

Review for the Generalist: Update on biologic therapies for pediatric rheumatic diseases

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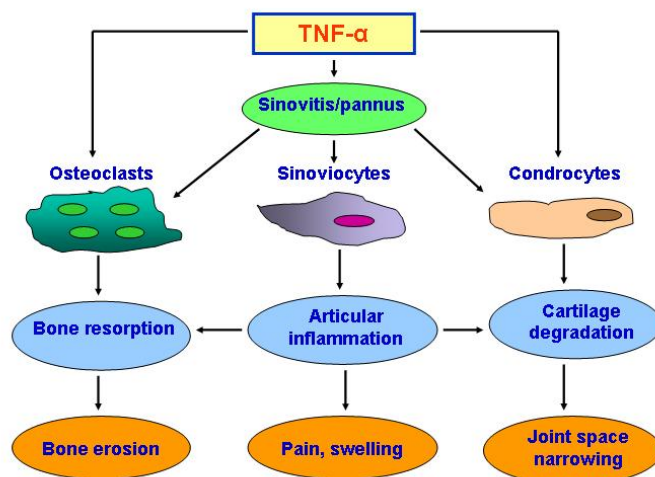
Introduction.

Pediatric rheumatic diseases are systemic inflammatory conditions of unknown etiology for which no curative treatment still exists [1]. A rational approach to therapy of these disorders has been hampered by the insufficient knowledge of the mechanism of action of the traditional anti rheumatic drugs. Recent advances in understanding the pathophysiology of the inflammatory response have led to the development of a new class of medications that are capable of inhibiting selectively the principal mediators of inflammation and tissue damage. The introduction of these new molecules, which are collectively termed biologic agents, has opened a new era in the treatment of rheumatic diseases in children. In the present paper, we review the characteristics of the biologic medications and the available information on their efficacy and safety in pediatric patients.

Tumor necrosis factor antagonists

The production of tumor necrosis factor (TNF) antagonists has been made possible by the demonstration of the pivotal role played by this cytokine in the pathogenesis of chronic arthritis (Figure 1) and by the characterization of its biochemical structure and receptor interactions [2,3].

Figure 1. Role of tumor necrosis factor (TNF)- α in the pathogenesis of chronic arthritis.



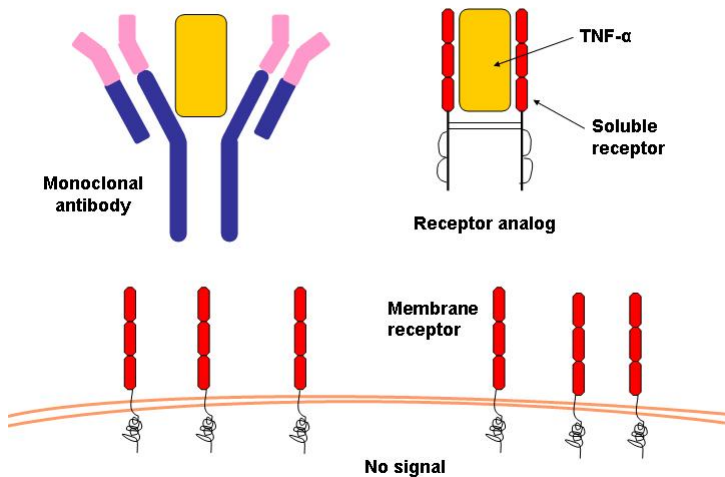
This knowledge has led to the development of strategies to block the link of TNF- α to its receptors. With tools from molecular biology, three different compounds have been created, all of which bind strongly to TNF- α and inhibit its proinflammatory activities (Table 1 and Figure 2). Etanercept is a fusion protein made up of two recombinant p75 TNF receptors fused with the Fc portion of a human IgG1. Infliximab and adalimumab are both monoclonal antibodies: the first is a chimeric molecule (composed by the variable region of a murine antibody grafted to the constant region of a human antibody), the second a human derived antibody.

Table 1. TNF antagonists' characteristics.

	Etanercept	Infliximab	Adalimumab
Biochemical structure	TNF-IgG1 fusion protein	Chimeric monoclonal antibody	Human monoclonal antibody
Binding target	TNF- α , lymphotoxin	TNF- α	TNF- α
Binding affinity	High, quick dissociation	High, slow dissociation	High, slow dissociation
In vitro cell lysis	No	Yes	Yes
Effect on Th1 cells	No suppression	Long-lasting suppression	Long-lasting suppression
Dosage	0.4 mg/kg (max 25 mg)	3-5 mg/kg	24 mg/m ²
Frequency of administration	Twice a week	Every 2 months*	Every 2 weeks
Route of administration	Subcutaneous	Intravenous	Subcutaneous

*In the maintenance phase

Figure 2. Mechanism of action of TNF- α antagonists. The monoclonal antibody (infliximab, adalimumab) and the receptor analog (etanercept) bind to circulating TNF- α and block its interaction with membrane receptor.



Although the overall efficacy and safety profile of these drugs is likely similar, there are important differences that must be taken into account in their clinical use. Because infliximab is a 25% murine molecule, its long-term use may induce the production of anti-chimeric antibodies, which may reduce its efficacy and lead to idiosyncratic reactions. For this reason, infliximab must be always administered in combination with an immunosuppressive drug, such as methotrexate. Then, when a monotherapy is chosen, it is better to use etanercept or adalimumab. The administration protocol is also different: etanercept and adalimumab are injected subcutaneously twice a week and every two weeks, respectively, whereas infliximab is infused intravenously every two months (in the maintenance phase). Although the longer half-life of monoclonal antibodies may represent an advantage for the disease control and, allowing a reduced frequency of injections, may facilitate children's compliance, it may raise more problems in the monitoring of drug toxicity.

The TNF antagonist for which more information is available in the pediatric age is etanercept, which is the only medication in this class that is registered to date for use in juvenile idiopathic arthritis (JIA). The efficacy of etanercept in JIA has been demonstrated in a controlled trial conducted in the US, which included 69 patients who either had an inadequate response or were not tolerant to methotrexate therapy [4]. In the open-label phase, a significant clinical benefit was observed in 74% of patients who received etanercept. In the subsequent randomized double-blind phase, in which etanercept was compared with placebo among responders, a significantly higher frequency of disease flare and a significantly shorter time to flare was observed in patients who were switched to placebo compared to those who were continued on etanercept.

The results of the long-term administration of etanercept in patients enrolled in the US trial [5] and in patients included in national registries in France and Germany [6,7] have been reported recently. These studies enabled the evaluation of the efficacy and toxicity profile of the drug in a large group of patients after a prolonged exposure (Table 2). In the US study [5], which included 58 patients, most side effects were

of mild to moderate intensity; 9 patients had serious adverse reactions, which, however, led to treatment discontinuation only in 2 cases. Significant laboratory abnormalities, including the occurrence of new autoantibodies or new autoimmune diseases, were never recorded. Two of the 3 patients who had varicella during treatment developed reversible central nervous system complications. For this reason, the authors recommend that children who are candidate to start etanercept receive vaccination, and that unvaccinated and not-immune children who are exposed to varicella are treated with specific immunoglobulins or acyclovir at the first sign of infection. As many as 81% of the 43 patients who completed 2 years of treatment in this study had sustained clinical response.

Table 2. Main side effects of etanercept reported in long-term studies in juvenile idiopathic arthritis.

Lovell et al [5]	Quartier et al [6]	Horneiff et al [7]
<p><u>Non infectious side effects</u></p> <ul style="list-style-type: none"> - Headache - Abdominal pain - Rhinitis - Nausea - Fever - Cutaneous rash <p><u>Infectious side effects</u></p> <ul style="list-style-type: none"> - Upper airways infections - Cutaneous infections - Flu-like syndrome - Otitis - Conjunctivitis - Appendicitis/peritonitis - Aseptic meningitis - Sepsis 	<p><u>Minor side effects</u></p> <ul style="list-style-type: none"> - Injection site reactions - Cutaneous rash - Gastrointestinal discomfort - Headache - Mood changes - Fatigue, anorexia <p><u>Serious side effects</u></p> <ul style="list-style-type: none"> - Pancytopenia - Psychiatric disorders - Uveitis flare - Retrobulbar optic neuropathy - Headache and marked dysesthesia - Cutaneous vasculitis 	<p><u>Non infectious side effects</u></p> <ul style="list-style-type: none"> - Cutaneous reactions - Liver enzyme increase - Exanthem, pruritus, urticaria - Abdominal pain, headache - Leukopenia, thrombocytopenia - Hair loss - Nausea, vomiting - Vertigo - Demyelinating syndrome with seizures <p><u>Infectious side effects</u></p> <ul style="list-style-type: none"> - Prolonged or febrile infections - Prolonged bronchitis - Lip herpes simplex - Varicella or herpes zoster - Pneumonia - Cellulitis - Urinary tract infection

Less encouraging results were obtained in the French registry [6], which enrolled 61 patients treated for an average period of 13 months. The rate of treatment withdrawal for serious side effects was 20%, and a remarkable decrease in the frequency of therapeutic response between the 3rd and the 12th month of treatment (from 73% to 39%) was noticed. Other relevant findings were the observation of a number of severe neurologic and psychiatric adverse events and a significantly lower efficacy in the subgroup of patients with systemic-onset JIA. The frequency of clinical response after 6 months (83%) observed in the German study [7], which included 334 patients, was comparable to that reported in other series. Similarly to the French experience, the therapeutic effect was poorer in systemic patients. The overall safety profile of etanercept was satisfactory, although one patient developed a demyelinating syndrome.

Further evidence that patients with systemic JIA do not respond as well to etanercept as those with other forms of JIA was provided by Kimura et al [8], who investigated through a questionnaire survey the response to etanercept of a cohort of 82 patients with this form of JIA followed by US pediatric rheumatologists. Forty-five percent of the patients had a poor response to treatment and an equal percentage experienced one or more disease flare; 35% discontinued therapy, mostly due to lack of response or flare. The reasons of the relatively poorer response to etanercept of patients with systemic JIA have been discussed recently [9]. In a small study, it was suggested that in systemic patients who do not respond to standard doses the administration of higher amounts of the drug (0.8 mg/kg/dose or above) may be required to induce response [10]. Etanercept has been tried with success in a patient with systemic JIA-associated macrophage activation syndrome [11]. The rationale for this intervention came from the demonstration that TNF- α may play a central role in the pathogenesis of the clinical and laboratory manifestations of this syndrome. However, there are reports of patients who developed this complication while taking TNF antagonists [12].

The preliminary results of the controlled trials with infliximab and adalimumab in JIA, which are ongoing, have been presented last year during the European Congress of Pediatric Rheumatology and the American College of Rheumatology meeting. The findings of the first analyses of the efficacy and safety of the two monoclonal antibodies were not dissimilar to those obtained with etanercept. The presentation of the final results of the trials will enable to establish the place of these medications in the current management of JIA. Recently, the efficacy and safety of infliximab, in association with methotrexate, have been evaluated in an open-label, 2-year study in 24 young adults with long-

lasting, refractory JIA [13]. After a median treatment duration of 9.1 months, significant improvement was observed in the number of active joints, pain scores, patient's and physician's global assessment of disease status, ESR, and CRP. The percentage of patients meeting the 20% American College of Rheumatology improvement criteria ranged from 54.2 to 86.7%. Twelve patients (50%) had adverse events, and 5 patients (20.8%) withdrew. Two patients experienced the transient occurrence of antinuclear antibodies and low-titer anti-double stranded DNA antibodies without developing features of systemic lupus erythematosus (SLE).

TNF inhibitors have been used with encouraging results in juvenile spondyloarthropathies [14-16]. Although evidence is still too limited to draw definite conclusions, it is likely that these medications will have a major role in these diseases. The effect of etanercept in treatment-resistant JIA-associated uveitis is unclear because the few therapeutic studies have provided conflicting results [17-19]. Furthermore, flares of uveitis during etanercept therapy in patients who had relapsing uveitis before the institution of treatment have been observed [16,19].

Following the satisfactory results obtained in chronic arthritides, the anti-TNF agents have been tested, generally with good results, in several other rheumatologic conditions refractory to conventional therapies, both in children and in adults [20]. However, most of these reports are anecdotal, and confirmation in controlled studies is warranted. This therapy has been proposed in the TRAPS (TNF receptor superfamily 1A-associated periodic fever syndrome), which is a hereditary antiinflammatory syndrome due to a specific genetic mutation that may cause a quantitative or qualitative abnormality of soluble TNF receptor. The resulting failure to inhibit the cytokine activity, which plays a major role in the induction of the inflammatory episodes, can be theoretically contrasted by etanercept, which is an analogue of the soluble physiologic receptor and can, therefore, compensate its deficiency [21]. Recently, a positive experience with etanercept has been reported in another antiinflammatory condition, the hyperimmunoglobulinemia D and periodic fever syndrome (HIDS) [22].

In clinical practice, it is important to consider that the administration of anti-TNF agents has been associated with an increasing risk of TB infection onset or reactivation. For this reason, an accurate screening for TB during baseline assessment and a careful monitoring for the entire duration of treatment are mandatory [23].

Anakinra

Several studies have shown that interleukin (IL)-1 is a key mediator of inflammation, bone resorption and cartilage destruction, which are the main determinants of joint damage in chronic arthritis. The proinflammatory action of IL-1 is contrasted by a natural inhibitor which, when present in excess, blocks the interaction of the cytokine with its receptor and, consequently, the transduction of the signal to the effector cells. Anakinra is a recombinant homolog of the human IL-1 receptor antagonist (IL-1Ra) that competitively inhibits binding of IL-1 with its receptor [24].

Anakinra has been evaluated in JIA in a non controlled trial [25]. This study has included 60 patients with polyarthritis who were treated for 12 weeks with daily subcutaneous injections of 1 mg/Kg/die. At the end of the treatment period, a significant response was observed in 61% patients. Anakinra was generally well tolerated and the most frequent adverse events were injection site reactions. Ten percent of the patients were discontinued prematurely from treatment. Nevertheless, IL-1 blockade with recombinant IL-1Ra did not gain much popularity in the treatment of JIA. Similarly, this approach did not prove to be significantly advantageous over anti-TNF blockade in adult rheumatoid arthritis, and did not show efficacy in patients who were failing anti-TNF treatment [26,27].

Recently, however, a number of reports have appeared regarding the excellent response of patients with the systemic subtype of JIA to anakinra [28-31]. Most patients cleared symptoms and laboratory abnormalities within days to week of therapy initiation, and prednisone dose was significantly tapered or discontinued in all. Many of these patients had failed etanercept. This effect has been related to an intrinsic dysregulation in the production of IL-1, which may play a critical role in the pathogenesis of this condition [31]. Interestingly, IL-1Ra therapy has been found to be effective in patients with refractory adult-onset Still's disease, which is the adult equivalent of systemic JIA [32]. The therapeutic effect of anakinra and the clinical similarities that exist between systemic JIA and autoinflammatory syndromes (see below) has led to postulate that at least some cases of systemic JIA could be due to gene mutations leading to uncontrolled IL-1 production [33]. Controlled clinical trials are likely to begin shortly for anakinra in systemic JIA.

Anakinra has demonstrated a remarkable efficacy in the autoinflammatory diseases that are associated with *C1AS1* gene mutations, which include Muckle-Wells syndrome, familiar cold autoinflammatory syndrome (FCAS), and chronic infantile neurological cutaneous and articular syndrome/neonatal-onset multisystem inflammatory disease (CINCA/NOMID). In 3 members of a family, all of whom had Muckle-

Wells syndrome, anakinra led to rapid and complete resolution of clinical and serologic evidences of active inflammatory disease [34]. IL-1Ra administration was found to prevent cold-induced symptoms and hematological and biochemical changes in patients with FCAS [35]. In two series of patients with CINCA/NOMID, this treatment was followed by rapid improvement in clinical symptoms and laboratory markers of inflammation [36,37]. The distinctive efficacy of treatment was confirmed by the reoccurrence of symptoms and laboratory abnormalities within few days from its discontinuation [38]. The mechanisms that lead to abnormalities in IL-1 release in autoinflammatory diseases and the rationale for their treatment with IL-1Ra have been reviewed recently [33].

Interleukin-6 inhibitor

As stated above, children with systemic JIA do not respond as well to etanercept as those with other forms of JIA. This poorer therapeutic effect is likely due to differences in the characteristics of the inflammatory response. A growing body of evidence suggests that in active systemic JIA the proinflammatory cytokine that plays a major role is IL-6 rather than TNF- α . IL-6 is a pleiotropic cytokine, which is believed to be responsible of the induction of fever, of the synthesis of several acute phase proteins, and of the development of the main complications of systemic JIA, such as growth failure, osteoporosis, and anemia [36].

IL-6 exerts its biologic activities through interaction with the transmembrane glycoprotein gp130, which mediates the activation of the intracellular signal. The cytokine molecule, however, is not able to bind directly to gp130, but can only do so after the link with its own receptor, either membrane (IL-6R) or soluble (sIL-6R), to form heterodimeric IL-6/IL6R complexes, which can bind to gp130. Of the various approaches that have been considered to block the biologic activity of IL-6, the most advantageous has been the one aimed at inactivating the cytokine receptors through the development of a humanized recombinant monoclonal antibody, named MRA [39].

Recently, Yokota et al [40] reported impressive clinical responses with the short-term use of escalating doses of MRA in 11 patients with corticosteroid-dependent systemic JIA. MRA administration led to prompt abatement of active disease manifestations, namely fever and active arthritis, and quick reduction of acute-phase reactants. No serious adverse events were recorded. This study confirms indirectly the pathogenetic role of IL-6 and suggests that this medication may have an important role in the future treatment of this disease, especially in corticosteroid-resistant patients. However, this

favorable preliminary experience warrants further investigation in a controlled clinical trial.

Abatacept

CTLA4-Ig or abatacept belongs to a new generation of medications that act at the beginning of the cytokines' pathway, blocking T-lymphocyte activation [41]. T-cells request at least two different signals to reach complete activation: the first generates after the presentation of the processed peptide to the T-cell receptor, in the context of a specific HLA antigen; the second is the so-called co-stimulatory signal, which is provided by the link between the CD28 receptor expressed on T-lymphocytes and the CD80/86 (B7-1 or B72) receptor expressed on the surface of the antigen presenting cells. The CTLA-4 is a second receptor that binds to both CD80 and CD86 with an affinity 500 to 2500 times higher than CD28.

Abatacept is a soluble protein that is composed by the extra-cellular portion of human CTLA4 and a fragment of the Fc region of a human IgG1. The binding between abatacept and the CD80/86 molecules prevents their interaction with the CD28 receptor and, therefore, blocks the second signal necessary for T-cell activation. The method of artificial modulation of the immunological response followed in the development of this drug is very interesting because it allows, at least theoretically, to avoid toxicity associated to cellular lysis through the specific block of the sole T-cells that have been stimulated to activation. No information still exists on the use of this medication in the pediatric age. A multicenter controlled trail is under way in JIA.

Rituximab

Rituximab is a humanized chimeric monoclonal antibody specific for the B-lymphocyte CD20 antigen. It is composed by the variable regions of a murine anti-human CD 20 B cell hybridoma fused to human IgG and κ constant regions [42]. Its administration produces a profound B lymphocyte depletion and its use is theoretically indicated in autoimmune diseases in which there is a pathogenetic autoantibody production, namely SLE. However, this drug doesn't seem to be completely adequate to decrease autoantibody generation because plasma cells, which are the main producers, do not express CD20 antigen. It has been hypothesized that the clinical improvement caused by rituximab in immune-mediated diseases is more related to the inhibition of others immunologic functions of B cells potentially implicated in the pathogenic process, such as the ability of behaving as antigen presenting cells, of producing cytokines and of stimulating T cells activation [43]. The mechanisms through which

rituximab destroys target cells is not clear, but it may involve antibody-dependent cytotoxicity, complement-mediated lysis, or apoptosis.

There are reports of the efficacy of this medication, either as monotherapy or in combination with immunosuppressive drugs, in patients with juvenile SLE who had severe clinical manifestations which were refractory to corticosteroids or conventional immunosuppressive treatments. These manifestations include autoimmune hemolytic anemia, thrombocytopenia, proliferative nephritis, and central nervous system involvement (isolated or associated with the presence of antiphospholipid antibodies) [44-46].

Although rituximab has generally been well tolerated in the few treated cases, it may produce a number of side effects, such as infusion reactions, hypogammaglobulinemia, anti-chimerical antibodies, and increased susceptibility to infection. Furthermore, although there is evidence that it may not affect the protective antibody levels induced by prior vaccination, presumably due to the lack of effects on long-lived plasma cells [47], there is the concern that children receiving treatment may not mount an effective response to vaccinations.

Anecdotal reports in refractory juvenile SLE and recent clinical trials in adult patients with proliferative lupus nephritis [48] suggest that rituximab may have an attractive safety and efficacy profile and may be associated with less risk than current regimens with cyclophosphamide, which may have a superior potential of impairing defenses from infection and is responsible for a significant risk of ovarian failure. However, further investigations in larger number of patients are required to support this hypothesis.

Conclusion

The introduction of biologic agents has led to a dramatic change in the approach to the treatment of childhood rheumatic diseases. For the first time, clinicians may target specific aspects of the pathologic process that produces the disease. It should be kept in mind, however, that, at the present time, these medications do not represent an alternative to the traditional anti-rheumatic drugs and that their use should be considered only in patients with the most severe and refractory forms, who are at risk of developing sustained active disease with impairment of quality of life, irreversible organ damage, or unacceptable drug toxicity [49]. The challenge for the next future will be to conduct trials and accumulate clinical information that will help to establish which patients are most likely to benefit from these treatments and when in the course of

disease these therapies should be introduced in order to achieve a right balance among efficacy, toxicity, and cost. Furthermore, data in larger number of patients treated for sufficiently protracted periods are needed to define the long-term safety of biologic therapies in childhood.

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Figure legends

Figure 1. Role of tumor necrosis factor (TNF)- α in the pathogenesis of chronic arthritis.