Headache	9 (64)	8 (47)	3 (14)	21 (53)	NR[d]	6 (21)	4 (36)	3 (27)	9 (33)	6 (38)	1 (1)	NR	37 (31)	NR	10 (42)	117/430 (27)	66/210 (31)
Malaise	NR	NR	NR	21 (53)	NR[d]	7 (24)[e]	NR	NR	13 (48)	8 (50)	9 (9)	4 (44)	40 (34)	NR	NR	102/341 (30)	
Arthritis/arthralgia	6 (43)	7 (41)	3 (14)	1 (3)	46 (65)	4 (14)[e]	1 (9)	NR	NR	7 (44)	2 (2)	NR	NR	NR	NR	77/320 (24)	33/230 (14)
Carotidynia	NR	3 (18)	1 (5)	NR	NR	1 (3)	NR	NR	NR	NR	4 (4)	NR	5 (4)	NR	0	14/311 (5)	
Dyspnea	3 (21)	NR	4 (19)	11 (28)	38 (54)	NR	3 (27)	1 (9)	4 (15)	NR	30 (30)	NR	28 (24)	NR	NR	122/415 (29)	49/210 (23)
Hypertension	13 (93)	11 (65)	12 (57)	29 (73)	60 (85)	22 (76)	8 (73)	11 (100)	15 (56)	10 (63)	71 (70)	3 (33)	79 (66)	13 (52)	13 (54)	370/535 (69)	199/241 (83)
Abdominal pain	NR	5 (29)	2 (10)	9 (23)	NR[d]	NR	1 (9)	4 (36)	4 (15)	5 (31)	4 (4)	NR	13 (11%)	NR	NR	47/363 (13)	33/199 (17)

(Continued)

TABLE 2 | (Continued)

Autor (REF)	Zhu (59)	Jales-Neto (54)	Szugye (6)	Goel (55)	Clemente (56)	Misra (57)	Eleftheriou (45)	Feng (58)	Aeschlimann (44)	Sahin (7)	Fan (46)	Lei (60)	Danda (52)	Bolek (61)	Karabacak (62)	Summary	Brunner (136)
Syncope	2 (14)	6 (35)	1 (5)	6 (15)	NR[d]	2 (7)	NR	NR	3 (11)	3 (19)	10 (10)	NR	9 (8)	NR	3 (13)	45/408 (11)	4/199 (2)
Skin features	NR	NR	0	3 (8)	NR	4 (14)	1 (9)	1 (9)	NR	NR	NR	NR	NR	NR	NR	9/112 (8)	12/230 (5)
Organ-specific features, *n* (%)																	
Decreased pulse	10 (71)	10 (59)	13 (62)	25 (63)	61 (86)	23 (79)	2 (18)	3 (27)	16 (59)	12 (75)	38 (38)	NR	73 (61)	9 (36)[i]	[k]	295/502 (59)	30/230 (13)
Bruits	3 (21)	10 (59)	12 (57)	19 (47)	53 (75)	14 (48)	5 (45)	3 (27)	15 (56)	14 (88)	52 (52)	[n]	55 (46)	NR	[l]	255/477 (53)	38/230 (17)
Claudication	NR	10 (59)	3 (14)	16 (40)	26 (37)	12 (41)	1 (9)	NR	6 (22)	6 (38)	23 (23)	NR	46 (39)	NR	5 (21)[m]	154/476 (32)	32/241 (13)
BP discrepancy	NR	11 (65)	15 (71)	NR	48 (68)	16 (55)	2 (18)	5 (45)	18 (67)	12 (75)	56 (55)	NR	NR	9 (36)	NR	192/329 (58)	NR
Stroke	0	3 (18)	0	3 (8)	NR[d]	2 (7)	2 (18)	NR	3 (11)	2 (13)	6 (6)	0	10 (8)	0	1 (4)	32/453 (7)	39/230 (17)
Cardiac disease	3 (21)[a]	3 (18)[b]	1 (5)	8 (20)[c]	13 (18)[d]	4 (14)[e]	3 (27)[f]	2 (18)	NR	1 (6)[g]	25 (25)[h]	[o]	18 (15)	0	NR	81/475 (17)	52/230 (23)
Ocular disease	3 (21)	5 (29)[b]	2 (10)	7 (18)[c]	15 (21)	6 (21)[e]	1 (9)	NR	4 (15)	2 (13)	38 (38)	NR	14 (12)	NR	NR	97/466 (21)	12/230 (5)[j]

BP, blood pressure; F, female; IQR, interquartile range; LAD, lymphadenopathy; M, male; NR, not reported; SD, standard deviation.

**median.*

[a]Chest pain in n = 3 (21%), cardiac murmurs n = 5 (36%), congestive heart failure = 4 (29%), pericardial effusion and cardiomyopathy n = 1 (7%) each. Bruits over subclavian artery and abdominal aorta n = 3 (21%) each.

[b]Cardiac disease reported as "myocardial infarction" in n = 1 (6%) and "heart failure" in n = 3 (18%) patients, ocular disease reported as "visual complaints."

[c]Reported as cardiomyopathy and severe aortic regurgitation in n = 1 (3%) patient, ocular disease reported as "visual blurring."

[d]"Constitutional symptoms" (fever, asthenia, and weight loss) in n = 55 (78%) patients, "neurological symptoms" (headache, stroke, syncope) in n = 50 (70%), "gastrointestinal symptoms" (abdominal pain, diarrhea, vomiting) in n = 41 (58%) patients. Cardiac disease reported as "heart failure."

[e]Malaise and weight loss reported as one item, arthralgia/myalgia reported in n = 4 (14%), arthritis in n = 1 (3%) patient, "cardiac disease" reported as congestive heart failure, "ocular disease" reported as "blurring of vision."

[f]"Cardiac disease" reported as ischemic cardiac pain in n = 2 (18%), as cardiomyopathy in n = 3 (27%), as congestive cardiac failure in n = 2 (18%), as valvular heart disease in n = 1 (9%), and as pericarditis in n = 1 (9%) patients.

[g]Reported as "heart failure," and "visual complaints."

[h]"Cardiac disease" was reported as heart failure in n = 25 (25%) and myocardial infarction/ischemia in n = 3 (3%) patients.

[i]Numbers combined for decreased pulses and blood pressure discrepancy.

[j]Reported as "uveitis."

[k]Pulse loss: carotid 22%, radial 35%, brachial 26%, femoral 35%, dorsalis pedis 26%.

[l]Bruits: carotid 39%, subclavian 35%, renal 39%, abdominal aorta 48%.

[m]5/ 24 (21) with claudication of upper extremity and 5/ 24 (21%) with claudication of lower extremity.

[n]Bruits: carotid 22%, subclavian 22%, abdominal 44%.

[o]Cardiac findings: unstable angina 22%, acute myocardial infarction 11%, heart failure 44%, silent 22%.

distinguishing active inflammation from chronic inactive disease. Thus, imaging is crucial for diagnosis, assessment of disease extent and follow-up management of TAK. Imaging modalities include conventional angiography, magnetic resonance (MR) angiography, computer tomography (CT) angiography, Doppler ultrasound (US), and fluorodeoxyglucose positron emission tomography (PET) (^{18}F-FDG-PET). Although listed in the EULAR/PRINTO/PReS classification criteria for childhood-onset TAK, conventional angiography is nowadays rarely used and restricted to very few, specific indications such as angiographic imaging prior to revascularization procedures (77).

In childhood-onset TAK, contrast-enhanced MR angiography is the most popular imaging modality (**Figure 2**). It is proposed as the first imaging for suspected TAK by the EULAR recommendations on imaging of large vessel vasculitis (77), and is particularly appealing for repeated evaluations in the pediatric population due to lack of invasiveness and of radiation (78). However, recent research evidenced accumulation of gadolinium in the brain and other human tissues with repeated exposure. This raises concerns about potential toxicity particularly in the pediatric population and underlines the importance to carefully consider the indications for each MRI (79). Similar to MR imaging, CT angiography provides information on anatomical changes of the vascular lumen and wall, and the extent of arterial lesions with good spatial resolution. However, radiation exposure remains an important concern, especially in children and with repeated exposure. Doppler US is non-invasive and non-radiating, it visualizes the arterial wall and lumen, as well as altered blood flow characteristics. Challenges with its use include the lack of pediatric radiologists with expertise in vasculitis imaging, as well as acoustic technical limits, restricting the accessibility of certain vessels such as the descending aorta, especially in children (80).

More recently, ^{18}F-FDG-PET has been suggested to support radiologic assessment of disease activity (81). In children though, ^{18}F-FDG-PET plays a minor role for routine imaging monitoring of disease activity, mainly due to the high radiation dose.

While these imaging modalities (MR angiography, CT angiography, Doppler ultrasound, and ^{18}F-FDG-PET) reliably detect signs suggestive of vascular inflammation and allow diagnosis of TAK even in the early pre-stenotic phase, their role for follow-up monitoring is less evident. As an example, vascular changes such as vessel wall thickening or ^{18}F-FDG uptake are not specific to active TAK, but may also be induced by healing processes or fibrotic remodeling. This causes difficulties for interpretation of imaging as there is no clear correlation of imaging results with disease activity during the course of disease. Hence, it is crucial to combine clinical, laboratory and imaging evaluation for disease management.

The interested reader is referred to a recent extensive review on imaging in adult and childhood-onset TAK for more information (82).

Efforts to describe angiographic patterns of vascular involvement in TAK have resulted in the identification of different patterns with distinct clinical presentation in various ethnicities (53, 83). Most recently, three distinct clusters with distinct clinical symptoms and outcomes were identified in a large cohort of 806 adults with TAK of Indian and North American origins (84). Yet, these angiography-based disease classifications require validation regarding prognostic prediction.

DIFFERENTIAL DIAGNOSIS

Given the variable clinical presentation with often non-specific symptoms, differential diagnosis of childhood-onset TAK is broad and also depends on disease presentation. For example, differential diagnoses of fever of unknown origin have to be considered during the early disease phase, when non-specific systemic inflammatory symptoms predominate. Infections including tuberculosis and syphilis may cause aortitis, bacterial infections such as *staphylococcus aureus*, *streptococcus*, *salmonella*, or *brucella* should be considered in children with more acute clinical presentations (85, 86).

Differential diagnosis also includes other primary vasculitides (Behçet disease, Kawasaki disease, polyarteritis nodosa) and vasculitides secondary to systemic lupus erythematosus, spondylarthritis or sarcoidosis. Non-inflammatory diseases such as aortic coarctation, Williams syndrome, Marfan or Ehlers-Danlos syndrome, and fibromuscular dysplasia (FMD) may mimic childhood-onset TAK. In contrast to TAK, FMD is not an inflammatory disease; but it may be difficult to differentiate from TAK during the "burned-out" disease phase as–unlike in adults–the characteristic angiographic "string of beads" pattern is rarely observed in childhood-onset FMD (87).

TREATMENT

Immunosuppressive Therapy

Because of progressive or relapsing disease most children with TAK require immunosuppressive therapy to control systemic and vascular inflammation. Challenges in clinical management include the timely treatment initiation and assessment of disease activity to guide therapeutic decision-making. Diagnostic delay can result in irreversible vascular damage even prior to diagnosis and assessment of treatment response is difficult, because reliable laboratory and radiological biomarkers for disease activity are lacking.

Treatment recommendations are extrapolated from adult TAK studies, as high-level evidence including randomized controlled trials is not available to guide treatment in childhood-onset TAK. To date, high-dose corticosteroids remain the mainstay for induction of remission (78, 88), although recent treatment approaches in adults have used protocols without corticosteroids (89). Relapses are common in patients on corticosteroid monotherapy (90), and side effects of long-term high dose corticosteroids may be devastating, especially in children. Therefore, early initiation of second-line, corticosteroid sparing agents has been recommended (78, 88, 91). Traditionally, cyclophosphamide has been used in children with extensive or life-threatening disease, while conventional disease-modifying antirheumatic drugs (DMARDs) such as methotrexate,

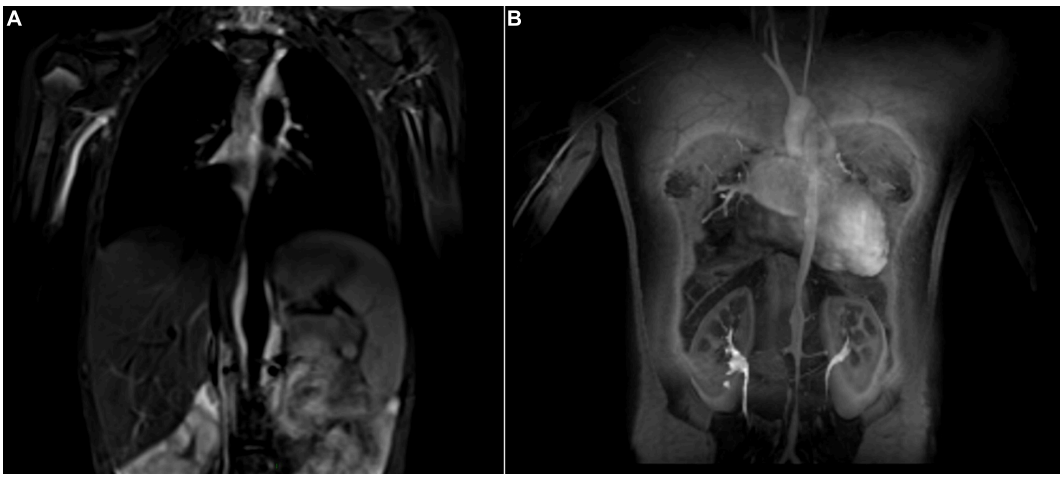

FIGURE 2 | Takayasu Arteritis in a 13-year old girl who presented with fatigue, dyspnea, anemia, and claudication of the lower extremities. The MR angiogram (T2 black blood sequence, coronal view) shows hypersignal (inflammation) of the abdominal aorta **(A)**. Post contrast angiography (coronal view) demonstrates multifocal narrowing of the aorta **(B)**.

azathioprine, and mycophenolate mofetil have been favored in less severe cases (45, 91).

Better understanding of disease pathophysiology has resulted in the use of cytokine- and pathway-targeting agents such as TNFα-, IL-6, and more recently JAK-inhibitors (15, 16, 27). Beneficial effects of TNFα- and IL-6-inhibitors have been reported for more than a decade in mainly retrospective case series and case reports. Based on these data, the use of biologic agents on a case-to-case basis was proposed in the recent European consensus-based recommendations for the treatment of childhood vasculitis (78). More recently, and particularly in children, biologic agents have been preferred over cyclophosphamide when they can be accessed and afforded as they present a more favorable toxicity profile.

For TNFα-inhibitors, evidence is mainly extrapolated from adults. The largest cohort study retrospectively included 209 adults with TAK and compared efficacy of TNFα-inhibitors (63% of patients) and the IL-6 inhibitor tocilizumab (37% of patients) (92). Efficacy was equivalent between biologic agents: complete response was observed in 66% of patients on TNFα-inhibitors and 70% of patients on tocilizumab. A total of 103 relapses (median of 36 months follow-up) were reported with similar rates between TNFα-inhibitors and tocilizumab (92). These results are supported by previous studies evaluating the efficacy of TNFα-inhibitors (93–96) and comparing rates of treatment response to TNFα-inhibitors and tocilizumab in patients with TAK (97, 98).

In children, data on TNFα-inhibitors are limited to small retrospective cohorts and case reports. In a retrospective cohort of childhood-onset TAK from Canada, eleven mostly treatment refractory children were treated with TNFα-inhibitors (n = 10 treatment episodes) or tocilizumab (n = 2 treatment episodes). Biologic agents were associated with significantly better 2-year flare-free survival rates and greater likelihood to reach inactive disease at last follow-up compared with conventional DMARDs or corticosteroids alone (44). Filocamo retrospectively reported four children with mainly refractory TAK treated with TNFα-inhibitors: two achieved remission and two partially responded (99). In addition, several other small case series and case reports have described the beneficial use of TNFα-inhibitors in children with treatment refractory TAK (100–102). TNFα-inhibitors with different mechanisms of action (monoclonal anti-TNFα antibodies and TNFα receptor) have been used, but most commonly the monoclonal anti-TNFα antibody infliximab, followed by adalimumab.

Beneficial effects and safety profiles of the IL-6 inhibitor tocilizumab have been reported in several adult and pediatric TAK cohorts (103–109). Two large retrospective cohort studies of mostly DMARD-refractory adults with TAK demonstrated significantly better event-free survival with tocilizumab compared to conventional DMARDs, and complete response rates in up to 70% of tocilizumab-treated patients (92, 109). However, a randomized, placebo-controlled trial of patients with TAK who had recently relapsed did not find a statistically significant difference between patients receiving tocilizumab and those in the placebo group, although patients receiving tocilizumab trended toward fewer relapses. Among the 36 enrolled patients, six children over the age of 12 years were included (four receiving TCZ, two placebo) and there were no new safety concerns (110). The long-term extension study confirmed a corticosteroid-sparing effect and stable/improved disease on imaging evaluation for up to 96 weeks (111). More recently, a prospective multicenter open-label trial showed high efficacy of tocilizumab in combination with corticosteroids in treatment-naïve patients with TAK, with high remission rates of 85% and corticosteroid discontinuation rates of 54% after 6 months of therapy. However, relapse rates were of 45% after tocilizumab discontinuation, highlighting the necessity of maintenance therapy (112).

In children with TAK, data on tocilizumab are scarce. Apart from the few patients included in the randomized controlled trial

(110) there are only a few retrospective case series published, reporting children with TAK with mostly DMARD-refractory disease and good response to tocilizumab with no adverse events (44, 104, 105, 113).

The discovery of the critical role of the JAK/STAT pathway in the pathophysiology of TAK paved the way for the use of JAK-inhibitors. Forty-two mainly refractory patients with TAK treated with a JAK-inhibitor (9/42 treatment-naïve patients, 3/42 with childhood-onset TAK) have been published to date with promising results (27, 114–121). Most patients were treated with the JAK 1/3 inhibitor tofacitinib (39/42) in combination with prednisone ± MTX or other conventional DMARDs. The largest cohort prospectively compared the efficacy and safety of corticosteroids and tofacitinib (n = 27 adults with TAK) with corticosteroids and methotrexate (n = 26 adults with TAK) (121). Patients receiving tofacitinib had significantly higher complete remission rates at 12 months (88.6 vs. 56.5%, p = 0.02), lower relapse rates (11.5 vs. 34.8%, p = 0.052) and significantly lower average corticosteroid doses during the study period compared to those on methotrexate. Treatments were well tolerated with a good safety profile (121).

Various other biologic agents have been used with partial success in adults with TAK. Rituximab has been proposed as a therapeutic option following evidence of an implication of B cells in the pathophysiology of TAK (31) and its potential benefits have been reported in retrospective case reports of treatment-refractory adult patients with TAK (31, 33). The use of rituximab in childhood-onset TAK has been described, but sound data are lacking (45). Ustekinumab, a monoclonal antibody against IL-12/IL-23 has been used following detection of *IL12B* as a susceptibility gene for TAK in genome-wide association studies (122). Clinical and laboratory response has been reported to be good, although improvement was not observed on imaging (123). Finally, a randomized, placebo-controlled trial in adult patients with TAK did not find better flare-free survival in patients treated with the T cell co-stimulation inhibitor abatacept compared with controls (124).

However, although biologic agents, and in particular TNFα-, IL- 6-, and JAK-inhibitors seem promising, not all patients respond to these treatments. For anti-TNFα agents, for example, some controversy emerges from reports of patients who developed TAK while they were being treated with a TNFα-inhibitor for another disease and primary non-response or even disease progression has been described under TNFα-, IL-6, and JAK-inhibitors (44, 114, 115, 125–129). Of note, assessment of disease activity is even more challenging in tocilizumab-treated patients, as biologic inflammation may be suppressed and disease activity scores that include acute phase reactants may not be sensitive enough (72, 129).

More data are required to better understand, when to start a biologic agent, which biologic therapy to choose for an individual patient and how long to continue treatment. While biologic agents are currently considered mainly in case of relapsing or refractory disease despite conventional DMARDs, recent treatment approaches have used them at treatment initiation and independently from disease severity in treatment-naïve adults (89, 112) and children (44), but the long-term outcome has yet to be determined. Further studies will be needed to provide more data to guide therapeutic management.

Antiplatelet therapy is often prescribed in the management of TAK, although there is no evidence to support its usefulness. Its benefits need to be weighed against potential side effects, principally gastrointestinal hemorrhage.

Vascular Interventions

Endovascular interventions or reconstructive surgery may be required to treat major vascular complications. Ideally, they should be performed in phases of stable remission, but urgent interventions may be necessary in case of arterial dissection or critical vascular ischemia (130). In children with TAK, endovascular interventions are performed mainly for treatment-resistant reno-vascular hypertension, restenosis is observed in about half of the patients within one year (131, 132).

ASSESSMENT OF DISEASE ACTIVITY AND DAMAGE

Assessment of disease activity is often difficult in clinical practice because an outcome measure that reliably reflects vascular inflammation does not exist. The current tools insufficiently reflect disease activity in pediatric large vessel vasculitis, although the Pediatric Vasculitis Activity Score (PVAS) has been validated in children. Other disease activity measurement tools such as the ITAS 2010 and ITAS-A, which additionally includes acute phase reactants, have been developed specifically for TAK, but are only validated in adults.

The US National Institute of Health (NIH) criteria, commonly used to assess disease activity in TAK, define active disease as the presence of constitutional symptoms, new bruits, increased acute phase reactants or new angiographic findings (133).

Although tools for assessment of disease damage exist for adults with TAK, none has been validated in children. These scores may help to assess accumulated damage over time, but discrimination between disease and treatment-related damage may be difficult (134).

PROGNOSIS/EVOLUTION

Children with TAK present with more systemic inflammation and more widespread vascular disease than adults. However, relapses and accrued damage are high and equally frequent in both groups and seem to be associated with longer duration of symptoms (44, 52, 61).

Recent advances in disease recognition and therapeutic strategies have decreased morbidity and mortality in TAK. Several recent studies have reported the benefit of biologic therapies such as TNFα-inhibitors or Tocilizumab in adults, with up to 80% of patients achieving complete remission at 6 months (92, 112). In children, data are scarce. A retrospective cohort study demonstrated significantly higher 2-year flare-free survival

rates and higher rates of inactive disease at last follow-up in children treated with biologic agents, compared with those on non-biologic therapies (44).

Young age and high CRP at disease onset, stroke, lower BMI, longer duration of symptoms and high accrued damage scores have been associated with poor outcomes including increased mortality in childhood-onset TAK (45, 46, 52). In the recent pediatric cohorts, mortality rate varied between 0 and 27% (6, 7, 44–46, 54–59). Despite growing literature, more data are needed, particularly in children, to better describe the long-term outcome of new therapeutic strategies and to identify factors predicting treatment response and relapses.

DISCUSSION

Timely diagnosis of childhood-onset TAK is important because the disease is associated with a significant morbidity and mortality. Despite persisting gaps in the knowledge of the pathophysiology of TAK, critical inflammatory pathways contributing to the disease begin to be elucidated and provide avenues for new treatment approaches. Treatment recommendations are mostly based on adult TAK studies with level of evidence two or three, although few randomized controlled trials have been published with biologic agents. Corticosteroids remain the mainstay for induction of remission, but biologic agents such as TNFα- or IL-6- and JAK-inhibitors are increasingly used, particularly in severe, relapsing or DMARD-refractory cases. Whether upfront use of biologic agents improve long-term outcome, yet needs to be investigated.

Large international collaborative efforts are required to conduct well-designed studies to determine efficacy of current therapeutic regimens, to identify reliable biomarkers that help to assess disease activity and guide treatment choice, and to better define the long-term outcome of pediatric TAK using validated pediatric outcome measures. One of the main goals is thereby finding therapeutic strategies to reduce cumulative corticosteroid use and to achieve the best possible efficiency-tolerance balance with minimal cumulative damage.

AUTHOR CONTRIBUTIONS

FA reviewed the literature and drafted the manuscript. RY and RL reviewed the literature and revised the manuscript critically for important intellectual content. All authors contributed to the article and approved the submitted version.

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Working Towards a Treat-to-Target Protocol in Juvenile Proliferative Lupus Nephritis – A Survey of Pediatric Rheumatologists and Nephrologists in Germany and Austria

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Background: To describe treatment practices for juvenile proliferative lupus nephritis (LN) class III and IV of pediatric rheumatologists and nephrologists in Germany and Austria in preparation for a treat-to-target treatment protocol in LN.

Methods: Survey study by members of the Society for Pediatric and Adolescent Rheumatology (GKJR) and the German Society for Pediatric Nephrology (GPN) on diagnostics and (concomitant) therapy of LN.

Results: Fifty-eight physicians completed the survey. Overall, there was a considerable heterogeneity regarding the suggested diagnostics and management of juvenile

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proliferative LN. Increased urinary protein excretion, either assessed by 24 h urine collection or spot urine (protein-creatinine ratio), and reduced estimated glomerular filtration rate were specified as important parameters for indication of kidney biopsy to diagnose proliferative LN and monitoring of therapy. Corticosteroids were generally proposed for induction and maintenance therapy, most often in conjunction with either mycophenolate mofetil (MMF) or cyclophosphamide (CP) as steroid-sparing immunosuppressants. MMF was clearly preferred over CP for induction therapy of LN class III, whereas CP and MMF were equally proposed for LN class IV. MMF was most often recommended for maintenance therapy in conjunction with oral corticosteroids and continued for at least 3 years and 1 year, respectively, after remission. Hydroxychloroquine was widely accepted as a concomitant measure followed by renin-angiotensin system inhibitors in cases of arterial hypertension and/or proteinuria.

Conclusion: The majority of pediatric rheumatologists and nephrologists in Germany and Austria propose the use of corticosteroids, most often in combination with either MMF or CP, for treatment of proliferative LN in children. The considerable heterogeneity of responses supports the need for a treat-to-target protocol for juvenile proliferative LN between pediatric rheumatologists and nephrologists.

Keywords: SLE, nephritis, T2T, mycophenolate mofetil, cyclophosphamide, corticosteroid, kidney biopsy

INTRODUCTION

Lupus nephritis (LN) is a substantial cause of morbidity and mortality among patients with systemic lupus erythematosus (SLE). Within 10 years of an initial SLE diagnosis, 5–20% of patients with LN develop end-stage kidney disease (1). In up to 20% of all SLE patients, the onset of the disease occurs in childhood or adolescence (2). By contrast to adults, 50 to 60% of patients with juvenile onset SLE will develop lupus nephritis (3–6).

In German registries [National Pediatric Rheumatologic Database and German Lupus Nephritis Registry of the German Society for Pediatric Nephrology (GPN)], approximately 20 patients with LN per year are newly documented (with the possibility of underrepresentation due to the level of awareness of the registries) (7). The small number of cases distributed over several centers hampers a standardized procedure for this difficult-to-treat disease.

To improve long-term outcomes in children and adolescents with rheumatic diseases, the definition and evaluation of therapeutic strategies (treat-to-target, T2T) is an important tool (8). To develop these tools, the PRO-KIND initiative (Projekte zur Klassifikation, Überwachung und Therapie in der Kinderrheumatologie/Projects on classification, monitoring and therapy in pediatric rheumatology) within the Commission of the Society for Pediatric and Adolescent Rheumatology (Gesellschaft für Kinder- und Jugendrheumatologie, GKJR) was founded in 2015. Their task is to develop T2T protocols for the most prevalent pediatric rheumatic diseases in Germany, some of which have been published (9–15). In 2019, the initiative received funding from the Joint Federal Committee (Gemeinsamer Bundesausschuss, GBA) to evaluate the practicability and effectiveness of these protocols. To achieve this aim, 500 patients with new-onset rheumatic diseases will be recruited in a register study and treatment of these patients will be prospectively followed for 12 months. The register is currently recruiting patients until September 2022.

For SLE and specifically for LN, there is currently no T2T therapy protocol, while consensus treatment plans (CTPs) of the Childhood Arthritis and Rheumatology Research Alliance (CARRA) and the Single Hub and Access point for pediatric Rheumatology in Europe (SHARE) initiative's recommendations are available (16, 17). Therefore, the development of an agreed consensus treatment protocol between pediatric rheumatologists

Abbreviations: ACE, angiotensin-converting enzyme; ACR, American College of Rheumatology; ASA, acetylsalicylic acid; ATII, angiotensin II; AZA, azathioprine; BILAG, British Isles Lupus Assessment Group index; BSA, Body Surface Area; CARRA, Childhood Arthritis and Rheumatology Research Alliance; C-HAQ, Childhood Health Assessment Questionnaire; CP, cyclophosphamide; CR, complete response; CsA, cyclosporin A; CTP, consensus treatment plan; CV, cardiovascular; ECLAM, European Consensus Lupus Activity Measurement; eGFR, estimated glomerular filtration rate; ERA-EDTA, European Renal Association-European Dialysis and Transplant Association; EULAR, Joint European League Against Rheumatism; GKJR, Society for Pediatric and Adolescent Rheumatology; GnRH, gonadotropin releasing hormone; GPN, German Society for Pediatric Nephrology; HCQ, hydroxychloroquine; IVIG, intravenous immunoglobulin; LMWH, low molecular weight heparin; LN, lupus nephritis; MMF, mycophenolate mofetil; MP, methylprednisolone; NSI, non-steroidal immunosuppression; PDN, prednisolone; POF, premature ovarian failure; PRO-KIND, Projekte zur Klassifikation, Überwachung und Therapie in der Kinderrheumatologie/Projects on classification, monitoring and therapy in pediatric rheumatology; RBC casts, Red Blood Cell casts; RTX, rituximab; SHARE, Single Hub and Access point for pediatric Rheumatology in Europe; SLE, systemic lupus erythematosus; SLEDAI-2K, Systemic Lupus Erythematosus Disease Activity Index 2000; SMILEY, Simple Measure of Impact of Lupus Erythematosus in Youngsters; T2T, treat-to-target; TAC, tacrolimus.

and nephrologists is a key goal. To develop such a protocol, the PRO-KIND SLE working group evolved and conducted a survey together with the SLE working group of the GPN. This survey addressed current diagnosis and treatment of patients with proliferative LN in Germany and Austria on the basis of different case vignettes. The survey was distributed *via* the mailing lists of GKJR and GPN, and 58 German-speaking pediatric rheumatologists and nephrologists completed this survey and the data is presented here.

MATERIALS AND METHODS

Survey

A survey (**Supplementary Appendix**) was developed by the PRO-KIND SLE working group and representatives of the GPN. The survey consisted of 25 closed and open-ended questions. Questions (a combination of Likert scale, multiple choice, and open comments) included:

- The respondent's field of activity and type of workplace, as well as their age group
- Whether the respondents are currently treating patients with SLE or how many they have treated in their career so far
- The description of patients with LN WHO class III or IV and further detailed questions on
  - Diagnostics,
  - Indication for kidney biopsy in SLE patients,
  - Activity assessment of SLE,
  - Therapy for proliferative LN class III or IV,
  - Definition of response to therapy in LN and,
  - Concomitant therapies and preventive measures in SLE or LN.

In August 2016, the survey link was mailed to pediatric rheumatologists and nephrologists *via* the mailing lists of GKJR and GPN. Responses were collected *via* SurveyMonkey®; a follow-up message was sent out once to encourage survey completion after a few weeks. Data collection was closed in January 2017.

Analysis

Percentages and mean values were determined from the Likert scale and multiple-choice question responses. Rating averages were calculated by adding up the score results of the Likert scale and dividing it by the number of respondents. Open-ended comments were analyzed.

Case Vignette

A 15-year-old previously healthy girl with a suspected diagnosis of SLE meeting 7 of 11 American College of Rheumatology (ACR) classification criteria (18) (malar rash, photosensitivity, oral ulcers, renal disorder, hematologic disorder, positive ANA titer, and immunologic disorder) was presented in a case vignette once with LN class III and once with LN class IV. Based on this case vignette, questions regarding further diagnostic and therapeutic procedures were queried in the survey (see **Supplementary Appendix** for full survey).

RESULTS

Respondent Demographics

Of all pediatric rheumatologists (n = 129) and nephrologists (n = 315) contacted, a total of 58 responded and 42 fully completed the survey, resulting in a response rate of 13 and 9.5%, respectively. Most respondents (n = 25) belong to the age group of 41–50 years, the others belong to the age groups 51–60 years (n = 19), 31–40 years (n = 8) and >60 years (n = 6), respectively (**Figure 1A**).

The participants were mostly pediatric rheumatologists (60%), followed by pediatric nephrologists (35%) and general pediatricians (5%). More than half (54%) work at a university hospital, 44% at a non-university hospital, and one participant in a general pediatric practice.

Of the participants 38% have cared for 11–20 SLE patients in their career to date, while 36% have cared for 21–50 SLE patients, 19% have treated 1–10 and 7% have treated more than 50 SLE patients (**Figure 1B**).

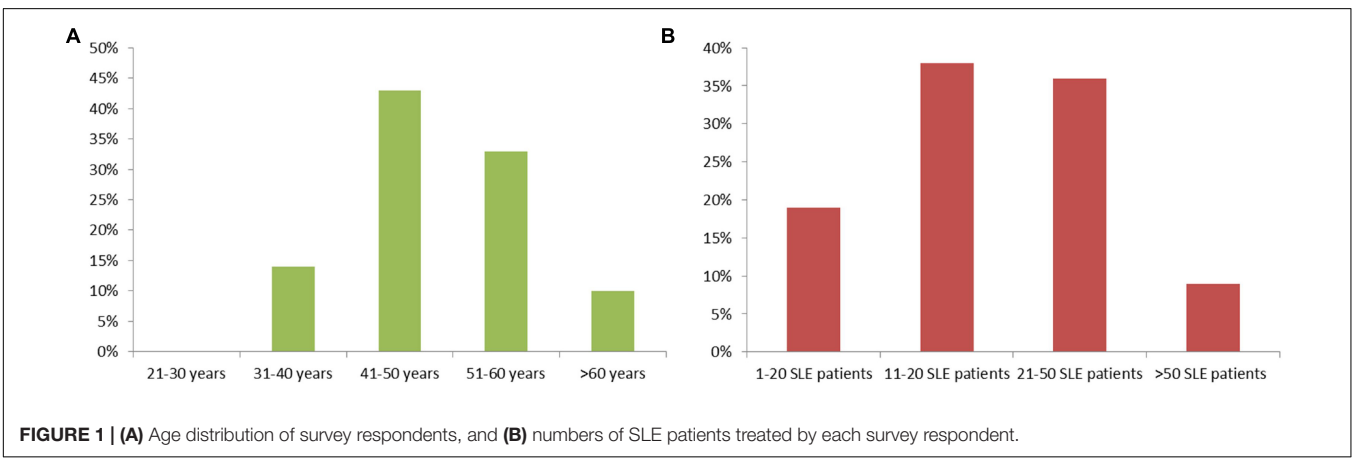

FIGURE 1 | (A) Age distribution of survey respondents, and **(B)** numbers of SLE patients treated by each survey respondent.

TABLE 1 | Consultants involved in the diagnosis and treatment planning of an SLE patient with suspected LN.

Discipline	Total number of respondents (%)
Pediatric nephrologist	38 (91)
Ophthalmologist (with fundus)	29 (69)
Pediatric cardiologist	24 (57)
Pediatric rheumatologist	23 (55)
Pediatric pulmonologist	11 (26)
Hematologist/Haemostaseologist	8 (19)
Neuropediatrician	7 (16)
Dermatologist	6 (14)
Psychologist/Psychiatrist	4 (9)
Gynecologist	2 (5)
Pediatric endocrinologist	1 (2)

Diagnostics

The vast majority of survey respondents (91%) would involve a pediatric nephrologist in the initial diagnosis and treatment planning of a patient with LN; other disciplines involved by the majority are ophthalmologists and cardiologists (see **Table 1**). 55% of respondents would suggest consulting a pediatric rheumatologist, which suggests that, depending on the presentation of the patient, pediatric rheumatologists are less frequently involved in the initial diagnosis and treatment planning.

When assessing the extent of LN, protein excretion in 24 h collection urine (>300 mg/m^2 and 24 h or ≥0.5 g per 24 h) was rated as most essential, above the protein-creatinine ratio in spot urine (>0.2 g/g or >20 mg/mmol). However, several other parameters, e.g., dip-stick protein, and serum creatinine were also considered helpful (see **Table 2**).

Kidney Biopsy for Diagnosis of Lupus Nephritis

According to the majority of the respondents (98%), the decision to perform a kidney biopsy is made on the basis of relevant pathological urine and kidney findings. A pathologic urine finding requiring kidney biopsy was agreed upon by 100% (n = 42) of respondents for nephrotic-range proteinuria [>1 g/m^2 per 24 h or protein-creatinine ratio > 2 g/g creatinine (>200 mg/mmol)], 98% (n = 41) for rapidly progressive proteinuria, 62% (n = 26) for pathologic urine status (e.g., >5 erythrocytes/high power field and/or detection of RBC casts) with mild-moderate proteinuria (≤1 g/m^2 per 24 h or protein-creatinine ratio 0.2–2 g/g creatinine or 20–200 mg/mmol), 48% for mild-moderate proteinuria with normal urine status, and 24% for pathologic urine status without mild-moderate proteinuria. Pediatric nephrologists tended to propose more frequently isolated mild-moderate proteinuria as an indicator for kidney biopsy as compared to rheumatologists (60 vs. 45%). Parameters also considered important for the indication of a kidney biopsy are listed in **Table 3**, including reduced eGFR < 60 ml/min per 1.73 m^2 and an increase in serum creatinine. By contrast, highly elevated double-stranded DNA antibodies alone and patients' ethnicity were considered not very important.

Activity Assessment of Systemic Lupus Erythematosus

To monitor SLE activity, more than 90% of respondents suggest the use of the Systemic Lupus Erythematosus Disease Activity Index 2000 (SLEDAI-2K) as a validated tool; further, Physician Global Assessment (76%), Parent/Patient Global Assessment (64%), and Childhood Health Assessment Questionnaire (C-HAQ) (52%) were considered relevant. Other tools such as Simple Measure of Impact of Lupus Erythematosus in Youngsters (SMILEY), which is not available in German, and European Consensus Lupus Activity Measurement (ECLAM) (10% each) and British Isles Lupus Assessment Group (BILAG) index (5%) were considered less relevant.

Therapy for Systemic Lupus Erythematosus With Proliferative Lupus Nephritis Class III

As the answers on therapy schemes were a combination of Likert scale, multiple choice, and open comments, the different dosing regimens are displayed in the **Supplementary Appendix**. Only significant differences are described, otherwise no clear preference for the proposed dosing regimens were seen.

The hypothetical patient with LN outlined in the case vignette, presented with proteinuria 500 mg/m^2 and protein-creatinine ratio 0.8 g/g creatinine (90 mg/mmol), erythrocyte cylinder Erys: 10/high power field, eGFR: 110 ml/min per 1.73 m^2 and blood pressure at the 75th percentile.

For **induction** therapy for the SLE patient with LN class III, as outlined in the case vignette, 54% (n = 22) of respondents opted for the combination of intravenous and oral corticosteroid therapy (**Table 4**), and similar numbers suggest mainly intravenous (n = 10) or mainly oral (n = 9) therapy.

For non-steroidal immunosuppressive therapy (NSI), 74% respondents (n = 31) suggest initiation of therapy with mycophenolate mofetil (MMF) at a dosage of 1000–1200 mg/m^2 per day, with either a maximum of 3 g (n = 15) or 2 g per day (n = 16). The lower MMF dosage was more frequently proposed by pediatric rheumatologists compared to nephrologists (50 vs. 27%). Other suggested additional immunosuppressants (multiple answers possible, see **Supplementary Appendix** for dosing regimens) were cyclophosphamide (CP) [n = 7 (17%), with no clear preference for the preferred dosage], azathioprine (AZA), and rituximab (RTX) (n = 3 each). Another 3 respondents indicated that they would not use any other immunosuppression in addition to corticosteroid therapy. In the open-ended comments, hydroxychloroquine (HCQ) was mentioned as an immunomodulatory. This concomitant drug for SLE was not part of the selection, as it is not specifically for the treatment of LN. Primary therapy with cyclosporin A (CsA) was not suggested by any respondent.

For **maintenance** therapy after achieving disease inactivity and after at least 6 months, 39% (n = 16) of respondents opted to discontinue corticosteroid therapy upon complete remission of the nephritis (based on normalization of proteinuria and eGFR) and 61% (n = 25) decided to continue corticosteroid therapy for at least one more year. There was no clear consensus for PDN

TABLE 2 | Laboratory parameters in terms of their importance in assessing the extent of LN (answers by Likert scale: 1 = very important, 2 = somewhat important, 3 = not very important, 4 = not important at all; with rating average of respondents).

	1 = very important; total number of respondents	2 = somewhat important; total number of respondents	3 = not very important; total number of respondents	4 = not important at all; total number of respondents	Rating average
24 h collection urine: protein excretion > 300 mg/m^2 per 24 h or ≥0.5 g/1.73 m^2 per 24 h	36	4	2	0	1.19
Spot urine collection: protein-creatinine ratio > 0.2 g/g (>20 mg/mmol) creatinine	29	13	0	0	1.31
Serum creatinine	26	13	2	0	1.41
Urine dip-stick: protein > twofold positive	19	19	4	0	1.64
Schwartz formula: estimated glomerular filtration rate (eGFR)	18	16	6	0	1.70
Cystatin C: estimated GFR (eGFR)	15	19	6	2	1.88
Creatinine clearance/BSA using 24 h collection urine	10	21	7	2	2.03

TABLE 3 | Other relevant parameters for the indication of a kidney biopsy (answers by Likert scale: 1 = very important, 2 = somewhat important, 3 = not very important, 4 = not important at all; with rating average of respondents).

	1 = very important; total number of respondents	2 = somewhat important; total number of respondents	3 = not very important; total number of respondents	4 = not important at all; total number of respondents	Rating average
eGFR < 60 ml/min per 1.73 m^2	37	3	0	1	1.15
Elevated serum creatinine levels	33	6	0	1	1.23
eGFR < 90 ml/min per 1.73 m^2	24	15	1	1	1.49
Elevated blood pressure (>95th percentile)	20	13	6	2	1.76
Combination of high auto-antibodies (dsDNA and/or nucleosomes) plus decreased complement levels (C3 and/or C4)	15	11	12	2	2.03
Strongly decreased C3	11	14	12	2	2.13
Strongly decreased C4	10	13	13	2	2.18
Patient ethnicity (African–American, Hispanic, Asian)	7	13	14	5	2.44
Strongly increased anti-dsDNA	6	11	11	9	2.62

dosing in maintenance therapy, with half of the subgroup opting for 5–7.5 mg per day (or 0.15–0.2 mg/kg per day). BSA adjusted corticosteroid dosing was preferred by pediatric nephrologists, whereas rheumatologists preferred dosing according to body weight. For further immunosuppression in the context of maintenance therapy, most respondents (n = 24, 57%) suggested MMF (with a dosage of 1000–1200 mg/kg per day, max. 2 g per day). 8 respondents (20%) would prefer therapy with AZA, 3 (8%) with RTX (with no clear preference for the proposed dosing regimens), and 2 (5%) with CsA.

In case of non-response to induction therapy in LN class III, 5% of respondents (n = 2) suggest continuing the basic medication and only increase PDN p.o. or MP i.v. dose. By contrast, the remaining 95% of respondents (n = 39) would add an immunosuppressive drug, depending on the previous therapy, in addition to corticosteroids. In general (multiple answers possible), 16 respondents (32%) suggested CP, another 16 respondents (32%) suggested MMF (see **Supplementary Appendix** for suggested dosage regimens, no clear preference emerged among respondents), 11 (22%) suggested RTX, and 7 (14%) CsA. Two respondents proposed plasmapheresis and one immunoadsorption. In the open comments, therapy with ofatumumab (alone or in combination with MMF) was suggested twice.

TABLE 4 | Suggested corticosteroid induction therapies for proliferative lupus nephritis class III or IV (adapted from Refs. 17, 63).

	Prednisolone/methylprednisolone (PDN/MP) therapy in the first 6 months
Mainly intravenous (i.v.)	MP i.v. 15–30 mg/kg (max 1 g) or 300–500 mg/m^2 for 3 days, then i.v. MP pulse therapy initially 1x/week, then 1x/month+ start PDN *per os* (p.o.) 0.5 mg/kg → reduction → target PDN 6–10 mg/m^2/48 h or 0.2 mg/kg (up to max 10 mg/d) p.o.
Mainly p.o.	MP once i.v. 15–30 mg/kg (max 1 g) or 300–500 mg/m^2 for 3 days+ start PDN p.o. 2 mg/kg or 60 mg/m^2 for 6 weeks → reduction → target PDN 6–10 mg/m^2/48 h or 0.5 mg/kg (max 20 mg/d)
Combined i.v. + p.o.	MP i.v. 15–30 mg/kg (max 1 g) or 300–500 mg/m^2 for 3 days, further optional i.v. MP pulse therapy (max 1x/month)+ p.o. PDN start 1(–1.5)mg/kg → reduction by 10% every (1–)2 weeks → target PDN 6–10 mg/m^2/48 h or 0.2 mg/kg (up to max. 15 mg/d)

TABLE 5 | Suggested criteria in assessing remission in lupus nephritis (answers by Likert scale: 1 = very important, 2 = somewhat important, 3 = not very important, 4 = not important at all; with rating average of respondents).

	1 = very important; total number of respondents	**2 = somewhat important; total number of respondents**	**3 = not very important; total number of respondents**	**4 = not important at all; total number of respondents**	**Rating average**
Protein-creatinine ratio < 0.2 g/g (<20 mg/mmol) crea or protein excretion < 200 mg/24 h in 24 h urine collection	31	9	0	0	1.23
eGFR > 90 ml/min per 1.73 m^2	23	14	0	0	1.38
Normalization of serum complement C3	16	21	4	0	1.71
Urine sediment (erythrocytes 5/high power field, no RBC casts detectable)	15	19	6	0	1.78
SLEDAI score < 2	3	23	10	1	2.24

Therapy for Systemic Lupus Erythematosus With Proliferative Lupus Nephritis Class IV

The hypothetical patient with LN outlined in the case vignette presented with prognostically unfavorable risk factors: histology with LN WHO class IV and 50% crescent formation, proteinuria 1.5 g/m^2 per day and urinary protein-creatinine ratio 2.1 g/g creatinine (237 mg/mmol), erythrocyte cylinder 10/high power field, eGFR 72 ml/min per 1.73 m^2, blood pressure 97th percentile.

For **induction** therapy, 67% of respondents (n = 28) would opt for a combined i.v. and p.o. corticosteroid therapy and 33% (n = 14) for oral therapy only. For additional immunosuppression (multiple answers possible), a similar number of respondents suggested the use of CP (n = 23, 40%), including 3 in combination with other immunosuppressants and MMF (n = 24, 41%). Other immunosuppressants or therapies suggested were RTX (n = 8, 14%), CsA (n = 1, 2%), MTX (n = 1, 2%), and plasmapheresis (n = 1, 2%).

For **maintenance** therapy after achieving disease inactivity and after at least 6 months, 82% (n = 31) proposed continuation of corticosteroid therapy for at least one more year. Unlike in LN class III, most respondents (n = 16, 42%) suggested a dose of 5–7.5 mg per day (or 0.15–0.2 mg/kg/d), 18% (n = 7) of respondents opted to discontinue corticosteroid therapy following complete clinical remission of nephritis. Furthermore, most respondents suggest MMF (n = 34, 69%) for maintenance therapy (multiple answers possible) and others suggest RTX (n = 6, 12%), AZA (n = 6, 12%), CsA (n = 3, 6%), and CP (n = 1, 2%).

In case of non-response to induction therapy, most respondents (n = 37, 97%) opt for an extension of the basic therapy beyond the increase of the corticosteroid dose, depending on previous therapy. This most often included (multiple answers possible) RTX (n = 21), followed by CP (n = 17), MMF (n = 11), CsA (n = 6), AZA (n = 3), plasmapheresis (n = 6), and immunoadsorption (n = 3). In the open comments, therapy with ofatumumab (alone or in combination with MMF) was indicated twice, as well as therapy with intravenous immunoglobulin (IVIG) (n = 1) and tacrolimus (n = 1) and combinations of immunosuppressants, e.g., MPN + RTX + MMF + CsA or RTX + MMF.

Definition of Response to Therapy in Lupus Nephritis

Parameters most frequently considered relevant for assessing a satisfactory response to LN therapy were either the urinary protein-creatinine ratio in a spot urine, or 24 h protein excretion

and normalization of eGFR (>90 ml/min per 1.73 m^2). However, normalization of urine sediment and normalization of serum complement C3 were also considered important decision tools (see **Table 5**).

As shown in **Table 5**, remission was defined by the following criteria: protein-creatinine ratio <0.2 g/g creatinine (<20 mg/mmol), eGFR > 90 ml/min per 1.73 m^2, and SLEDAI score < 2. Time acceptable to achieve remission was selected by participants.

In case of LN class III, 71% (n = 29) of participants considered an interval of 8–12 weeks until remission, following induction therapy, as acceptable. Seven% of respondents considered an interval of 24 weeks as acceptable, while 5% would expect a therapeutic response after only 2 weeks, or 17% after 4 weeks, following induction therapy.

In cases of LN class IV, 49% (n = 20) of respondents considered a period of 8–12 weeks until reaching a therapeutic response (see **Table 5**) to be acceptable, whereas 5% would require this after only 2 weeks, or 34% after 4 weeks, following induction therapy, and 10% stated the acceptable interval until response to be 24 weeks and 2% even 52 weeks.

In case of a satisfactory treatment response, most respondents (64%, n = 27) suggest continuing immunosuppressive therapy for at least 3 years, whereas 10% (n = 4) suggest stopping treatment after 1 year and 26% (n = 11) suggest continuing for more than 3 years. Pediatric nephrologists proposed longer treatment durations.

Table 6 shows different scenarios for repeat kidney biopsies. Respondents saw different indications, but most would rather perform a repeat kidney biopsy in the event of a suspected recurrence of nephritis. Other reasons included persistence of proteinuria for over one year on maintenance therapy, partial response after 6–12 months, or after 3–4 months in case of non-response at the end of induction therapy.

Concomitant Therapy and Preventive Measures for Lupus Nephritis

There was general agreement that patients should receive HCQ as a concomitant therapy for LN (**Table 7**). Other important measures included therapy with an angiotensin-converting enzyme (ACE) inhibitor or angiotensin II (ATII) receptor antagonist in cases of arterial hypertension and/or proteinuria, followed by gonadotropin releasing hormone (GnRH) analogs or fertility preservation, prior to therapy with CP, prescription of progestogen (especially in antiphospholipid syndrome), vitamin D substitution and the implementation of vaccinations and infection prophylaxes.

DISCUSSION

This study provides new insights into treatment practices of pediatric subspecialists caring for patients with proliferative LN class III and IV in Germany and Austria. As early diagnosis and prompt treatment of LN can improve long-term renal survival (19), the two working groups (PRO-KIND SLE working group and the GPN SLE working group) have the following common goal: to develop consensus protocols for clinical practice with clearly defined treatment goals including timelines for achieving these goals.

The principle of T2T has been successfully introduced for several rheumatic diseases including juvenile idiopathic arthritis, recently published (10–15). Identifying appropriate therapeutic targets and translation of these targets into clinical practice will lead to improved care for patients and, subsequently, to a better outcome (20). International and German consensus treatment recommendations for LN in children are available (16, 17, 21, 22), but lack a T2T approach.

Overall, the answers to the survey questions reflect a large heterogeneity in the management of juvenile proliferative LN in Germany and Austria, supporting the need to design T2T strategies which should be consented by the relevant subspecialties caring for SLE patients.

Rheumatologists participating in this survey are more likely to involve a nephrologist in the diagnosis and treatment planning of an SLE patient with suspected LN than vice versa, while international recommendations emphasize the inclusion of both disciplines (16, 21). That only 55% consult a rheumatologist might also be partly due to the fact that the majority of respondents are themselves pediatric rheumatologists. Since isolated lupus nephritis is a very rare condition (23–25) and SLE is a multisystem disease, interdisciplinary collaboration is important and worthy of support, to which the joint establishment of a treatment protocol could contribute.

When assessing the extent of LN, protein excretion in 24 h collection urine (>300 mg/m^2 per 24 h or ≥0.5 g per 24 h) and protein-creatinine ratio (>0.2 g/g creatinine or >20 mg/mmol) in spot urine collection were evaluated as key parameters. Recently, Smith et al. did not find significance of proteinuria in differentiating SLE patients with and without development of LN longitudinally (26). However, proteinuria is generally noted in patients with juvenile proliferative LN (7) and remains an important tool for detecting subclinical renal involvement in SLE (16). In our survey, serum creatinine and eGFR were also assessed as important parameters in evaluating the extent of LN. It is worth mentioning, that these two parameters failed to discriminate between patients with and without LN in the United Kingdom JSLE Cohort Study (26).

The definition of therapeutic targets is obviously a core element of the T2T approach. To date, the literature does not offer a uniform definition of complete remission in LN. The Joint European League Against Rheumatism and European Renal Association-European Dialysis and Transplant Association (EULAR/ERA-EDTA) recommendations define proteinuria as <0.5 g/24 h and normal or near normal (within 10% of normal eGFR if previously abnormal) eGFR as complete response (CR), and this definition has also been adopted by the SHARE Initiative (16, 27). In our survey, respondents also rated the increase of eGFR to >90 ml/min/m^2 as a very important target for remission, as well as protein excretion in 24 h urine collection < 200 mg/24 h, which is somewhat stricter than the above recommendations. Furthermore, normalization of serum complement C3 is also an important decision tool to define CR to the respondents, while it has been shown to have modest

TABLE 6 | Indications for repeat kidney biopsy during follow-up of lupus nephritis (answers by Likert scale: 1 = fully agree, 2 = tend to agree, 3 = partly/partly, 4 = tend to disagree, 5 = do not agree; with rating average of respondents).

	1 = fully agree; total number of respondents	2 = tend to agree; total number of respondents	3 = partly/partly; total number of respondents	4 = tend to disagree; total number of respondents	5 = do not agree at all; total number of respondents	Rating average
In case of suspected recurrence of nephritis	16	16	10	0	0	1.86
In maintenance therapy if proteinuria persists > 1 year	13	15	7	4	0	2.05
Persistent eGFR < 90 ml/min per 1.73 m^2	3	10	15	11	0	2.87
Not necessary in case of confirmed LN class III, IV, or V	4	11	11	4	6	2.92
At the end of induction therapy:	0	0	7	8	7	4.00
• regardless of response to therapy	0	0	0	10	19	4.66
• in case of only partial response after 6–12 months	7	15	9	3	2	2.39
• in case of no response after 3–4 months	6	16	10	3	0	2.29
In remission prior to discontinuation of maintenance therapy	0	0	2	12	25	4,59

specificity for active LN (28). On the other hand, in a recent British cohort, C3 levels at baseline were a significant predictor for subsequent LN development (26). In summary, targets in the management of LN need to be defined and should be the subject of consensus findings.

When renal involvement is suspected in patients with SLE, kidney biopsy is the widely accepted gold standard (16, 29). In our survey, respondents stipulated that nephrotic-range or rapidly progressing proteinuria were important indicators for kidney biopsy, reflecting the consensus in adult SLE (27, 30–32). The fact that respondents of this survey failed to rate ethnicity as an important parameter in the indication for kidney biopsy, is in discordance with the literature: African Americans, East Asians, and Hispanics with SLE are more likely to develop LN than are SLE patients of European descent (33, 34). This result may reflect the historically lower prevalence of these ethnicities in Germany and Austria and the lack of awareness of this risk factor. Many pediatric nephrologists and rheumatologists continue to follow ACR recommendations when deciding on the necessity of a kidney biopsy (17, 35).

For induction therapy of proliferative LN, our survey suggests that the use of corticosteroids is mandatory, with respondents preferring combined intravenous and oral administration. The majority of participants suggested maintaining PDN treatment for at least one year, but consider discontinuation thereafter, in order to avoid long-term side effects (36). However, there was no consensus on optimal dose and duration of PDN treatment in children in order to balance efficacy and side effects. A recent study conducted by the GPN in children with LN class III or IV, showed corticosteroid toxicity in 42% and growth failure in 78% of children in the first year of treatment (7). Therefore, a consensus for optimal corticosteroid dosing is of utmost importance.

Mycophenolate mofetil was clearly preferred over CP for induction therapy, in addition to corticosteroids in patients with LN class III. By contrast, CP (0.5 g/m^2/month for 6 months) and MMF were rated equally for induction treatment of LN class IV. This approach is supported by recent registries and cohort studies suggesting the comparability of MMF and CP in induction therapy for proliferative LN in children, although no difference between MMF and CP with respect to treatment-associated side effects was noted with a follow-up of maximum 13 months (7, 37, 38). The use of high-dose intravenous CP (0.5–0.75 g/m^2 monthly for 6 months) was recommended to be reserved for adult patients with proliferative LN class III/IV showing unfavorable clinical (nephritic urine sediment and impaired renal function with an eGFR between 25 and 80 ml/min/1.73 m^2), or histologic (crescents or necrosis in >25% of glomeruli) prognostic factors (21). Of note, there was no consensus on the MMF dosage regimen to be used during induction treatment with half each of the participants proposing 2 and 3 g, respectively. The latter was more frequently proposed by pediatric nephrologists and is in line with recent guidelines for treatment of proliferative LN in adults (21).

Most physicians considered an interval of 12 weeks as acceptable to assess treatment response, which is in agreement with a survey of North American pediatric nephrologists and rheumatologists (39). This timeline may be rather optimistic, as recent registry data showed that 25 and 17% of German patients with juvenile LN class III/IV receiving induction treatment with corticosteroids in combination with either MMF of CP showed persistent proteinuria after 3 and 6 months, respectively (7). Again, consensus on timelines for treatment targets need to be

TABLE 7 | Useful concomitant therapies or preventive measures in patients with lupus nephritis (answers by Likert scale: 1 = very important, 2 = somewhat important, 3 = not very important, 4 = not important at all; with rating average of respondents).

	1 = very important; total number of respondents	2 = somewhat important; total number of respondents	3 = not very important; total number of respondents	4 = not important at all; total number of respondents	Rating average
Hydroxychloroquine	37	5	0	0	1.12
ACE inhibitor or ATII receptor antagonist in case of arterial hypertension	34	7	0	0	1.17
Indication vaccinations (e.g., influenza, pneumococcus)	26	15	0	0	1.34
Sperm or oocyte preservation before CP	16	9	3	0	1.54
Passive use of Low Molecular Weight Heparin (LMWH) (in case of immobility and/or nephrotic syndrome)	21	15	5	0	1.61
Low-dose acetylsalicylic acid (ASA) in case of positive antiphospholipid antibodies	17	21	3	0	1.66
GnRH analogs in post-pubertal patients and CP	19	13	5	1	1.68
Pneumocystis prophylaxis under CP	19	15	6	0	1.68
IgG substitution in case of IgG deficiency after RTX	19	16	6	0	1.68
ACE inhibitor or ATII receptor antagonist in case of proteinuria	7	15	1	0	1.74
Calcium supplementation	20	7	9	1	1.76
Gynecology consult for Post-pubertal patients once yearly with Pap smear	16	17	6	1	1.80
Vitamin D	9	10	8	0	1.96
• fixed dose of 1000 IU/d	10	10	11	1	2.09
• level-adapted (target 30 μ g/l or 75 nmol/l)	5	18	16	2	2.37
Pneumocystis prophylaxis under RTX	13	14	10	1	1.97
Start contraception for patients of childbearing age	8	16	7	0	1.97
• always a progestogen-only contraceptive pill	6	8	6	4	2.33
• progestogen-only contraceptive pill only if antiphospholipid antibodies are positive	15	19	5	1	1.80
Monitoring of CMV viral load in relapses of the underlying disease or before intensification of immunosuppression	6	23	10	1	2.15

better defined. This is important, as it will guide physicians toward switching to second-line treatments.

In case of non-response to induction therapy, most respondents opt for a switch of medication beyond the increase of the corticosteroid dose, depending on previous therapy. This most often included RTX (preferred by 8% among nephrologists vs. 25% among rheumatologists) (39), followed by CP, MMF, and CsA, whereas other measures such as plasmapheresis and immunoadsorption were rarely proposed. This reflects what is currently recommended for adult patients with proliferative LN in case of treatment failure or partial response only, i.e., switching to MMF, a calcineurin inhibitor, intravenous CP or RTX (21, 40–49).

Mycophenolate mofetil was most often recommended for maintenance therapy in LN class III/IV, in conjunction with oral corticosteroids, whereas AZA or CsA were rarely suggested,

which is in line with recommendations for adults with proliferative LN (21, 49).

As for concomitant therapies and preventive measures in childhood LN, results of our survey echo the published data, that pediatric SLE patients should all be treated with HCQ (50). As there is evidence in adult SLE patients that ACE inhibitors or ATII receptor antagonist have a protective effect on the kidneys in case of proteinuria (51, 52), its use is recommended in children with LN and proteinuria (16), a view widely shared by respondents of this survey. In addition, respondents of this survey confirm the importance of using inhibitors of the renin-angiotensin system in arterial hypertension, as documented in international recommendations (53).

The question of fertility preservation in therapy with CP is particularly relevant in adolescent patients. Low-dose intravenous CP does not seem to impact ovarian reserve as measured by anti-Mullerian hormone (54) and the SHARE initiative did not include recommendations for fertility preservation (16). Still, the occurrence of premature ovarian failure (POF) and the risk of permanent sterility in young men the with CP exposure is a rare but serious event (55, 56). In addition to the CP dose limitation that appears to minimize the risk of fertility reduction (57), the combined use of GnRH analogs with CP therapy was shown to be associated with a significant reduction of POF among premenopausal women with SLE, suggesting that the addition of GnRH analog can be a strategy to prevent POF among premenopausal women (58). In addition to endorsing this measure, participants of the survey also consider sperm or oocyte preservation before CP to be useful which, of course, must be discussed individually with each patient (59).

It was shown that low-dose ASA may be beneficial in the primary prophylaxis of cardiovascular (CV) events in SLE patients (60, 61). Considering the general increased risk for a CV event in SLE patients (62) and especially with positive antiphospholipid antibodies, a low-dose acetylsalicylic acid (ASA) therapy in case of positive antiphospholipid antibodies can be considered useful, as suggested by our respondents and also in the literature (50).

The limitations of our study are low participation/response rates (which is not unusual for an online survey distributed *via* mail) and which may be related to the treatment of LN being primarily in highly specialized centers. However, LN in children and adolescents is a rare condition. Therefore, the number of rheumatologists and nephrologists treating children with LN is also low and likely only those felt consequently addressed to answer the survey. In addition, there is a possible selection bias in only addressing members of the mailing lists of GKJR and GPN. We realize that the definitions of treatment response and failure need to be more clearly delineated. Finally, the role of adherence and therapeutic drug monitoring to optimize treatment with MMF, and the use of "multitarget therapy" (i.e., MMF in combination with a calcineurin inhibitor) for induction of LN were not included in this survey, as these measures have only recently gained attention. The same accounts for new therapeutic options, such as belimumab, which has been approved as an add-on therapy for adult SLE patients with LN in Germany since 2021. In this 2017 survey, belimumab was not yet considered as a treatment option, but which may gain importance in childhood LN therapy.

Several additional aspects should be discussed when treating children and adolescents with LN, such as treatment adherence (possibly promoting intravenous drug administration), the issue of growth (corticosteroid dose limitation), fertility, necessitating CP dose limitation, as well as the psychosocial aspects, such as schooling and socialization with peers. In a study conducted by the GPN in children with LN class III or IV, 80% of patients had drug-related complications in the first year of treatment, including glucocorticoid toxicity in 42% of children and growth retardation in 78% (7).

In conclusion, our survey reveals that the majority of German and Austrian pediatric rheumatologists and nephrologists would use corticosteroids, most often in combination with either MMF or CP for induction treatment of juvenile proliferative LN. Minimization of steroid-exposure remains a major challenge in these children and adolescents, asking for well-designed clinical trials to define the optimal dosage and duration of corticosteroid treatment. The considerable heterogeneity of responses highlights the need for a treat-to-target protocol (T2T) between pediatric rheumatologists and nephrologists. This goal is to be achieved, among other measures, through interdisciplinary cooperation in consensus conferences followed by either controlled or register studies, in which the value of the T2T protocols is tested.

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.

AUTHOR CONTRIBUTIONS

CS, FS, CMH, CH, and KT designed the survey. KM, JB, UN, AH, TK, NW, BT, LW, and DH revised the survey design. CS, KT, and KV were involved in interpretation of the data and analyzed the data. KV drafted the manuscript. KT, CMH, BT, FS, and DH substantively revised the manuscript. All authors critically revised the manuscript and approved the final draft.

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SUPPLEMENTARY MATERIAL

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Number of Episodes Can Be Used as a Disease Activity Measure in Familial Mediterranean Fever

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Objective: To evaluate the number of episodes in the past 12 months as an indicator of the overall disease activity status in Familial Mediterranean fever (FMF).

Methods: In this cross-sectional study, patients were recruited from tertiary pediatric hospitals. Demographic data, main clinical symptoms of the episodes, treatment modalities, and genetic mutations were recorded. The patients were grouped as no episodes (Group 1), 1–4 episodes (Group 2), and more than 4 episodes (Group 3) according to the number of episodes in the past 12 months. The Pediatric Quality Life Inventory (PedsQL), the Children's Depression Inventory (CDI), and the Wong-Baker FACES Pain Rating Scale (FACES) scores were compared between groups. Concurrent validity between the number of episodes and the patient-reported outcome measures (PROMs) was assessed using Spearman's rank correlation coefficient (ρ).

Results: A total of 239 patients were included. There were 74 patients (31%) in Group 1, 99 (41.4%) in Group 2, and 66 (27.6%) in Group 3. Groups were similar according to age, age at diagnosis, gender, consanguinity, family history, history of amyloidosis, clinical symptoms, and in terms of allele frequency ($p > 0.05$). According to PROMs completed by parents, moderate correlations were found between the number of episodes and the PedsQL score ($\rho = -0.48$; 95% $CI = -0.58$ to -0.35, $p < 0.001$) and between the number of episodes and the Wong-Baker FACES score ($\rho = 0.47$, 95% $CI = 0.35$–0.57, $p < 0.001$).

Conclusion: The number of episodes was positively and moderately correlated with patient- and parent-reported outcomes in our cohort. The number of episodes in patients with FMF can be used as a single measure to assess disease activity.

Keywords: Familial Mediterranean fever, disease activity, quality of life, patient reported outcomes, convergent validity

INTRODUCTION

Familial Mediterranean fever (FMF) (OMIM #249100) is the most common monogenic autoinflammatory disease (AID) characterized by recurring febrile episodes of 1–3 days accompanied by inflammation in the serous membranes causing peritonitis, pleuritis, or synovitis. Colchicine is the first-line treatment, and if a patient is resistant or a non-responder, biologics can be used to suppress episodes and systemic inflammation. The most devastating complication is amyloidosis in untreated and non-compliant patients with FMF. There are some phenotypic features associated with a severe disease course, such as the presence of one (or two) M694V mutations, ethnicity, and country of residence (1).

Monitoring disease activity in FMF is essential to measure the effectiveness of treatments, prevent complications, and quantify the effect of the disease on the overall health and quality of life (QoL). The importance of regular monitoring of disease activity was highlighted in the international recommendations for the management of FMF (2, 3). During the past decade, there were several attempts to develop instruments to measure disease severity, damage, and activity for FMF and other autoinflammatory diseases (AIDs) (4, 5). There are a few patient-reported outcome measures (PROMs) validated for use in FMF (6). The only available patient-reported tool to measure disease activity for FMF is the Autoinflammatory Disease Activity Index (AIDAI) (7), which was developed and validated by an international consortium (8), but its use in both research and clinical practice has been limited (9). It is challenging to complete a prospective diary for a long time, especially in adolescents with FMF. Except for the use reported in the publication describing its validation, there has been no uptake of the AIDAI as an outcome instrument related to the FMF.

We propose that the number of episodes could reasonably be used as an indicator of disease activity status in patients with FMF. We assessed the concurrent validity of the number of episodes as a feasible stand-alone measure of disease activity. To do so, we developed *a priori* predictions of the associations that the number of episodes in a year would have with particular PROMS, based on the evidence in the literature regarding observed associations with the level of disease activity in patients with FMF. Specifically, we predicted the following associations in children with FMF: functional status and QoL would be negatively associated, while the level of depressive symptoms and pain would be positively associated with the number of episodes in the past year.

MATERIALS AND METHODS

Participants

Consecutive patients referred to the pediatric rheumatology outpatient clinics were recruited. Patients who had a diagnosis of FMF based on the pediatric FMF criteria or the Tel-Hashomer criteria were eligible (10, 11). All participating parents and children $\geq$ 8-year-old-age gave written informed assent and/or consent to participate in this study. The study protocol was approved by the institutional ethics committee.

Clinical Assessment

All patients were evaluated by a pediatric rheumatologist cross-sectionally. Face-to-face interviews were used to collect data on demographics (age, sex, age at diagnosis, consanguinity, and history of amyloidosis), treatment, mutations, and main clinical symptoms. The number of episodes in the past 12 months was obtained from patients or their parents. Then, patients were assigned into three groups by the number of FMF episodes: no episodes (Group 1), 1–4 episodes (Group 2), and more than 4 episodes (Group 3). Among this referred population, we included patients for whom we had data on three PROMs, the Pediatric Quality Life Inventory (PedsQL^{TM}) Generic Core Scale score, the Children's Depression Inventory (CDI) score, and the Wong-Baker FACES^{R} pain rating scale (FACES^{R}) score. In addition, to see if there are any differences among the patient groups, the elements of the AIDAI symptom scale were also collected (7). Medication adherence was assessed for medication-taking behavior, given that it is such an important confounder in research and a challenge in clinical care.

Genetic Screening

The QIAamp DNA mini kit (Qiagen, Germany) was used for DNA extraction. A reverse-hybridization method (Vienna Lab Diagnostics, Vienna, Austria) was performed for mutation analysis (12). Eleven variants in the *MEFV* gene were genotyped, such as E148Q, P369S, F479L, M680I (G > C and G > A), I692 del, M694V, M694I, K695R, V726A, A744S, and R761H.

Patient Reported Outcome Measures

Patients completed the following patient reported outcome measures (PROMs) during the face-to-face interview during their clinical visit.

The PedsQL^{TM} Generic Core Scale

Pediatric Quality Life Inventory, developed in 1999, by Varni et al. (13) is a short, standardized assessment tool to evaluate children with chronic diseases according to patients' and parents' perceptions of health-related quality of life (HRQoL). In 2005, the reliability and validity of the Turkish version of PedsQL were reported (14, 15). The PedsQL Generic Core Scale includes two summary scores with four scales and 23 items: the Physical Health Summary Score consisting of a physical functioning scale (8 items) and the Psychosocial Health Summary Score consisting of emotional functioning (5 items), social functioning (5 items), and school functioning (5 items) scales. Higher scores indicate better HRQoL. In this study, both parents and children reported the PedsQL.

Children's Depression Inventory

Kovack's CDI (16) is a 27-item self-report questionnaire to assess depressive symptoms experienced in the past 2 weeks in children 7–17 years old. The validated and reliable Turkish version was published in 1991 (17). Higher scores indicate the necessity to refer the patient for further evaluation in terms of clinical depression. In our research, both children and their parent(s) completed the CDI. Higher scores indicate more depressive symptoms.

Wong-Baker FACES^{R} Pain Rating Scale (FACES^{R})

The Wong-Baker FACES Pain Rating Scale (FACES) was developed for children to communicate about their pain (18). The FACES scale uses six hand-drawn, gender-neutral faces depicting smiling (0) to crying (10) placed at equal intervals horizontally: 0 (no hurt) and 10 (hurts worst). In this research, pain experienced by children < 8 years of age was evaluated by their parents. Higher scores indicate more pain.

Autoinflammatory Disease Activity Index

The AIDAI symptom scale includes 12 variables: fever, overall symptoms, abdominal pain, nausea/vomiting, diarrhea, headache, chest pain, painful nodes, arthralgia, or myalgia, swelling of the joints, eye manifestations, and skin rash. The calculation of the score is based on simple math; the sum of all 12 variables was divided by the number of months over which the diary was completed (0–372 in a month of 31 days). For the purposes of the current study, all the elements of the AIDAI symptom scale were asked for the last 1 year to the patients and their parents during the face-to-face interview. Instead of calculating the scores, we compared the elements of the AIDAI among the groups and hypothesized that the difference in the disease activity is mainly generated by the frequency of episodes. To test this hypothesis, we empirically chose to score dichotomously each element of the AIDAI depending on the presence or the absence of the individual item.

Statistical Analysis

Statistical analysis was performed using the Statistical Package of Social Science (SPSS) for Windows, version 26.0 (SPSS Inc., Chicago, IL). Descriptive statistics were presented as frequencies and percentages for categorical variables and median [interquartile range (IQR)] for continuous variables as appropriate. The variables were investigated using visual (histograms and probability plots) and analytical methods (Kolmogrow–Simirnov test) to evaluate the normal distribution. The chi-squared test or Fisher's exact test was used to compare categorical variables where appropriate. The Kruskal–Wallis test was used to compare non-normally distributed variables in the three groups. The Mann–Whitney *U*-test was performed to test the significance of pairwise differences using the Bonferroni correction to adjust for multiple comparisons. Concurrent validity was assessed using the associations of three PROMS with the number of FMF episodes in the past 12 months using the Spearman rank correlation coefficient (ρ). Correlation coefficients of $\rho < 0.39$ were considered as weak; 0.40–0.69 as moderate; and ≥ 0.70 as strong (19). A $p < 0.05$ was considered a statistically significant result.

RESULTS

Participants

There were 270 patients enrolled in the registry. A total of 31 patients were excluded from the study because of incomplete response to PROMS, as mentioned in the Materials and Methods section. Forms were collected on 239 patients (44.4% men and 55.6% women) with FMF from seven different pediatric rheumatology centers in Turkey. A total of 176 forms were completed by parents and patients, and 63 forms were completed by parents who have children < 8 years old. There were 74 patients (31%) in the no FMF episode group (Group 1), 99 patients (41.4%) in the 1–4 episode group (Group 2), and 66 patients (27.6%) in ≥ 4 episode group (Group 3). The median age at the time of enrollment was 11 years (IQR: 7–14 years), the median age at disease onset was 3 years (IQR: 1–6 years), and the median age at diagnosis was 6 years (IQR: 3–9 years). Consanguinity, family history of FMF, and amyloidosis were reported as 29.7% (n = 71), 52.7% (n = 126), and 17.6 (n = 41), respectively. The three groups formed by the number of FMF episodes were similar according to age, age at diagnosis, gender, consanguinity, family history, and history of amyloidosis ($p > 0.05$), but the age at disease onset was significantly higher in Group 2 than the others ($p = 0.001$) (**Table 1**). Allele frequencies of the MEFV gene mutations in the groups were 60.4, 57.8, and 60% for M694V; 11.4, 15.6, and 12.1% for M680I; and 11.4, 7.8, and 9.9% for V726A, respectively (**Table 1**). The groups were similar in terms of M694V and V726A alleles ($p = 0.843$ and $p = 0.46$). Only the M680I allele was significantly more frequent in Group 2 ($p = 0.01$) (**Table 1**). The comparison of the genotypes for each group was also given in **Table 1**, and the groups were similar for homozygosity, compound heterozygosity, and heterozygosity ($p = 0.94$). Nearly all the patients (232 of 239 patients, 97.1%) were on colchicine treatment. The rest of the patients did not use colchicine because of intolerance (n = 2) and colchicine resistance (n = 5). Five patients were treated with biologic disease-modifying antirheumatic drugs (DMARDs) (2 Anakinra, 1 Canakinumab, and 2 Etanercept). Otherwise, medication adherence was similar among the groups.

The characteristic signs and symptoms for each group are presented in **Table 2**. The most common symptoms reported were recurrent fever (92.1%), abdominal pain (91.6%), fatigue (79.9%), arthralgia (79.9%), leg pain (65.3%), myalgia (61.5%), headache (52.7%), and vomiting (51.9%). Groups were similar according to the clinical symptoms ($p > 0.05$) (**Table 2**). The groups were compared according to each item on the AIDAI symptom scale and there were no statistically significant differences among the groups (**Table 2**).

Patient-Reported Outcome Measures

The PedsQL median (IQR) score was 77.3 (65.2–84.1) according to parents and 78.4 (67.8–85.6) according to children. For parent and child PedsQL scale scores (physical and psychosocial functioning scales) and total scores, patients in Group 1 had higher scores that meant better HRQoL than Group 2, and Group 2 had higher scores (better HRQoL) than Group 3 ($p < 0.05$) (**Table 3**). The median (IQR) CDI score was 8.0 (4.0–12.0) according to parents and 8.0 (5.0–12.0) according to children. Patients in Group 2 had higher parent CDI scores than those in Group 1 ($p < 0.001$). Child CDI scores were significantly lower in Group 1 than Group 2 ($p = 0.01$), and in Group 2 than Group 3 ($p = 0.03$) (**Table 4**). The FACES median (IQR) score was 2.0 (0–6.0) according to both parents and children. Both parent and child FACES scores were significantly lower in Group 1 than in Group 2 ($p < 0.001$), and in Group 2 than in Group 3 ($p < 0.001$) (**Table 3**).

TABLE 1 | Demographic features and comparisons among the groups by the number of Familial Mediterranean fever (FMF) episodes.

	Group 1 (*n* = 74)	Group 2 (*n* = 99)	Group 3 (*n* = 66)	Total(*n* = 239)	*P*
Age, median (IQR) in years	12.0 (8.0–14.0)	11.0 (8.0–15.0)	10.0 (7.0–13.0)	11.0 (7.0–14.0)	0.156
Symptom onset age, median (IQR) in years	3.0 (1.0–5.0)	4.0 (1.0–7.0)	2.0 (1.0–5.0)	3.0 (1.0–6.0)	0.001*
Age at diagnosis, median (IQR) in years	5.0 (3.0–8.0)	7.0 (4.0–11.0)	6.0 (3.0–9.0)	6.0 (3.0–9.0)	0.06
Gender, *n* (%)					
Male	39 (52.7)	44 (44.4)	23 (34.8)	106 (44.4)	0.105
Female	35 (43.7)	55 (55.6)	43 (65.2)	133 (55.6)	
Consanguinity, *n* (%)	26 (35.1)	24 (24.2)	21 (31.8)	71 (29.7)	0.272
Family history, n (%)	32 (43.2)	54 (54.5)	40 (60.6)	126 (52.7)	0.108
History of amyloidosis, *n* (%)	12 (16.2)	19 (19.2)	11 (16.7)	41 (17.6)	0.856
Duration of episodes					
0–48 h	-	51 (61.4)	27 (49.1)	78 (56.5)	0.15
> 48 h	-	32 (38.6)	28 (50.9)	60 (43.5)	
Allele frequency [*n* (%)]					
M694V	64 (60.4)	74 (57.8)	51 (63.0)	189 (60.0)	0.843
M680I	12 (11.4)	20 (15.6)	6 (7.4)	38 (12.1)	0.01*
V726A	12 (11.4)	10 (7.8)	8 (9.9)	30 (9.5)	0.46
Genotype [*n* (%)]					
Homozygote	26 (40.6)	34 (41.0)	29 (46.8)	89 (42.6)	
Compound heterozygote	21 (32.8)	25 (30.1)	17 (27.4)	63 (30.1)	0.94
Heterozygote	17 (26.6)	24 (28.9)	16 (25.8)	57 (27.3)	

No episode/year: Group 1, 1–4 episodes/year: Group 2, more than 4 episodes/year: Group 3.
**1–4 episode group is significantly higher than others.*

Concurrent Validity

According to PROMs completed by parents, moderate correlations were found between the number of episodes and PedsQL total score ($\rho = -0.48$; 95% $CI = -0.58$ to -0.35, $p < 0.001$), CDI ($\rho = 0.27$; 95% $CI = 0.13$–0.40, $p < 0.001$) and between the number of episodes and FACES score ($\rho = 0.47$, 95% $CI = 0.35$–0.57, $p < 0.001$). In addition, there were moderate correlations between the number of episodes and PROMs completed by children themselves (**Table 4**).

TABLE 2 | The main clinical symptoms in line with the autoinflammatory disease activity index (AIDAI) symptom scale and their comparison among the groups by the number of FMF episodes.

	Group 2 (*n* = 99)	Group 3 (*n* = 66)	Total (*n* = 165)	p
	n (%)	*n* (%)	*n* (%)	
Recurrent fever	90 (90.9)	62 (93.9)	152 (92.1)	0.47
Abdominal pain	90 (90.9)	60 (90.9)	150 (90.9)	1.00
Nausea-vomiting	50 (50.5)	37 (56.1)	87 (52.7)	0.48
Diarrhea	30 (30.3)	26 (39.4)	56 (33.9)	0.22
Headache	49 (49.5)	42 (63.6)	91 (55.2)	0.07
Chest pain	43 (43.4)	30 (45.5)	73 (44.2)	0.79
Arthralgia	84 (84.8)	47 (71.2)	131 (79.4)	0.03
Myalgia	69 (69.7)	37 (56.1)	106 (64.2)	0.07
Arthritis	37 (37.4)	25 (37.9)	62 (37.6)	0.94
Erysipelas like erythema	10 (10.1)	8 (12.1)	18 (10.9)	0.68

Group 2:1–4 episodes/year, Group 3: more than 4 episodes/year.

DISCUSSION

Assessment of disease activity in patients with AIDs remains a challenge due to the nature of these disorders, such as an episodic course, phenotypic differences, and a low likelihood of being able to see the patient during an acute episode. We have provided preliminary results suggesting that the number of episodes may offer a valid measure of disease activity in patients with FMF that can be easily administered in a clinic.

The european alliance of associations for rheumatology (EULAR) consensus recommendations for the treatment of FMF are that those patients should be seen two times a year (3). For the management of AIDs, it is mandatory to evaluate the disease activity (2). Hence, an international group of experts developed an activity score to assess the disease activity, called AIDAI, for four major hereditary periodic fever syndromes, such as FMF. It has not been widely adopted, however, since it is not practical for use in clinical trials or practice (9). Since it is not feasible to expect families to complete a prospective diary for the long period between clinical appointments, it is important to have a valid measure of disease activity that is easy to administer during clinic visits.

The AIDAI is a valid and reliable patient diary to assess the disease activity in four major hereditary syndromes. According to the AIDAI, a 3-month period is more suitable for surveying FMF, and it is not easy and applicable for defining the disease activity in FMF, especially if the patient is experiencing fewer episodes during the year. In the AIDAI Consensus Conference, the experts agreed that fever, joint symptoms, serositis, chest and skin symptoms, and the number and duration of episodes

TABLE 3 | The comparisons of the scores of PedsQL, FACES, and CDI among groups by the number of FMF episodes.

		a	b	c					
		Group 1	Group 2	Group 3	Total	a–b	a–c	b–c	
		Median (IQR)	Median (IQR)	Median (IQR)	Median (IQR)	*P*	*p*	*p*	*p*
PedsQL (parent)		*n* = 61	*n* = 89	*n* = 57	*n* = 207				
	Physical health	60.9 (53.1–62.5)	56.3 (43.7–62.5)	42.2 (31.3–59.4)	56.3 (40.6–62.5)	0.005	<0.001	<0.001	<0.001
	Psychosocial health*	91.7 (86.7–96.7)	83.4 (74.2–93.4)	73.4 (60.8–85.0)	85.0 (73.4–93.4)	<0.001	<0.001	0.001	<0.001
	Total score	83.3 (79.1–87.2)	75.9 (65.5–83.3)	65.9 (54.6–76.5)	77.3 (65.2–84.1)	<0.001	<0.001	<0.001	<0.001
PedsQL (child)		*n* = 56	*n* = 75	*n* = 41	*n* = 172				
	Physical health	60.9 (56.3–62.5)	56.3 (41.4–62.5)	42.2 (33.6–50.0)	56.3 (40.62–62.5)	0.001	<0.001	0.001	<0.001
	Psychosocial health*	93.4 (86.7–98.4)	81.7 (75.0–93.4)	78.4 (69.2–90.8)	86.7 (76.7–94.6)	<0.001	<0.001	0.89	<0.001
	Total score	84.9 (79.1–88.8)	75.5 (68.1–84.1)	68.1 (59.1–80.4)	78.4 (67.8–85.6)	<0.001	<0.001	0.02	<0.001
CDI (parent)		*n* = 63	*n* = 88	*n* = 55	*n* = 206				
		6.0 (3.0–9.0)	8.0 (4.0–12.0)	9.0 (6.0–15.0)	8.0 (4.0–12.0)	0.054	<0.001	0.09	<0.001
CDI (child)		*n* = 55	*n* = 75	*n* = 42	*n* = 172				
		7.0 (2.0–10.0)	8.0 (6.0–11.0)	11.5 (6.75–16.0)	8.0 (5.0–12.0)	0.011	<0.001	0.03	<0.001
FACES (parent)		*n* = 74	*n* = 99	*n* = 66	*n* = 239				
		0 (0–2.0)	0 (0–6.0)	6 (0–8.0)	2 (0–6.0)	0.006	<0.001	<0.001	<0.001
FACES (child)		*n* = 58	*n* = 76	*n* = 42	*n* = 176				
		0 (0–2.0)	2 (0–6.0)	6 (4.0–8.0)	2 (0–6.0)	0.008	<0.001	<0.001	<0.001

No episode/year: Group 1, 1–4 episodes/year: Group 2, more than 4 episodes/year: Group 3, PedsQL, Pediatric Quality Life Inventory; CDI, Children's Depression Inventory; FACES, Wong-Baker FACES Pain Rating Scale.
**Representing summary of emotional, social, and school subscales.*

TABLE 4 | Results of Spearmen's correlations between the number of episodes and PROMs.

	PROM	Episode groups-Spearman correlation (ρ)	95% confidence interval		*p*-value
			Lower	Upper	
Parents	PedsQL total score	−0.48	−0.58	−0.35	<0.001
	PedsQL physical health score	−0.44	−0.54	−0.31	<0.001
	PedsQL psychosocial health score	−0.44	−0.55	−0.31	<0.001
	CDI	0.27	0.13	0.40	<0.001
	FACES	0.47	0.35	0.57	<0.001
Children	PedsQL total score	−0.44	−0.56	−0.30	<0.001
	PedsQL physical health score	−0.45	−0.57	−0.33	<0.001
	PedsQL psychosocial health score	−0.39	−0.52	−0.24	<0.001
	CDI	0.30	0.15	0.44	<0.001
	FACES	0.45	0.32	0.57	<0.001

PROM, Patient-reported outcome; PedsQL, Pediatric Quality Life Inventory; CDI, Children's Depression Inventory; FACES, Wong-Baker FACES Pain Rating Scale.

were all important in the evaluation of disease activity for patients with FMF (7). AIDAI consists of 12 disease-related symptoms and the calculation of the score is based on simple math; the sum of all 12 variables divided by the number of months over which the diary was completed (0–372 in a month of 31 days). In terms of those criteria, there were no differences among the groups in our cohort except for the number of episodes. On the basis of our results, the number of episodes itself alone is a valid indicator of disease activity in patients with FMF.

Patients with AIDs should also be followed with clinical evaluation, laboratory test, QoL, tolerance, and treatment adherence. Relationships of patient-parent reported outcomes with disease activity have been studied in juvenile idiopathic arthritis (JIA) (20–26), juvenile idiopathic myositis (23), rheumatoid arthritis (27–29), systemic lupus erythematosus (SLE) (30–35), Behcet disease (36), and ankylosing spondylitis (AS) (34, 37). The data on the relationship between disease activity and patient-parent reported outcomes in FMF are very limited. In the present study, PedsQL, CDI, and FACES scores were used as patient-parent reported outcomes.

Quality of life is an important factor in determining disease status and defining and evaluating the effects of management

strategies (38). The concurrent validity of the number of episodes was assessed using PedsQL and a moderate correlation was found, which is not surprising in our study. PedsQL scores differed across groups, decreasing when the number of episodes increased in our cohort. Buskila et al. showed that the QoL in patients with FMF is inversely correlated with the number of FMF episodes for a year (39). Alayli et al. compared the HRQoL between patients with FMF and healthy people and indicated that the QoL is impaired in children with FMF (40). Sahin et al. have reported no relationship between QoL and the number of episodes in adult patients using SF-36 (41). On the contrary, the studies conducted with FMF patients during their episode-free period, reported that QoL is even better in patients with FMF compared with healthy controls (42). Taken all these together, it is clear that the number of episodes is inversely correlated with HRQoL in patients with FMF.

The CDI scores were higher in groups with more episodes in our study population. Makay et al. reported that the CDI scores of children and adolescents with FMF were significantly higher than those of a healthy control group (43). Sonmez et al. evaluated depression by using CDI in patients (remission) with FMF and healthy controls and found no difference between patients and healthy controls (44). It was reported in adults that depression was more frequent in patients with FMF than in healthy controls using the Hospital Anxiety and Depression Scale (HADS) (45, 46) and the Hamilton Depression Scale (HDS) (47). Our study is the first one that compared the CDI scores according to the number of episodes.

We used FACES as a pain scale in our cohort, and the results showed that pain scores were similarly higher with more episodes reported. We showed that worse health-related QoL (PedsQL) and increased depression (CDI) were correlated with the number of episodes.

The limitations of the present study need to be mentioned. One of the major limitations of our study is that we were not able to analyze the AIDAI score because of poor patient and parent adherence. On this occasion, we have faced the difficulty of using AIDAI in a large patient cohort, especially in adolescents. Another limitation that needs to be mentioned is that the current study was designed as cross-sectional and it is important to see the changes with PROMs, also prospectively, to complete all validation steps. We just performed concurrent validity due to the nature of the current study.

CONCLUSION

In conclusion, the present study showed that a larger number of episodes are related to worse patient- and parent-reported outcomes. The PedsQL, CDI, and FACES scores were significantly different among the groups divided according to the number of FMF episodes in a year, in a homogeneous study population in terms of demographic features, mutation types, clinical symptoms, and treatment adherence. This study showed that the number of episodes is the key element of disease activity in patients with FMF and can be used on its own to assess disease activity.

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 Clinical Trials Ethics Committee of GMMA, Ankara, Turkey. Written informed consent to participate in this study was provided by the participants' legal guardian/next of kin.

AUTHOR CONTRIBUTIONS

DP and KS: data analysis and interpretation. DK, NA, BM, YB, HP, and OK: collecting patient data and providing clinical information. DP, ZA, and MR: writing—original draft preparation. DP, KS, ZA, MR, RL, RB, and ED: writing—review and editing. ED: as a PI had full access to all the data in the study and takes responsibility for the integrity of the data and the accuracy of the analysis. All authors have read and agreed to the published version of the manuscript.

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Hereditary Systemic Autoinflammatory Diseases: Therapeutic Stratification

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Hereditary systemic autoinflammatory diseases (SAIDs) are rare, often severe conditions characterised by mutations in the key regulators of innate immune responses. Dramatic advances in the molecular genetics and next-generation sequencing in the past decade enabled identification of novel mutations that play a pivotal role in the mechanistic pathways of inflammation. Although genetic testing may not always provide straightforward guidance in diagnosis and clinical decision making, through translational research, it sheds light into molecular immunopathogenesis, particularly in IL-1 inflammasome and cytokine signalling pathways. These remarkable insights provided a better understanding of autoinflammatory conditions and their association with the innate and adaptive immune systems, as well as leading to development of cytokine-targetted biologic treatments. Use of targetted therapeutics not only helps control disease flares, reduce acute-phase responses and prevent devastating complications such as amyloidosis, but also improves health-related quality of lives and support patients to pursue almost a normal life. Herein, we discuss the commonest monogenic SAIDs, describe their immunopathology, and summarise the approaches in the management and targetted treatment of these conditions, including presentation of novel data based on a cohort of children with these rare diseases from a single quaternary referral centre in London.

Keywords: genomics, IL-1 inhibitors, innate immunity, interferonopathies, JAK 1/2 inhibitors, periodic fever, systemic autoinflammation

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INTRODUCTION

The concept of systemic autoinflammatory diseases (SAIDs) was first proposed by McDermott et al. in 1999, as a group of hereditary conditions characterised by recurrent unprovoked inflammation, without presence of autoantibodies or antigen-specific T-lymphocytes (1). Abundant inflammatory response is predominantly mediated by the cells and molecules of the innate immune system in the presence of host predisposition (1). The autoinflammatory nomenclature sought to provide a unified classification for this ever-growing list of diseases that can be distinguished from autoimmune conditions, without major involvement of adaptive immune system which is the hallmark for autoimmunity (2).

Systemic autoinflammatory diseases (SAIDs) usually present with unexplained recurrent episodes of fever and multisystem inflammation; mainly involving serosal surfaces, synovium, skin and eyes (3). Inflammation in muscles, vasculitis affecting small, medium and large vessels, and systemic amyloidosis may also occur in some patients (4). Hereditary recurrent fevers (HRFs) constitute a subgroup of SAIDs which involves familial Mediterranean fever (FMF), tumour necrosis factor receptor-associated periodic syndrome (TRAPS), cryopyrin-associated periodic fever syndrome (CAPS) and hyperimmunoglobulin-D with periodic fever syndrome (HIDS, now referred to as mevalonate kinase deficiency, MKD) as prototypes for this diagnostic category (2). Nevertheless, in addition to HRFs, the concept of autoinflammation has now been extended to a number of clinical entities encompassing more recently identified Mendelian diseases such as deficiency of adenosine deaminase-2 (DADA-2) and monogenic interferonopathies; as well as diseases with a polygenic form of inheritance (such as Behçet's and Still's disease) (2).

Advances in molecular genetics and the increased accessibility to genetic testing have extended recognition and treatment of SAIDs to a wider range of populations and ethnicities, which in turn provided important insights into genotype-phenotype associations (5). Diagnosis of SAIDs relies fundamentally on good history taking with a detailed family history, and clinical judgement. Molecular genetic analyses provide a definitive diagnosis for many cases, although results require careful interpretation as they can be misleading or inconclusive especially in the context of variants of uncertain significance (VUS) (6, 7). Over the last two decades, at least 30 different genes have been identified in hereditary diseases (Infevers[1]); as well as detailed descriptions of a growing number of polygenic "complex" syndromes (3). Recognition of underlying mutations in monogenic SAIDs has led to the identification of key regulators of innate immune responses. The innate immune system with its myeloid effector cells and pattern-recognition receptors (PRRs) for pathogen and danger-associated molecular patterns drives the immune responses in SAIDs (2, 8). NOD-like receptors (NLRs) that are a group of PRRs in innate immunity, have been identified as intracellular sensors with an ability to sense non-microbial danger signals, and subsequently form large cytoplasmic inflammasomes that activates caspases and results in secretion of pro-inflammatory cytokines IL-1ß and IL-18 (2, 9, 10). Recognition of the disease-associated mutations in the genes encoding inflammasome pathway, as an example mutations in *MEFV*, *NLRP3*, and *TNFRSF1A*, has dramatically improved our understanding of disease pathogenesis, and thereby had a vital impact on the development of targetted-therapeutic approaches (11). Excessive IL-1ß production and IL-1 signalling as a consequence of inflammasome assembly and activation upon *NLRP3* stimulation in CAPS spectrum represents an exemplar of targetted-therapeutic approach based on selective cytokine blockade to control inflammation (11). Similarly, "pyrin" protein encoded by the *MEFV* gene is linked with cytoskeleton in myeloid/monocytic cells and modulates IL-1ß processing, nuclear factor NF-κB activation and apoptosis which can explain the hyperinflammatory state during FMF attacks (12).

The underlying mechanisms of SAIDs is now better elucidated and it has been clarified that autoinflammation can be triggered in the context of activation of various inflammatory pathways, cytokine signalling or accumulation of misfolding proteins. In addition to above-described inflammasomopathies in FMF and CAPS, other underlying mechanisms for SAIDs can be summarised as follows: intracellular stress that causes production of reactive oxygen species; aberrant apoptosis; protein-misfolding and aberrant cytokine production as in TRAPS and HIDS; increased interferon signalling as in SAVI and CANDLE; NF-κB activation disorder as in Blau syndrome; and deficiency of enzymes such as adenosine deaminase 2 causing autoinflammation and vasculitis (2, 3) (**Table 1**).

Recently discovered inherited SAIDs such as the Behcet's mimic haploinsufficiency of A20 (13), VEXAS (vacuoles, E1 enzyme, X-linked, autoinflammatory, somatic) syndrome (14), autoinflammation with infantile enterocolitis (AIFEC) (15), periodic fevers, immunodeficiency and thrombocytopenia (PFIT) (16) and NEMO 5-associated autoinflammatory syndrome (NEMO-NDAS) (17) (**Table 1**) have further expanded the knowledge on immunobiology of innate immunity and autoinflammation, which in turn provided important insights for the treatment of these conditions.

This review summarises the immunopathological and clinical features of SAIDs with the most recent advances in the targetted-therapeutic approaches in line with the discoveries in basic and translational science. It will also outline the caveats in the management and treatment of SAIDs and finally, will point out the importance of precision medicine in SAIDs with an emphasis on how molecular insights can form the conceptual basis for targetted treatment within a real-life clinical framework.

FAMILIAL MEDITERRANEAN FEVER

Familial Mediterranean Fever (FMF) is the most prevalent and well-described hereditary SAID primarily affecting ethnic groups originating from eastern Mediterranean region, such as non-Ashkenazi Jews, Greeks, Turks, Armenians and Arabs, though it is now increasingly recognised in different populations owing to enhanced accessibility to genetic testing and raised disease awareness amongst physicians (18, 19).

The gene responsible for FMF, *MEFV* (MEditerranean Fever), is composed of 10 exons on chromosome 16p13.3 and encodes pyrin (or marenostrin) protein which is a component of IL-1 inflammasome pathway, hence regulates IL-1ß processing and activation (20, 21). According to INFEVERS database, more than 380 *MEFV* sequence variants have hitherto been reported[2] some of which are clearly pathogenic, whereas a large number of variants currently remain as of unknown significance (22). FMF is traditionally known as an autosomal recessive disease, nevertheless substantial number of patients with clinical FMF

[1]http://fmf.igh.cnrs.fr/ISSAID/infevers

[2]http://fmf.igh.cnrs.fr/infevers/

TABLE 1 | Monogenic systemic autoinflammatory diseases.

Disease	Gene/chromosome	Protein	Mode of inheritance
IL-1ß activation disorders (inflammasomopathies)			
FMF	*MEFV* (16p13.3)	Pyrin (marenostrin)	Autosomal recessive/or gene-dosage dependent autosomal dominant
CAPS [FCAS/MWS/CINCA (NOMID)]	*NLRP3* (1q44)	NLRP3 (prev. cryopyrin, NALP3)	Autosomal dominant
PAPA	*PSTPIP1* (15q24-25.1)	PSTPIP1	Autosomal dominant
AIFEC	*NLRC4 (2p22.3)*	NLRC4	Autosomal dominant
Intracellular stress leading to inflammation (protein misfolding, dysregulated ubiquitination, abnormal intracellular accumulation and intracellular trafficking of mutant proteins)			
TRAPS	*TNFRSF1A (12p13.31)*	TNFR1	Autosomal dominant
MKD/HIDS	*MVK (12q24.11)*	Mevalonate kinase	Autosomal recessive
Haploinsufficiency A20	*TNFAIP3 (6q23.3)*	TNFAIP3	Autosomal dominant
PFIT	*WDR1 (4p16.1)*	WDR1	Autosomal recessive
VEXAS	*UBA1 (Xp11.3)*	UBA1	X-linked
Defective regulatory mechanisms (affecting cytokine signalling)			
DIRA	*IL1RN (2q14.1)*	IL-1Ra	Autosomal recessive
DITRA	*IL36RN (2q14.1)*	IL-36Ra	Autosomal recessive
Majeed syndrome	*LPIN2* (18p11.31)	Lipin-2	Autosomal recessive
Defects in NF-κ B signalling pathway			
Blau syndrome	*NOD2 (CARD15) (16p12)*	NOD2 (CARD15)	Autosomal dominant
NEMO-NDAS	*IKBKG (Xq28)*	IKBKG	X-linked
ADA-2 Deficiency			
DADA-2	*ADA-2 (prev. CECR1) (22q11.1)*	ADA-2	Autosomal recessive
Increased intracellular Ca^{+2} signalling			
APLAID	*PLCG2 (16q23.3)*	PLCG2	Autosomal dominant
Interferonopathies			
CANDLE/PRAAS	*PSMB8 (6p21.32)* *PSMB4 (1q21.3)* *PSMA3 (14q23.1)* *PSMB9 (6p21.32)* *PSMB10 (16q22.1)* *PSMG2 (18p11.21)* *POMP (13q12.3)*	PSMB8, PSMB4, PSMA3, PSMB9, POMP	Autosomal recessive
SAVI	*TMEM173 (STING1) (5q31.2)*	STING1	Autosomal dominant
AGS	*TREX1(3p21.31)* *IFIH1 (2q24.2)* *SAMHD1 (20q11.23)* *RNASEH2A-C (19p13.13, 13q14.3, 11q13.1)* *ADAR (1q21.3)* *RNU7-1 (12p13.31)* *LSM11 (5q33.3)*	TREX1 IFIH1 SAMHD1 RNASEH2A-C DRADA	Autosomal dominant and autosomal recessive

ADA-2, Adenosine deaminase-2; ADAR, Adenosine deaminase RNA specific; AGS, Aicardi-Goutières Syndrome; AIFEC, autoinflammation and infantile enterocolitis; APLAID, PLCG2-associated antibody deficiency and immune dysregulation with autoinflammation; CANDLE, Chronic Atypical Neutrophilic Dermatosis with Lipodystrophy and Elevated temperature; CAPS, Cryopyrin-associated periodic syndrome; CARD15, caspase recruitment domain-containing protein 15; CECR1, cat eye syndrome critical region protein 1; CINCA, Chronic infantile neurological cutaneous and articular syndrome; DADA-2, deficiency of adenosine deaminase-2; DRADA; Double stranded RNA binding protein; FCAS, Familial cold autoinflammatory syndrome; FMF, familial Mediterranean fever; HIDS, hyperimmunoglobulin D syndrome; IFIH1, Interferon induced with helicase C domain 1; IKBKG, inhibitor of nuclear factor kappa B kinase regulatory subunit gamma; IL-1ß, interleukin 1 beta; IL1RN, interleukin 1 receptor antagonist; IL36RN, interleukin 36 receptor antagonist; LPIN2, lipin 2; LSM11, U7 Small nuclear RNA-associated protein; MEFV, MEditerranean Fever; MKD, mevalonate kinase deficiency; MVK, mevalonate kinase; MWS, Muckle-Wells syndrome; NEMO-NDAS, NF-κB essential modulator delta exon 5-autoinflammatory syndrome; NF-κB, nuclear factor kappa B; NLRC4, NLR-family CARD domain containing protein 4; NLRP3, NOD, LRR and pyrin domain-containing protein; NOD2, nucleotide binding oligomerisation domain containing protein 2; NOMID, neonatal-onset multisystem inflammatory disease; PAPA, pyogenic arthritis, pyoderma gangrenosum, and acne; PFIT, periodic fevers immunodeficiency and thrombocytopaenia; PLCG2, phosphatidylinositol-specific phospholipase C gamma 2; POMP, Proteasome maturation protein; PSMA3, Proteasome 20S subunit alpha 3; PSMB 4/8/9, Proteasome 20S subunit beta 4/8/9; PSMG2, proteasome assembly chaperone 2; PSTPIP1, proline-serine-threonine phosphatase interacting protein 1; RNASE H1A-C, ribonuclease H1A-C; RNU7-1, RNA, U7 Small Nuclear 1, SAMHD1, SAM and HD domain containing deoxynucleoside triphosphate triphosphohydrolase 1; SAVI, STING-associated vasculopathy of infancy; STING1, stimulator of interferon response CGAMP interactor 1; TMEM173, transmembrane protein 173; TNFAIP3, TNF alpha induced protein 3; TNFR1, tumour necrosis factor receptor 1; TNFRSF1A, TNF receptor superfamily member 1A; TRAPS, tumour necrosis factor receptor-associated periodic syndrome; TREX1, three prime repair exonuclease 1; UBA1, ubiquitin like modifier activating enzyme 1; VEXAS (vacuoles, E1 enzyme, X-linked, autoinflammatory, somatic) syndrome; WDR1, WD repeat domain 1.

phenotype demonstrate only 1 identifiable *MEFV* mutation. To investigate this further, Booty *et al.* searched the existence of a second mutation in patients clinically diagnosed with FMF and revealed that none of the patients had a second mutation (23). This study has demonstrated that FMF may not be a simple monogenic inflammatory disease and patients with only 1 *MEFV* mutation can present with FMF phenotype in the presence of other permissive alleles or environmental factors (23). Similarly, Marek-Yagel et al. investigated heterozygote FMF patients and performed haplotype analyses which revealed that heterozygote disease was indistinguishable from homozygote form, thus FMF can be considered as a dominant condition with low penetrance (24). The Single Hub and Access point for pediatric Rheumatology in Europe (SHARE) initiative in 2015 recommended that the presence of homozygous mutations in p.M694V, p.M680I, p.M94I or compound heterozygous mutations with two of these genes were associated with increased risk of severe disease (22). In contrast, although very common, presence of the p.E148Q variant as the only *MEFV* variant was recommended not to be labelled as FMF (evidence strength level B) (22). These recommendations were also demonstrated in the meta-analysis by Gangemi et al. (7) supporting the evidence regarding the diagnosis of FMF being based on clinical criteria, supported with genetic testing. Booty et al. (23) showed that almost 30% of FMF patients with clinical symptoms had only one identifiable mutation in *MEFV*. Thus it is suggested that FMF is best described an autosomal dominant condition with variable penetrance, and with gene mutation dosing effect influencing phenotypic severity. The variability of attack presentation and symptoms is currently explained by the effect of different MEFV mutations and compound heterozygotes, as well as by the contribution of heterogeneity among disease-modifying proteins (25). In 2012, experts reached consensus on performing genetic test for the 14 most common MEFV variants, nine of which are clearly pathogenic and five are VUS (6).

Familial Mediterranean fever (FMF) presents with self-limited inflammatory episodes of fever accompanied by polyserositis, arthritis and/or an erysipelas-like skin disease, all of which spontaneously resolve in 48 to 72 h (18). One of the potential underlying mechanisms is a massive increase in the chemotactic activity of the polymorphonuclear leucocytes resulting in rapid granulocyte influx into the affected tissues, driving autoinflammation (18). Increased understanding of innate immune system responses to different pathogens and pattern recognition receptors (PRRs) have led to the elucidation of potential immune mechanisms: pyrin inflammasome activation was triggered by the inhibition of RhoA, a member of the Ras homology family of small GTPases (26). In line with this hypothesis, following inactivation of RhoA by *Clostridium difficile* virulence factor, cytotoxin TcdB, pyrin mediated caspase 1-inflammasome activation (26). Indeed, Xu et al. demonstrated robust activation of caspase-1 and IL-1ß production by a recombinant Clostridium cytotoxin TcdB. This hypothesis was later underpinned by Park et al. (27) demonstrating pyrin inflammasome upon inhibition of Rho GTPases by certain bacterial toxins. Unlike other pathogens, *Yersinia* species were shown to possess a specific human pyrin inflammasome inhibiting toxin, YopM which facilitated binding of inhibitory proteins to the pyrin (28). IL-1ß release was substantially reduced in wild-type *Yersinia pestis* infected bone-marrow derived macrophages, whereas FMF patients with mutated pyrin could effectively produce IL-1ß upon being infected with *Y. pestis* (29). Park et al. (29), then demonstrated that YopM binding to FMF mutant human pyrin was markedly decreased compared to binding of toxin to the wild type human pyrin. Moreover, levels of IL-1ß secretion in the presence of different FMF-associated mutations and wild-type pyrin were measured. Interestingly, the cells expressing classical pathogenic (*MEFV* p.M694V, p.M680I, p.V726A) FMF mutations, hence FMF-associated mutant pyrin, secreted significantly higher levels of IL-1ß in comparison to the cells expressing wild-type pyrin or those with the *MEFV* p.E148Q variant (29). Taken together, these studies provided valuable knowledge about FMF and inflammasome pathophysiology, and opened avenues for future research.

In terms of morbidity, systemic AA amyloidosis is the most severe complication of FMF that generally presents with renal involvement (11%), though the adrenals, spleen, intestine, lung, and testes can also be affected (30, 31). Of note, AA amyloidosis used to cause long-term morbidity and mortality in majority of the patients before discovery of colchicine. Indeed, colchicine has been successfully used as a first line medication in FMF since 1972 not only for controlling attacks but also for preventing and treating amyloidosis (30, 32). Interestingly, in the abovementioned study by Park et al. (27), colchicine was shown to activate RhoA or reverse inhibition of it by depolymerisation of intracellular microtubules, and ultimately inhibited inflammasome and IL-1ß release. Recently, evidence-based recommendations for the management of FMF have been published by European League Against Rheumatism (EULAR) with international collaboration (33), which suggested prompt start of prophylactic colchicine as soon as the clinical FMF diagnosis is confirmed. Notably, in the absence of clinical FMF diagnosis or subclinical inflammation, genetic diagnosis is not a prerequisite to start treatment, although regular monitoring of these patients was recommended (33).

It is important to emphasise that colchicine is a safe and well-tolerated life-long treatment for the prophylaxis of FMF attacks, the commonest side effect being gastrointestinal disturbance with diarrhoea occurring predominantly in the first month of treatment (19). Dose reduction and a lactose-free diet may alleviate side effects, as colchicine is considered to unmask lactose intolerance (34). It has been reported that up to 5% of patients may remain colchicine intolerant, and in 5-10% disease is only partially controlled with colchicine (35). EULAR recommendations highlight that reduced compliance should be seriously considered in apparent colchicine resistant FMF patients (33). The underlying aetiology for intolerance has not been completely clarified yet; however, it is likely to be multifactorial, potentially associated with genetic variants and pharmacokinetics such as absorption and intracellular transport as well as interaction with other medications (36, 37). Clinicians should be vigilant whilst assessing patients, especially those with increased attack frequency and/or severity or colchicine unresponsiveness (19) as treatment adherence

can be a major problem for some cases, particularly during adolescence. Colchicine-intolerant or inadequately controlled cases or those with hepatobiliary dysfunction and/or severe renal failure are candidates for alternative treatment options, namely IL-1 inhibitors (38).

Given the roles of mutated pyrin protein in regulating caspase-1 and IL-1ß activation in inflammasome pathway, recent studies have demonstrated successful use of anti-IL1 therapies for the treatment of FMF (21, 25, 39, 40). To date, there are three different anti-IL1 medications effectively used in clinical practice (19): anakinra, a recombinant homolog of the human IL-1 receptor antagonist, competitively blocks binding of IL-1alpha and IL-1ß to the IL-1 receptor. Canakinumab, a fully human immunoglobulin G_1 monoclonal antibody against IL-1ß and rilonacept, a dimeric fusion protein capturing IL-1 (19, 25).

Non-steroidal anti-inflammatory drugs (NSAIDs) can be helpful as on-demand therapy to control symptoms during attacks, although they are not promising in preventing further episodes. The only indication for corticosteroid use in FMF is protracted febrile myalgia which is a very rare vasculitic complication (41).

TUMOUR NECROSIS FACTOR RECEPTOR-ASSOCIATED PERIODIC SYNDROME

Tumour Necrosis Factor Receptor-Associated Periodic Syndrome (TRAPS) is a monogenic AID caused by mutations in the extracellular domain of the TNF receptor (*TNFRSF1A*) on chromosome 12 which is recognised to have a central role in the regulation of innate immune responses and inflammation (4). The biologic effects of TNF include expression of adhesion molecules on leucocytes and endothelial cell surfaces, stimulation of cytokine secretion, leucocyte activation, angiogenesis and pyrexia (4). It was initially thought that mutations in type 1 TNF receptor (TNFR1) caused reduction in well-functioning soluble receptors leading to excess circulating TNF that would fuel inflammatory responses (11). Based on this pathophysiological mechanism, the TNF-inhibitor etanercept seemed to be the best possible therapeutic option at that stage. However, lack of efficacy of etanercept resulted in questions regarding the true pathogenesis of TRAPS (42). Defective clearance and intracellular trafficking of TNFR1 ultimately leads to accumulation of mutant receptor in endoplasmic reticulum (ER), potentially increasing intracellular stress and production of reactive oxygen species by mitochondria (43). Interaction between ER stress, ROS production and IL-1ß secretion has been established not only in TRAPS but also for other autoinflammatory diseases; moreover, this association might be a plausible explanation for the effectiveness of IL-1 inhibition in TRAPS (44). Indeed, initial anecdotal reports on promising use of anti-IL1 agents have been followed by the Eurofever Registry data (45), international expert consensus reports (46) and eventually a placebo-controlled, randomised study of canakinumab (39) proving IL-1 blockade as a safe and effective therapy for TRAPS, emphasising the pivotal role of IL-1 in the pathogenesis.

Regarding the presenting symptoms during attacks, alongside episodic fever, serositis and arthritis, patients also experience conjunctival involvement and/or periorbital oedema and myalgia. Another feature of this periodic fever syndrome is longer attack duration as compared with other hereditary SAIDs. Many TRAPS episodes last from less than one week to up to three weeks and minority of patients may have continuous inflammation with exacerbations (3, 4).

Evidence for treatment of TRAPS attacks is limited to retrospective or small prospective studies (46). NSAIDs have been shown to provide symptom relief in approximately 75% of TRAPS patients, although they are not effective in controlling inflammatory episodes. Likewise, corticosteroid effect was assessed in only retrospective studies and favourable outcomes were reported as on-demand therapy, nonetheless, initial response reduced over time, in addition to corticosteroid related side effects (47). In the Eurofever Registry, patients with the mild R92Q variant seemed to respond better to NSAIDs and colchicine compared to the other TNFRSF1A mutations, though overall colchicine use was not found beneficial (45). In prospective and retrospective studies, TNF-inhibitor etanercept demonstrated favourable outcomes accompanied with reduction in inflammatory parameters; nevertheless, efficacy declined over time (45, 46). Treatment failure, and even deterioration was observed with monoclonal TNF-inhibitors – infliximab and adalimumab, thus use of these medications are no longer recommended (48). In the Eurofever Registry (45) anti-IL1 treatment with anakinra was shown to be superior to etanercept, and indeed, recently an open-label canakinumab study (49) and placebo-controlled trial (39) confirmed efficacy of anti-IL1 therapies in TRAPS which led to licencing of canakinumab by U.S. Food and Drug Administration and European Medicines Agency.

CRYOPYRIN-ASSOCIATED PERIODIC SYNDROME

Cryopyrin-associated periodic syndrome (CAPS) is a rare, heterogenous inflammasomopathy associated with gain-of-function or *de novo* mutations in *NLRP3* that encodes a protein which is known as *NLRP3* or cryopyrin, a regulatory protein in interleukin-1 inflammasome (50) (**Figure 1**). Mutations in *NLRP3* result in excessive IL-1ß production causing a wide range of symptoms from cold-induced urticaria to severe neurological inflammation. Indeed, the clinical spectrum of CAPS is broad and comprises distinct and rare subgroups in regards to symptom severity (51). From mild to severe: familial cold autoinflammatory syndrome which can present with cold-induced urticaria, fever and constitutional symptoms; Muckle-Wells Syndrome (MWS) with temperatures, skin rashes, arthritis and sensorineural hearing loss; and the most severe form being chronic infantile neurological cutaneous articular syndrome (CINCA) [or neonatal-onset multisystem inflammatory disease (NOMID)] which can present with temperature episodes, arthritis or myalgia, cutaneous symptoms, chronic aseptic meningitis and epiphyseal overgrowth of the long bones (51).

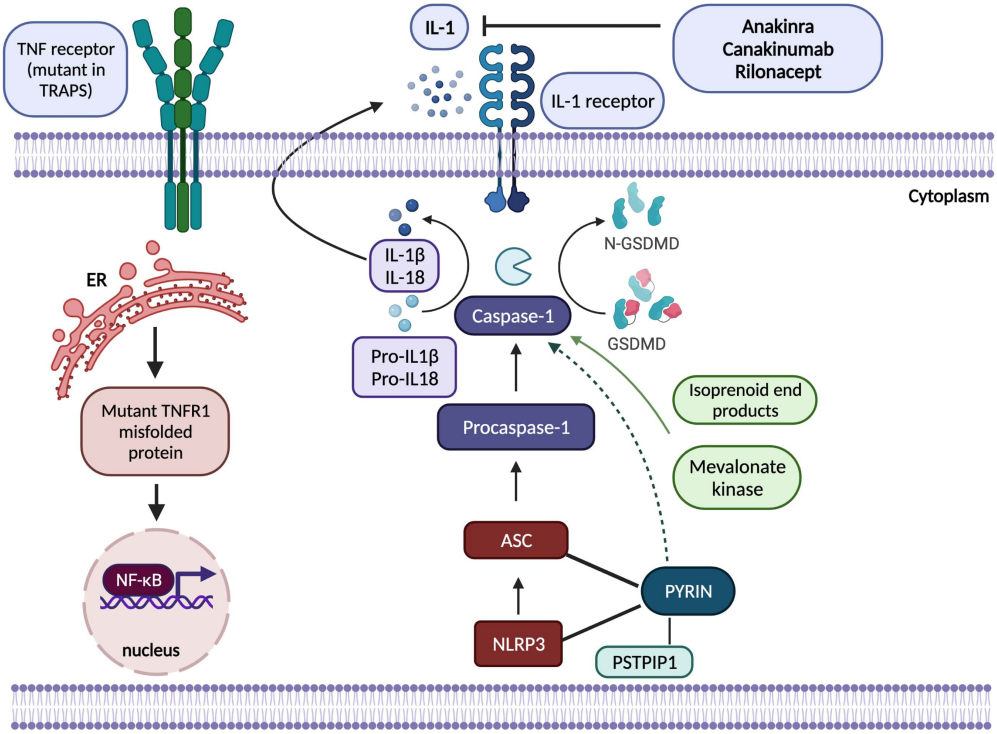

FIGURE 1 | Adapted from Kastner et al. (2) a schematic showing pathogenesis of hereditary autoinflammatory diseases regulated by IL-1ß (inflammasomopathies) and NF-κB (Created by Biorender). In CAPS, NLRP3 protein interacts with the adaptor protein ASC and caspase-1 to form the inflammasome complex which activates IL-1ß and IL-18 and results in inflammatory responses. Mutations in pyrin, PSTPIP1, NLRP3, mevalonate kinase proteins shown in the figure disrupt normal functioning of inflammasome complex. Mutations in NLRP3 increase the activation of the complex; however, mechanisms by which pyrin protein regulates inflammasome functioning have yet to be elucidated as theories involve both gain-of-function activation of pyrin-inflammasome complex and loss-of-function in its inhibitory effects on NLRP3. In TRAPS, mutant TNFR1 protein is misfolded in ER that causes accumulation of this protein, hence overactivation of NF-κB resulting in abnormal inflammatory immune responses. IL-1-targetted biologic agents, anakinra, canakinumab and rilonacept have been effectively used to control inflammatory state in these prototypic monogenic SAIDs. ASC, Apoptosis-associated speck-like protein; ER, endoplasmic reticulum; GSDMD, Gasdermin D; IL-1, interleukin-1; NF-κB, nuclear factor κB; NLRP3, NOD, LRR and pyrin domain-containing protein; PSTPIP1, proline-serine-threonine phosphatase interacting protein 1; TNF, tumour necrosis factor, TNFR1, tumour necrosis factor receptor 1; TRAPS, TNF-receptor associated periodic syndrome.

In the light of *NLRP3* being a component of inflammasome which senses danger signals and activates caspase-1, thereby initiating IL-1ß and IL-18 processing, IL-1 blockade resulted in complete therapeutic responses which have been life-altering in this monogenic inflammasomopathy (45, 50). Long-term IL-1 inhibition is now indicated for the whole spectrum of CAPS at any age, and the consensus recommendation is to initiate treatment as early in life as possible (46). In addition to IL-1 blockade, use of corticosteroids and/or non-steroidal anti-inflammatory drugs (NSAIDs) as on-demand therapy during attacks has also proven beneficial for some patients (46).

Systemic AA amyloidosis, a life-threatening complication of SAIDs that mainly presents with renal involvement, was reported to occur in approximately 25% of CAPS patients prior to targetted treatment with IL1 blockade (52). In a double-blind, place-controlled study, treatment with canakinumab demonstrated a rapid and sustained clinical response in CAPS patients with a substantial reduction in acute-phase reactants, especially in serum amyloid A, indicative of reduced AA amyloidosis risk (52). Canakinumab was considered as superior to other IL-1 inhibitors for multiple reasons. Firstly, subcutaneous administration of canakinumab is every four to eight weeks, whereas other IL-1 inhibitors anakinra and rilonacept are given daily or weekly, respectively. Undoubtedly, less frequent injections will increase adherence among adolescent and adult patients. Secondly, longer plasma half-life up to 28-30 days presumably provides prolonged resolution of symptoms and autocrine downregulation of IL-1ß production may be another beneficial disease-modifying impact (52). And finally, in the placebo-controlled, double-blind trial, at the end of week 24, all canakinumab patients remained in remission as compared with 25% in the placebo arm (52).

MEVALONATE KINASE DEFICIENCY OR HYPERIMMUNOGLOBULIN D WITH PERIODIC FEVER SYNDROME

Mevalonate Kinase Deficiency (MKD)/Hyperimmunoglobulin D With Periodic Fever Syndrome (HIDS) (OMIM #260920) is a rare autosomal recessive SAID characterised by bi-allelic mutations in the mevalonate kinase (*MVK)* gene (12q24.11) resulting in defective cholesterol biosynthesis and increased

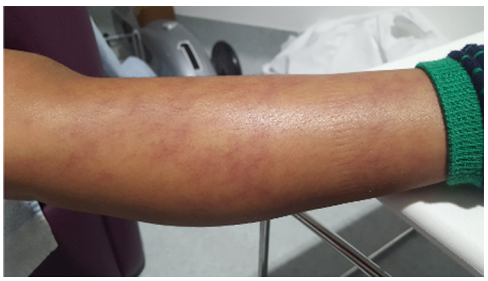

FIGURE 2 | Livedo racemosa type vasculitic skin rash in a DADA-2 patient. DADA-2, Deficiency of adenosine deaminase-2.

urinary excretion of mevalonic acid (53). The disease spectrum is primarily a continuum of two clinical phenotypes with different severity: at the milder end, MKD/HIDS sits as an autoinflammatory condition with early-onset febrile episodes usually without infection, skin rash, arthralgia, hepatosplenomegaly, lymphadenopathies, gastrointestinal involvement, but absence of neurological impairment. The metabolic disease mevalonic aciduria (MVA) remains at the severe end of the spectrum. MVA presents early in life with similar features, but later on the clinical phenotype includes neurodevelopmental delay, muscular hypotonia, ataxia associated with cerebellar atrophy and ocular symptoms (53). Both conditions are caused by homozygous or compound heterozygous mutations in *MVK* (53). The enzymatic activity of MVK can be measured in fibroblasts and lymphoblasts and varies from 1.8 to 28% in the autoinflammatory form; whereas it is usually below 0.5% in MVA (53, 54).

Symptom onset is usually in the first 6 months of life with recurrent 3- to 7-day temperature episodes that can be precipitated by specific factors such as vaccination, infections, surgery, physical or emotional stress. Macrophage activation syndrome (0.9%) and AA amyloidosis (4%) are rare but severe complications (54).

The aetiopathogenesis of autoinflammation in MKD has not been fully elucidated yet, although recent studies emphasise the role of defective prenylation in RhoA inactivation (27). Mevalonate kinase (MVK) is a central enzyme catalysing the isoprenoid biosynthesis pathway, generating sterol and non-sterol isoprenoids utilised in essential cellular functions (55). Autoinflammation and pyrin inflammasome activation in MKD has indicated the role of isoprenoids in the regulatory innate

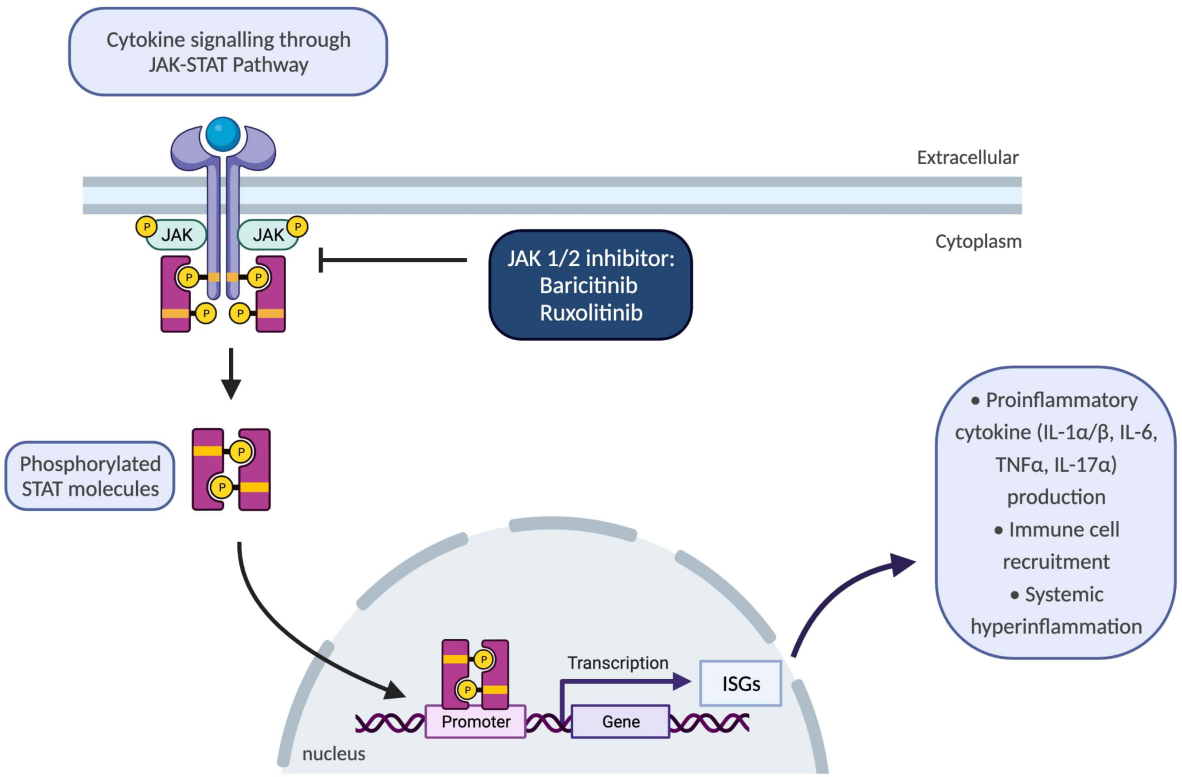

FIGURE 3 | Schematic showing JAK-STAT pathway and the use of JAK 1/2 inhibitors to block inflammatory responses. JAK/STAT pathway plays a key role for the downstream signalling of inflammatory cytokines encompassing interleukins and interferons. Upon binding of cytokines to their cognate receptors on cell surface, associated JAKs become activated and phosphorylate STAT proteins. Following phosphorylation, STATs translocate to the nucleus and regulate transcription of ISGs which drive activation of immune responses including proinflammatory cytokine production, differentiation, and proliferation of innate and adaptive immune cells, and consequently resulting in systemic hyperinflammation. IL-1α/β, interleukin-1 alpha and beta; ISGs, interferon-signature genes; JAK, janus kinase; STAT, signal transducer and activator of transcription proteins; TNFα, tumour necrosis factor alpha.

immune mechanisms (55). Downstream molecules in cholesterol biosynthesis such as geranylgeranyl pyrophosphate (GGPP) were shown to be used in protein prenylation by post-translational attachment of these molecules to the target proteins for optimum membrane localisation (55, 56). As an explanatory mechanism, Park et al. (27) demonstrated that membrane targetting of RhoA was also dependent on geranylgeranylation, which was compromised in the absence of GGPP resulting in RhoA inactivation and consequent pyrin inflammasome activation.

Treatment of MKD has been challenging and different medications have been trialled. Colchicine and statins were not effective in the majority of patients (54, 57). NSAIDs and corticosteroids have been used with some benefit for symptomatic relief, but neither of them was completely efficacious (54).

Maintenance therapy with IL-1 blockade and etanercept has been recommended in the international consensus guidance (46), although therapeutic success with daily anakinra is generally limited, with only 22% complete remission; and 89% partial remission (45). In an open-label study, Arostegui *et al.* (58) demonstrated that canakinumab was an effective treatment choice to control MKD attacks as well as to suppress inflammation-related transcriptional responses (58). More recently, a placebo-controlled trial has also shown favourable outcomes with canakinumab treatment which led licencing of this medication in MKD (39).

DEFICIENCY OF ADENOSINE DEAMINASE-2

Deficiency of Adenosine Deaminase-2 (DADA-2) is a recently described autosomal recessive SAID caused by loss-of-function homozygous or compound heterozygous mutations in adenosine deaminase-2 *(ADA-2)* (previously *CECR1)* (59). Navon Elkan et al. (60) first identified mutations in this gene by whole exome sequencing (WES) in families with polyarteritis nodosa (PAN) (60). Zhou et al. (59) reported that skin, liver and brain biopsies revealed vasculopathic changes with compromised endothelial integrity leading to endothelial cellular activation

TABLE 2 | Summarised features of our cohort with monogenic and autoimmune interferonopathies treated with selective JAK 1/2 inhibitor baricitinib.

Patient	Age	Sex	Diagnosis	Genotype	Peripheral blood ISG assay	Duration of baricitinib treatment (months)	Current dose	PGA before treatment	PGA at last visit	Comment
Pt 1	13	M	SAVI	*STING1* (p.C206Y)	Abnormal	24	4 mg TDS	6	1	Improved QoL
Pt 2	5	F	Unclassified IFNopathy	Awating WES	Abnormal	27	2 mg TDS	6	2	Improved chilblains, stable neurology and MRI brain scans
Pt 3	8	F	Unclassified IFNopathy	Awating WES	Abnormal	5,5	2 mg TDS	5	2	Significant improvement
Pt 4	2	M	Unclassified IFNopathy	Awating WES	Abnormal	7,5	2 mg BD	4	0	Complete response
Pt 5	8	M	AGS	*SAMHD1* Compound heterozygous (c.400C > T/c.1244A > G)	Abnormal	5,5	2 mg TDS	5	3	Improved chilblains, stable neurology
Pt 6	3	M	SAVI	*STING1* (p.F279L)	Abnormal	11	2 mg TDS	3	1	Post-allo BMT, damage accrued prior to treatment
Pt 7	6	M	JDM	2 VUS *OTULIN* (p.Q115H) *ADA-2 (p.R154C)*	Abnormal	9	2 mg BD	N/A	N/A	Resolution of skin disease, reduction in steroid use, weaning IVIg
Pt 8	4	F	AGS	*TREX1* (p.D73N)	Abnormal	9,5	2 mg TDS	4	1	Reduction in fever and panniculitis episodes, neurology stable
Pt 9	16	F	SLE	N/A	Abnormal	11	4 mg BD	3	0.5	DLQI at start: 15/30 DLQI last visit: 0/30
Pt 10	15	F	SLE	N/A	Abnormal	6,5	4 mg BD	N/A	N/A	Unclear, compliance issues
Pt 11	3	F	Autoimmune hepatitis	STAT1 Gof	Not done	10	2 mg am/pm 4 mg lunch	7	2	Significant improvement

ADA-2, Adenosine-deaminase-2; AGS, Aicardi-Goutières Syndrome; Allo-BMT, allogeneic bone marrow transplantation; BD, bis in die (twice a day); DLQI, dermatology life quality index; Gof, gain-of-function; IFNopathy, interferonopathy; ISG, interferon signature gene; JDM, juvenile dermatomyositis; N/A, not applicable; OTULIN, OTU deubiquitinase with linear linkage specificity; pt, patient; SAMHD1, SAM and HD domain containing deoxynucleoside triphosphate triphosphohydrolase 1; SAVI, STING-associated vasculopathy of infancy; SLE, systemic lupus erythematosus; STAT1, signal transducer and activator of transcription protein 1; STING1, stimulator of interferon response CGAMP interactor 1; QoL, quality of life; TDS, ter in die (three times a day); TREX1, Three prime repair exonuclease 1; VUS, variant of uncertain significance; WES, whole exome sequencing.

and inflammation (59). ADA-2 enzyme is produced by myeloid cells and promotes differentiation of monocytes and anti-inflammatory M2 macrophages, hence deficiency of ADA-2 results in a predominance of pro-inflammatory M1 macrophages that secrete pro-inflammatory cytokines, mainly TNFα (59, 61).

The clinical and histopathological features are very similar to PAN, and characterised by systemic inflammation, livedo racemosa (**Figure 2**), and early-onset vasculopathy which may cause haemorrhagic and ischaemic lacunar strokes (62). Multifaceted phenotypes with immunodeficiency and/or haematological involvement ranging from pure red-cell aplasia (Diamond-Blackfan anaemia) and neutropaenia to multi-lineage bone marrow failure have been reported (63, 64).

Definitive diagnosis depends on mutation detection and demonstration of reduced ADA2 enzyme activity in serum (61). Retrospective cohort studies have demonstrated profound therapeutic efficacy and safety of TNF-inhibitors which provided complete control of inflammation, reduced vasculitic disease activity and prevented occurrence of vascular events without causing severe complications (61, 62, 65). Infusion reactions to infliximab (human-mouse chimeric monoclonal antibody) that require switching to another anti-TNF agent (etanercept or adalimumab) have been reported (61). Given that DADA-2 patients require lifelong treatment, development of anti-drug antibodies especially against monoclonal antibodies and reduction in treatment efficacy has been a major concern for anti-TNF therapies. Furthermore, TNF-inhibitors have not been beneficial in treating DADA-2 patients with haematological manifestations or immunodeficiencies, although allogeneic haematopoietic stem cell transplantation has been proven successful to control these symptoms as well as vascular inflammation (64–66). Aspirin usage has been debatable in DADA-2; however, in some cases with non-haemorrhagic ischaemia and peripheral vascular disease, judicious use of aspirin to obtain acute anti-thrombotic effect may be beneficial (61, 67). Gene therapy is currently being studied and is a potential future therapeutic option for DADA-2 patients as it has been promising in other monogenic diseases (61).

INTERFERONOPATHIES

Interferon (IFN)-mediated systemic autoinflammatory diseases are innate immune dysregulatory diseases that present early in life with fever, systemic inflammation, neuroinflammation, and upregulated type I IFN response gene signatures (ISGs)

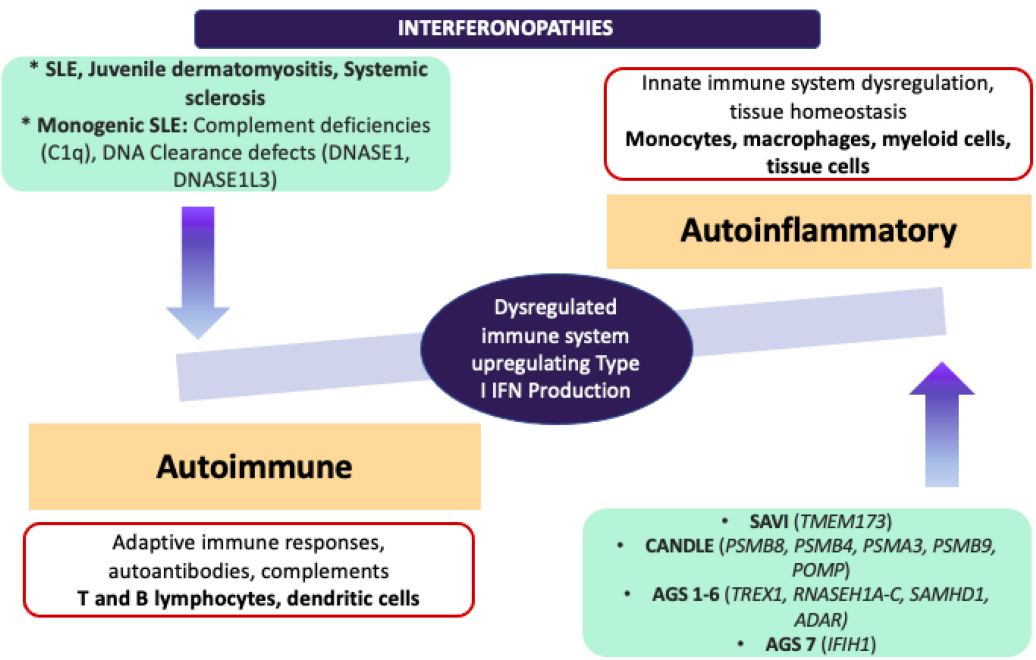

FIGURE 4 | Adapted from Kim et al. (68) comparison of autoinflammatory and autoimmune interferonopathies. Monogenic autoinflammatory interferonopathies that are demonstrated on the right end, are currently defined as CANDLE/PRAAS, SAVI and AGS, and driven by the mutations in proteasome complexes resulting in dysregulation in innate immune responses and increased transcription of IFN signature genes without immune complex deposition. On the left end, monogenic SLE, JDM and SSc are shown under autoimmune interferonopathies, since fundamentally adaptive immune system drives the underlying autoimmune pathology with production of autoantibodies, deposition of immune complexes and activation of T and B lymphocyte subsets. Pathogenic immune complexes can trigger IFN production in these conditions through activation of B lymphocytes and dendritic cells. ADAR, Adenosine deaminase RNA specific; AGS, Aicardi-Goutières Syndrome; CANDLE, Chronic Atypical Neutrophilic Dermatosis with Lipodystrophy and Elevated temperature; C1q, complement 1q; DNASE, deoxyribonuclease; IFIH1, Interferon induced with helicase C domain 1; IFN, interferon; JDM, juvenile dermatomyositis; POMP, Proteasome maturation protein; PSMA3, Proteasome 20S subunit alpha 3; PSMB 4/8/9, Proteasome 20S subunit beta 4/8/9; RNASE H1A-C, ribonuclease H1A-C; SAMHD1, SAM and HD domain containing deoxynucleoside triphosphate triphosphohydrolase 1; SLE, systemic lupus erythematosus; TMEM173, transmembrane protein 173; TREX1, three prime repair exonuclease 1.

in peripheral blood cells. They usually have high morbidity and mortality rates (68, 69). Monogenic interferonopathies include *C*hronic *A*typical *N*eutrophilic *D*ermatosis with *L*ipodystrophy and *E*levated temperature (CANDLE), STING-associated vasculopathy of infancy (SAVI), and Aicardi-Goutières Syndrome (AGS) (68). CANDLE [also referred as proteasome-associated autoinflammatory syndrome (PRAAS)] is caused by loss-of-function mutations in genes encoding proteasome-immunoproteasome components that regulate protein degradation. Brehm et al. (70) revealed that mutations in proteasome genes had an impact on protein expression, protein folding, proteasome assembly and activity. The outcome is sustained IFN-gene expression signature, regardless of genotype. Likewise, SAVI is known to be caused by gain-of-function mutations in *STING1*, the gene encoding stimulator of interferon genes (STING) which plays a central role in innate immune responses by stimulating type I IFN production (71). Disease pathogenesis is similar and considered to be driven by the elevated ISGs; thus, these conditions present with overlapping clinical phenotypes (71).

Until recently, there were no available treatment options to block type-I IFN signalling pathways; however, better understanding of molecular disease mechanisms guided development of selective janus kinase (JAK) 1/2 inhibitors, baricitinib and ruxolitinib (69) (**Figure 3**). To date, various JAK inhibitors have been approved as treatment options in inflammatory conditions ranging from rheumatoid arthritis and psoriasis to inflammatory bowel disease (72). Safety and efficacy of baricitinib were evaluated in a recent longitudinal study which demonstrated improvement in quality-of-life scores, growth and development of patients with reduced inflammatory markers, disease activity and ISGs (69). The commonest adverse events were reported as upper respiratory tract infections, gastroenteritis, and viral reactivation with BK virus (69).

Use of Janus Kinase Inhibition in Children With Interferonopathies at Great Ormond Street Hospital

Herein, novel unpublished data regarding patients diagnosed with interferonopathies and followed-up under Great Ormond Street Hospital (GOSH) paediatric immunology and rheumatology specialities are presented. In our cohort, JAK 1/2 inhibition has been proven to be successful in monogenic and autoimmune interferonopathies. Baricitinib has been used for a median of 9,5 months (range: 5,5 – 27 months). Eleven patients followed by rheumatology (n = 10) and immunology (n = 1) specialities are reported. Median age was 6 years (range: 2 – 16 years). Seven of 11 patients were diagnosed with monogenic interferonopathies: 2/7 with SAVI had confirmed mutations in *STING1*, 2/7 with AGS (*TREX1* and *SAMHD1* mutations), 3/7 with unclassified interferonopathy. All three unclassified patients had undergone whole exome sequencing that were awaited at the time of writing of this manuscript. The remaining four patients had the following autoimmune interferonopathies: 2/4 systemic lupus erythematosus (SLE), 1/4 juvenile dermatomyositis (JDM),

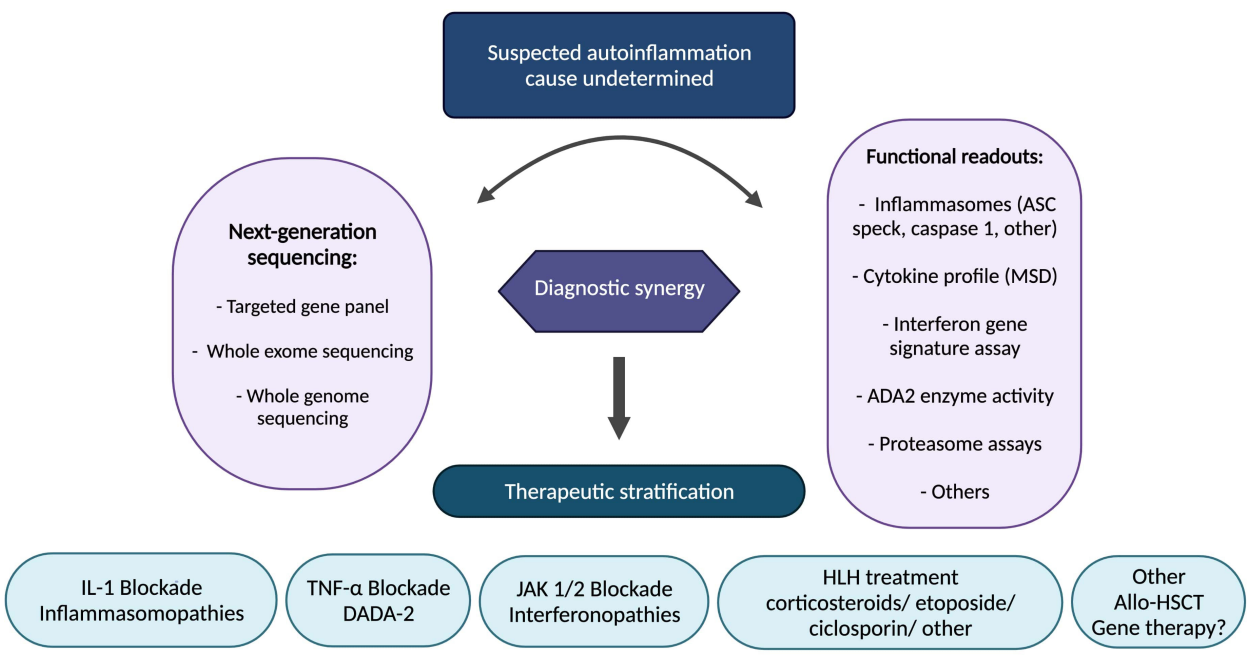

FIGURE 5 | Stratified therapeutic approach for autoinflammation. Functional readouts listed are non-exhaustive examples; other functional readouts pertinent to any genetic findings include STAT signalling (interferon pathway); ADA-2 enzyme activity; leucocyte intracellular MVK enzyme activity; peripheral blood RNA interferon signature, amongst others. ADA-2, adenosine-deaminase 2; Allo-HSCT, allogeneic haematopoietic stem cell transplantation; ASC, apoptosis associated speck-like protein containing a CARD; DADA2, deficiency of adenosine deaminase 2; HLH, hemophagocytic lymphohistiocytosis; IL-1, interleukin-1; JAK, janus kinase; MSD, meso scale discovery; TNF, tumour necrosis factor.

1/4 autoimmune hepatitis with a detected gain-of-function mutation in STAT1 (**Table 2**). Physician global assessment (PGA) of the disease activity is a subjective score given by the evaluating clinician and ranges from 0 to 10; 0 indicating well-controlled disease activity. Assessments were carried out by different clinicians, although there has been a remarkable decrease in average PGA from 4.7/10 to 1.3/10 from start of treatment to the last assessment.

It would be important to emphasise that in addition to monogenic interferonopathies, ISGs have been found upregulated in other autoimmune conditions such as SLE, JDM, and systemic sclerosis. Further scrutiny of the molecular pathogenesis in type I IFN signature has not only led to the development of novel targetted-therapeutic options for Mendelian interferonopathies and for other autoimmune diseases, but also has increased our appreciation of the continuum between the autoinflammatory and autoimmune conditions (73) (**Figure 4**).

CONCLUSION

The list of monogenic SAIDs has been ever-growing with the advances in molecular genetic testing and increased awareness amongst physicians. Although the notion that autoinflammatory conditions are driven by innate immune dysregulation is generally true, identification of novel mutations in genes causing overlap with autoinflammation, immunodeficiency, and/or autoimmunity has strongly indicated the crosstalk between the adaptive and innate immune systems.

Elucidation of the underlying innate immune mechanisms with translational and reverse-translational research has facilitated precision medicine in this space, particularly resulting in therapeutic stratification to IL-1blockade (inflammasomopathies), anti-TNF (DADA2), and JAK 1/2 inhibitors (interferonopathies). Ongoing challenges as more and more patients have access to next generation genetic sequencing include how to interpret novel genetic variants; functional assays to probe the pathogenicity of genetic variants are increasingly necessary in routine clinical practice. Gene therapies are on the horizon for autoinflammation: *ex vivo* lentiviral transduction of haematopoietic stem cells; gene editing; and gene silencing are all likely to impact patient care in the coming decade, and offer hope especially for treatment-resistant/inadequately controlled cases. In the meantime, we present a summary of our therapeutic stratification strategy for autoinflammation including fulminant inflammation caused by monogenic diseases associated with haemophagocytic lymphohistiocytosis and related entities (**Figure 5**).

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.

ETHICS STATEMENT

This study was approved in full by the NRES Committee London – Bloomsbury, ethics number 08/H0713/82. Written informed consent was obtained from the minor(s)' legal guardian/next of kin for the publication of any potentially identifiable images or data included in this article.

AUTHOR CONTRIBUTIONS

OK drafted the manuscript. AP, KW, and OK designed the figures and tables. DE and PB revised and finalised the manuscript. All authors contributed to the article and approved the submitted version.

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REVIEW
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Cell Based Treatment of Autoimmune Diseases in Children

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Mesenchymal stem cells have recently been recoined as medicinal signaling cells (MSC) for their ability to promote tissue homeostasis through immune modulation, angiogenesis and tropism. During the last 20 years, there has been a plethora of publications using MSC in adults and to lesser extent neonates on a variety of illnesses. In parts of the world, autologous and allogeneic MSCs have been purified and used to treat a range of autoimmune conditions, including graft versus host disease, Crohn's disease, multiple sclerosis, refractory systemic lupus erythematosus and systemic sclerosis. Generally, these reports are not part of stringent clinical trials but are of note for good outcomes with minimal side effects. This review is to summarize the current state of the art in MSC therapy, with a brief discussion of cell preparation and safety, insights into mechanisms of action, and a review of published reports of MSC treatment of autoimmune diseases, toward the potential application of MSC in treatment of children with severe autoimmune diseases using multicenter clinical trials and treatment algorithms.

Keywords: stem cells, mesenchymal, transplant, treatment, autoimmune, children

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CURRENT CHALLENGES IN PEDIATRIC RHEUMATOLOGY

The subspecialty of pediatric rheumatology cares for children with autoimmune, autoinflammatory and immune dysregulatory illnesses that occur with an incidence of 1 in 10,000 to 1 in a few million children per year. Although the prevalence is not fully known, it is estimated that in the United States alone, 24 million people or over 5% of the population have an autoimmune disease and a proportion of the affected are children requiring care from a pediatric rheumatologist (NIH Autoimmune Diseases Coordinating Committee: Progress in Autoimmune Diseases Research, March 2005). **Figure 1** shows the types of conditions cared for by the subspecialty; these include those confined to children, such as Juvenile Idiopathic Arthritis (JIA), and those that can affect a wide age range, such as systemic lupus erythematosus (SLE), dermatomyositis (JDMS), scleroderma (SSc), rheumatoid arthritis (RA), and inflammatory bowel disease (IBD). Within this group, children constitute about 10–20% of the total number representing the tail end of the bell-shaped curve for age of onset (1). Not only do children have longer time span to cope with the illness, but also the evidence suggests, on average, the severity of illness can be more pronounced (2, 3). This brings challenges to control disease activity and damage over time to ensure the child's growth into a productive adulthood.

Current treatment modalities are designed primarily to provide immunomodulation without any direct support to *de novo* regeneration (4–7). Steroids are powerful to down regulate various inflammatory pathways, but prolonged usage is unacceptable for numerous adverse effects at young ages (8). In the last 20 years, targeted treatment using biological response modifiers have been

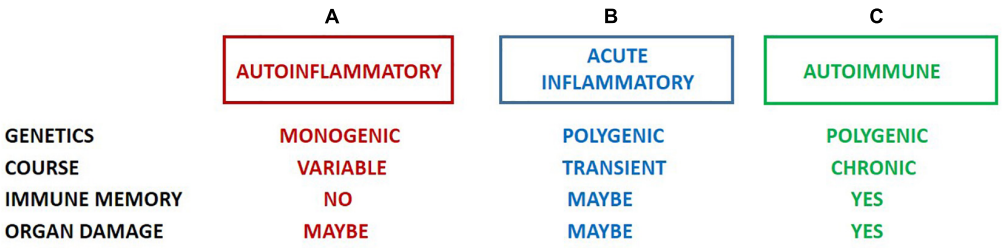

FIGURE 1 | Pediatric rheumatology is involved in inflammatory conditions in children that range from monogenetic **(A)**, i.e., autoinflammatory syndromes to polygenic **(B,C)**. The latter can be one time occurrence (**B**; such as Kawasaki Disease or MIS-C) or chronic and long term **(C)**. Autoimmune conditions **(C)** can be systemic (i.e., affecting 2 or more target organs; such as SLE, JDMS, SSc) or single organ specific (such as Rheumatoid factor + RA, T1DM, autoimmune thyroiditis, uveitis, IBD and Multiple Sclerosis). We postulate that most conditions under B are triggered by infections and the determining factor between the two polygenic inflammatory conditions **(B,C)** is the presence or absence of an adversary immune memory. Should breakage of tolerance occur, there might be a progression from **(B,C)** (such as reactive arthritis to chronic arthritis) at varying speed and intensity based on host HLA, genetic risk factors, immune -repertoire and -memory, and the properties of the triggering event.

successful steroid sparing agents particularly in arthritis, however, long term adverse effects of these medicines remain unknown. Successful treatment of systemic illnesses has been more limited; potent immune suppression to dampen immune memory requires combination therapy using steroids, chemotherapy, biologic response modifiers and recently Jak kinase inhibitors. Although, these agents bring increased treatment options, this is at the expense of escalated risk for serious infections and, yet unknown, adverse repercussions. While there has been significant progress on the treatment protocols for our patients, still, in long-term follow-ups, immune mediated inflammatory diseases (IMID) ranked among the top ten leading causes of death and emphasizes the high burden of inflammation (9).

CELL BASED TREATMENT FOR AUTOIMMUNE DISEASES

Humankind is dependent on two kinds of multipotent progenitor cells throughout life (10) both are harbored in the bone marrow (BM): hematopoietic stem cells (HSC) and mesenchymal stem cells (MSC). The latter, recently recoined as Medicinal Signaling cells (11), are pericytes located over the abluminal surface of blood vessels, and found not only in BM, but also throughout tissues (12, 13). While HSC are the progenitors of blood cells (i.e., leukocytes, erythrocytes and platelets), MSC can differentiate in somatic cells including adipose tissue, chondrocytes, osteocytes and myocytes necessary for growth, regeneration, and tissue repair (14). In addition, MSC can modulate leukocytes to reduce inflammation and preserve tissue homeostasis by angiogenesis and tissue tropism (15). MSC can be expanded *ex vivo* into large numbers without senescence or malignant transformation. Morphologically they are adherent fibroblast-like cells with surface markers positive for CD105, CD73, and CD90 and negative for CD34, CD45- (16). Functionally, MSC are immunomodulatory through evolutionarily highly conserved paracrine factors [such as indoleamine 2,3-dioxygenase (IDO), prostaglandin E2 (PGE2), Heme Oxygenase-1 (HO-1), transforming growth factor β (TGF β)], as well as, by release of exosomes carrying compact cargo customized to the needs in microenvironment, and by cell to cell contact (17–19). As a result, there is down regulation of innate and specific immune system and upregulation of regulatory feedback loops as evidenced by increased M2 Macrophages, IL-10 and T regulatory cells (Treg).

It is important to note that information encoded within the HSC provides the blueprint for the composition of the immune repertoire and the set points of immune regulation toward environmental insults. This concept was proven experimentally in the 1980s by achieving cure upon myeloablative BMT of inbred lupus mice models using allogeneic donor cells from healthy strain (20, 21). Similar results were shown using myeloablative mixed chimerism protocols suggesting importance of immune regulatory networks (22, 23). Non-myeloablative mixed chimerism BMT was effective for survival (71.4%) and preserved kidney histopathology in treated lupus mice at 62-week follow-up, but it required co-transplant of MSC (24). Response to treatment with MSC alone varied based on lupus strain (25, 26). However, a comparative assessment of treatment response among different lupus strains to the same MSC protocol remains to be seen.

There are case reports confirming that transplant of allogeneic (related or unrelated donor) HSC transplant can lead to cure in certain autoimmune diseases. Most studies involved oncology patients with co-existing autoimmune disease who underwent BMT for cancer. Although, so far this is the only known treatment that can promote cure, it can be associated with over 20% mortality and high risk for acute or chronic graft versus host disease (GVHD) (27). In late 1990s, the concept of "setting the clock back" so as to eradicate immune memory by myeloablative autologous (patient's own) BMT was envisioned (26). Over 1,500 patients with various autoimmune diseases were treated. The long-term outcomes of this approach is summarized in Tyndall

TABLE 1 | Cell based treatment of autoimmune diseases.

Cells	Donor	Pro's	Con's
HSC	Allogeneic	Cure	Requires conditioning High risk for GVHD, Requires HLA match High TRM
	Autologous	No risk for GVHD	Requires conditioning No need for HLA match May or may not be a cure
MSC	Allogeneic	Do not require conditioning No need for HLA match No risk for GVHD So far, high safety profile	Not cure Expect transient improvement
	Autologous	Patient's own cells	Concern for genetic factors limiting efficacy

(28) and Farge et al. (29): 100-day treatment related mortality (TRM) was 1% for RA and 11% for lupus patients. The 5-year survival was at 85%, remission rate was about 30%. About 5% of all treated were under 18 years old; among those, 65 were patients with JIA. During long-term follow-up of 34 children for up to 5 years, 53% achieved remission, 21% were resistant to treatment and 9% were deceased mostly from infection (30). There have been only a few studies on non-myeloablative transplant protocols (31–33); it is based on gentle conditioning; therefore, it can be a promising direction for reduced TRM on selected patients.

In analogy to HSC, it has been suggested that autoimmune diseases may in part be propagated by abnormal properties of MSC (34). There is limited evidence in support of this concept when *ex vivo* expanded MSC from patients with various autoimmune diseases are examined by a battery of tests including cell morphology, doubling time, signs of senescence, cell surface markers, and functional studies on immune modulation and angiogenesis. For instance, bone marrow derived MSC from patients with SLE (25, 35–37) showed evidence of distorted cell morphology, early senescence, and slow growth to confluence *in vitro* even though the surface markers and differentiation potential remain compatible to those from healthy controls. Functionally, the immunomodulatory activities may vary from normal (36) to impaired (35). Similar observations have been reported in scleroderma patients: when bone marrow derived MSC from scleroderma patients were cultured *in vitro*, the percentile of endothelial like MSC was significantly decreased, along with signs of early senescence and impaired capillary morphogenesis when compared with healthy controls (38–41). Interestingly, the senescence and immunomodulatory activities of MSC from SLE or scleroderma patients can be improved by inhibition of JAK-STAT or activation of mTOR pathways, respectively (42, 43). There have been similar observations that properties of MSC may (37) or may not (44) be altered in organ specific autoimmune diseases. The evidence so far does not suggest a prominent effect of iatrogenic influences on MSC that the patient may be exposed to Mancheño-Corvo et al. (45), but the literature in this area has been sparse and does not allow for full conclusions.

Nonetheless, these studies have encouraged applications of allogeneic MSC in clinical trials and paved the way for development of off the shelf products. In clinical trials discussed below, the MSC were prepared from adipose tissue, umbilical cord or bone marrow samples. Properties of MSC based on the source tissue is an ongoing area of research (46–48). Although surface phenotype remains similar, there are significant differences in gene expression profiles and differentiation potential based on the tissue of origin (49) even when they are derived from the same donor (50). The treatment outcomes, however, appear to be comparable irrespective of tissue of origin that correlates with the report that the immunomodulatory activities of MSC derived from different tissues of a single donor were reported comparable (51).

Pro's and Con's of cell based treatment is summarized in **Table 1**. While HSC is a once in a life- time event, MSC has the potential to be developed as a "rescue measure" that can be repeated on as needed basis. It is important to point out that the success of HSC transplant is dependent on engraftment. This is not the case for MSC. So far, there is no proven method to promote engraftment of MSC (52, 53) and the efficacy of MSC is likely to be based on paracrine factors to modulate immune regulations, promote angiogenesis and support vitality of stromal cells to improve and/or sustain homeostasis as depicted in **Figure 2**.

IMPORTANT CONSIDERATIONS IN CELLULAR TREATMENT PROTOCOLS BASED ON HISTORICAL FOUNDATION

Since the early 2000s (54, 55), there have been numerous open label phase I/II studies on MSC involving over one thousand patients globally to assess safety and feasibility of MSC transplant. In review of the literature, studies vary for cell source, cell type, treatment protocol, disease selection, and patient selection.

The groundbreaking studies that led this trend were the results of MSC treatment for steroid resistant acute (aGVHD) (56) on a 9-year-old child with malignancy. Shortly after, the protocols used for aGVHD were adapted in trials on autoimmune diseases based on the justification that the pathogenesis of both overlaps for immune mediated microvascular damage (57).

Most protocols involved introducing single cell suspensions of *ex vivo* expanded MSC at early passages (< passage 6; i.e., cells are harvested at less than 6th generation of culture expansion) into a host. The subjects were allowed to continue current medications.

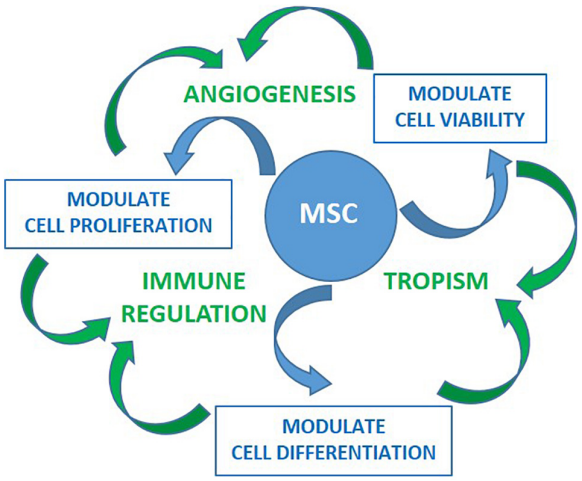

FIGURE 2 | Preclinical studies have shown effects of MSC on cell viability, proliferation and differentiation toward preserving homeostasis. These are highly coordinated activities delivered through evolutionarily conserved mediators as well by cell-to-cell contact toward promoting angiogenesis, tropism and/or immune modulation. These activities are tailored based the signals received from the microenvironment such as those through proinflamatory cytokines and Danger- Associated Molecular Patterns (DAMPs) receptors. Once activated, MSC can modulate both innate and specific immune system *in vitro*. This is accomplished by inhibiting activation and proliferation of effector cells of myeloid (neutrophil, monocyte/macrophage, dendritic) and lymphoid (Th1, Th17, B, NK) lineages, as well as, by promoting differentiation and expansion of regulatory cells (Treg, M2 macrophages, and myeloid derived suppressor cells). *In vivo* immunomodulatory activities of MSC have been supported by the findings of increased Treg and decreased Th17 cells in several studies. Improvement of immune regulation coupled with tropism and angiogenesis is promising for MSC treatment allowing reparation of tissues damaged by inflammation.

There was no conditioning except a small group of patients received cyclophosphamide as noted below. The variables include the source of cells (autologous versus allogeneic), type of cells (bone marrow derived, umbilical cord derived, or adipose tissue derived stem cells), route of infusion (systemic by intravenous, or intra-arterial, versus local injection), dose of cells (usually 1–2 million/kg) and frequency of infusions (once or given intermittently every few days to months). IV has been the most commonly used route of MSC treatment. The majority (>95%) of donor cells are trapped in lung vasculature and become undetectable within 2–3 weeks post infusion (58). It is postulated that most are taken out by the host's killer lymphocytes (59, 60).

Assessment of disease activity and treatment response has been, by and large, by clinical tools including validated disease activity measures, basic laboratories and imaging. Few studies included advanced testing on immune parameters. To our knowledge, there has not been a histopathologic investigation to correlate tissue changes with reported outcomes in humans.

In general, the patient selection has been targeted to those with moderate to severe disease activity who failed to respond or had limitations that did not allow them to continue on conventional treatment. Among those, some had established tissue damage and impending organ failure. The treatment protocols for autoimmune diseases, so far, involved adults at ages of 18 years and above. There have been only few patients at ages down to 16 years old who were included in cumulative results without separating the data by age groups (61). To our knowledge, we were the first to report the experience on MSC treatment in Pediatric Rheumatology (62).

SAFETY DATA FOR MSC BASED THERAPIES

MSC therapy is tantalizing to consider in autoimmune diseases as patients are chronically ill and current therapies are not curative. Most treatment regimens have significant immunosuppression and often have adverse side effects. MSC is generally thought to be devoid of major side effects and based on a review of the literature, over a thousand patients have received MSC treatment world-wide. The early concerns regarding the possibility of under reporting of adverse effects is slowly dissipating with increasing cumulative data through global engagement.

In two systematic analyses, the safety of MSC therapy was explored. In the first, Lalu et al. (63) used the MEDLINE, EMBASE, and the Cochrane Central Register of Controlled Trials and reviewed 2,347 studies with 36 studies that met inclusion criteria. The primary outcome adverse events were grouped according to immediate events (acute infusional toxicity, for example: fever), organ system complications, infection, and longer-term adverse events (death, malignancy). There were 1,012 participants with diverse clinical conditions (ischemic stroke, Crohn's disease, cardiomyopathy, myocardial infarction, GVHD, and healthy volunteers). Eight studies were randomized control trials (RCTs) with 321 participants. Meta-analysis of the RCTs did not detect an association between acute infusional toxicity, organ system complications, infection, death, or malignancy. The major significant association with MSC therapy was a transient fever. Based on these reviews, the authors concluded that MSC therapy appeared to be safe, but more studies were needed. In another systematic analysis, Can et al. reviewed 93 peer-reviewed full-text articles and abstracts published by August 2017 that investigated the safety, efficacy and feasibility of UC- MSCs in 2,001 patients with 53 distinct pathologies. All studies noted therapeutic benefit and there were no long-term adverse events or tumor formation (55).

A retrospective study in a cohort of 404 patients with different autoimmune diseases who received MSC transplants from 2007 to 2016 was done in Nanjing University Medical School (64). Their endpoint was to evaluate the frequency of adverse events by using the Common Terminology Criteria for Adverse Events version 4.0 (CTCAE v4.0) (65). Based on this grading system, five grades were defined as: grade 1, mild: asymptomatic or mild symptoms, clinical or diagnostic observations only, intervention not indicated; grade 2, moderate: local or non-invasive intervention indicated; grade 3, severe or medically significant but not immediately life-threatening, hospitalization or prolongation of hospitalization indicated; grade 4, life-threatening consequences, urgent intervention indicated; and grade 5, death related to AEs. In this system, grades 3–5 are

considered serious. Hyperacute adverse events were defined as occurring during and immediately after the infusion, while acute adverse events were defined as occurring from the second day to the first month after infusion. After the first month, subsequent infections and malignancies were analyzed. There were 11.9% of patient with hyperacute adverse events that included fever, headache, palpitation, facial redness, insomnia, and stomach discomfort, but all were classified as grade 1–2; mild. Patients with polymyositis or dermatomyositis (6/30 or 20%) or those over 40 years old (25/182 or 13.7%) had proportionately more hyperacute adverse events, but the numbers were small. Acute adverse events occurred in 4% in the first month after transplant including fever, hair loss, peeling skin, facial rash and cervical lymphadenopathy, that were mild, but there were 6 patients with infection, two with encephalorrhagia, and one cirrhosis with bleeding from esophageal varices resulting in 5 deaths. In this cohort, there were 45 deaths that occurred an average of 29.6 months after the MSC infusions. After 1 month, there were no cardiac, gastrointestinal, renal, pulmonary, neurological, or hematological adverse events. Death occurred in 45 patients, with 64.4% developing 3 years after MSC infusion. Infections remained a major concern, with 26.7% developing an infection. The most common cause of death was disease relapse (62.2%). Cancer occurred in 6.7% of patients. Again, those with dermatomyositis and polymyositis had proportionately the highest mortality. In this study, 26 patients were children (<18 yo). At the time of the report, 24 of the children had good outcomes during the 4–5 years following MSC transplantation. Two died from disease complications more than 100 days after the MSC transplant. The authors conclude that MSC therapy in autoimmune disease is safe and shows efficacy and concluded that the incidences of adverse events was acceptable to warrant MSC therapy in patients with autoimmune disease.

After infusion, the majority of the MSC are found in the lungs and the MSC are viable for about 24 h. At 24 h the MSC were also found in the liver. After 24 h, there are no viable MSC noted (66). The consequences of the MSC in the lung is not well known, but in patients with lung and cardiac disease there is concern that this massive influx of cells could result in activation of the cytokine and complement system. In patients with pulmonary hypertension, activation of the vascular system could result in acute ischemia that may be difficult to reverse. Although pulmonary embolism is a concern as a treatment related adverse effect, so far it is rarely reported. To this point, two recent studies on MSC treatment on severe COVID-19 infection did not report TRM (67, 68).

One of the later sequelae of MSC transfusion is the risk of teratoma formation, undifferentiated proliferation, or malignancy. In one clinical trial of MSC for treatment of advanced neovascular age-related macular degeneration, a MSC from a patient was found to have a mutation and the trial was stopped. It is not clear if this mutation was pre-existing or occurred during cellular preparation and re-programming (69). Further studies are needed for optimal preparation of MSC infusions and long-term data collection essential to determine the long-term risks of MSC. Although, the risk for interstitial lung disease or accelerated fibrosis initially was a great concern - for the potential of trapped MSC within the lung to differentiate into fibroblasts -, this, so far, has not been a reported adverse effect (70). Further studies are needed for optimal preparation of MSC infusions and long-term data collection essential to determine the long-term risks of MSC.

MSC TREATMENT OF AUTOIMMUNE DISEASES—OVERVIEW OF PUBLISH DATA

In the last two decades, there has been considerable data accumulated on applications of MSC for various autoimmune diseases. This is through the pioneering work mostly by the investigators of Far East and Middle East in single center-based trials at various academic institutions (64, 71–73). The major rheumatological illnesses studied, so far, include SLE, SSC, and Rheumatoid Arthritis (RA). There are only a few reports of use of MSC in dermatomyositis and vasculitis. There are also learning points from the experiences on other organ specific autoimmune diseases (MS, IBD, and DM) as well as from applications of MSC on intractable conditions of the newborns.

Lupus has been one of the most extensively studied disease models. In 2009, Dr. Sun and colleagues reported the first groundbreaking pilot study on four patients treated with allogeneic bone marrow derived MSC who achieved clinical and serological improvement during 12–18 month follow-up period (25). Similar disease control was achieved when umbilical cord derived MSC were used in some (74) but not all trials (75). The selection criteria included ongoing active lupus activity with SLE disease activity index (SLEDAI) score $\geq$ 8, inadequate disease control with high dose steroids (>20 mg/day) along with at least 6 monthly treatment of intravenous cyclophosphamide or at least 3 months of oral mycophenolate mofetil, refractory immune-mediated thrombocytopenia and refractory lupus nephritis (WHO IV/V with proteinuria $\geq$1,000 mg/24 h, serum creatinine $\geq$ 1.5 mg/dl or decreased creatinine clearance without end-stage renal failure. The MSC harvested from bone marrow or umbilical cord, expanded *in vitro* in media with fetal bovine serum. Cells from passage 3 to 5 were infused to patients intravenously at 1×10^6/kg body weight. The outcomes were similar when MSC was given once weekly for in two intervals (76). Recently, the same center has published cumulative experience on 81 lupus patients for long-term outcomes (77). The treatment involved a total of 104 MSC infusions using bone marrow derived (22/81) or umbilical cord derived (59/81) MSC given intravenously once (66/81), twice (11/81), or up to 4 (4/81) times during the follow-up. In addition, 39/81 also received IV cyclophosphamide at 10 mg/kg/day × 3 just prior to MSC. The cohort was composed of moderate to severe, SLE who were resistant to various treatments (including cyclophosphamide in 59 out of 81 patients) prior to enrollment. Overall, the MSC treatment was safe and effective. Five-year survival was 68/81 and 37/81 achieved remission. Out of 37, 22 had complete remission (4 off treatment), 6 had partial remission and 9 relapsed. Fifteen out of 81 patients died from various non-treatment related events, 8 occurred within

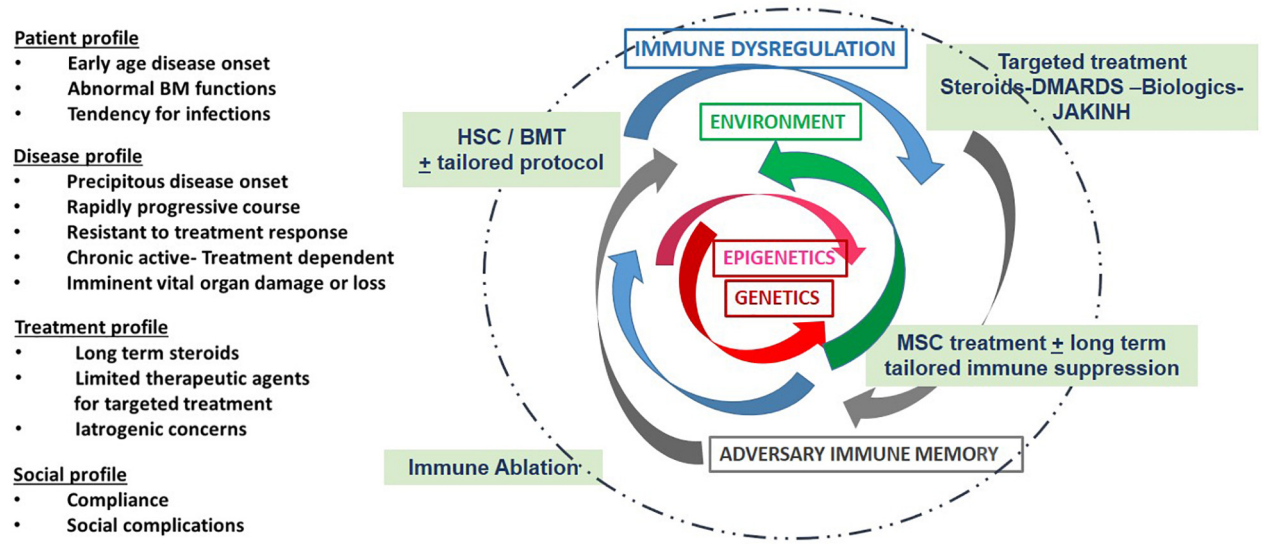

FIGURE 3 | Depicts some of the considerations and challenges with MSC treatment: Treatment regimens are usually based clinical considerations as listed in the first column, i.e., genetic influences and disease course as well as the history of treatment response and social concerns. Genetic and epigenetic factors (red arrows) and their environment (green arrows) are unique to each patient. These combined factors may result in immune dysregulation (blue arrows) and a subsequent adversary immune memory (gray arrows). Therapies (in green text box) are designed to dampen inflammation. In selected patients, personalized cell based treatment protocols can be introduced to improve long-term outcomes and minimize damage. New algorithms are needed based on data derived from expanded laboratory panels and real time assessment tools that are now available through adaptations of existing technology and essential for patient centered care.

the first 12 months post MSC: 4 out of 8 of the deceased had pulmonary infection and 2 had cardiac compromise. Four of remaining 7 deceased at 31–83 months post MSC had continuing disease progression and ESRD. During the follow-up, majority of adverse events were centered on infections while 51 subjects remained on varying extents of immunotherapy. Laboratory parameters showed significant improvement in proteinuria and cytopenia, serum albumin and complement levels. Initial reports included decreased titers of double stranded DNA antibody, as well as increased blood T-regulatory (Treg) cells (CD4 + CD25 + Foxp3 +)—and decreased Th17- populations in the peripheral blood samples (73, 78). A follow-up case report on two lupus patients treated with autologous MSC also had increased Treg cells, but the clinical improvement was marginal (79). Increased levels of Treg post MSC is a reproducible finding, but further investigations are warranted to explore time course, and sustainability of blood lymphocyte profiles post treatment for its impact on treatment outcomes.

There is significant interest in MSC treatment of SSC for the paucity of effective treatment options, as well as, for the pathogenesis of the illness that is tightly coupled with the progeny of MSC, i.e., fibroblasts and endothelial cells (70). Initial results were encouraging on a small case series of four patients with leukemia who developed sclerodermatous chronic GVHD after bone marrow transplant (80). These patients improved after treatment with unrelated allogeneic bone marrow derived MSC injected *via* intra-osseous route. Follow up labs were significant for increased ratio of peripheral blood Th1 to Th2 cells. Keyszer et al. reported (81) their experience on five patients with severe and life-threatening SSC with positive Scl70 (n = 4) or positive anti-RNP (n = 1) autoantibodies. All 5 patients received a single intravenous infusion of related bone marrow derived MSC (0.2–1.8 × 10^6/kg body weight). There was no treatment related mortality following shortly after infusion. The beneficial effect was observed mostly on skin findings; starting at 3 months post treatment, there was improvement of skin score for thickness and healing of ischemic ulcers. Two patients with cardiac involvement died at 6 and 23 months post MSC. Two patients with lung disease progressed- one requiring lung transplant. A case report from Italy (82) observed significant improvement of gangrenous ischemic ulcers after 3 monthly intravenous infusions of autologous bone marrow derived MSC (almost 1 × 10^6/kg body weight/dose). There have been trials involving local injections of MSC in patients with scleroderma: A recent report from Japan (83) on 40 patients with peripheral arterial disease (11 with SSC and 29 with arteriosclerosis obliterans) reported improvement of ischemic ulcers based on a protocol involving surgical debridement followed by local intramuscular injections of autologous bone marrow derived stem cells (0.4–5 × 10^{10} total) and finally skin grafting to cover the open ulcers. At the 2-year follow-up, non-treatment related mortality rate, and recurrence rates were 27 and 18%, respectively. Nine percent progressed to require limb amputation. For treatment of childhood onset limited sclerosis, Scuderi et al. (84), injected autologous adipose tissue derived stem cells mixed with hyaluronic acid solution (8 × 10^5/ml up to 10 ml) locally at the affected areas of skin in 6 patients (including one with generalized morphea, and one with En Coup De Sabre). There were no adverse effects. One patient had moderate and 4 had considerable levels of improvement at 1-year follow-up.

Treatment of refractory Rheumatoid Arthritis with MSC has been a global interest and a platform for industry sponsored trials using off the shelf MSC in the pipeline. Trials on arthritis started after a pilot study in Korea on 4 patients receiving autologous adipose derived MSC IV ± IA with a combined dose up to 500×10^6/patient. The treatment was tolerated well without TRM. So far, there are over 400 patients treated with single or up to 3 weekly doses of allogeneic MSC at doses of ranging from 1 to100×10^6 IV per infusion. Follow-up was 1–36 months (median 12 months), among 8 trials (85). A recent clinical trial from China (86) reported observations on 172 patients with RA who had history of partial response to conventional treatment. There were two study arms (1:1), one, with umbilical cord derived MSC ($4 \times 10^7 \times 1$) and two, with cell free culture supernatant of MSC cultures. All subjects continued on DMARDS. There was significant improvement in the first arm, but not in the second arm. Furthermore, the improvement correlated with decreased serum proinflammatory cytokines (TNFα, IL6) as well as increased Treg that lasted for 3–6 months. There were no serious adverse reactions or treatment related mortality. Long-term follow-up of the same cohort was reported on 64 subjects (including 3 juvenile onset arthritis and 4 ankylosing spondylitis) 36 months post MSC treatment (61). The disease activity score (DAS28, HAQ), autoantibody titers for RF and cyclic citrullinated peptide antibody (anti- CCP) as well as blood inflammation markers (ESR, CRP) showed steady and significant decline over the 3 years. CBC, serum total immunoglobulins, liver and renal functions remained normal. Treatment of ankylosing spondylitis (AS) with MSC infusions also were safe and effective. In a study 31 patients with treatment resistant AS were treated with 4 weekly IV infusions of BM derived allogeneic MSC at 1×10^6/kg/dose. There was no TRM or serious adverse effects. The clinical improvement correlated with MRI improvement at 20 weeks post treatment (87).

CONCLUSION AND NEXT STEPS

Cell based treatment with HSC has cured many diseases in the last 5 decades (88) when there is no other remedy for illnesses like cancer or immune deficiency. Adaptation of this modality to autoimmune diseases, however, is challenging for TRM or GVHD. Even with autologous protocols, the conditioning regimens are concerning for high risk of infection. Adaptation of non-myeloablative protocols can be promising particularly for young children with known genetic risk factors and poor prognosis. This will require available full match donor and cross-disciplinary teams.

Recently, MSC treatment has been promising for multifaceted medicinal properties as it offers not only immune tolerance, but also vascular and somatic wellness (89, 90). This is important particularly for autoimmune diseases as long-term outcomes are determined by the balance between immune mediated damage and tissue regeneration. Unlike treatment with HSC where transplanted cells result with a binary outcome, i.e., all or none, MSC treatment should be considered as a transient, but personalized, therapy, and not a cure.

Treatment paradigms in complex diseases, particularly in rheumatology, are a moving target that is reconfigured along with advances in predictive biomarkers, preventive measures and targeted treatments. In the last 25 years, there has been a transition from an upright to a downward pyramid (91). We suggest MSC has the potential to become a component of a new treatment paradigm particularly for early intervention. While currently cell-based treatment is considered for life threatening conditions, this may change in time as the comfort level of using this therapeutic modality improves once further evidence becomes available on safety and efficacy. MSC may work better in early phases of the illness before permanent tissue changes develop. It is likely that some, if not most, of the patients treated with MSC will continue to require immunosuppressive regimens, albeit to a lesser extent, to prevent organ damage. MSC is not a treatment that can bring vitality back once there is effacement of tissue architecture and loss of tissue specific progenitor cells. Currently there is no effective protocol to accomplish engraftment of donor MSC and repair late-stage tissue damage *de novo*.

It is worth pointing out that, as a natural result of aging, it is well known that there is a decline in the numbers as well as the telomere length of MSC (92). This process is accelerated in patients with chronic inflammation. The mechanisms involved are not fully known but epigenetic changes are likely to be important. Advantage of introducing MSC may include sustained homeostasis through supporting *in situ* pericyte populations. Knowledge gain in reference biomarkers to assess *in vivo* landscapes for tropism and regeneration are important for successful applications of MSC and cell-free products of MSC (including exosomes) in the near future. In line with this concept, as the children have escalated regenerative capacity (7, 30) with ongoing natural physiology of growth, they may benefit from MSC more robustly when compared with adults.

Currently there is no protocol tailored for pediatric autoimmune patients (**Figure 3**). Although, the 1st case reports for successful application of hematopoietic stem cells (HSC), as well as MSC treatment in medicine were on children for treatment of immune deficiency and malignancy, in 1968 (93) and 2004 (57), respectively. With the advancements of cellular therapy, commercial MSC products have been licensed for the indication of for pediatric steroid refractory GVHD in a number of countries including Japan, Canada, and New Zealand (94). On an important note, there has been significant progress on applications of MSC on intractable newborn diseases. In neonates, there are two recent review articles that site benefits of MSC in case reports or small trials in certain neonatal diseases including severe intraventricular hemorrhage (IVH), bronchopulmonary dysplasia (BPD), and necrotizing enterocolitis (NEC). The reports are encouraging in that there are no adverse events, the studies are small, but promising (95, 96). Most of these studies note the need for multiple infusions. There are now five phase I clinical trials in neonatal patients: 3 in BPD, 1 in IVH, and I in hypoxic ischemic encephalopathy (HIE) (96).

As the public becomes informed *via* the internet, patients and parents demand explanations and consideration of potential

treatments. In the reported case of the three pediatric patients (1 with SLE, 1 with mixed connective tissue disease (MCTD) and one with JIA) who received MSC transplants, all were parent or patient initiated with great cost to the family (62). All reported improvement, but this may have been influenced by the difficulties and financial burden entailed to get the MSC transplant. Two of the patients had to travel outside of the US to receive the MSC transplant. As more information is available, patients and their families may seek this therapy, which on the internet has promoted as curative in some cases and benign. As pediatric rheumatologists, we strongly believe, it is for the benefit of our patients to bring awareness of this therapeutic modality and actively engage in its research to determine -first hand- its promise and, equally importantly, its potential adverse and long-term effects.

We do believe coordinated and multilateral initiatives involving academics, government, industry and patient advocacy groups are key for fast-track progress on multi-center and patient centered research to push the limits to reach cure.

AUTHOR CONTRIBUTIONS

OYJ and DM envisioned, crafted, wrote, and edited the manuscript. Both authors contributed to the article and approved the submitted version.

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Health disparities in outcomes of pediatric systemic lupus erythematosus

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Healthcare disparities exist throughout the United States, and disparities in healthcare delivery are responsible for a substantial portion of preventable morbidity and mortality. SLE disproportionately affects racial and ethnic minoritized groups, including Blacks, Hispanics, and Asians/Pacific Islanders. Specifically, Black females have a 3 to 4-fold increased risk of developing SLE than White females. Population studies funded through the Centers for Disease Control have examined variations in disease outcomes among the different populations around the United States. For example, studies have shown that lupus nephritis, anti-phospholipid syndrome, and thrombocytopenia are more likely to affect racial and ethnic minorities than Whites. In addition, the Center for Disease Control WONDER (Wide-ranging Online Data for Epidemiologic Research) database found SLE was the seventh leading cause of death for all women aged 15–25 years and the fifth leading cause of death for African American and Hispanic females. From these studies, we know SLE primarily affects racial and ethnic minorities, but we do not know why these groups are at increased risk of developing the disease or have worse outcomes. By examining the underlying mechanisms of health disparities within our patient populations and mitigation strategies, we will further understand and provide better treatment for our patients. This review will discuss current research related to health disparities and health outcomes in childhood-onset SLE (cSLE).

KEYWORDS

health disparities, systemic lupus erythematosus, implementation science, population studies, pediatrics

Introduction

Healthcare disparities exist throughout the United States, and disparities in healthcare delivery are responsible for a substantial portion of preventable morbidity and mortality (1). SLE disproportionately affects racial and ethnic minoritized groups, including Blacks, Hispanics, and Asians/Pacific Islanders. Specifically, Black females have a three to four-fold increased risk of developing SLE than White females (2, 3), Population studies funded through the Centers for Disease Control have examined variations in disease outcomes among the different populations around the United States. For example, studies have shown that lupus nephritis, anti-phospholipid syndrome, and thrombocytopenia are more likely to affect racial and ethnic

minorities than Whites (3–5). In addition, the Center for Disease Control WONDER (Wide-ranging Online Data for Epidemiologic Research) database found SLE was the seventh leading cause of death for all women aged 15–25 years and the fifth leading cause of death for Black and Hispanic females. From these studies, we know SLE primarily affects racial and ethnic minorities, but we do not know why these groups are at increased risk of developing the disease or have worse outcomes. By examining the underlying mechanisms of health disparities within our patient populations and mitigation strategies, we will further understand and provide better treatment for our patients. This review will discuss current research related to health disparities in health outcomes of childhood-onset SLE (cSLE) and quality improvement strategies to address disparities.

Methodology

We performed a PubMed search (Figure 1) with the query including pediatric/children/child, systemic lupus erythematosus/SLE/lupus, health disparities/social vulnerability/adverse childhood events/ACE, and patient outcomes. The search resulted in 33 articles from 2010 to present, of which 10 articles were of relevance. The eligibility of studies focused on pediatric SLE or adult SLE studies that assessed SLE outcomes and disparities. Exclusion criteria included articles discussing medication treatment regimens, including pharmacokinetics and safety and efficacy of new treatment regimens, description of patient registries, and effect of smoking on SLE. There were limited papers focused on cSLE, health disparities, and patient outcomes, therefore we included a few studies pertaining to adults that we felt were relevant. One adult study pertained to the history of pediatric outcomes (adverse childhood events). Quality improvement studies, including a review of a quality framework, were also included due to the relevance in health outcomes and the discussion of three different areas where healthcare quality improvement can be implemented.

Review of the literature

At this time, there is limited published research investigating disparities in patient outcomes in cSLE. In assessing health disparities in patient outcomes, the primary studies have been large population-based studies, looking at demographics of hospitalizations and associated comorbidities. There is limited data looking specifically at SLE disease activity and health disparities. Another vital area of research in health disparities and outcomes involves improving patient outcomes using care continuum models and quality improvement/ implementation science. Below, we will discuss current health disparities research

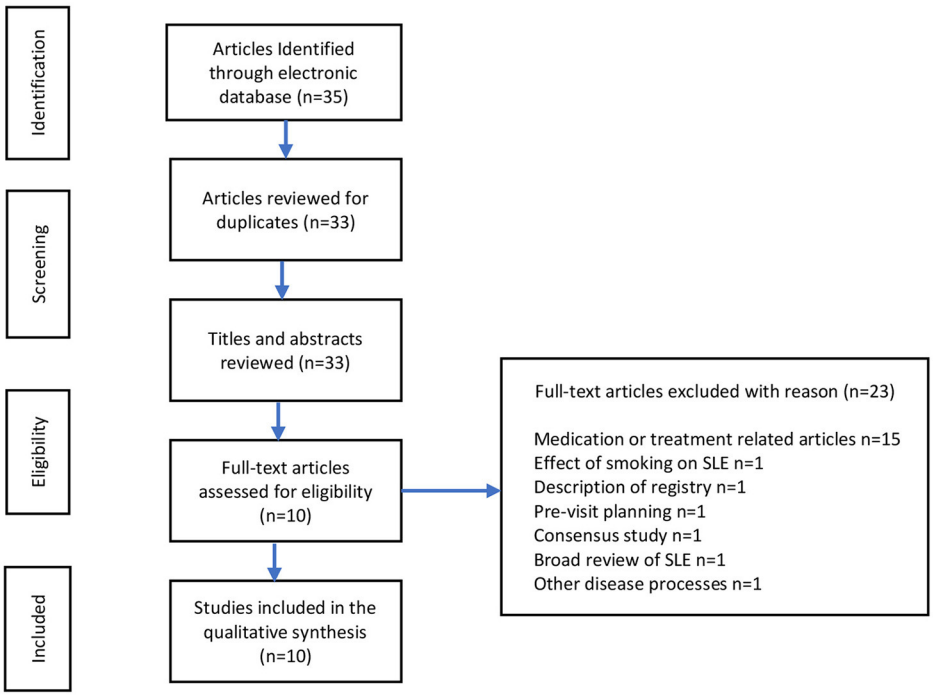

FIGURE 1
Flow chart for PubMed query for pediatric SLE, health disparities, and patient outcomes.

TABLE 1 Patient demographics for study evaluating cSLE outcomes from PHIS database from Son et al. (6).

Demographics	
Race	
White	39%
Black	35.4%
Asian	5.3%
Ethnicity	
Hispanic	26.6%
Insurance	
Yes	85%
Public insurance	53%

using population-based studies. We will then transition to studies discussing quality improvement and implementation science to improve patient outcomes.

In assessing health disparity outcomes, we will discuss three studies that examined different patient outcomes. In the first study, Son et al. (6) look at the rate of hospital/ICU admissions, end-stage renal disease, and mortality in SLE. In the second study, Knight and her colleagues discuss health disparities in SLE in relation to depression and anxiety. Lastly, in the third study, an adult SLE study, DeQuattro et al. (7) examines adverse childhood events (ACEs) and their relationship with SLE.

With the assessment of disparities in patient outcomes, Son et al. (6). examined the admissions rate to better understand health disparities in child onset SLE (cSLE). Son et al. investigated whether there was an association between sociodemographic information (Table 1) and variation in the volume of admissions for child onset SLE (6). The outcomes of interest included ICU admissions, ESRD, and in-hospital mortality. The study used pediatric health systems (PHIS) database that included hospitalization information from 43 free-standing pediatric hospitals within the United States. Admission data was analyzed for children between the age of 3 and 18 years with at least 1 International Classification of Diseases (ICD)-9 code for SLE between January 2006 and September 2011. The outcomes of interest in the assessment of sociodemographic health disparities using the PHIS data set, included ICU admissions, ESRD, and in-hospital mortality. There were 10,724 admissions among 2,775 patients in the 43 pediatric hospitals within the United States.

The average follow-up for patients was approximately 1 year. Roughly 85% of patients had insurance, of which 53% of patients had public insurance. A multivariable logistic regression model was performed and controlled for patient gender, age, race, ethnicity, insurance type, hospital volume, US census region, and severity of illness. In the study, Hispanics were noted to have longer length of stays, more readmissions, and increased in-hospital mortality. There was also a significant association between Black patients and increased ICU admissions. Regarding ESRD, about 5.8% of patients with cSLE developed ESRD, with Black and Hispanic patients at higher risk for ESRD. In hospital mortality was 1.5% ($n = 41$), of which 11% of the patients had ESRD. Black patients were also noted to be significantly over-represented in the SLE hospitalizations, accounting for 43.6% of all cSLE admissions. A limitation of the study is we do not know to what degree Black patients were overrepresented in hospitalizations relative to SLE prevalence, or why. There are likely unmeasured risk factors at play, including potentially modifiable social and environmental factors, more so than genetic susceptibility. The Southern region of the United States had a significantly larger population of cSLE patients with renal disease (6). This study by Son et al. (6) demonstrated differences in SLE outcomes based on sociodemographic factors within the United States. Specifically, it noted increased risk for ESRD and mortality in Black and Hispanic minority population groups with SLE. Most recently, a follow-up study evaluated PHIS data from 2006-2019, demonstrated overall improvement in frequency of ESRD and dialysis but continued racial disparities when it comes to ESRD and dialysis and need for interventions to address disparities in renal outcomes (8).

Another examination in health disparities and outcomes in SLE patients, involves the assessment of depression and anxiety. Knight et al., performed a population-based study evaluating the prevalence of depression and anxiety in pediatric patients aged 10 to 18 years old with SLE (9). Data was obtained from the US Medicaid Analytic Extract database from 2006 to 2007. The study included 970 children with SLE, of which 15% identified White, 42% identified Black, 27% identified Latino, and 16% identified as other races or ethnicities (which included Asian, Pacific Islander, Native American, and other). The study used ICD-9 codes for depression, anxiety, adjustment disorder, and other psychiatric disorders to determine the prevalence of mental health disorders in cSLE.

Of the 970 patients, 19% had depression, 7% had anxiety, 6% had acute adjustment disorder, and 18% had other psychiatric disorders. The analysis was adjusted for age, sex, urban vs. rural environment, presence of lupus nephritis, presence of seizure/strokes, glucocorticoid use, and the number of outpatient visits. In the adjusted analysis, there was a significant difference in diagnosis of depression and anxiety in Black patients compared to White patients, with Black patients less likely to be diagnosed with depression and anxiety. There was no significant difference between Whites and other races or ethnicities (9).

Among the 970 patients, 20% were prescribed antidepressants, 7% were prescribed anxiolytics, and 6% were prescribed antipsychotics. For the patients diagnosed with a psychiatric diagnosis, approximately 61% were prescribed at least 1 psychotropic medication. For the patients who did not have a psychiatric diagnosis, approximately 17% had

been prescribed at least 1 psychotropic medication, leading to concern for under-diagnosis vs. other medical indications. Additionally, when prescription demographics were further classified, Black patients were significantly less likely to be prescribed anxiolytics. The study also noted a significant increase in depression and anxiety in patients with increased medical visits (9).

Overall, the study illustrates the high burden of depression (19%) and anxiety (7%) in cSLE patients, which was significantly more than the overall prevalence of depression and anxiety noted in the general Medicaid population (9). The study also illustrates the concern for decreased treatment of depression and anxiety in Black patients within the Medicaid cohort. A study in adolescent psychiatry also noted racial and ethnic minorities were less likely to be prescribed treatment for depression (10). There could be numerous reasons for treatment, such as the use of therapy rather than medication. Additionally, family or culture stigma related to mental health and treatment may also play a role in treatment of depression (9, 10). Within the clinical setting, language concordance between patient and provider could also be a factor (10).

An additional area of health disparities research is whether adverse childhood events (ACEs) contribute to the development of SLE. Most recently, DeQuattro et al. examined whether there was an association between ACEs and systemic lupus erythematosus in adult patients (7). Although this study does not assess the association of ACEs in a pediatric population with SLE, the study was included because of the relevance in the implication of ACEs in association with SLE. The prevalence of ACEs in childhood of patients with SLE from the California Lupus Epidemiology Study (CLUES) was compared to population survey estimates from California's Behavioral Risk Factor Surveillance System (BRFSS). The BRFSS survey at the time of the study did not include neglect; therefore, the neglect portion of the ACE questionnaire was omitted. They then evaluated for associations in overall ACE level with patient-reported outcomes and physician assessed health status measures. A multivariable regression analysis was performed and controlled for sociodemographic, nephritis, and cSLE (7). Results of the study found that the distribution of ACE levels was similar for the CLUES and BRFSS groups ($p = 0.42$). Two potential reasons for the similar prevalence values include selection and survival bias in the CLUES group, with patients with more severe disease activity or lower socioeconomic level less likely to participate in the study (7).

Further examination of the CLUES group and association with SLE disease activity showed the median ACE level was 1 and about 20% of participants had ≥4 ACEs. An ACE level ≥1 was more likely to be seen in an older patient of Hispanic ethnicity or Black race and with a history of lupus nephritis. A patient with an ACE score greater than 0 was also less likely to have a 4-year college degree. It was also noted that patients who reported increased SLE disease activity, damage, and depression had increased ACE levels. There was also a decrease in physical function and health status with increasing ACE levels. Overall, there was a noted "dose-response" association between patient-reported health outcomes and ACE level (7). The associations remained significant even after adjustment for age, sex, race and ethnicity, cSLE, and educational attainment. However, interestingly there was not a significant association between ACE levels and SLE disease activity with physician associated measures. It is unclear why there was an association between patient reported outcomes and ACE level and not physician reported outcomes. It was speculated overall health status and mood may also play a role in the patient reported outcomes and impact the score (7). This study is one of the first to evaluate ACE levels in SLE patients and demonstrated overall higher ACE levels with patient reported outcomes. ACE levels are an important consideration for future research because of the association between toxic stress and worse long-term health outcomes, particularly in people with chronic diseases.

An additional area of research in health disparities involves ways to improve patient outcomes. The next two studies focus on using frameworks to improve outcomes for SLE patients. A key part to the studies is examining how improving health disparities can improve patient outcomes.

For the first study, Bartels et al. (11) were interested in evaluating retention in care as a mechanism to improve patient outcomes. The retention in care model was a framework for human immunodeficiency virus (HIV) from World Health Organization (WHO), Institute of Medicine (IOM), and Centers for Disease Control and Prevention (CDC) to improve patient outcomes. By developing strategies related to information gained from the continuum of care model, viral suppression has improved from 61 to 80% between 2012 and 2016. Bartels et al. (11) were interested in the HIV continuum of care model because HIV disproportionately impacts young adults in minority groups and socioeconomically disadvantaged. They wanted to develop and validate a similar model for SLE. They were interested in the relationship of race, socioeconomic disadvantage, and retention in care. The 5 steps of the SLE care continuum include diagnosis of SLE, link to rheumatology care, retain in care, immunotherapy, and low disease activity/damage (11).

In developing the SLE care continuum model, the primary care clinic visit was of importance to assess for other comorbidities. Patient demographics were notable for 91% female, 39% Black, 5% other, and 4% Hispanic. Black patients were more likely to live in disadvantaged neighborhoods (51 vs. 5% of White patients) and more likely to receive public insurance (75 vs. 40% for White patients). In defining retention in care for SLE, they focused on 2 annual visits and 2 lab defined every 6 months. When assessing predictors for the care model, living in a disadvantaged neighborhood was the strongest predictor in lower retention (OR 0.41, 95% CI 0.18, 0.93) as opposed to an individual's race. In general, the neighborhood

has a significant impact on one's health, including access to food, pharmacies, clinics, as well as safety in a patient's daily life. Being aware that neighborhoods play an important factor for retention in care, knowing which neighborhoods have limited resources is an important consideration. The Centers for Disease Control and Prevention (CDC) created the social vulnerability index (SVI), which compiles 15 social factors, based on census tract information, into an interactive map to identify communities that may need more support. Using the SVI could be a helpful screening tool for clinicians to determine which patients are at increased risk for lower retention in care and develop strategies in clinic to mitigate effects and improve outcomes (12). Overall, authors concluded that success reducing disparities in HIV highlights the need to measure SLE retention in care as a necessary first step toward designing interventions, policies, and building patient partnerships to eliminate lupus outcome disparities (11).

A review from Lawson used Donabeidan's framework for assessment of healthcare quality in SLE patients (13). The Donabeidan framework divides factors into 3 areas: structures, processes, and outcomes. Using this framework allows further understanding of potential factors and underlying mechanism impacting SLE outcomes and develop strategies for improvement. Structure includes attributes related to the clinical setting, such as facilities, financial resources, and equipment. Accessing care, such as making to clinical appointments with a rheumatologist, was associated with age, insurance status, socioeconomic status, distance to healthcare providers, and neighborhood factors. A population study using United States Renal Data System (USRDS) data in California found that the incidence of ESRD from SLE varied by zip code (14). There was an increased incidence of ESRD in zip codes with a greater proportion of public insurance or uninsured and a higher incidence of hospitalizations for conditions treated in ambulatory clinics. These findings were independent of an individual person's socioeconomic status. Additionally, geographic distance to a medical center can contribute to decrease in care. In the Lupus outcomes study from 2002-2004, Medicaid patients often traveled further to their rheumatologist than those with private insurance. The patients were also more likely to obtain care for their SLE through their primary care practitioner or the Emergency Department. An example of using a factor within the structure branch of the framework is developing a coordinated clinic appointments for patients with multiple subspecialists. With coordinated appointments, they have shown the potential of reducing hospitalizations, cost, and improve quality in chronic illnesses (13).

The second factor included in the Donabeidan framework is process of care. Process of care includes actions performed in giving and receiving care. The majority of quality improvement projects focus on process of care because actionable targets can be easily created. The development of cSLE quality indicators is an example of process care actions. The quality indicators for cSLE include 26 indicators focused on diagnosis, health maintenance measures, diagnosis and treatment for lupus nephritis, general preventive strategies, surveillance for medication safety, counseling and evaluation of cardiovascular risk, and transition planning. Since the development of the 26 quality indicators, there have been a couple of studies that have investigated adherence with specific quality indicators (15). Authors also remarked that even though quality indicators have emerged as an important tool to measure quality, further validation is necessary to define not only their validity but also feasibility in clinical practice and whether they are associated with improved clinical outcomes (13).

In a benchmarking study evaluating the adherence of quality indicators for cSLE, 7 centers from the United States, India, and Brazil, Mina et al. (16) found wide variability in assessing cardiovascular risks factors (21–100%), bone mineral density evaluation (7–90%), and discussion of sun exposure prevention (58–99%) among the different centers. Within the United States, there was not a significant difference among the 4 centers between private and public insured patients in quality indicators (16). In addition, Harris et al. (17) evaluated the cSLE quality indicators: hydroxychloroquine use, vitamin D recommendations, meningococcal vaccination, pneumococcal vaccination, influenza vaccination, ophthalmology screening, and bone mineral density evaluation at a single center. Adherence to quality indicators ranged between 28.6 and 94.4%, with bone mineral density evaluation having the lowest adherence and Plaquenil recommendations having the highest adherence. During this time, they also compared the quality indicators to SLE disease damage and race. There was not a significant association between the individual quality indicators and race or ethnicity, but there was a significant association between disease damage and minority race and ethnicity. The study was at a single center and may have had inadequate power to evaluate whether following quality indicators leads to improvement in racial health disparities. Further studies at other centers will be crucial in monitoring whether quality indicators improve racial health disparities and whether additional quality indicators or barriers improve health disparities (17).

The pneumococcal vaccine rate is one of the quality indicators often with poor adherence. At Nationwide Children's hospital, Sivaraman et al. (18) used quality improvement methodology to improve pneumococcal vaccine rate amongst cSLE patients. They determined the barriers (updated electronic health record with vaccine records and provider understanding of vaccine administration recommendations) for administering pneumococcal vaccine, and within 18 months their administration rate improved from 2.5 to 87% (18). The study highlights evaluating adherence to quality indicators, assessing for barriers to improved health outcomes, and how to effect clinical change to provide a sustained improvement in patient health.

Future directions

SLE is a chronic disease that disproportionately affects racial and ethnic minority groups. Current research evaluating health outcomes in cSLE is limited but does show that minoritized populations are disproportionately affected and have worse outcomes, such as increased frequency of hospitalizations, ESRD, and mortality in Hispanic and Black patients (6). Additionally, SLE patients are at increased risk for depression and anxiety, which can impact medication adherence.

The science of health care disparities is unique. To be done well, it needs to include a comprehensive investigation into an individual's circumstances and the communities we serve and our health care systems over time. Recognition that health disparities are driven by social and economic inequities that are embedded into our health care system is of utmost importance.

Currently, there is limited research examining pediatric health disparities in childhood onset SLE and outcomes. Future research is needed to evaluate the association of health disparities and cSLE disease outcomes. It is important to evaluate and determine solutions to pediatric health disparities from different angles. For example, multi-center observational studies need to be performed to evaluate the association between SLE disease outcomes and pediatric health disparities. Additionally, the use of a standardized tool, such as children's healthcare of Philadelphia's childhood lupus index, to assess care quality for cSLE will allow universal data collection across centers to better assess cSLE outcomes (19). It will allow for a more comprehensive evaluation of quality indicators and whether or not they are indeed an important tool to measure quality and moreover, if they are even associated with improved outcomes. From there we can see what areas specific for the medical center and nationally need improvement.

One area of patient outcomes noted in previous studies is that larger medical centers often have improved patient outcomes compared to smaller centers (19). Further investigation examining why larger centers have improved outcomes is an important area to pursue, such as examining whether specific resources improve outcomes. Often, smaller centers do not have access to a social work or a lupus patient navigator, which play a critical role in assessing for health disparities and their knowledge in regional resources. An intervention to consider would be funding opportunities for small centers to provide a social worker or lupus patient navigator and see if cSLE outcomes improve. Once we understand cSLE outcomes using a standardized tool, we can evaluate areas needing improvement, monitor for areas of disparities, and use implementation science and quality improvement frameworks to improve patient outcomes.

As a mechanism to improve health disparities, implementation science and quality improvement have been used to improve health outcomes (11, 13). Implementation science and quality improvement frameworks provide flexibility and the ability to localize to regional issues related to health disparities. As part of the design, process, and implementation phases, it is important to determine the best approach and modifications, if necessary, that are inclusive and reflective of the unique aspects of health disparity populations in the real-world setting (1, 20). Over the next few years, further research will be available that will provide more insight into interventions to lessen the effect of health disparities and better advocate for our patients regarding health policy.

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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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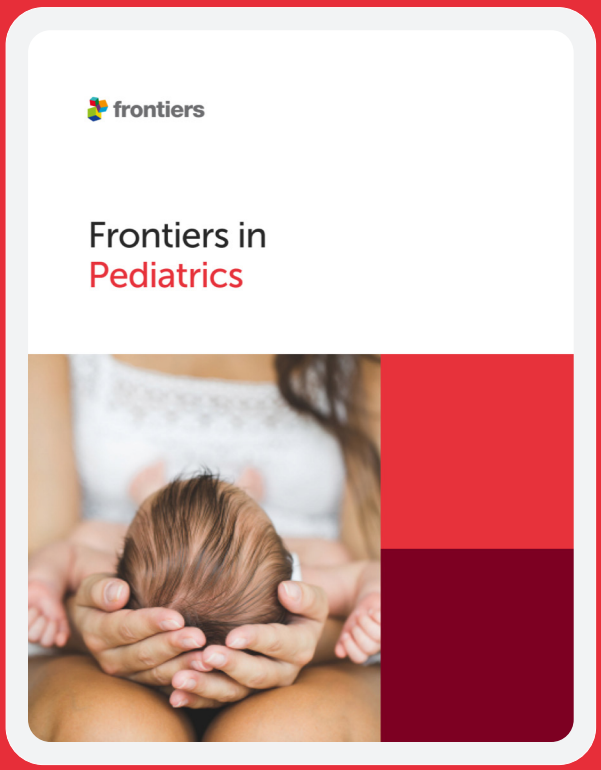

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