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REVIEW

Biologics in juvenile idiopathic arthritis: a narrative review

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Abstract In the past years, pediatric rheumatology has seen a revolution in the treatments for rheumatic diseases, particularly juvenile idiopathic arthritis. Even if nonsteroidal anti-inflammatory drugs (NSAID), intra-articular corticosteroids (IAC) injections, and methotrexate remain the mainstay of the treatment for JIA patients, in aggressive disease, these treatments may be not sufficient to reach disease remission and to prevent long-term disability. Comprehension of immunological mechanisms involved in the pathogenesis of the diseases allowed to conceive new drugs targeting specific steps of the immune response. Several cytokines, like TNF alpha and IL-1, represent a very interesting target for biologic therapies. Due to the efficacy of these therapies, nowadays, "disease remission" in pediatric rheumatology is more and more frequent, especially in juvenile idiopathic arthritis patients, and the long-term outcomes have been significantly improved. Crucial to these advancements have been multicenter controlled clinical trials and long-term safety monitoring.

Conclusions: Research in pediatric rheumatology has resulted in dramatic advances in diseases management. Biologic treatments have improved physical and functional outcomes and quality of life of patients with rheumatic disease.

What is Known:

- *NSAID, intra-articular injection of corticoids, and methotrexate are the mainstay in treatment of JIA.*
- *In aggressive JIA, these treatments may be not sufficient to reach disease remission and to prevent long term disability.*

What is New:

- *In recent years, management of JIA has significantly improved with the development of biologic therapies that allowed children with arthritis to reach a normal growth and to achieve a good long-term functional outcome.*

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Abbreviations

DMARD	Disease-modifying anti-rheumatic drug
JIA	Juvenile idiopathic arthritis
IL-1	Interleukin-1
IL-6	Interleukin-6
MAS	Macrophage activation syndrome
NSAID	Nonsteroidal inflammatory drugs
sJIA	Systemic juvenile idiopathic arthritis
TNF	Tumor necrosis factor

Introduction

Juvenile idiopathic arthritis (JIA) is defined as arthritis of unknown etiology that begins before the 16th birthday and persists for at least 6 weeks, with other known conditions excluded [32] (Table 1). Nonsteroidal anti-inflammatory drugs (NSAID) and intra-articular corticosteroids (IAC) injections are the mainstay of the treatment for JIA patients with oligoarticular involvement. Methotrexate is the most commonly used disease-modifying anti-rheumatic drug (DMARD) in JIA management, mainly as a second-line agent in children with insufficient response to IAC injections or as initial treatment for patients with aggressive disease. Comprehension of mechanisms involved in inflammatory process led to development of biological molecules that target specific steps of the immune response, interfering with cytokines or cellular interactions involved in the activation and regulation of the immune system. Due to the efficacy of biologic therapies, nowadays, "disease remission" in pediatric rheumatology has become a realistic goal, especially for JIA patients, and the long-term outcomes have been significantly improved. In this review, we present the current available biologics used in JIA (Table 2).

Interference with cytokines

A major part of clinical manifestation associated with JIA can be related to the effect of cytokines released by activated T cell and monocytes [12]. Therefore, these cytokines became a very interesting target for biologic therapies.

Anti-tumor necrosis factor (TNF)-α gents

The crucial role of TNF-α in the pathogenesis of various inflammatory diseases, including JIA, has been widely demonstrated [9]. Etanercept and adalimumab are the anti-TNF-α agents approved for JIA treatment, whereas infliximab, golimumab, and certolizumab pegol are approved for adult rheumatoid arthritis. Anti-TNF-α agents are indicated in the latest international recommendations as a second- or third-line agent in patients with JIA with persistent active disease despite an adequate treatment with DMARD, methotrexate in particular [36, 37].

Table 1 ILAR classification of juvenile idiopathic arthritis

Systemic arthritis
Oligoarticular JIA
a. Persistent
b. Extended
Polyarthritis (rheumatoid factor negative)
Polyarthritis (rheumatoid factor positive)
Psoriatic arthritis
Enthesitis-related arthritis
Undifferentiated arthritis

Etanercept is a fully human, dimeric fusion protein of the human p75 TNF-α receptor and the Fc region of human IgG1 that binds to circulating TNF-α, preventing its interaction with the cell surface receptor and the subsequent inflammatory response.

In 1999, etanercept was the first biologic agent approved by the US Food and Drug Administration (FDA) for the treatment of moderate to severe polyarticular JIA in children older than 2 years old, based on a randomized, double-blind withdrawal study comparing etanercept to placebo. At the end of this study, etanercept was effective in 80% of patients [23]. The promising results of this trial, that showed sustained effectiveness and long-term safety of etanercept in the open-label phase, have been then confirmed by numerous observational and open-label studies, which have clearly demonstrated efficacy of etanercept in reducing joint count, morning stiffness and inflammatory parameters and in improving growth, functional ability and quality of life of JIA patients [15, 19, 25, 38, 51].

Etanercept is indicated for JIA patients with polyarticular course who demonstrate insufficient response or intolerance to methotrexate, and its initial clinical effect usually manifests in 2–3 weeks [23]. It is not usually prescribed in patients with systemic-onset JIA, where different pro-inflammatory cytokines have a pivotal role in the disease pathogenesis.

Adalimumab is a fully humanized monoclonal IgG1 antibody against TNF-α that acts binding both soluble and membrane-bound TNF-α. Adalimumab has been approved by FDA in 2008 for the treatment of polyarticular JIA in children from 4 years of age and older, based on a randomized, double-blinded, placebo-controlled withdrawal study, that showed a good efficacy and a reduced disease flare in placebo-controlled phase, with a sustained response rate during open-label extension [26].

In Europe, adalimumab is indicated in combination with methotrexate for the treatment of active polyarticular juvenile idiopathic arthritis, in patients from the age of 2 years who have had an inadequate response to one or more DMARDs. Appraisal of anti-adalimumab antibodies is described and can be considered an early marker associated to a poor clinical response [17].

Infliximab is a chimeric human–mouse monoclonal antibody directed against TNF-α in its soluble and membrane-bound forms, leading to TNF-α neutralization and to antibody-dependent cytotoxicity of TNF-α producing cells. In 2007, a multicenter randomized double-blind placebo-controlled trial suggested the efficacy of infliximab in polyarticular subtype, showing a rapid improvement as early as week 2 [40]. The effectiveness of infliximab in polyarticular JIA has been reported in the last years in many case series and open-label trials [47].

Table 2 Target and relatives drugs

Target	TNF-α			IL-1			IL-6	CTLA-4	CD20
Drug	Etanercept	Adalimumab	Infliximab	Anakinra	Canakinumab	Rilonacept	Tocilizumab	Abatacept	Rituximab
Dose	0.8 mg/kg sc OW max = 50 mg/ week	24 mg/m^2 sc q2w	5 mg/kg IV initially, 3–10 mg/kg 2nd dose at 2 w, then q4–8 w	1–2 mg/kg sc od	2–4 mgg/kg sc q4w	2.2–4.4 mg/kg sc ow	12 mg/kg (body weight < 30 kg), 8 mg/kg (body weight > 30 kg) IV q2w	10 mg/kg IV at w 0, 2, 4 then q4w	750 mg/m^2 IV, two doses 2 w apart; or 375 mg/m^2 IV weekly for 4 w
Effective in	pcJIA psJIA ERA	pcJIA JIA associated uveitis	pcJIA, psJIA, JIA associated uveitis	sJIA CAPS	sJIA CAPS (TRAPS) (MKD)	CAPS	pcJIA sJIA	pcJIA	JSLE JDM

The tolerability of infliximab infusion is a major concern: there is a relevant risk of infusion-related reactions, development of anti-nuclear antibodies, and of human anti-chimeric antibodies; all these events are probably related to low dose regimes (3 mg/kg) [40]. Human anti-chimeric antibodies seem to be responsible for a higher clearance of infliximab and subsequently to its lack of efficacy and also to an increased rate of infusion reactions [28]. Concurrent administration of MTX can help to prevent the development of human anti-chimeric antibodies, improving infliximab effect.

Golimumab is a fully humanized monoclonal antibody against soluble and transmembranous TNF-α. A randomized, double-blind, placebo-controlled study had evaluated the efficacy and safety of golimumab in pediatric patients with active polyarticular JIA and poor response to methotrexate The rate of disease's flares during the withdrawal phase in responder patients was not significantly different between golimumab + MTX group and MTX group [reported in abstract form [7]]. A phase III multicenter, open-label trial, with the purpose of evaluating the pharmacokinetics of golimumab administered intravenously in poliarticular JIA is ongoing.

Certolizumab pegol is a pegylated anti-TNF-α inhibitor. Pegylation enhances the half-life of the drug and allows a subcutaneous 2–4-week dosing schedule. There is a clinical trial underway for the use of certolizumab in children with JIA.

Anti-interleukin-1 (IL-1) agents

IL-1 is a pivotal pro-inflammatory cytokine, produced by monocytes, macrophages, and dendritic cells, whose activity is physiologically controlled by soluble IL-1 receptor antagonist. Evidence from the literature confirmed that IL-1 blockade is the cardinal treatment for several auto-inflammatory diseases [221] that share several features with systemic-onset juvenile idiopathic arthritis (sJIA). The activation of the innate immune system, the presence of systemic features the absence of autoimmunity suggest that sJIA is an auto-inflammatory rather than an autoimmune disease. The discovery of the efficacy of IL-1 inhibition in sJIA is an interesting example of inverse translational research. The efficacy of IL-1 blockade, was accidentally observed in two sJIA patients [30, 50], paving the way for several immunological studies (from the bed to the bench) that have definitely demonstrated the pivotal role of IL-1 in the pathogenesis of the disease. In fact, systemic JIA patients usually show an excellent response to IL-1 inhibitors, whereas anti-TNF agents are less effective in this JIA subtype [23, 34].

Anakinra is a human recombinant form of IL-1 receptor antagonist that binds to the IL-1 receptor on cell surfaces preventing its interaction with IL-1 and subsequent cell signaling. Due to his short half-life, anakinra is administered in

daily subcutaneous injection and this dose scheduling might be a concern for children compliance. Anakinra administration in sJIA patient can lead to a rapid improvement of systemic features and laboratory parameters [30, 54]. Since the first description of its efficacy in sJIA response to IL-1 blockade revealed to be variable; in fact two subsets of sJIA can be identified, according to patient response to anakinra [14]. One (accounting for about 50% of patients) with a dramatic, complete response to IL-1 blockade, the other resistant to treatment or with an intermediate response. Complete responders had a lower number of active joints and an increased absolute neutrophil count, compared to patients showing an incomplete or no response.

In a prospective study, anakinra was used as first-line therapy in patients with sJIA with an excellent response within 3 months and treatment could be stopped within 1 year with sustained remission [49]. Nevertheless, the use of anakinra as first-line treatment in sJIA is still debated because controlled data are lacking.

Canakinumab is a fully human anti-IL-1β monoclonal antibody. The long half-life of this drug justifies its subcutaneous administration every 4 weeks in sJIA [42]. Canakinumab is approved for sJIA treatment in children aged 2 years and older, based on two international randomized, placebo-controlled trials that revealed the efficacy of canakinumab in children with sJIA and active systemic features [39]. In trial 1, after a single injection, 33% of the patients present an inactive disease within 15 days. Trial 2 confirmed these results with a sustained efficacy in 82% of patients after 2 years of treatment.

Rilonacept is a fully human dimeric fusion protein that incorporates the extracellular domains of the IL-1 receptor components required for IL-1 signaling, linked to the Fc portion of IgG1. Efficacy and safety of rilonacept in sJIA was studied in a double-blind placebo-controlled trial that showed a good safety of the product but a positive clinical response only in half of the patients treated over 2 years [24]. This drug is still neither approved by FDA nor available in Europe.

Anti-interleukin-6 (IL-6) agents

IL-6 plays a central role in clinical and laboratory manifestations of sJIA. Several studies have shown that levels of IL-6 correlate with spikes of fever, thrombocytosis, and joint involvement [11].

Tocilizumab is a humanized, monoclonal antibody against the IL-6 receptor that competes with the soluble and the membrane-bound IL-6 receptor to prevent cell signaling. Tocilizumab is approved in patients >2 years with persistently active sJIA and is administered every 2 weeks, via intravenous infusion. Efficacy of tocilizumab in sJIA was proved in a randomized, double-blind, phase III study in which the drug tocilizumab was administered to children (aged 2–19 years) with disease refractory to conventional treatment. Tocilizumab was effective on 91% of patients by week 6 of the open-label lead-in phase. Responders were included in the open-label extension phase in which tocilizumab was effective in 98% of patients at week 48 [52]. These findings were confirmed in a multicenter double-blind placebo-controlled trial [10]. Tocilizumab administered intravenously every 4 weeks has shown to be effective in treating polyarticular JIA patients with inadequate response to or that were intolerant to methotrexate [8].

Inhibition of cellular function and cell-cell interaction

Targeting lymphocyte activation and cellular functions might be an alternative approach for the management of JIA, in particular refractory polyarticular subtype that shows inadequate response to other therapies, including one or more anti-TNF agents.

Abatacept is a soluble fusion protein that selectively modulates the CD80/CD86:CD28 co-stimulatory signal for T-cell activation and is administered via intravenous infusion. A double-blind randomized controlled withdrawal trial has shown efficacy in children with polyarticular JIA subtype [41]. In this study, 190 patients with active polyarticular JIA and an inadequate response or intolerance to at least one DMARDS were treated with abatacept. Of 170 patients that completed the open-label period, 123 responded to treatment. Effectiveness of abatacept was confirmed in the double-blind phase; however, patients that previously received a TNF inhibitor appeared to demonstrate a minor response, possibly due to a more aggressive disease.

Rituximab is a chimeric, monoclonal mouse-human antibody against CD20 B cell receptor present on pre-B and mature B cells, but not on stem cells or plasma cells. Rituximab acts by antibody-dependent and complement-dependent cellular cytotoxicity and removes B lymphocytes by the circulation inducing apoptosis. Anti-CD20 therapy is approved for adult RA, but only isolated reports support efficacy of rituximab in JIA patients [2, 21].

JIA-related uveitis

JIA-related uveitis is a chronic, non-granulomatous, anterior uveitis that involves the iris and the ciliary body (iridocyclitis) and can cause severe visual impairment. It is the more frequent extra-articular manifestation of JIA and is usually asymptomatic. Biologic drug may be considered for uveitis treatment, in case of limited response to topical (or systemic) corticosteroids and methotrexate. Both adalimumab and infliximab have been proved to be effective for the treatment of JIA-

related uveitis [46, 53], whereas etanercept is not indicated [43].

Efficacy of tocilizumab in treating severe and therapy-refractory uveitis associated with juvenile idiopathic arthritis have been recently described [45].

Macrophage activation syndrome

Macrophage activation syndrome (MAS) is a potentially life treating complication of sJIA which is seen most frequently in systemic juvenile idiopathic arthritis (sJIA) and other rheumatologic conditions. Clinical features of MAS are coagulopathy, pancytopenia, and liver and central nervous system dysfunction. Prahalad and colleagues [33] reported the efficacy of etanercept in a boy with MAS, whereas other authors described the onset of MAS in patients with sJIA who were receiving etanercept [35] suggesting that this therapy may not be ideal for MAS occurring in children with sJIA. Recently, several cases of sJIA-associated MAS have been reported who benefited dramatically from the administration of the IL-1 inhibitor, anakinra, after incomplete response to corticosteroids and Cyclosporine A [6, 18]. However, MAS occurring in sJIA patients treated with anti-IL1 have been described [27]. In the reported cases, cause-effect relationship is often difficult to establish and paradoxically increasing the dose of anakinra resolved MAS is most cases [29]. Due to its efficacy in treating sJIA, targeting IL-6 has been proposed as a possible approach also in sJIA-associated MAS patients. However the role of tocilizumab in the treatment of MAS is still unclear at present, because cases of MAS attributed to anti–IL-6 therapy have been reported [20].

Tolerability and safety

Skin reactions at the injection site with subcutaneously administered agents are a common minor adverse event, in particular with etanercept and adalimumab, although these reactions usually do not determine a drug withdrawal. Acute infusion reactions occur especially with infliximab and may also be observed with tocilizumab and abatacept. Cytopenia is only occasionally reported upon treatment with anti-TNF-α [25], while neutropenia is a concern in patients treated with tocilizumab even if an association between neutropenia and the occurrence of serious infection has not been demonstrated [5, 52]. All the biologic therapies potentially increase the risk of infection, tuberculosis in particular. Data coming from registries suggest that serious infection is more frequent in patients treated with biologics compared to patients treated with methotrexate alone [5, 16]. Due to the increased risk of tuberculosis reactivation during biologic therapies, especially with anti-TNF agents, a careful screening for latent mycobacterial infection is strictly recommended before starting a biologic treatment and during its course. A potential link between anti-TNF-α medication and demyelinating disorders have been suggested but not proven [48], nevertheless it seems reasonable avoid utilization of anti-TNF-α agents in subjects that shows demyelinating diseases as multiple sclerosis. Treatment with TNF-α inhibitors and other biologics has been associated with an increased risk of developing autoantibodies, but usually without any clinical manifestation [3], and autoimmune disorders like systemic lupus erythematosus or vasculitis have been rarely reported [31].

A major concern especially with anti-TNF agents has been the possible increased risk of malignancies. In 2009, the FDA reported 48 cases of malignancies in children treated with anti-TNF agents. A large part of these patients was diagnosed with an inflammatory bowel disease and 88% had received other immunosuppressive treatments [13]. To date, a causal relationship between malignancy and biologic therapy could not be defined, even because JIA patient shown an increased baseline incidence of tumors [4, 44]. The increasing use of biologic treatment in clinical practice raises questions on long-term safety of these drugs and for this reason registries for long term monitoring of patients under biologic therapies are crucial.

Conclusions

In recent years, research in children with JIA has resulted in dramatic advances in disease management.

The advent of the biologic therapies has highly improved physical and functional outcomes of patients with rheumatic disease. Nevertheless, many questions are still unanswered, for example whether there is a best therapeutic option for a specific subtype of patients or which is the correct time for drug withdrawal once remission has been reached.

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Dr. Minoia and Dr. Malattia corrected the initial draft of the manuscript and approved the final manuscript as submitted.

Compliance with ethical standards

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