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REVIEW

Biologics in children's autoimmune disorders: efficacy and safety

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Abstract Advances in understanding the pathogenesis of rheumatic diseases have led to the discovery of mechanisms of inflammation and autoimmunity and have made possible the invention of new target-specific drugs. Biologic drugs, designed to inhibit specific components of the immune system, such as cytokines, cytokine gene expression, and their complex interactions, have revolutionized the treatment options in pediatric rheumatology. Only three agents are currently available for treating juvenile idiopathic arthritis (JIA): etanercept, at the dose of 0.8 mg/kg once weekly, adalimumab at the dose of 24 mg/m^2 every 2 weeks, and abatacept at the dose of 10 mg/kg at weeks 0, 2, 4, and then every 4 weeks. They are well tolerated and relatively safe in children: Side effects are generally mild and include injection site reactions and infections. Infliximab, rilonacept, and canakinumab are also approved by the Food and Drug Administration for treatment of pediatric autoimmune disorders and are currently investigated in JIA. This review summarizes the current state of biologic drugs, their clinical application, and their efficacy and safety in the pediatric age.

Keywords Biologic drugs · Pediatric rheumatology · Efficacy · Safety · Juvenile idiopathic arthritis

Abbreviations

ACR	American College of Rheumatology
ANCA	Anti-neutrophil cytoplasmic antibodies
CAPS	Cryopirin-associated periodic syndrome
CD	Crohn's disease
CINCA	Chronic infantile neurological cutaneous and articular syndrome
CRP	C-reactive protein
CTLA4	Cytotoxic T-cell-associated antigen 4
DMARDs	Disease-modifying anti-rheumatic drugs
ELISA	Enzyme-linked immunosorbent assay
EMEA	European Medicines Agency
ERA	Enthesitis-related arthritis
ESR	Erythrocyte sedimentation rate
FCAS	Familial cold-induced autoinflammatory syndrome
FDA	Food and Drug Administration
FMF	Familial Mediterranean fever
HACAs	Human anti-chimeric antibodies
HSTL	Hepatosplenic T-cell lymphoma
IBD	Inflammatory bowel disease
IL-10	Interleukin 10
IL-18	Interleukin 18
IL-1ra	Interleukin 1 receptor antagonist
IL-6	Interleukin 6
IVIG	Intravenous immunoglobulin
JIA	Juvenile idiopathic arthritis
LT-α	Lymphotoxin alpha
MTX	Methotrexate
MWS	Muckle–Wells syndrome
NICE	National Institute for Health and Clinical Excellence
NOMID	Neonatal onset multisystemic inflammatory disease
PGE2	Prostaglandin E2
RA	Rheumatoid arthritis
soJIA	Systemic onset juvenile idiopathic arthritis
TB	Tuberculosis
TNF-α	Tumor necrosis factor alpha

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TRAPS	Tumor necrosis factor receptor-associated periodic syndrome
UC	Ulcerative colitis

Introduction

Since the 1990s, advances in the understanding of the immune system and its mechanisms involved in inflammation provided new targets for the treatment of rheumatic diseases. A major step forward in the treatment of adult rheumatoid arthritis (RA) and juvenile idiopathic arthritis (JIA) was the introduction of biologic drugs.

Biologics are genetically engineered drugs targeting specific sites of the inflammatory cascade such as cytokines, cell surface molecules, and adhesion molecules [39].

The biologic therapies that are currently available are divided into those that target cell surface molecules and those interacting with circulating molecules. Cell surface molecules can serve as markers for specific cells and can be targeted and deleted by a monoclonal antibody, the first class of biologics [39]. The first antibodies available were murine proteins produced from murine "hybridomas" but with the limitation of their immunogenicity. The next step in antibodies engineering was the production of humanized antibodies with a consequent reduction of immunogenicity [40]. Lately, various "fully human" antibodies have been developed (Table 1).

The second class of molecules interferes with cytokines. Cytokines, the soluble mediators of inflammation, bind to cell surface receptors. They may be divided in proinflammatory ones, such as tumor necrosis factor alpha (TNF-α) and interleukin-6 (IL-6), and anti-inflammatory, such as interleukin-10 and interleukin-1 receptor antagonist (IL-1ra). Most biologics bind to the soluble cytokines or prevent their binding to specific receptors [30]: They are fusion proteins, with the extracellular domain of a cell surface receptor fused to the C region of an IgG1 in order to create a soluble form of the receptor [39].

In recent years, the application of biologic has expanded to a great number of pediatric autoimmune diseases. Moreover, a limitation of biologic therapies is that the response to treatment is not predictable, and it is not yet known how to identify patients who will effectively respond. Besides, careful safety monitoring is necessary due to the risk of infections, anaphylactic reactions, possible neurologic side effects, and low response to vaccinations.

In April 2009, the Food and Drugs Administration (FDA) published an important warning on TNF-α blockers' safety profile. During recent years, many cases of lymphoma and other cancers have been reported both in adult and children. About 48 reports of malignancies have been identified in children and adolescents of which approximately half were lymphomas, including Hodgkin's and non-Hodgkin's lymphoma. Among the 48 cases, there were 11 deaths. A higher rate of malignancy was reported in patients treated with infliximab and etanercept. No official data are available for adalimumab because of its minimal use in pediatric patients. The majority of these patients (88%) were also using other immunosuppressive drugs such as azathioprine and methotrexate (MTX).

This article will review the clinical applications of biologic drugs in children and discuss what is currently known about factors associated with clinical response and the safety in pediatric age.

Anti-tumor necrosis factor alpha agents

Knowledge of the role of TNF-α in inflammation, its overproduction in murine models of inflammation and in serum and synovial fluid in arthritis, has permitted the successful use of anti-TNF-α therapy: Anti-TNF-α agents have been used in pediatric rheumatology since 1990s and have radically changed the outcome of several diseases, especially in children with JIA who failed to respond adequately to MTX or have been unable to tolerate it due to adverse side effects; anti-TNF-α drugs are also helpful in other autoimmune diseases like uveitis, Crohn's disease (CD), sarcoidosis, ophthalmologic manifestations of Behçet disease, and anti-neutrophil cytoplasmic antibodies (ANCA)-associated vasculitis [41, 61, 72]. Three anti-TNF-α agents are currently approved for the use in the pediatric age: etanercept, infliximab, and adalimumab.

Treatment with TNF-α antagonists has been recognized as a risk factor for active tuberculosis (TB); some cases of latent TB could reactivate soon after treatment initiation. For this reason, worldwide health authorities recommend screening patients for latent TB and treating them before initiating anti-TNF-α treatment [18]. The mechanism by which the anti-TNF-α treatment reactivates latent TB is not fully understood: In animal models, TNF-α plays a central role in mediating mycobacterial infections, and soluble membrane-bound TNF-α is essential in protecting from TB infection [68].

A major problem with anti-TNF-α drugs is immunogenicity, depending mainly on their constitution. Chimeric drugs containing murine particles could induce antibodies against the drug (human anti-chimeric antibodies (HACAs). As a consequence, a reduction in effectiveness of long-term treatment or the induction of allergic reactions is registered [1]. Infliximab has been the most studied regarding immunogenicity, which can be significantly reduced by the association with immunosuppressive drugs, the most important being MTX [1]. Anti-etanercept antibodies have been demonstrated both in treated adults and children, but they do not interfere with the drug action and its safety profile [1]. On

Table 1 Biologic therapeutics in use or in development for use in juvenile idiopathic arthritis (JIA; modified from Hayward et al. [33] and Isaacs [39])

Drug	mAb category	Target	Therapeutic dose
Etanercept (Enbrel®)	Fusion proteins Suffix: -cept	TNFα	0.8 mg/kg/dose once weekly, maximum 50 mg/dose Subcutaneous injection
Infliximab (Remicade®)	Chimeric Suffix: -ximab	TNFα	6–10 mg/kg/dose once weeks 0, 2, 6 and then every 4 to 8 weeks Intravenous infusion
Adalimumab (Humira®)	"Fully human" Suffix: -mumab	TNFα	24 mg/m^2 every 2 weeks, maximum 40 mg/dose Subcutaneous injection
Anakinra (Kineret®)	"Fully human" receptor antagonist Suffix: -ra	IL-1 receptor	1 to 2 mg/kg/day, maximum 100 mg/dose Subcutaneous injection
Rilonacet (Arkalist®)	Fusion proteins Suffix: -cept	IL-1	2.2.–4.4 mg/kg once weekly Subcutaneous injection
Abatacept (Orencia®)	Fusion proteins Suffix: -cept	Cytotoxic T-lymphocyte-associated antigen 4 (CTLA4 Ig)	10 mg/kg weeks 0, 2, 4, and then every 4 weeks, maximum 1,000 mg/dose Intravenous infusion
Rituximab (Rituxan®)	Chimeric Suffix: -ximab	CD20	750 mg/m^2; two doses 2 weeks apart or 375 mg/m^2; 4 doses, weekly per 4, maximum 1,000 mg/dose Intravenous infusion
Tocilizumab (RoActemra®)	Humanized Suffix:-zumab	IL-6	8–12 mg/kg every 2 weeks Intravenous infusion
Canakinumab (Ilaris®)	"Fully human" Suffix:-umab	IL-1β	2 mg/kg/dose every 8 weeks Intravenous infusion or subcutaneous injection

the contrary, the completely human composition of adalimumab makes it less immunogenic [1]. Side effects and contraindications for the use of anti-TNF-α are summarized in Table 2.

Etanercept (Enbrel®)

The TNF-α inhibitor etanercept (Enbrel®) is a genetically engineered fusion protein consisting of two identical chains of the recombinant extracellular human TNF-receptor p75 monomer fused with the Fc domain of a human IgG1. Etanercept effectively binds both TNF-α and lymphotoxin alpha and inhibits their activity [12]. It is given by subcutaneous injection at a dose of 0.4 mg/kg twice weekly or 0.8 mg/kg once weekly [35]; it is licensed and recommended by the FDA in the USA in children over 2 years. The National Institute for Health and Clinical Excellence in the UK and the European Medicines Agency of the EU approved etanercept in children over 4 years with polyarticular JIA unresponsive or intolerant to MTX (Table 3) [70]. The efficacy of this drug was demonstrated for the first time on 69 children with polyarticular JIA, refractory or intolerant to MTX, in a double-blind, placebo-controlled trial by Lovell and colleagues [51]. Subsequent studies have shown long-term safety and efficacy of etanercept up to 8 years of continuous treatment in patients with polyarticular course JIA [25, 53]. Unfortunately, these results are not applicable to all JIA sub-types; in particular, children with systemic onset JIA (soJIA) do not respond to etanercept.

Etanercept has also been shown to be effective in juvenile spondyloarthropathy, enthesitis related arthritis (ERA), psoriatic arthritis, and extended oligoarthritis, but today's data are limited. [7, 13, 62, 88].

Table 2 Side effects and contraindications for the use of anti-TNF-alpha

Major adverse effects	Contraindications for the use
Injection site reaction	Absolute
Infusion reaction	Active infections
Infections (varicella)	History of recurrent or chronic infections
Reactivation of a latent infection	Previous and untreated TB
Demyelinating disease	Multiple sclerosis or optic neuritis
Neuropsychiatric side effects as fatigue, headaches, vertigo, depression, pain amplification syndromes, anxiety.	Combination treatment with anakinra (IL-1 receptor antagonist)
Heart failure	Active or recent history of malignancy (past 10 years), except for skin cancer
Malignancy	Relative
Immunogenicity	Pregnancy
	Lactation
	HIV, HBV, and HCV infections

Chronic uveitis occurs in up to 30% of JIA patients, particularly in those with oligoarticular or seronegative polyarticular subsets [82]. It has been showed that blocking TNF-α inhibits autoimmune uveitis in experimental animal models [17]. Until recent years, JIA-associated uveitis unresponsive to corticosteroid therapy was commonly treated with MTX, and some authors have reported a 59% success rate of MTX as monotherapy in JIA-associated uveitis [81]. To date, there have been no published controlled studies of etanercept for JIA-associated uveitis, and there are limited controlled data about the use of TNF inhibitors in the treatment of uveitis [82, 85]. In a small double-blind, placebo-controlled study, there was no apparent difference in the anterior segment inflammation between patients treated with etanercept or placebo [85]. On the contrary, Reiff and co-workers prospectively evaluated ten patients with pauciarticular JIA-associated uveitis and found successful treatment with etanercept, but they did not include a control group. Besides, seven of ten of those children did not achieve complete treatment response [74]. Other studies did not report significant efficacy of etanercept in JIA uveitis [21]. It must be stated that these studies were limited by the small size of study population.

Etanercept is the only anti-TNF-α licensed in children, and this reason, together with a good long-term efficacy and safety profile, make it the first choice among biologics in children with JIA [70].

Side effects of etanercept are generally mild and include injection site reactions, headaches, upper respiratory infections of mild to moderate severity, urticarial reactions, and gastrointestinal symptoms [31, 36]. With long-term use of anti-TNF agents in adults, there have been reports of increased serious infections, lymphoma, and demyelinating disorders [61]. A few cases of malignancy are reported in children treated with etanercept: Long-term data suggest that there is no increase in incidence of tumors, but the risk of malignancy in children remains undefined. On literature review, three reports of deaths in patients with JIA on etanercept could be identified [70].

Moreover, it is recommended that patients do not receive live vaccines during treatment; they should promptly interrupt treatment in case of exposure to viruses and bacteria [52]. Currently, no guidelines are available about when and how to stop etanercept in JIA patients who achieved a good clinical response. Prospective, multicenter observational studies are needed to answer this question. Finally, etanercept has been recently well tested in 18 children with new-onset type 1 diabetes preserving β-cell function and improving glycemic control after a 24-week course [60].

Infliximab (Remicade®)

Infliximab is a chimeric human/murine monoclonal antibody directed against TNF-α [30]. It possesses a human IgG1 C region and murine V regions effective in binding TNF-α. Due to the murine fragment, infliximab retains immunogenicity and can cause anaphylaxis (fortunately rare), lack of efficacy, and infusion reactions [39]. Infliximab is given by intravenous infusion, at the dose of 3 to 6 mg/kg at 0, 2, and 6 weeks followed by maintenance every 8 weeks [23]. It has a longer half-life than etanercept, and it may yet have the effect of inducing TNF-α producing T cell through apoptosis [95].

Infliximab has been shown to be efficacious in children with juvenile ERA and in the management of refractory JIA uveitis: It appears more effective than etanercept for JIA-associated uveitis [61]. In JIA, studies reported improvement in pain, morning stiffness, reduction of fatigue, reduction in number of active joints, and reduction in C-reactive protein levels (52.6%) and in the erythrocyte sedimentation rate (42.3%) after the first infusion of infliximab. Besides,

Table 3 Comparative indications approved for pediatric use (in italics) by FDA and EMEA

Drug	FDA approvals	EMEA approvals
Etanercept (Enbrel®)	Rheumatoid arthritis	Rheumatoid arthritis
	Psoriatic arthritis	Psoriatic arthritis
	Ankylosing spondylitis	Ankylosing spondylitis
	Plaque psoriasis	Plaque psoriasis
	Polyarticular JIA (>4 years)	*Pediatric plaque psoriasis (>8 years)*
		Polyarticular JIA (>4 years)
Infliximab (Remicade®)	Rheumatoid arthritis	Rheumatoid arthritis
	Crohn's disease	Crohn's disease
	Psoriatic arthritis	Psoriatic arthritis
	Ankylosing spondylitis	Ankylosing spondylitis
	Plaque psoriasis	Plaque psoriasis
	Ulcerative colitis	Ulcerative colitis
	Pediatric Crohn's disease (>6 years)	*Pediatric Crohn's disease (>6 years)*
Adalimumab (Humira®)	Rheumatoid arthritis	Rheumatoid arthritis
	Psoriatic arthritis	Psoriatic arthritis
	Ankylosing spondylitis	Ankylosing spondylitis
	Crohn's disease	Crohn's disease
	Plaque psoriasis	Plaque psoriasis
	Polyarticular JIA (>4 years)	*Polyarticular JIA (13–17 years)*
Anakinra (Kineret®)	Rheumatoid arthritis	Rheumatoid arthritis
Rilonacept (Arkalist®)	CAPS (>12 years)	CAPS (>12 years)
Abatacept (Orencia®)	Rheumatoid arthritis	Rheumatoid arthritis
	Polyarticular JIA (>6 years)	Polyarticular JIA (>6 years)
Rituximab (MabThera®)	Rheumatoid arthritis	Rheumatoid arthritis
	Non-Hodgkin's Lymphoma	Non- Hodgkin's Lymphoma
	Chronic lymphocytic leukemia	Chronic lymphocytic leukemia
Tocilizumab (RoActemra®)	Rheumatoid arthritis	Rheumatoid arthritis
Canakinumab (Ilaris®)	*CAPS (>4 years)*	*CAPS (>4 years)*

infliximab plus MTX seem to be highly effective and safe in short and medium term (2 weeks–12 months) and more efficacious than MTX alone at conventional or higher dosages with one or more other conventional disease-modifying anti-rheumatic drugs (DMARDs) [27].

In a randomized placebo-controlled trial, infliximab proved to be a beneficial option for the treatment of 122 children with polyarticular JIA resistant to previous therapies; besides, patients treated with infliximab at the dose of 3 mg/kg exhibited rapid improvement, but the safety profile was less favorable in comparison with the dose of 6 mg/kg dose [77, 78]. The authors concluded that both infliximab 3 and 6 mg/kg, in combination with MTX, are effective in joint symptoms of JIA, but the 3 mg/kg dose registered higher serious adverse events, such as infusion reactions and the production of antibodies against infliximab [77]. In the open-label extension of this trial, the authors confirmed safety and efficacy but reported a high discontinuation rate in a period of 4 years of follow-up. Furthermore, infliximab seems to be more effective than etanercept in JIA-associated uveitis [91].

Infliximab is also approved for the use in pediatric CD [30] as it has been demonstrated to induce clinical remission in patients with active luminal inflammatory CD in several studies [11]. It is also effective in patients with abdominal or perianal fistulas, although pediatric studies on the use of anti-TNF-α in inflammatory bowel diseases are limited, and the long-term outcome and safety have not yet been established. In a retrospective study of 30 children with CD treated with infliximab and followed for a mean of 2 years, there was evidence that some continued to maintain the response achieved over a long period of time [16]. In recent years, an alarming side effect was reported in eight adolescents and young adults with inflammatory bowel disease (IBD), mainly CD, who developed, after a few years of treatment with infliximab, a hepatosplenic T-cell lymphoma (HSTL). However, all the IBD cases with HSTL had a long-term combination of infliximab with other

immunomodulators; no cases of HSTL have been reported in infliximab-treated-patients with other autoimmune disorders [11]. Trials have also shown that infliximab can induce and maintain remission in patients with moderate and severe active ulcerative colitis (UC) [80]. Furthermore, emerging data suggest efficacy of infliximab for the treatment of children with Kawasaki disease resistant to intravenous immunoglobulin [6]. Infliximab has been proven to be well tolerated in children. About 40% of treated patients can develop mild adverse effects, the most frequent being upper respiratory infections, which does not require the discontinuation of treatment; such data suggest a need to promptly survey treated patients in order to prevent severe infections. Serious infusion reactions are reported in about 2.6% of children, the majority occurring in HACAs-positive patients [78].

Adalimumab (Humira®)

Adalimumab is a fully human IgG monoclonal anti-TNF-α antibody [54]. It offers a higher binding activity, a role in cell lysis and in apoptosis, and a less immunogenic effect based on its fully humanized structure. This latter property avoids the need of concomitant MTX administration [42, 61].

Adalimumab is licensed for the use in RA, ankylosing spondilitis, psoriatic arthritis, and severe CD [84]. The dose is 24 mg/m^2 (maximum dose 40 mg), given subcutaneously every other week [59, 87]. Preliminary data from a randomized placebo-controlled trial of 171 children with polyarticular JIA aged 4–17 years demonstrated a rapid beneficial effect of adalimumab with a reassuring safety profile over a 1-year period [55]. In a more recent controlled trial, Lovell et al. showed that adalimumab, administered with or without MTX, improved signs and symptoms of disease in children with polyarticular course JIA, and the higher responses were among children receiving adalimumab in combination with MTX [54].

Adalimumab has been investigated also for the treatment of JIA-associated uveitis. Tynjälä et al. retrospectively observed 20 JIA children with chronic uveitis under adalimumab treatment; the authors found improvements of ocular inflammation in 35% of patients during the period of observation, especially in those with shorter disease duration and of a younger age [90]. No data are currently available about the treatment of Behçet disease-associated uveitis in children; only a few cases are recorded among the adult population.

Based on the data of trials, in February 2008 the US FDA approved adalimumab for the treatment of active polyarticular JIA in children 4 years of age and above [33, 37].

Adalimumab does not require laboratory monitoring, and the most common side effects are injection site reactions and mild upper respiratory tract infections [55]. Like other anti-TNF agents, it increases the risk of infections, requiring TB screening before starting therapy [89].

IL-1 antagonists

IL-1 is a proinflammatory cytokine secreted by monocytes and macrophages. It activates antigen-presenting cells and CD4+ lymphocytes and promotes lymphocyte differentiation; it increases prostaglandin E2, collagenases, and neutral proteinases production [2, 83]. This cytokine plays a critical role in the maintenance of chronic inflammation. In JIA, Martini et al. and Madson et al. demonstrated an increased production of IL-1 by peripheral blood monocytes and synovial fluid monocytes, respectively [46, 56, 58, 71].

IL-1 receptors are found in bone marrow, endothelium, hypothalamus, and many other cells. Natural IL-1ra is produced by macrophages and blocks the biological functions of IL-1; this mechanism was used to produce the recombinant IL-1ra biologic agent anakinra that competitively binds to both type I and type II IL-1 receptors [3, 33, 84]. IL-1 blocking therapy is currently in use in children with JIA, while several other IL-1 blocking agents are under development [33]. It is particularly useful for the treatment of cryopyrin-associated periodic syndrome (CAPS), a rare disorder characterized by overproduction of IL-1.

Anakinra (Kineret®)

Anakinra is a fully human IL-1ra, licensed in 2001 by FDA for the treatment of adults affected by RA [33, 83, 84]. It competitively binds to the IL-1 receptor, thus blocking endogenous IL-1 signaling [33]. Anakinra is a short-acting agent that requires daily subcutaneous administration at the dose of 1–2 mg/kg, maximum 100 mg/dose [33, 93].

It can be combined with MTX or other DMARDs, and it seems to be clinically and radiologically effective.

A randomized, placebo-controlled trial of anakinra (1 mg/kg/day, maximum 100 mg) in 50 children with JIA suggested a better efficacy in soJIA. IL-1 seems to be the major mediator of inflammation in soJIA, particularly fever, providing a rationale for an IL-1 blocking therapy [32, 38]. Lequerrè et al. enrolled 35 patients with soJIA and adult-onset Still disease on anakinra: Steroid dosage was reduced or stopped, but less than half of soJIA achieved a sustained improvement of laboratory and clinical features [49].

Gattorno et al. selected and treated with anakinra 22 soJIA children, unresponsive to a long-term corticosteroid therapy, mostly in association with a second-line agent. The authors proposed that soJIA can be divided into two different subgroups according to the clinical and laboratory response to anakinra and marked by different outcome: The first group

responded strongly within a few weeks of treatment; the second exhibited incomplete or no response. The greater response was associated with a lower number of involved joint and a higher neutrophil count, while in vitro IL-1β and IL-18 secretion by monocytes were not in accordance with the treatment outcome [25].

The identification of the molecular basis of Muckle–Wells syndrome (MWS), familial cold-induced autoinflammatory syndrome (FCAS), and neonatal onset multisystemic inflammatory disease/chronic infantile neurological cutaneous and articular syndrome (NOMID/CINCA), also known as CAPS, supported evidence for the role of IL-1β in the pathogenesis of these group of diseases. As a consequence, IL-1β blockade is an option for treatment of these syndromes [9, 22, 28, 29, 50].

Neven et al. followed up for 26–42 months ten patients, aged 3 months–20 years, with NOMID/CINCA syndrome treated with anakinra: Data suggested a remarkable long-term efficacy if the treatment was initiated as soon as possible, but it was difficult to achieve a complete resolution. In particular, there was a mild improvement in neurological involvement, hearing, and visual acuity, but mental retardation remained stable [64]. One of the largest studies by Goldbach-Mansky et al. reported a rapid response to anakinra in 18 children with NOMID/CINCA syndrome with improvement in magnetic resonance imaging neurologic lesions and disappearance of cutaneous lesions [28].

Gattorno et al. enrolled four children and one adult patient with tumor necrosis factor receptor-associated periodic syndrome (TRAPS) in a study: The response to anakinra treatment (1.5 mg/kg/day) was similar to that observed in other autoinflammatory diseases: Fever and other symptoms disappeared, but when anakinra was withdrawn, after a few days, patients experienced disease relapse. The authors concluded that anakinra provides a short- and long-term efficacy in TRAPS, controlling clinical and laboratoristic manifestations and preventing diseases relapses [24].

Several reports confirm the dramatic efficacy of anakinra in young children affected by other autoinflammatory syndromes, decreasing frequency of attacks and normalizing laboratory tests. It neutralizes attacks of Hyper-IgD syndrome and also improves symptoms and reduces the long-term risk of amyloidosis in familial Mediterranean fever (FMF) patients resistant to colchicine [65, 67, 75, 92].

Adverse reactions during anakinra therapy are neutropenia, nausea, diarrhea, cardiopulmonary arrest, influenza-like symptoms, production of anti-anakinra antibodies, and serious infections [83]. However, the most frequent and common side effects are injection site reaction with burning and pain and infections [83, 84]. There are also some case reports of visceral leishmaniasis, varicella, and osteonecrosis in soJIA patients treated with anakinra [37, 49].

Rilonacept (Arkalist®)

Rilonacept is an IL-1 blocking agent currently on trial for children with soJIA. Rilonacept is a recombinant fusion protein of IL-1 receptor protein components and the Fc portion of a human immunoglobulin. It is a longer IL-1α and IL-1β blocker and is administered once weekly by subcutaneous injection. Preliminary results of a controlled trial of rilonacept in soJIA were presented by Lovell and colleagues at the 2007 American College of Rheumatology (ACR) scientific meeting. The authors enrolled 21 children on rilonacept at 2.2–4.4 mg/kg/week with 10/21 (47%) patients achieving an ACR 70 response at 42 weeks [33].

In February 2008, after proven efficacy demonstrated by Hoffman et al., rilonacept was approved by the FDA for the treatment of the two CAPS disorders FCAS and MWS in adults and children aged 12 years and older [34]. Recent data indicate a beneficial effect of rilonacept in other inflammatory conditions including FMF and gouty arthritis [9].

Canakinumab (Ilaris®)

Canakinumab is a fully human anti-IL-1β monoclonal antibody that selectively blocks IL-1β and is administered by subcutaneous injection or intravenous infusion at the dose of 2 mg/kg every 8 weeks [47]. In a multicenter, randomized, double-blind, placebo-controlled trial, canakinumab showed rapid and sustained clinical efficacy in 45 patients, between the ages of 4–75 years with CAPS syndrome [47]. The drug was administered for a total of 48 weeks. The use of canakinumab was not associated with life-threatening adverse effects other than an increased rate of infections [47]. The prolonged duration of action and the low incidence of injection site reaction represent an advantage of this drug compared to rilonacept and anakinra in the treatment of CAPS syndrome.

This new biological agent is currently undergoing several international trials for use in CAPS syndrome, FMF, and JIA. Particularly, it is being investigated in two different randomized, double-blind, placebo-controlled withdrawal studies in children, aged 2–19, affected by soJIA: the first to evaluate the flare prevention and the second to assess the initial efficacy and safety in a single-dose at disease onset. Data are therefore expected to better evaluate the use of this drug in pediatric age.

IL-6 blockers

IL-6 is a proinflammatory cytokine syntetized by mononuclear cells, vascular endothelial cells, and fibroblasts in response to stimulation by IL-1 and TNF-α. It stimulates

B-cell growth, osteoclast activation, and hepatocyte synthesis of acute phase reactants [15]. IL-6 also plays an important role in the pathogenesis of anemia and growth failure of children with soJIA [15]. Furthermore, increased serum and synovial fluid levels of IL-6 have been found in children with soJIA and polyarticular JIA [14, 56]. For these reasons, the potential role for IL-6 as a therapeutic target was investigated both in adult RA patients and in children with JIA [94].

Tocilizumab (MRA, RoActemra®, Actemra®)

Tocilizumab is a recombinant, humanized monoclonal antibody that binds to the IL-6 receptor blocking the IL-6 signal transmission [97]. The clinical application of tocilizumab has been evaluated in a series of clinical trials in adult RA [57, 66]. In a double-blind, placebo-controlled trial, intravenous tocilizumab at 8 mg/kg every 2 weeks had an excellent and rapid effect in children with soJIA [96]. Currently, the long-term efficacy, tolerability, and safety in children under tocilizumab are still being observed. An international study of tocilizumab in polyarticular JIA (aged 2–17) is currently ongoing: It is a 24-week randomized double-blind, placebo-controlled trial with 16-week open-label lead-in phase and 64-week open-label follow-up. The estimated completion date of the study is on January 2014, and significant data are awaited. Common adverse events are mild gastrointestinal and upper respiratory tract infections [96]. Infusion reactions, an increase in serum cholesterol, and transient neutropenia have also been reported [63].

Abatacept (Orencia®)

During a normal immune response, activated T cells express a molecule named cytotoxic T-cell-associated antigen 4 (CTLA4), which binds to CD86 with higher affinity than CD28; this leads to the activation of cytotoxic T-cells [5]. Abatacept is a fully human soluble fusion protein consisting of the extracellular domain of the CTLA4 antigen and a fragment of Fc domain of IgG [37, 59]. Abatacept is given as intravenous infusion monthly at the dose of 10 mg/kg [69].

It is the first of a new class of biologic agents that block a cell activation signal from antigen-presenting cells to T-cells. It results in the depletion of T-cells, inhibition of their function, and activation of naive T cells and memory T cells [30, 43, 59]. The signal is mediated by CD80 and CD86, expressed on antigen-presenting cells, and by CD28 of T cells [43]. Abatacept has been studied in randomized clinical trials in adult patients with RA who had inadequate response to anti-TNF drugs or MTX; data indicate significant clinical benefits [26, 44]. Consequently, abatacept was approved by FDA in 2006 for moderate-to-severe RA refractory to other DMARDs [84]. More recently, Ruperto and colleagues reported clinical benefit in a randomized double-blind, placebo-controlled trial for JIA patients irrespective of the clinical subtype (excluding children with soJIA and active systemic manifestations in the previous 6 months) [79].

Following this trial, in April 2008, abatacept received FDA approval for treatment of severe polyarticular JIA in children aged 6 years or older, especially in moderate–severe cases refractory or with an inadequate response to other DMARDs or anti-TNF therapy [33, 84].

Infusion reactions such as nausea, headache, dizziness, hypotension, or hypersensitivity are generally mild [69]. Few serious adverse events were reported in the JIA trial including varicella, encephalitis, and hematoma, all completely resolved without sequelae [79]. Specific antibodies against entire abatacept molecule or CTLA-4 portion, measured by enzyme-linked immunosorbent assay, were frequently observed in patients on continuous therapy [45].

B-cell-targeted therapy

In recent years, a growing body of evidence suggested an important role of B lymphocytes in the pathogenesis of several autoimmune diseases: B cells are the precursors of immunoglobulin-secreting plasma cells and also produce cytokines that regulate the function of other cells.

Rituximab (Rituxan®, MabThera®)

Rituximab is a chimeric murine–human monoclonal antibody directed against CD20+ B cells: It selectively and profoundly depletes CD20+ B lymphocytes, inhibits cell growth, and induces apoptosis [76, 84]. It was approved in 1997 by FDA for the treatment of non-Hodgkin's B-cell lymphoma. In July 2006, rituximab was licensed in EU for the treatment of severe RA in monotherapy or in combination with MTX or cyclophosphamide [10, 19, 20, 48, 83]. Rituximab appears to be effective in autoimmune disorders and is given by intravenous infusion at different doses [8]. The most common protocol is 375 mg/m^2/week intravenously, for a total of four infusions; some patients need a second infusion cycle after a variable time [93].

Although the mechanism of this drug in arthritis is unclear, B-cell depletion seems to produce anti-inflammatory effects via decreased antigen presentation and disruption of T-cell costimulation [33].

There are no trials about the use of rituximab in JIA; only a few cases reported the use of this drug in children

[23, 33, 93]. However, studies about chronic autoimmune cytopenias in childhood have demonstrated general safety and tolerability in children [4, 73]. Recent findings have reported efficacy of rituximab in the treatment of refractory ANCA-associated vasculitis both in adults and children. Jones et al. retrospectively observed a 75% complete remission rate and 23% of partial remission among 65 patients aged 7–77 years, unresponsive to other immunosuppressants [41].

Adverse reactions are mild and generally include infusion reactions such as hypertension, hypotension, nausea and abdominal pain, pruritus, rash or urticaria, pyrexia, cough and bronchospasm, dyspnea, asthenia, muscle spasm, and anxiety [43, 93]. Infusion reactions decreased to 2% after the second infusion and may be further lessened by pretreatment with glucocorticoids or acetaminophen [43, 86, 93].

Other possible adverse events are infections and hypogammaglobulinemia; consequently, some authors recommend intravenous infusion of immunoglobulin 400 mg/monthly for at least 1 year after the treatment discontinuation [93].

Conclusions

Biologic drugs have changed the treatment of JIA and many other autoinflammatory syndromes in the pediatric age, producing significant clinical improvement as never previously observed. Furthermore, the application of biologic drugs in pediatric age is expanding. Until now, an important proportion of patients have not responded to standard treatment for children. So, in the future, the use of biologic treatment may be tailored to the patient's cytokine and genetic profile and to the type and severity of the disease. Nowadays, there is the need to better define which patients should be considered for a specific biologic treatment. The potential side effects and the possible new applications of these drugs represent a challenge for pediatric rheumatologists.

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