Review of biologics in children with rheumatic diseases

The advent of biological drugs has revolutionized the management of various pediatric rheumatologic diseases, primarily juvenile idiopathic arthritis. These drugs enable better disease control and prevent or retard damage due to active disease in a substantial number of children. Their use in the periodic fever syndromes has enabled the control of active inflammation leading to symptom control and prevention of long-term consequences such as amyloidosis and renal failure. In this review, we discuss the efficacy and safety of the various biologics used to treat a number of childhood rheumatic diseases, with particular emphasis on juvenile idiopathic arthritis.

KEYWORDS: biologics ▪ JIA ▪ juvenile dermatomyositis ▪ juvenile SLE ▪ periodic fevers

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In recent years, the advent of new drugs has led to a dramatic change in the management of rheumatic diseases in children. Central to this, is the development of a new class of agents termed biologics, which has virtually revolutionized management of juvenile idiopathic arthritis (JIA), such that 'complete disease remission' is a frequent reality today. Prolonged treatment of JIA with traditional disease modifying antirheumatic drugs such as methotrexate and sulfasalazine leads to persistence of active disease in approximately 50% of children [1]. Thus there is a need for more aggressive therapy, especially early in the course of the disease, which could lead to better outcomes.

Currently available biologics include TNF-α blockers, agents that target IL-1 and IL-6, T-cell costimulation inhibitors and antibodies against the CD20 molecule present on B cells.

In this review, we present data relating to the efficacy and safety of the different biologics used to treat various childhood rheumatic diseases, with particular focus on JIA.

JIA

JIA is the most common idiopathic inflammatory arthritis of childhood, with prevalence rates ranging from 0.07 to 10 per 1000 children [2,3]. It is defined as arthritis that begins prior to 16 years of age, is of unknown etiology and persists for longer than 6 weeks. According to the International League Against Rheumatology (ILAR) classification, JIA is subdivided into seven distinct categories (Table 1) [4]. For decades, the primary aim of management of JIA was control of pain and inflammation. However, with the increasing range of drugs available today, especially biologics, induction of complete remission is a logical goal. However, not all the biologics available are either US FDA or EMA approved, and most are currently used as off-label medications.

The general treatment goals of JIA include elimination of active disease and normalization of joint function, so as to preserve normal growth and development, and to prevent long-term joint damage and deformities. To assess improvement in clinical trials, an important requirement is a set of validated outcome measures. To this end, the 'core-set' criteria have been developed and validated for JIA. These six pediatric American College of Rheumatology (ACR-Pedi) criteria are shown in Box 1. An ACR-Pedi 30 response is defined as 30% improvement in three out of six criteria without worsening of >30% in more than one of the remaining criteria. ACR-Pedi 50 and 70 responses include 50 or 70% improvement, respectively, in at least three out of six criteria with worsening of 30% in no more than one criterion.

Anti-TNF-α agents

TNF-α has been found to play an important role in the pathogenesis of a variety of inflammatory diseases, including JIA [5–7]. TNF-α-blocking agents bind to and antagonize the effects of TNF-α, acting on both the free molecule in serum and the cell surface-bound molecule. Etanercept, adalimumab and infliximab are the three TNF-α agents used in the therapy of JIA, especially the polyarticular subtype, and juvenile psoriatic arthritis, with polyarticular

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Table 1. International League Against Rheumatology classification of juvenile idiopathic arthritis.

Oligoarthritis – Persistent – Extended	Arthritis of four or fewer joints in the first 6 months – Affecting not more than four joints throughout the disease process – Extending to affect more than four joints after the first 6 months
Polyarthritis – RF positive – RF negative	Arthritis of five or more joints within the first 6 months Subdivided according to the presence of RF
Systemic arthritis	Arthritis with or preceded by quotidian fever for at least 3 days accompanied by one or more of: – Evanescent erythematous rash – Lymphadenopathy – Hepatomegaly and/or splenomegaly – Serositis
Psoriatic arthritis	Arthritis and psoriasis or arthritis with at least two of: – Dactylitis – Nail pitting or onycholysis – Psoriasis in first-degree relative
Enthesitis related arthritis	Arthritis and enthesitis or arthritis or enthesitis with two of: – Sacroiliac joint tenderness or inflammatory lumbosacral pain – HLA-B27 positive – Onset after 6 years of age in a male – Acute (symptomatic) anterior uveitis – History of HLA-B27-associated disease in a first-degree relative
Undifferentiated arthritis	Arthritis that fulfills criteria in none of the above categories, or fulfills criteria in two or more of the above categories

RF: Rheumatoid factor.

involvement. Etanercept is a soluble TNF receptor fusion protein, consisting of the extracellular domain of the TNF-α receptor combined with the Fc portion of human immunoglobulin. It binds to soluble TNF-α and thus decreases downstream TNF-α receptor-mediated signaling. Infliximab is a chimeric human–mouse monoclonal antibody directed against TNF-α, whereas adalimumab is a fully humanized monoclonal antibody against TNF-α. Both infliximab and adalimumab bind to both the soluble and membrane-bound TNF-α, neutralizing its effect. These different mechanisms of action between the soluble receptor fusion protein and monoclonal antibodies have implications in choice of and side effects associated with biologics.

Etanercept

The design of the study that evaluated etanercept's effectiveness in JIA has become the model for subsequent studies of biologic agents in children [8]. Children with JIA refractory or intolerant to methotrexate, enrolled in the trial, enter an open-label lead-in phase, where all are treated with etanercept. Responders then enter a double-blind placebo-controlled phase, in which half continue to receive etanercept and the other half are given placebo. Children who flare on placebo are restarted on etanercept in an open-label extension phase. This strategy enables all children to receive the drug, making the study more ethical and acceptable to patients/parents.

In this study, 69 children with active arthritis despite 10 mg/m^2/week of methotrexate were given etanercept 0.4 mg/kg twice weekly in an open-label fashion for 3 months. A total of 74% of children had an ACR-Pedi 30 response, and were entered into a randomized, double-blind, placebo-controlled withdrawal phase, in which half continued etanercept and the other half received placebo. Flare rates 4 months after randomization were 21/26 (81%) in those receiving placebo and only 7/25 (28%) in those children receiving etanercept. Those who flared were again restarted on etanercept in an open-label fashion, resulting in response rates equivalent to the initial open-label phase. Of these children, 82% were able to either completely discontinue or taper corticosteroids below 5 mg/day [9]. It was also noted that in those children with systemic-onset JIA (SOJIA), etanercept was less effective. Long-term sustained effectiveness over 8 years of the continued open-label phase has been demonstrated for a total of 318 patient-years of exposure [10]. This study also showed safety of long-term etanercept use, where the overall rates of serious adverse events (0.12 per patient-year) did not increase with continuous long-term use of the drug.

In the German Etanercept Register, which has data of approximately 1300 children, high rates of adherence to etanercept therapy were noted, with approximately 66% of children on the drug for 4 years, which again suggests a favorable efficacy and tolerability [11,12].

The Dutch Etanercept Registry evaluated the effectiveness of etanercept in 146 children with JIA with a median follow-up of 2.5 years [13]. They found significant improvement within 3 months and in the years thereafter. Initial effectiveness was found to vary with the subtype of JIA. Children with SOJIA responded less favorably in the initial 3 months and had significantly more withdrawal of etanercept due to inefficacy. However, after 15 months of therapy, response rates were similar to other subgroups. In addition, 38% of these children had complete remission of their disease. Rates of serious adverse events were low. The inferior response rates of SOJIA were also observed in another multicenter French study, where 61 children with JIA, 22 with systemic-onset disease, responded less favorably as compared with other subtypes throughout the entire course of the study [14].

The Dutch Etanercept Registry recently analyzed the costs and treatment success of etanercept [15]. The cost analysis revealed that although the costs of etanercept are substantial, other direct medical costs, such as costs related to hospitalization and concomitant medication had decreased after the start of etanercept therapy. A significant reduction in outpatient consultations at the outpatient clinic was observed. All the JIA core set variables had also improved significantly. Thus the authors concluded that, as these children were refractory to conventional treatment and at risk of long-term disability, the costs are potentially justifiable [15].

The Biologics and New Drugs Registry (BNDR) of the British Society for Paediatric and Adolescent Rheumatology (BSPAR) recently published the reasons for discontinuation of etanercept therapy [16]. Four hundred and eighty three etanercept-treated JIA patients from 30 centers were enrolled in the registry, with 941 patient-years of follow-up. After a median follow-up of 2 years, 69% remained on the drug. One hundred (20.7%) discontinued etanercept, nine due to disease control and 88 because of treatment failure (53 due to inefficacy, 14 due to noncompliance and 21 due to adverse events). In two patients, the reasons for discontinuation were unknown and in one the diagnosis was changed. Cessation of therapy for inefficacy was associated with systemic arthritis subtype (odds ratio [OR]: 2.55), chronic anterior uveitis (OR: 2.39) and inefficacy of methotrexate before starting etanercept (OR: 8.3).

Etanercept is administered by subcutaneous injection, at a dose of 0.4 mg/kg (maximum 25 mg) twice weekly. It has recently received FDA approval for treatment of moderate-to-severe polyarticular JIA in children as young as 2 years of age.

Adalimumab

Adalimumab is a fully humanized monoclonal IgG1 antibody against TNF-α. It was the second anti-TNF agent to receive FDA approval for the treatment of moderate-to-severe active polyarticular JIA in children over 4 years of age. It is administered subcutaneously at a dose of 20 mg every other week in children weighing less than 30 kg, and 40 mg every other week in children weighing more than 30 kg.

In a multicenter study of 171 children with polyarticular course of JIA, with a similar trial design as the initial etanercept trial, comprising an open-label lead-in phase, followed by a double-blind, placebo-controlled phase, and an open-label extension phase, children were treated with 24 mg/m^2 of adalimumab [17]. Eighty-four children were receiving concomitant methotrexate. A total of 74, 64, 46 and 26% of children receiving adalimumab monotherapy, and 94, 91, 71 and 28% children receiving a combination of methotrexate and adalimumab achieved ACR-Pedi 30, 50, 70 and 90 responses, respectively. In the placebo-controlled phase, significantly more children receiving placebo flared (71 and 65% on placebo and placebo plus methotrexate, vs 43 and 37% on adalimumab and adalimumab plus methotrexate combination). The drug was found to be reasonably safe, with only minimal adverse effects. In the 2 years of the open-label

Box 1. Core set criteria for improvement in juvenile idiopathic arthritis†.

- Number of active joints
- Number of joints with limited range of motion
- Physicians global assessment of disease activity
- Parents/child's global assessment of overall well-being
- Childhood health assessment questionnaire
- Erythrocyte sedimentation rate

†Pediatric American College of Rheumatology (ACR-Pedi) 30 response: 30% improvement in three out of six criteria without worsening of >30% in no more than one of the remaining criteria; ACR-Pedi 50 response: 50% improvement in at least three out of six criteria with worsening of 30% in no more than one criterion; ACR-Pedi 70 response: 70% improvement in at least three out of six criteria with worsening of 30% in no more than one criterion.

extension phase, ACR-Pedi responses were sustained, and 40% of children had ACR-Pedi 100 responses. This study demonstrated the safety and efficacy of adalimumab, with and without combined methotrexate, in the treatment of polyarticular course of JIA.

Biologics including infliximab and adalimumab have been used in clinical practice in children with refractory JIA-associated uveitis. No good quality evidence in the form of controlled trials is currently available in the literature. Small case series and retrospective studies have also suggested the effectiveness of adalimumab in the treatment of JIA-associated uveitis, which can occur in about 10–15% of children with JIA [18,19]. This is a potential advantage over etanercept, which is not effective in treating uveitis and has potentially been associated with flares and new onset of uveitis in children with JIA [20–22]. Compared to adults, children experience a higher incidence of hypersensitivity reactions with adalimumab (6 vs 1% in adults) and antibodies to adalimumab (16 vs 5% in adults) [17].

Infliximab

Infliximab is a chimeric human–mouse monoclonal antibody directed against TNF-α. Unlike etanercept, it triggers apoptosis of cells bearing TNF-α. It is administered as an intravenous infusion, at a dose of 3–6 mg/kg at 0, 2 and 4 weeks and subsequently intervals of 4–8 weeks. Higher doses or shorter dosing intervals may also be used.

A multicenter randomized double-blind placebo-controlled trial of infliximab in 122 children with polyarticular JIA, did not find a significant effect of infliximab 3 mg/kg intravenous infusion therapy on ACR-Pedi responses as compared with placebo at 14 weeks [23]. After 14 weeks, following crossover from placebo to infliximab 6 mg/kg, ACR-Pedi 50 and 70 responses at week 52 were achieved by 70 and 52% of the children. Infliximab 3 mg/kg had a less favorable safety profile, with a higher incidence of infusion reactions, often severe, and formation of antibodies to infliximab, antinuclear antibody or anti-dsDNA antibodies.

In the open-label extension (52–204 weeks) phase of the study involving 78 of 122 patients, 34% discontinued infliximab prematurely, often by withdrawing consent due to lack of efficacy [24]. Infusion reactions were also frequent, occurring in 32% of the children. Overall, 30% of the children continued the study to week 204. The open-label extension phase was thus enriched with responders. Though the trial demonstrated that infliximab was safe, it had a high drop-out rate, mainly due to lack of efficacy.

Infliximab has not been formally approved by the FDA for the treatment of JIA, although it is often used. It is approved for the therapy of refractory Crohn's disease in children over 6 years.

Safety of anti-TNF-α agents in JIA

Reported adverse effects with anti-TNF-α blockers are generally mild and transient. Local skin reactions/infusion reactions are generally mild and transient. Minor infections are common, usually upper respiratory tract infections, but there is also a higher risk of developing tuberculosis. This risk is higher with the monoclonal antibodies infliximab and adalimumab, as compared with etanercept [25,26]. Autoimmune phenomena such as drug-induced lupus, demyelinating disease, uveitis, psoriasis and inflammatory bowel disease are rare. The risk of malignancies has been reported to be increased in children treated with anti-TNF-α agents. The postmarketing surveillance data on anti-TNF-α agents collected by the FDA reported 48 malignancies developing in children, of which 20 occurred in children with rheumatic conditions [27]. However 88% of these children were also receiving other immunosuppressive drugs, including corticosteroids, azathioprine and methotrexate. Approximately half of the malignancies reported were lymphomas, leukemias, melanoma and other solid tumors were also reported. The FDA has added a boxed warning with regard to the possible increased risk of malignancy, especially lymphomas, in children treated with anti-TNF-α agents. Despite this, a recent summary of worldwide pediatric malignancies in children treated with etanercept did not find an overall increased risk. However the authors acknowledge that it is difficult to assess the actual risk due to the rarity of malignant events, the underlying higher risk of lymphomas and leukemias in children with JIA and the confounding use of other immunosuppressants [28].

Others

Certolizumab pegol is a PEGylated Fab fragment of a humanized anti-TNF-α antibody, and golimumab is a humanized monoclonal anti-TNK-α antibody. Both of these drugs have been found to be effective for the management of adults with rheumatoid arthritis, psoriatic arthritis and Crohn's disease. Currently

there are no published data from randomized controlled trials on the efficacy of these drugs in JIA. A multicenter trial of golimumab in JIA is ongoing [101].

IL-1 blockers

SOJIA is characterized by spiking fever, often associated with rash, pericarditis, arthritis and hepatosplenomegaly. IL-1β is a proinflammatory cytokine, synthesized by monocytes/macrophages and dendritic cells. It induces systemic features such as fever, and also the production of other proinflammatory mediators such as prostaglandins, IL-6 and TNF-α. Its effects are downregulated by a receptor antagonist, IL-1RA, which binds to the IL-1 receptor, but does not cause downstream stimulation. This cytokine is thought to play a major role in the pathogenesis of SOJIA, along with IL-6. Mononuclear cells from children with SOJIA spontaneously produce large amounts of IL-1, and serum samples from these children were found to induce production of IL-1 from healthy peripheral blood mononuclear cells, and anakinra treatment lead to normalization of disease-specific gene expression profile [29,30].

Three inhibitors of IL-1 are currently available: anakinra, which is a recombinant IL-1 receptor antagonist, rilonacept, an IL-1 receptor fusion protein and canakinumab, a human IL-1 β antibody.

Anakinra

Being an IL-1 receptor antagonist, it competitively binds the IL-1 receptor, without inducing downstream stimulatory signaling. It is administered at a dose of 1–2 mg/kg (maximum 100 mg daily) by subcutaneous injection.

In an initial open-label trial of anakinra in 80 children with a polyarticular course of JIA, although overall it had only a modest effect on ACR-Pedi 30 response, 73% of children with SOJIA responded, as compared with 54% with combined polyarticular and oligoarticular subtypes [31]. In another study of 20 children with corticosteroid-dependent active SOJIA, 95% having previously received methotrexate, and 70% anti-TNF-α therapy, 15 (75%) improved [32]. However ACR-Pedi 30, 50 and 70 responses were only modest at 3 months; 55, 30 and 0% respectively, and at 6 months; 50, 25 and 10%. Corticosteroid dose was reduced by 15–78% in nine children. Four children stopped therapy due to lack of efficacy. Overall safety was acceptable.

Another multicenter double-blind placebo-controlled trial of 24 children with SOJIA was recently published [33]. Part one of the trial was placebo-controlled, where 12 children each received either anakinra or placebo for 1 month, to demonstrate a higher proportion of responders in the active treatment group. Part two was an open-label treatment, where all children received anakinra after 1 month. At the end of 1 month, significantly more children receiving anakinra (67%) responded as compared with those receiving placebo (8%). Ten children switched to anakinra in the open-label phase, of whom nine responded. Gene-expression profiles were studied in the blood, and their normalization was observed in responders. Tolerability and side effects were similar in the anakinra and placebo groups. However loss of response was observed in most of the patients over time. The study concludes that anakinra is efficacious at least in the short term.

The recent US/ACR guidelines propose treatment with anakinra as a first-line steroid-sparing drug [34]. It has short-term efficacy, but these responses are not usually sustained in the long term. It needs daily injections, which may be painful and lead to local injection-site reactions. Infections are also increased. In the multicenter trial, a total of 46 infections were reported. Most were minor respiratory tract infections. Three children developed varicella infection and two had vulval candidiasis. Atypical pneumonitis and urinary tract infection were also reported. In four children, the infections were considered serious. In a cohort of 33 children with SOJIA from three centers in the USA were treated with anakinra, one child developed macrophage activation syndrome (MAS) [35]. However anakinra has also been reported to be effective in the treatment of MAS associated with SOJIA [36–38]. These factors may hamper its widespread use in SOJIA. However the favorable experience with anakinra is encouraging further studies of IL-1 inhibitors in SOJIA.

Rilonacept

Rilonacept is an IL-1 R/IL1RacP/Fc fusion protein, which binds to soluble IL-1β, preventing it from binding to its receptor, having a longer half-life as compared with anakinra. Nine children with SOJIA were treated with rilonacept in the open-label phase of a randomized controlled, double-blind study [39]. ACR-Pedi 50 responses were impressive, with 55 and 78% attaining this at the end of 2 and 4 weeks, respectively. In those who had fever, an immediate disappearance of the fever was observed. Tolerability was acceptable. In the long-term

open-label phase, outcomes at 24 months were recently presented [40]. Responses were sustained and therapy was generally well tolerated. However, two children developed MAS during therapy with rilonacept. A double-blind, randomized, placebo-controlled trial of rilonacept is ongoing [102].

Canakinumab

Canakinumab is a human IL-1β antibody that binds to IL-1β, blocking its activity. It has a long plasma half-life and is administered at a dose of 4 mg/kg subcutaneously once a month. In a Phase II dose-escalation trial, 23 children were treated with canakinumab, in doses ranging from 0.5 to 9 mg/kg [41]. Seventeen of them had been previously treated with anakinra. A total of 59% of the children reached ACR-Pedi 50 response within 15 days, and 18% achieved inactive disease. Six out of 11 nonresponders to anakinra, responded to a single dose of canakinumab. A randomized, placebo-controlled double-blind study of monthly subcutaneous injection of canakinumab is currently underway [103].

Anti-IL-6 therapy

Tocilizumab

Tocilizumab is a humanized recombinant antibody that binds to IL-6 receptor, and inhibits the downstream signaling of IL-6 and thus its proinflammatory effects. Serum and synovial fluid levels of IL-6 have been found to be elevated in children with SOJIA and correlate with disease activity [42–45].

In a dose-escalating study of 11 children with active refractory SOJIA, in which all children were initially given 2 mg/kg of tocilizumab, repeated for two more doses 2 weeks apart in those who responded, or 4 mg/kg in those who flared, again repeated for two doses 2 weeks apart or 8 mg/kg, repeated as above for two more doses, abrupt reduction of disease activity was observed in ten out of 11 children, as assessed by fever, arthritis, childhood health assessment questionnaire or acute phase reactants [46]. A total of 90.9% of children achieved 30% response 2 weeks after a third fixed dose.

In another open-label single dose trial, 18 Caucasian children with active SOJIA despite receiving >0.2 mg/kg/day of prednisolone were recruited [47]. Fifteen out of 18 children enrolled were treated with 2, 4 or 8 mg/kg of body weight of tocilizumab intravenously. A marked clinical response was observed within 48 h in all children, which lasted up to 4–8 weeks. Eleven, eight and three children achieved ACR-Pedi 30, 50 and 70 responses (as defined by Giannini *et al.*) [48]. The most dramatic responses were observed in the 4-mg/kg dose, and responses were most prolonged in the 4- and 8-mg/kg doses. Clinical improvement was accompanied by a parallel improvement of laboratory variables, such as C-reactive protein (CRP), anemia, white blood cell count and albumin.

There is only one double-blind placebo-controlled trial of tocilizumab in SOJIA [49]. This trial like the etanercept trial had an open-label lead-in phase of 6 weeks, a randomized double-blind placebo-controlled phase of 12 weeks and an open-label extension phase of at least 48 weeks. Fifty-six children were enrolled, and received 8 mg/kg of tocilizumab by intravenous infusion, every 2 weeks. At the end of the open-label lead-in phase ACR-Pedi 30, 50 and 70 responses were achieved in 91, 86 and 68% children, respectively. CRP concentration declined to <50 mg/dl in 86% children within 2 weeks. In the double-blind placebo-controlled phase, ACR-Pedi 30, 50 and 70 responses and CRP levels <15 mg/dl were maintained in 80, 80 and 75% children who received tocilizumab, versus 20, 17 and 13% who received placebo, respectively. Efficacy was sustained for a significantly longer duration in those receiving tocilizumab. At the end of the 48-week open-label extension phase, 96% children were still receiving tocilizumab, indicating good efficacy and tolerability. ACR-Pedi 30, 50 and 70 responses were 98, 94 and 90, respectively. Tolerability profile was good, much like other biologicals.

Interim results at 52 weeks of the ongoing multicenter, three part, 5-year TENDER trial of tocilizumab in SOJIA were recently presented at the The European League Against Rheumatism meeting [50]. Efficacy data at 52 weeks was available in 88 children and safety data in all 112 children. ACR 30 plus absence of fever and ACR 70/90 responses progressively improved in 88, 89 and 65% of children, respectively. There was also a marked reduction in the corticosteroid dose, with 48% children discontinuing corticosteroids. The drug was generally well tolerated. Thirty three serious adverse events were observed in 25 children, of which 12 were considered related to tocilizumab. Fifteen serious infections occurred; six considered related to the drug. All of these resolved and none led to drug discontinuation. One child died of a suspected tension pneumothorax, which was considered unrelated to tocilizumab.

Various side effects that can occur with the use of tocilizumab include serious infusion reactions, infections, transient increases in liver enzymes, which usually occur early in the course and tend to improve over time, neutropenia, formation of antitocilizumab antibodies, anaphylactoid reactions and hypercholesterolemia.

Inhibition of T-cell costimulation

Abatacept

Abatacept is a fully human soluble fusion protein that contains the Fc portion of IgG1 linked to CTLA-4. It binds to CD80 or CD86, and inhibits T-cell activation. It has been studied in children with polyarticular course of JIA, including some who were refractory to other biologics [51]. The trial design was again similar to the etanercept trial. One hundred and ninety children were enrolled, among which one third were refractory to anti-TNF-α therapy. They were treated with 10 mg/kg of abatacept, given every 4 weeks, with or without methotrexate. Two-thirds achieved ACR-Pedi 30 response during the open-label lead in phase. Significantly more children who had not received anti-TNF-α therapy responded, as compared with those who had previously received anti-TNF-α therapy (76 vs 39%). During the double-blind, placebo-controlled phase, 53% of children on placebo flared, as compared with 20% receiving abatacept, with median time to flare being shorter in those on placebo. ACR-Pedi 30, 50, 70 and 90 responses in the abatacept and placebo group were 82, 77, 53 and 40% versus 69, 52, 39 and 16%, respectively. Few serious adverse events were reported.

One hundred and fifty three children entered the long-term extension open-label phase [52]. Among those who received abatacept in both the double-blind and open-label extension phase, 90, 88, 75, 57 and 39% attained ACR-Pedi 30, 50, 70, 90 and 100 responses, respectively. Responses were either maintained or progressively improved. Response rates were similar among those who had received biologics prior to abatacept to those who had not. Clinical responses were also similar in those children who were randomized to receive placebo in the double-blind phase, suggesting that interruption of the drug for as long as 6 months is well tolerated. The safety profile was found to be favorable. A total of 73% of the children who did not attain ACR-Pedi 30 response at the end of the open-label lead-in phase, and thus were not randomized, attained this response during the open-label long-term extension phase. This suggests that responses in some children may be delayed.

A case series of seven children with JIA-associated uveitis, refractory to immunosuppressants and ≥2 anti-TNF-α agents reported the efficacy of abatacept in the treating the uveitis and maintaining its remission for a mean of 9 months [53]. The mean frequency of uveitis flares was also decreased.

Abatacept was FDA approved in 2008 for the treatment of moderate-to-severe polyarticular JIA, in children more than 6 years old. It is administered as an intravenous infusion over 30 min, at a dose of 10 mg/kg, up to a maximum of 1000 mg at 0, 2 and 4 weeks, and then every 4 weeks.

Anti-B-cell therapy

Rituximab is a chimeric anti-CD20 antibody that binds to and causes apoptosis of CD20-positive cells, causing prolonged depletion of B cells. It has been found to be an effective treatment option for the treatment of rheumatoid arthritis. There is just one trial of its efficacy in children with refractory JIA [54]. Fifty-five children with refractory polyarticular and systemic JIA were given 4 weekly infusions of rituximab at a dose of 375 mg/m^2/dose, repeated if necessary. At week 24, ACR-Pedi 30, 50, 70 responses were attained by 98, 50 and 40% respectively. At 96 weeks, these responses were attained by 98, 93 and 93% of 25 patients. High rates of remission were also noted with repeated courses, with 25% patients after the first course and 98% after the fourth course attaining remission. It has been found to be effective in some case reports and case series [55–57]. Contrary to the experience in adults treated with rituximab, children may develop long-lasting B-cell depletion and hypogammaglobulinemia, sometimes requiring replacement immunoglobulin replacement [58]. Incomplete maturation of the immune system in children may limit widespread B-cell depletion therapy in children.

Hereditary periodic fever syndromes

The hereditary periodic fever syndromes consist of a spectrum of rare, inherited, chronic, multisystem, auto-inflammatory syndromes. They include familial Mediterranean fever, hyperimmunoglobulin D syndrome (HIDS), TNF receptor associated periodic fever syndrome (TRAPS) and the cryopyrin associated periodic fever syndrome (CAPS), which is comprised of three entities: familial cold auto-inflammatory syndrome (FCAS), Muckle-Wells syndrome (MWS) and neonatal-onset multisystem inflammatory disorder (NOMID; also called chronic

infantile neurological cutaneous articular syndrome [CINCA]). These disorders are characterized by recurrent episodes of fever, rash, arthralgias and arthritis, serositis and in some instances conjunctivitis, sensorineural deafness, chronic meningitis and intellectual impairment. Systemic amyloid associated amyloidosis can develop due to chronic ongoing inflammation with significant morbidity and mortality.

TRAPS is associated with missense mutations in the p55 subunit of the TNF receptor, leading to aberrant signaling of the TNF-α receptor. The age of onset, frequency and severity of attacks and response to corticosteroids are highly variable. HIDS is caused by mutations in the mevalonate kinase gene, which encodes an enzyme involved in cholesterol biosynthesis. Polyclonal IgD levels are elevated. TNF-α levels are elevated in the serum in both of the above disorders and are potential targets for therapy [59]. CAPS are characterized by mutations in *NLRP3*, the gene encoding cryopyrin, a component of the IL-1 inflammasome, leading to the overproduction of IL-1β. Therapies targeting this cytokine have shown promising results.

Anti-TNF-α therapy

In a series on seven patients with TRAPS, all having active disease and either not responding to or requiring high doses of corticosteroids, etanercept was given at a dose of 25 mg subcutaneously twice weekly for 24 weeks [60]. Clinical activity as assessed by pain and overall well-being improved, and CRP levels decreased in five patients during follow-up. However one patient required a subsequent course after a 3-month washout period. This study demonstrated the short-term efficacy of etanercept in TRAPS. Etanercept has also demonstrated efficacy in the treatment of nephrotic syndrome and amyloidosis associated with TRAPS in case reports [61,62]. However case reports have also documented failure of anti-TNF-α therapy, especially infliximab, which may be complicated by a severe paradoxical inflammatory reaction [63–66].

Anti-IL-1 blockade

Anakinra

Since IL-1 is the predominant cytokine involved in CAPS, therapies targeting this cytokine have shown promising results. A study on 18 patients with NOMID, with at least two of either urticarial rash, CNS symptoms or epiphyseal or patellar overgrowth on radiography, and active disease despite NSAIDs, corticosteroids or disease-modifying-antirheumatic drugs, when treated with anakinra, demonstrated disappearance of rash and conjunctivitis, and improvement of CNS symptoms such as headache after 6 months of therapy [67]. CSF pressure and white blood cell count improved, as did the leptomeningeal and cochlear lesions on MRI. Another study in ten patients demonstrated sustained efficacy for 26–42 months in the treatment of systemic inflammation, and in some cases neurologic involvement and growth parameters in patients with NOMID/CINCA [68]. Case reports have also demonstrated its efficacy in the management of TRAPS, sensory deafness in MWS, febrile crisis in HIDS and hydrocephalous in CINCA syndrome [69–72].

Rilonacept

An open-label study on five patients with FCAS treated with rilonacept demonstrated long-term sustained benefit and safety [73]. Improvement in clinical and laboratory measures of inflammation was observed. A recent randomized, double-blind placebo-controlled trial in patients with FCAS or MWS was published [74]. This was a two part study, which lasted 6 weeks and 18 weeks. In part one, patients were treated with a loading dose of 320-mg rilonacept or placebo administered subcutaneously, followed by weekly injections of 160-mg rilonacept or placebo for 6 weeks. This was followed by part two, which again consisted of two parts. In part A, patients were given weekly rilonacept 160 mg for 9 weeks in a single-blinded manner, followed by part B where they were treated with rilonacept in the same dose, or placebo in a double-blinded manner for a further 9 weeks. Forty-four patients completed both the studies. At the end of 6 weeks, rilonacept was found to be significantly superior to placebo in reducing symptoms and flare rates. In Phase II, patients who received rilonacept in Phase I continued to demonstrate benefit, and those who had received placebo and were switched to rilonacept demonstrated a rapid improvement in symptoms and decrease in inflammatory markers. During part B, rilonacept was superior to placebo in maintaining clinical and inflammatory response. Safety and tolerability were generally favorable. This drug has been approved by the FDA for the treatment of FCAS and MWS in patients over 11 years of age.

Canakinumab

A multicenter randomized, double-blind, placebo-controlled trial of canakinumab 150 mg every 8 weeks, in which patients with CAPS having the *NLRP3* mutation was recently

published [75]. Patients included those who had received previous anakinra (49%) or rilonacept or those who had flared on canakinumab (26%). Part one was an open-label phase lasting for 8 weeks; part two was a randomized placebo-controlled phase for 24 weeks; and part three was an open-label extension phase, in which all patients received canakinumab. Of the 35 patients enrolled in Phase I, complete response to a single dose was observed in 34 (97%). During the double-blind phase, all the patients who received canakinumab maintained remission, whereas 81% receiving placebo flared. CRP and serum amyloid A levels remained low in those on canakinumab, in contrast to those on placebo. A total of 97% of patients who entered Phase III had sustained clinical and biochemical remission on canakinumab. Suspected infections were more prevalent in those on canakinumab; however, the infections were not serious.

Canakinumab has been FDA approved for the treatment of FCAS and MWS in adults and children who are 4 years or older.

Others

A recent case report has shown the efficacy of tocilizumab, an IL-6 inhibitor in the management of a patient with TRAPS [76]. Following treatment, an improvement in clinical features and markers of acute inflammation were observed. This cytokine may be a potential target for future therapeutic trials in TRAPS.

Juvenile dermatomyositis

Juvenile dermatomyositis is the most common inflammatory myositis of childhood, characterized by proximal muscle weakness and the pathognomonic rash, comprising Gottron's papules or heliotrope rash. Corticosteroid use has dramatically decreased the morbidity and mortality associated with the disease. However, up to 70% of patients show an incomplete response, including 10% who may be refractory to or relapse on corticosteroids [77]. These drugs are also associated with a variety of side effects, including weight gain, glucose intolerance, osteoporosis and cataracts. Although randomized controlled trials are lacking, drugs such as methotrexate, azathioprine, cyclosporine and more recently mycophenolate mofetil are often used as steroid-sparing agents. Although there are no randomized controlled trials on the use of rituximab in this disease, case series have reported the effectiveness and safety of this agent in the treatment of refractory disease [78,79]. Rituximab is administered at a dose of 375 mg/m^2 weekly, for a total of four doses.

Juvenile systemic lupus erythematosus

Systemic lupus erythematosus in children is a more aggressive disease than in adults, having a higher frequency and severity of nephritis. There is a paucity of studies on the utility of biologics, especially B-lymphocyte depletion therapy in juvenile systemic lupus erythematosus. Retrospective series and case reports have reported efficacy of rituximab in children with aggressive disease not responding to conventional treatment [80–83]. Extrapolating from trials of adult lupus, drugs such as rituximab and belimumab show promise in treating manifestations of the disease not responding to conventional therapy [84–87].

Future perspective

Research over the next few years will focus on understanding the pathogenesis of the various juvenile rheumatic diseases more thoroughly, and better defining the various cytokines and small molecules involved. Efficacy of small-molecule inhibitors, which have the major advantage of being orally administered, and are currently being studied in rheumatoid arthritis, will be studied in JIA. There will be more large-scale registries available to fully understand the as yet unknown side effects. Collaborative efforts, especially between the developing nations and the west will be a major step forward. Studies on the withdrawal of biologics and the rates of sustained remission of drugs will be needed. Finally, pharmacogenomics will help in more accurately predicting those children who will respond to a particular biologic, require long-term medication or develop major side effects due to a particular drug.

Conclusion

Management of pediatric rheumatologic diseases has evolved considerably. Development of biologics is a major factor contributing to this. Collaborative efforts are a major factor in the conduct of multiple trials. These developments raise the hope of overall improved outcomes and better long-term functional outcomes in children suffering from rheumatologic diseases.

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Executive summary

Biologics & juvenile rheumatic diseases

- Currently available biologics have revolutionized the management of pediatric rheumatic diseases.
- These target various cytokines such as TNF-α, IL-1, IL-6, block T-cell costimulation and act against the CD20 molecule present on B cells.

Juvenile idiopathic arthritis

- It is the most common idiopathic inflammatory arthritis of childhood.
- Etanercept, adalimumab and infliximab are the three TNF-α agents used.
- Etanercept is a soluble TNF receptor fusion protein, whereas infliximab and adalimumab are antibodies directed against TNF-α.
- Etanercept and adalimumab are highly effective for the management of severe or refractory polyarticular, extended-oligoarticular and juvenile psoriatic arthritis with polyarticular involvement.
- Efficacy of infliximab is less, as compared with etanercept and adalimumab. It has been approved for the therapy of refractory Crohn's disease.
- Adalimumab has also been found to be effective in uveitis associated with juvenile idiopathic arthritis.
- Use of these agents has been found to be cost beneficial.
- Systemic-onset juvenile idiopathic arthritis responds less well to anti-TNF-α therapy. IL-1 blockers such as anakinra and more recently rilonacept and canakinumab, as well as tocilizumab, which is an antibody directed against the IL-6 receptor, are effective therapies.
- Abatacept, a T-cell costimulation blocker, is also effective in the management of refractory polyarticular, extended-oligoarticular and juvenile psoriatic arthritis with polyarticular involvement.

Hereditary periodic fever syndromes

- Anti-TNF-α therapy has been effective in small case series and case reports.
- Therapies targeting IL-1, which is the major cytokine involved in the pathogenesis of familial cold autoinflammatory syndromes have shown beneficial effects.

Others

- Trials of rituximab for the management of severe or refractory juvenile dermatomyositis and systemic lupus erythematosus are ongoing.

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- ▪ of interest
- ▪▪ of considerable interest

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