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PEDIATRIC RHEUMATOLOGY (S OZEN, SECTION EDITOR)

Biologics in Pediatric Rheumatology: Quo Vadis?

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Abstract The past two decades have brought immense satisfaction to pediatric rheumatologists and families of children with rheumatologic diseases. We have been able to better classify, recognize, and diagnose rheumatologic diseases, but most importantly, the discovery of biologic therapies and their efficacy and relative safety in treating multiple rheumatologic conditions, improving quality of life for the patients we care for. We will review the advances of the past two decades and discuss potential areas for new discoveries.

Keywords TNF inhibitors · IL-1 inhibitors · IL-6 inhibitors · Abatacept · Rituximab · Tofacitinib · Juvenile idiopathic arthritis (JIA)

Introduction

Pediatric rheumatologic conditions encompass many diseases, with the common characteristics of: (1) being of unknown etiology, (2) pathogenesis involves mediators of the immune system, and (3) autoimmune or autoinflammatory in nature.

Over the past two decades, outcomes have dramatically improved and lifetime remissions are within reach. The developments in therapies have been monumental; patients have gone from living with contractures and irreversible disability to leading a "normal" life. Despite all the benefits of newer therapies, we are still learning about their potential long-term side effects, which therapy is ideal, and when to start or discontinue these treatments. Individual therapy plans are envisioned as a "trial and error" for each new or difficult to treat patient. The future of pediatric rheumatology lies in possibly advancing to "personalized" treatments; accounting for the unique characteristics of every patient, widely including variables, from gene expression to clinical manifestations. Ideally, we would avoid exposing patients to therapies that might not benefit them and avoid the potential side effect that these medications might have.

The pathogenesis of rheumatologic diseases is still not entirely known, but biologics and emerging therapies have been developed to target certain identified pathogenic pathways. In this article, we will discuss the new developments of the past 15 years and the directions our therapies are taking.

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Biologics that Interfere with Cytokine Function

Cytokines play a crucial role in the inflammatory response in multiple autoimmune and autoinflammatory conditions. The presence of increased levels of cytokines and increased gene expression of these cytokines has led to the development of our newer and most effective therapies. Barnes et al. found distinct cytokine gene expression profiles for different subtypes of juvenile idiopathic arthritis (JIA) [1].

Although the role of a specific cytokine in polyarticular and oligoarticular JIA is not entirely understood, T cell and monocyte-derived cytokines are known to be responsible for the synovial changes in JIA [2]. TNF inhibitors were the first biologic disease-modifying anti-rheumatic drug (DMARD) to be used for treating JIA. TNF inhibitors currently in use or being evaluated for their use in children include etanercept, infliximab, adalimumab, golimumab, and certolizumab. Anti-TNF therapy has resulted in the biggest impact on outcomes of

disease, especially in polyarticular course JIA [3, 4, 5•]. They all have a similar safety profile, which includes increased risk of infection, specifically reactivation of latent tuberculosis, fungal infections, and hepatitis B virus. Increased risk of malignancy has been shown in young men with inflammatory bowel disease, but not in JIA [6]. Etanercept was the first drug to be trialed already over 15 years ago. The initial trial in polyarticular JIA showed that 74 % of patients met ACR 30 at 3 months of initiating therapy [7]. It has been widely prescribed since it became available, and studies have shown major improvement in health-related quality of life in patients receiving etanercept [8–10].

Infliximab is a chimeric monoclonal antibody that binds both soluble and membrane-bound TNFα. The initial multicenter, double-blind, placebo-controlled study did not meet its endpoint. The rationale was that pediatric patients metabolize the drug faster than adults and may require higher doses [11]. Case series and open-label trials suggest efficacy and safety in treating non-systemic JIA, as well as JIA-associated uveitis.

Adalimumab is a fully human monoclonal antibody, similarly binding both soluble and membrane-bound TNFα. It is approved by the FDA for the treatment of polyarticular JIA since 2008. It was found to be more effective when used in combination with methotrexate than methotrexate alone for JIA [12••]. Although no randomized studies, open-label trials have found it to be effective in treating JIA-associated uveitis as well [13, 14].

Golimumab is a fully human monoclonal antibody to soluble and transmembranous TNFα. It has been approved in adults for rheumatoid arthritis, psoriatic arthritis, and ankylosing spondylitis. In children with polyarticular disease, the GO-KIDS trial, a placebo-controlled, three-phase withdrawal study, showed pediatric ACR 30 response in 87 % of patients and 36 % achieved inactive disease at the end of the first phase at week 16. The study failed to meet its primary endpoint. Both groups had a sustained pediatric ACR 30 response (89–95 %), and there was no difference in disease flare [15•]. Further investigation in children is needed.

Certolizumab pegol is a pegylated anti-TNFα inhibitor. Pegylation enhances the half-life of the drug and allows a 2- to 4-week dosing schedule. There is currently a clinical trial underway for the use of certolizumab in children with JIA [16•].

IL-1β and IL-6 have been targeted in systemic juvenile idiopathic arthritis (SJIA) and other autoinflammatory conditions. Efficacy of IL-1 has been demonstrated in SJIA, cryopyrin-associated periodic fever syndromes (CAPS), and macrophage activation syndrome [17, 18•, 19, 20•, 21••, 22, 23]. IL-1 inhibitors include anakinra, canakinumab, and rilonacept.

Anakinra is a recombinant human interleukin-1β receptor antagonist (IL-1RA). Pascual et al. administered this recombinant IL-1 receptor antagonist to nine SJIA patients who were refractory to other therapies. Seven out of the nine patients demonstrated a complete response, and the other two patients showed partial response to this therapy [17]. A multicenter, randomized, double-blind, placebo-controlled trial with anakinra in SJIA showed response in 8 out of 12 patients in the anakinra arm versus one patient in the placebo arm at 1 month of treatment ($p = 0.003$) [18•]. At month 2, of the ten patients that were switched to anakinra from the placebo arm, nine responded to anakinra treatment. In a retrospective study, 46 patients with SJIA were treated with anakinra. Fever and rash resolved within 1 month in >95 % of patients, while C-reactive protein and ferritin normalized by 1 month in >80 % of patients. Eleven percent of patients still had active arthritis after 6 months of starting therapy. Bacterial infections were seen in two patients and hepatitis in one patient [19]. Efficacy and relative safety of anakinra has been evidenced in other studies as well.

In neonatal onset multisystem inflammatory disease (NOMID), the use of anakinra has been related to prompt resolution of rash; improvement in daily symptoms, levels of CRP, ESR, and amyloid A; and improvement in cochlear and leptomeningeal lesions with recurrence of symptoms after withdrawal of medication and improvement once again after reinstating therapy [20•].

Canakinumab is a humanized monoclonal antibody against IL-1β. It was approved by the Food and Drug Administration (FDA) in the USA for the treatment of CAPS in 2009 and treatment of SJIA in 2013. In SJIA, two sequential randomized, double-blind, placebo-controlled trials showed canakinumab to be effective in treating systemic features in SJIA in patients 2–19 years old with active SJIA. These studies showed canakinumab to be effective in treating systemic features in SJIA. Pediatric ACR30 was reached in 84 % of the patients on canakinumab at day 15 in the first trial vs. 10 % in the placebo group ($p < 0.001$). At the end of the second trial, 73 % had reached pediatric ACR50 and 31 % had inactive disease. In the open-label phase, 74 % of the patients on canakinumab had no flare vs. 25 % in the placebo group. There were no reports of opportunistic infections, tuberculosis, or malignancy in these two trials, but increased risk of infection, disease flare, and MAS occurred. One patient developed pulmonary hypertension [21••].

Rilonacept is a fusion protein composed of the IL-1 receptor and the Fc portion of IgG1. A study on the efficacy and safety of rilonacept in patients' ages 4 to 20 years with SJIA was published in 2013. The study found no difference in efficacy of treatment between rilonacept- and placebo-treated patients during the initial double-blind phase but complete resolution of fever, and rash after 3 months of starting the open-label phase of the study occurred in the vast majority of treated patients. Clinical and laboratory measures showed improvement in more than 50 % of the rilonacept-treated patients still at 2 years after initiation of therapy, and no serious adverse

events were attributed to the medication [22]. Data from the RAPPORT study (The RAndomized Placebo Phase Study Of Rilonacept in the Treatment of Systemic Juvenile Idiopathic Arthritis) showed rilonacept had better efficacy when compared to placebo at 4 weeks, with 79 % of patients meeting ACR pediatric 30 response criteria vs. 39 % of patients in the placebo, 60 % meeting ACR pediatric 50 response criteria vs. 30 % in the placebo arm, and 40 % of patients meeting ACR pediatric 70 response criteria vs. 12 % in the placebo arm. Adverse events were similar in the two arms, with four patients developing elevation of transaminases twice the upper level of normal, two patients developed transaminases five times the upper level of normal, and one patient developed EBV-induced MAS [23].

Tocilizumab is a humanized monoclonal antibody against the IL-6 receptor. It competes with natural soluble and membrane-bound IL-6 receptors. The TENDER trial showed tocilizumab was effective in treating SJIA when compared to placebo. In the double-blind phase, at week 12, significantly more patients in the tocilizumab group than in the placebo group (64 of 75 (85 %) vs. 9 of 37 (24 %), $P < 0.001$) had absence of fever and achieved ACR 30, and in the open-label extension phase at week 52, 80 % of patients had at least 70 % improvement and remained afebrile. Adverse events were more commonly seen in the tocilizumab group including serious infections, neutropenia, and transaminitis [24]. The CHERISH trial, a randomized, double-blind, placebo-controlled withdrawal trial, of tocilizumab in polyarticular JIA, had three phases, including an open-label phase, where 89 % of patients achieved pediatric ACR 30 response. Of the patients previously exposed to biologics, who had treatment failure prior to the study, 48 % achieved pediatric ACR 70 with tocilizumab [25••]. Tocilizumab is approved in the USA by the FDA for the treatment of SJIA in 2011 and for the treatment of polyarticular JIA in 2013.

Ustekinumab is a fully human monoclonal antibody against the p40 subunit common to IL-12 and IL-23. Th17 cells are inhibited by IL-23 and IL-12 has effects on Th1 cells. There is no current trial data in pediatric rheumatic diseases but studies in adults show promising results in psoriatic arthritis and ankylosing spondylitis [26–29].

Biologics that Interfere with Cellular Function

Rituximab is a chimeric monoclonal antibody that binds to the CD20 receptor on the B cells. The CD20 receptor is in the pre-B cells and mature B cells. Due to its mechanism of action, it can potentially be used to treat conditions in which autoantibodies play a major role in the pathogenesis of disease. There are no randomized trials on rituximab, but there is some evidence of its benefits in ANCA-associated vasculitis, systemic lupus erythematosus (SLE), JIA, and inflammatory central nervous system disease. Alexeeva et al. evaluated 55 patients with polyarticular and systemic JIA who had failed first- and second-line therapies after administration repeat courses of rituximab once a week for 4 weeks. At week 24, 98 % of patients achieved pediatric ACR 30 response, 50 % achieved ACR 50, and 40 % achieved ACR 70 response. By week 96, pediatric ACR 30, 50, and 70 responses were achieved by 98, 93, and 93 % of 25 patients, respectively, and remission was seen in 25 % at 24 weeks, 52 % at 48 weeks, 75 % at 72 weeks, and 98 % of patients at 96 weeks, having received 1, 2, 3, and 4 courses of rituximab, respectively [29]. Dale et al. published a retrospective multicenter study of rituximab in 144 pediatric patients with autoimmune and inflammatory CNS disease, including patients with neuropsychiatric SLE. A definite, probable, or possible benefit was reported in 87 % of patients [30]. In 2011, Lehman et al. reported a case of ANCA-associated vasculitis, with pulmonary hemorrhage, that attained remission after receiving combination therapy with rituximab and cyclophosphamide and in 2014 published data from a pilot study of rituximab and cyclophosphamide combination therapy in patients with SLE and diffuse proliferative glomerulonephritis in eight patients, or steroid-dependent disease in four patients. The study showed significant reduction in mean prednisone dosage, erythrocyte sedimentation rate, and SLEDAI and increase in C3, albumin, and hemoglobin at 1- and 5-year follow-up [31•, 32]. A small case series of nine patients with juvenile dermatomyositis (JDM), from the French Autoimmunity and Rituximab registry, with refractory disease; suggests that rituximab might be effective in these patients as well [33•]. Side effects include infusion reactions, prolonged reduction of immunoglobulin levels, increased risk of infection including reactivation of hepatitis B virus, and in rare cases, when used with other agents, risk of progressive multifocal leukoencephalopathy [34].

Belimumab is a human monoclonal antibody against B lymphocyte stimulator or BLyS. It is expressed on macrophages and monocytes, and it enhances the proliferation of B cells. It was approved in 2011 by the FDA to treat active SLE, making it the first medication to be approved in over 50 years. Although the data available is from adult studies, some of the newer studies have included a subset of pediatric patients. Hui-Yuen et al. included 39 patients with childhood-onset, 65 % responded favorably at 6 months, and 35 % discontinued corticosteroids [35]. Side effects include infusion reactions, anaphylaxis, and infections (Table 1) [34].

Abatacept inhibits the activation of T cells by blocking the co-stimulatory signal required. It is a fully human soluble fusion protein, containing the extracellular portion of CTLA-4 and the Fc portion of IgG1. It was approved by the FDA in 2008 for the treatment of JIA based on the results of an international, multicenter, randomized, double-blind, placebo-controlled, withdrawal study. In the study, 53 % of patients who went on to receive placebo after the initial phase had a flare vs. 20 % in the abatacept group. The endpoint was time to flare. In

Table 1 Biologics used for pediatric rheumatologic conditions

Medication	Suggested dosing
Etanercept	0.8 mg/kg subcutaneous injection once a week
Infliximab	6–10 mg/kg intravenous infusion at weeks 0, 2, 6, and every 6–8 weeks thereafter
Adalimumab	Patients 15–30 kg 20 mg subcutaneous injection every other week
	Patients >30 kg 40 mg subcutaneous injection every other week
Golimumab	30 mg/m^2 subcutaneous injection once a month
Certolizumab pegol	*400 mg loading dose at weeks 0, 2, and 4, then 200 mg every 2 weeks or 400 mg every 4 weeks subcutaneous injection*
Anakinra	1 mg/kg subcutaneous injection daily
	(max. dose 100 mg/day)
Canakinumab	4 mg/kg subcutaneous injection every 4 weeks (for SJIA)
	150 mg every 8 weeks (for CAPS)
Rilonacept	4.4 mg/kg (max 320 mg) loading dose, then 2.2 mg/kg subcutaneous injection once a week (max 160 mg)
Tocilizumab	Polyarticular JIA:
	>2 years <30 kg 10 mg/kg intravenous infusion every 4 weeks
	>2 years >30 kg 8 mg/kg intravenous infusion every 4 weeks
	SJIA:
	>2 years <30 kg 12 mg/kg intravenous every 2 weeks
	>2 years old >30 kg 8 mg/kg intravenous every 2 weeks
Ustekinumab	45 mg subcutaneous injection on weeks 0 and 4, then every 12 weeks
Rituximab	500 mg/m^2 (max dose 1000 mg) intravenous infusion on weeks 0 and 2 or 375 mg/m^2 intravenous infusion weekly for 4 doses (may repeat every 6 months)
Belimumab	10 mg/kg intravenous infusion at weeks 0, 2, and 4 then every 4 weeks
Abatacept	<75 kg 10 mg/kg intravenous infusion over 30 min on weeks 0, 2, and 4 then every 4 weeks
	>75 kg 750 mg intravenous infusion over 30 min on weeks 0, 2, and 4 then every 4 weeks
Tofacitinib	5 mg by mouth twice a day

Medications in italics in the chart above display adult doses; no pediatric dosing available

the placebo group, the median time to flare was 6 months. The events were too few in the abatacept group and median time to flare was not possible to calculate [36].

New and Emerging Therapies

Despite all the advances, newer therapies continue to emerge as different immunological pathways are found to be, at least partially, responsible for the pathogenesis of the diseases.

Tofacitinib is an inhibitor of the Janus kinase (JAK); it selectively inhibits Jak1, Jak2 to a lesser extent, and Jak3, blocking multiple cytokines implicated in the pathogenesis of synovitis. It is an oral preparation and has been approved for the treatment of adult RA by the FDA. All biologics used and approved to date are administered either by intravenous or subcutaneous route, making tofacitinib a very attractive option [36]. There is a clinical trial underway to evaluate this agent in children with JIA.

Other Jak inhibitors and spleen kinase (Syk) are being studied for adult rheumatologic diseases and if favorable results are found we will likely see pediatric-based studies in the near future.

Tailored Treatment

Risk of exposing pediatric patients to biologics and new drugs that have been on the market for only a few years or that are off label is always of great concern to their families, especially because there is not a way of knowing which medication will induce remission in each individual patient. Biomarkers have become the target for many researchers, not only as a marker of disease activity or specific organ involvement, but also as a prognostic marker and as a way to narrow the therapeutic options and avoid exposing patients to unnecessary side effects.

Foell et al. published the first study showing that patients on methotrexate that reached clinically inactive disease and had higher than normal levels of MRP8/14 (S100A8/9), a serum protein, had a greater change of flare after stopping

methotrexate than those with normal levels [37] Further studies have been published to support the presence of markers that may aid in choosing a therapeutic approach, these which serologic, transcriptomic, and genetic markers [38••, 39, 40].

It is of utmost importance to discuss the expectations and goal of therapy with each individual family and to continuously reassess the progress

Conclusions

The improvements made in the past two decades are the biggest motivation to continue finding answers. As aspects of the pathogenesis of rheumatologic diseases are better understood, newer and improved therapies will slowly become available. Targeting specific areas of the immune response will aid in avoiding some unnecessary side effects. This and newer markers of prognosis, as they become available, will allow in the future for tailored, more individualized, treatment plans [41, 42].

Compliance with Ethics Standards

Conflict of Interest YS declares that she has no conflict of interest. NI reports funding from Novartis, outside the submitted work.

Human and Animal Rights and Informed Consent This article does not contain any studies with human or animal subjects performed by any of the authors

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- •• Of major importance

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