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Rolando Cimaz, Gabriella Maioli & Giulia Calabrese

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REVIEW

Current and emerging biologics for the treatment of juvenile idiopathic arthritis

Rolando Cimaz[a,b], Gabriella Maioli[c] and Giulia Calabrese[c]

[a]Pediatric Rheumatology Department, ASST-Gaetano Pini-CTO, Department of Clinical Sciences and Community Health, University of Milan, Milan, Italy; [b]Pediatric Rheumatology Department, ASST-Gaetano Pini-CTO, University of Milan, Milan, Italy; [c]University of Milan, Milan, Italy

ABSTRACT

Introduction: The management of a child with juvenile idiopathic arthritis (JIA) requires a combination of pharmacological, physical, and psychosocial therapies in order to induce disease remission, by controlling articular and systemic inflammation. This review aims to provide a comprehensive discussion on the biological therapies currently in use in the treatment of JIA referring to existing recommendations and clinical evidence. We also discuss on the emerging biological drugs actually under consideration.

Areas covered: Recent findings on immunological mechanisms involved in the pathogenesis of the disease allowed us to identify several specific targets for biologic therapies. A systematic literature review was conducted between January 1997 and January 2020 on PubMed including national and international guidelines and recommendations, trials and case–control studies.

Expert opinion: There is now a plethora of therapies that are directed against variable targets, and the physician has to choose the most appropriate available medication in order to achieve early and sustained remission with as few side effects as possible. Research is advancing very fast in order to be more and more specific in suppressing inflammatory pathways without harming natural defenses. Finally, pharmacoeconomic considerations will also be very important to deal with, considering the high cost of most of these molecules.

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Juvenile idiopathic arthritis; pediatric rheumatology; biologic therapy; clinical evidence

1. Introduction

1.1. Juvenile idiopathic arthritis

Juvenile idiopathic arthritis (JIA) is defined as arthritis of unknown etiology that affects children before the 16th birthday and persists for at least 6 weeks, with other known conditions excluded. This term encompasses several disease categories, each of which has distinct clinical manifestations, genetic background, and etiopathogenesis. The International League of Associations for Rheumatology (ILAR) recognizes seven main categories, on the basis of the clinical and laboratory features present in the first 6 months of illness: oligoarthritis (oJIA), rheumatoid factor (RF)-negative polyarthritis, RF-positive polyarthritis, juvenile psoriatic arthritis (JPsA), systemic JIA (sJIA), enthesitis-related arthritis (ERA), and undifferentiated arthritis [1]. This classification has been subject to several criticisms so that a proposal for a new classification of JIA has been recently discussed [2].

A systematic literature review was conducted between January 1997 and January 2020 on PubMed including national and international guidelines and recommendations, randomized controlled trials, controlled trials, nonrandomized prospective studies, case–control and cohort studies. We also searched for previously published meta-analyses and systematic literature reviews.

1.2. Treatment principles for the management of JIA

The optimal approach to the management of a child with JIA requires a combination of pharmacological, physical, and psychosocial therapies aiming to induce disease remission and preserve daily functioning, by controlling articular and systemic inflammation. Inactive disease achievement could be considered as a minimal treatment goal.

Nonsteroidal anti–inflammatory drugs (NSAIDs) and intra-articular corticosteroid (IAC) injections are the mainstay of the treatment for JIA patients with oligoarticular involvement. Systemic corticosteroids administration is mainly restricted to sJIA, particulary to manage the extra-articular manifestations (severe anemia, myocarditis, sierositis, and macrophage activation syndrome). Among disease-modifying anti-rheumatic drugs (DMARDs) methotrexate is used in patients with oJIA featuring high disease activity and poor prognostic factors, whereas it is the first-line treatment in patients with polyarticular JIA [3]. In case of MTX intolerance leflunomide is an alternative option but it is not approved for JIA and is rarely used as a switch to a biologic agent is preferred [4]. Sulfasalazine may be considered in patients affected by ERA, with relatively limited efficacy, mostly on peripheral arthritis than on axial disease and enthesitis [5,6].

The increasing knowledge about physiopathological mechanisms of the disease led to the development of drugs that target specific cytokines or cellular interactions, interfering with the activation and regulation of the immune system. According to specific subtypes in JIA, several different immunopathological mechanisms are implicated and, therefore, different biologics are variably effective on specific categories of patients [7].

CONTACT Rolando Cimaz rolando.cimaz@unimi.it Pediatric Rheumatology Department, ASST-Gaetano Pini-CTO, Department of Clinical Sciences and Community Health, University of Milan, via Gaetano Pini n.9, Milan 20122, Italy

Article highlights

- Biologic therapy, by targeting specific cytokines or cellular interactions, interferes with the activation and regulation of the immune system.
- Since these drugs have been introduced in clinical practice the prognosis for children with JIA has dramatically improved.
- Variable clinical responses have been observed to specific biological drugs among different JIA subtypes.
- Evidence for new agents are promising; these review describes recent and ongoing clinical trials on emerging biologic drugs and small molecules available.
- In clinical practice pharmacoeconomic aspects have to be considered; biosimilars are also an effective option to increase access to biologic treatment in patients with JIA worldwide.

Since these new therapies are available, an important improvement in outcome has been observed in the past two decades, and a pronounced reduction of functional disability has been registered [8].

2. Biologic drugs

2.1. Overview

The American College of Rheumatology (ACR) recommendations suggest that patients that fail to respond to, or are intolerant to, DMARDs are candidates for biologic therapy. These guidelines have been recently updated and, according to these new recommendations, biologic therapy may be considered as initial therapy for patients with risk factors (positive anti–cyclic citrullinated peptide antibodies, or joint damage) and involvement of high-risk joints (e.g. cervical spine, wrist, or hip), high disease activity, and/or those at high risk of disabling joint damage [9]. This actually represents a topic of debate since previous studies were not conclusive enough to support biologics as initial therapy, but currently, ongoing studies may allow to clarify which patients are most likely to benefit from initial biologic therapy [10–12].

The biological drugs that are currently used for JIA are represented by monoclonal antibodies and recombinant proteins that block cytokine receptors, or neutralize cytokine activity, or modulate lymphocyte functioning (Table 1).

Increased knowledge on JIA pathogenesis has highlighted the pivotal role of tumor necrosis factor α (TNF-α), interleukin-6 (IL-6) and interleukin-17 (IL-17) as proinflammatory cytokines. TNF-α induces up-regulation of other cytokines, chemokines and endothelial adhesion molecules, and inhibits regulatory T cell function. IL-6 is an inflammatory cytokine that contributes to synovial inflammation inducing acute phase reactants release and an imbalance between Th17 and regulatory T cells [13,14].

Based on the JIA categories, variable clinical responses have been observed to specific biological drugs, even among patients belonging to the same clinical category. These differences could be due to pharmacological aspects, genetic polymorphisms, and epigenetic factors affecting the expression of cytokine genes [15].

2.2. Currently used biologic drugs

2.2.1. Anti-TNF-α

According to ACR recommendations, TNF-α inhibitors should be used for patients with oligoarticular and polyarticular JIA (pJIA) who have received MTX for 3 months at the maximum tolerated dose and have moderate or high disease activity, or after 6 months of methotrexate administration with low disease activity [3].

Anti TNF-α agents are also recommended after 3 months of MTX without adequate improvement or for patients with axial involvement who failed to respond to NSAIDs.

Etanercept and adalimumab are the only anti-TNF-α licensed for JIA by the Food and Drug Administration (FDA) and the European Medicines Agency (EMA). Golimumab has recently been approved for polyarticular JIA by the EMA.

2.2.1.1. Etanercept

2.2.1.1.1. Pharmacodynamic and pharmacokinetic properties. Etanercept (ETN) is a dimeric protein composed of the Fc region of human immunoglobulin IgG fused with the human p75 TNF receptor that binds to circulating TNF-α, preventing its interaction with cell surface receptors and subsequent activation of the inflammatory cascade. ETN is administered subcutaneously, reaching the highest concentration 48 h after a single dose. ETN half-life is approximately 70 h. The usual dose is 0.4 mg/kg twice a week (max 25 mg) with an interval of 3– 4 days between doses, or 0.8 mg/kg (max 50 mg) given once a week.

2.2.1.1.2. Clinical indications in JIA. Etanercept is the first biologic agent approved for children older than 2 years with moderate to severe polyarticular JIA (RF positive or negative) and extended oJIA who have had an inadequate response to, or who have proved intolerant to MTX. In Europe, the indication was extended to adolescents (aged more than 12 years old) affected by JPsA and ERA, who have had an inadequate response to, or who have proven intolerant to conventional therapy.

2.2.1.1.3. Clinical evidence of efficacy. A randomized, placebo-controlled withdrawal trial proved ETN efficacy and safety in patients with a polyarticular disease course refractory or intolerant to DMARDs [16]. Several extension studies have subsequently confirmed its long-term efficacy and adequate safety profile [17–19].

In an open, non-randomized German study, the combined therapy of etanercept and MTX showed better results than etanercept monotherapy. The response rate was assessed according to the ACR Pedi criteria. After 12 months, 376 patients treated with combined therapy and 55 patients treated with etanercept alone had ACR Pedi 30/50/70% responses of 81/74/62% and 70/63/45%, respectively, [20,21].

Etanercept has also proven to be effective in arthritis and enthesitis as well as in bone erosion prevention both in ERA and PsJIA patients [22,23].

ETN, and in general TNF-α antagonists are not recommended as first-line treatment for sJIA; however, in this JIA subtype, ETN can represent an additional therapeutic option in patients who do not respond to IL-1 or IL- 6 antagonists, acting as a valid corticosteroid-sparing agent, especially in

Table 1. Currently available biologic drugs for JIA.

Biologic (originator)	Biosimilar	Pediatric indication	Mechanism of Action	Route	Dosing	Half-life
Etanercept (Enbrel)	Benepali Erelzi Eticovo[a]	pJIA (≥2 yrs) JPsA (≥12 yrs) ERA (≥12 yrs) PsO (≥ 4 yrs)	Binding to TNF-α	s.c.	0.4 mg/kg/twice a week or 0.8 mg/kg/ week	70 hours
Infliximab (Remicade)	Flixabi Inflectra Ixifi[a] Remsima Renflexis[a] Zessly	JIA-related uveitis (off label) pJIA (off-label) CD (≥6 yrs) UC (≥6 yrs)	Binding to soluble and membrane-bound TNF-α	I.V.	5–10 mg/kg at 0, 2, 6 weeks and then every 4–8 weeks	7.5– 9.5 days
Adalimumab (Humira)	Amgevita Amjevita[a] Cyltezo Hadlima[a] Hyrimoz Hulio Idacio Imraldi	pJIA (≥2 yrs) ERA (≥6 yrs) Uveitis (>2 yrs) CD (≥6 yrs) HS (≥12 yrs)	Binding to soluble and membrane-bound TNF-α	s.c.	20 mg every 2 weeks (<30 kg); 40 mg every 2 weeks (>30 kg)	10 – 20 days
Golimumab (Simponi)	N.A.	pJIA (≥2 yrs)	Binding to soluble and membrane-bound TNF-α	s.c.	30 mg/m2 every 4 weeks (<40 kg); 50 mg every 4 weeks (>40 kg)	9 – 15 days
Certolizumab pegol (Cimzia)	N.A.	pJIA (PASCAL trial on going)	Binding to soluble and membrane-bound TNF-α	s.c.	NA	14 days
Tocilizumab (RoActemra)	LusiNEX (ongoing trial) BAT 1806 (ongoing trial)	sJIA (≥ 2 yrs) pJIA (≥2 yrs)	Binding to soluble and membrane-bound IL-6R	I.V. s.c.	sJIA I.V.: 8 mg/kg every 2 weeks (≥30 kg); 12 mg/kg every 2 weeks (<30 kg). sJIA s.c.: 162 mg/week (≥30 kg); 162 mg every 2 weeks (<30 kg). pJIA I.V.: 8 mg/kg every 4 weeks (≥30 kg); 10 mg/kg every 4 weeks (<30 kg). pJIA s.c.: 162 mg every 2 weeks (≥30 kg); 162 mg every 3 weeks (<30 kg).	23 days (sJIA) 16 days (pJIA)
Anakinra (Kineret)	-	sJIA (≥ 8 months and ≥ 10 kg) – only approved by EMA, not approved by FDA. CAPS	Binding to IL-1Rα	s.c.	1–2 mg/kg/day (<50 kg); 100 mg/day (≥50 kg).	4–6 hours
Canakinumab (Ilaris)	N.A.	sJIA (≥2 yrs) CAPS (≥4 yrs) TRAPS HIDS/MKD FMF	Binding to IL-1β	s.c.	4 mg/kg every 4 weeks (up to a maximum of 300 mg)	22–25 days
Abatacept (Orencia)	N.A.	pJIA (≥ 2 yrs)	Inhibits costimulatory signal by binding to CD80/CD86	I.V. (≥ 6 yrs) s.c. (≥ 2 yrs)	I.V. route: 10 mg/kg (<75 kg); 750 mg (>75 kg to <100 kg); 1000 mg (≥100 kg), at 0, 2, 4 weeks and then every 4 weeks. s.c. route: 50 mg/0.4 mL syringe (≥10 to <25 kg); 87.5 mg/0.7 mL syringe (≥25 to <50 kg); 125 mg/mL syringe (≥50 kg).	11 days
Rituximab (Mabthera)	Truxima Rixathon	pJIA (off label)	Binding to CD20	I.V.	375 mg/m^2 once a week for 4 weeks	N.A.

[a]only approved in United States

CAPS, Cryopyrin-Associated Periodic Syndromes; CD, Crohn's Disease; EMA, European Medicines Agency; FDA, Food and Drug Administration; FMF, Familial Mediterranean Fever; HIDS Hyperimmunoglobulin D Syndrome; HS, hidradenitis suppurativa; I.V., intravenous; MKD, Mevalonate Kinase Deficiency; N.A., not available; PsO, psoriasis; s.c., subcutaneous; TRAPS, Tumor Necrosis Factor Receptor Associated Periodic Syndrome; UC, ulcerative colitis; pJIA, polyarthritis juvenile idiopathic arthritis (JIA); JPsA, juvenile psoriatic arthritis; ERA, enthesitis-related arthritis; sJIA, systemic JIA.

those children with prevalence of joint involvement rather than systemic manifestation [24].

2.2.1.1.4. Safety and monitoring. Klotsche et al. published a study evaluating the safety of ETN in 1414 patients with pJIA where significantly more serious adverse events, infections, and medically important infections were observed (ETN: 4.5, 5.7, 0.9 per 100 exposed years) compared with those treated with MTX alone (2.6, 5.5, 0.5 per 100 exposed year) [25]. The risk for malignancies was not significantly increased for ETN compared with MTX (0.09 and 0.07/100 person-years). Patients under ETN monotherapy developed more frequently incident inflammatory bowel disease (IBD) and incident uveitis (0.5 and 0.8/100 exposed year) than patients treated by ETN in combination with MTX (0.1 and 0.2/100 exposed year) or MTX alone (0.03 and 0.1/100 exposed year). Other studies showed more uveitis flares in JPsA, ERA and extended oJIA, compared to pJIA [26]. A multicentric Italian retrospective study enrolled 1038 JIA patients treated with ETN (with a median duration of therapy of 2.5 years). Clinically significant adverse events were reported in 27.8% of patients and ETN was discontinued in 9.5% because of side effects. The most common adverse events were new onset or recurrent uveitis (10.2%), infections (6.6%), injection site reactions (4.4%), and neuropsychiatric (3.1%), gastrointestinal (2.4%). and hematological disorders (2.1%). Ten patients developed an inflammatory bowel disease and two developed a malignancy. One patient died of fulminant streptococcal sepsis. These results confirmed that ETN was overall well-tolerated, as only one quarter of patients experienced clinically significant adverse events and less than 10% experienced treatment discontinuation for drug toxicity [27]. Other rare adverse events have been described, such as skin vasculitis, drug-induced lupus, pancytopenia, aplastic anemia, mood changes, weight gain, autoimmune hepatitis, cholecystitis, macrophage activation syndrome (MAS) [28,29].

Concerning the increased incidence of uveitis and IBD in patients with JIA receiving ETN rather than other anti-TNFα, a causative link between the drug and the development of these conditions has not been found. At the same time, there are publications showing that ETN is not effective in the management of idiopathic uveitis and Crohn's disease [30,31]. Since that, it is reasonable to consider the occurrence of these conditions as a clinical manifestation of JIA. Conversely, in case of IBD the development of arthritis could be the first manifestation of the gastroenterological disease.

With regard to monitoring, treatment with ETN, as for all biological therapies, should not be initiated in patients with active infections, including chronic or localized infections, and patients should be monitored for infections before, during, and after such treatment [32].

2.2.1.2. Adalimumab

2.2.1.2.1. Pharmacodynamic and pharmacokinetic properties. Adalimumab (ADA) is a fully humanized monoclonal antibody that binds both soluble and membrane-bound TNF-α [33]. It has been shown, in rheumatoid arthritis, that adalimumab can induce Foxp3 + T-reg cell expansion, thus promoting Th17 cell suppression [34].

It is administered every 2 weeks by subcutaneous injection at a dose of 20 mg for patients whose weight is less than 30 kg, and 40 mg if weight is more than 30 kg. For patient older than 12 years a dose of 40 mg is administered regardless of weight.

2.2.1.2.2. Clinical indications in JIA. According to EMA recommendations, ADA can be prescribed to patients from the age of 2 years affected by active pJIA. It should be used in combination with MTX in patients who have had an inadequate response to one or more DMARDs. ADA can be given as monotherapy, in case of intolerance to MTX or when continuing the treatment with MTX is not effective, as no additional benefit is evident. Moreover, ADA is indicated for the treatment of active ERA in patients aged 6 years and older, who have had an inadequate response to, or who are intolerant to conventional therapy. Importantly, ADA is indicated for the treatment of pediatric chronic noninfectious uveitis in patients from 2 years of age. Other extra-rheumatologic pediatric indications approved by EMA are pediatric plaque psoriasis, Crohn's disease and hidradenitis suppurativa in adolescents.

2.2.1.2.3. Clinical evidences of efficacy. Adalimumab efficacy and safety have been shown in a randomized, double-blind, multicenter trial including 171 children aged 4 years or older, affected by pJIA, with or without concomitant MTX therapy: after 16 weeks, 94% of patients treated with ADA+MTX and 74% of those receiving adalimumab alone achieved ACR Pedi 30 response, and the rate of disease flares was higher among patients treated with adalimumab alone than in those receiving concomitant MTX (43% and 37%, respectively) [8]. This led to the recommendation of using ADA in combination with MTX, except for patients for whom MTX use is not appropriate. Another randomized, placebo-controlled study including 46 pediatric patients (aged 6 to 17 years) showed the efficacy of ADA in ERA after 12 weeks, with clinical improvement maintained during the following 52-week-open label phase. Therefore, the EMA license for ADA was extended to ERA [23]. Several studies found that ADA was effective in refractory uveitis associated with JIA, in particular, ADA seems to have a higher efficacy when used as first anti-TNF-α treatment in chronic uveitis [35–39]. The administration of ADA without MTX possibly results in an increased formation of anti-drug antibodies, increased clearance, and, consequently, reduced efficacy of biologic therapy. In patients with pJIA, from 4 to 17 years old, with or without concomitant MTX treatment, anti-ADA antibodies were identified in 15.8% and 25.6% of patients, respectively. However, no correlation between the presence of anti-ADA antibodies and the occurrence of adverse events was noticed [8].

2.2.1.2.4. Safety and monitoring. Like other TNF-α antagonists, infections due to bacterial, mycobacterial, fungal, parasitic, viral agents, have been described during therapy with ADA and cases of reactivated tuberculosis and reactivation of HBV in chronic carriers have occurred, so that patient should be closely monitored [29,32]. As a minimal routine follow up, complete blood count, transaminases, albumin, should be obtained every 8–12 weeks.

2.2.1.3. Infliximab

2.2.1.3.1. Pharmacodynamic and pharmacokinetic properties. Infliximab (IFX) is a chimeric monoclonal antibody against TNF-α, including both human and murine

components. IFX binds both soluble and membrane-bound TNF molecule leading to antibody-dependent and complement-dependent cytotoxicity [40]. The estimated half-life is about 7.5– 9.5 days.

2.2.1.3.2. Clinical indications. Currently, in rheumatic diseases IFX is licensed only for adults. The only pediatric indication is the treatment of ulcerative colitis and Crohn's disease for children older than 6 years. In these clinical setting IFX is administered i.v. at a dose of 5 mg/kg at 0, 2 and 6 weeks, then every 4–8 weeks (intervals between consecutive administration can be adjusted according to the individual response). Pharmacokinetic and pharmacodynamics studies established that IFX at a dose of 3 mg/kg was completely cleared from the body before the following injection, indicating that higher doses should be used in pediatric patients or that shorter intervals between infusions could be required [41].

2.2.1.3.3. Clinical evidences of efficacy. Infliximab is not licensed for use in JIA since it failed to achieve its primary endpoint in an international, randomized trial involving patients with polyarticular JIA not responsive to MTX [42]. This trial consisted of a first phase of double-blind treatment with IFX (3 mg/kg) or placebo, with all of the 122 patients included on treatment with MTX. The second phase (30 weeks) consisted in an open-label treatment with IFX at a dosage of 3 mg/kg in patients who were previously in the IFX group, and 6 mg/kg in those previously placed in the placebo group. After the first phase the differences between the two groups were not statistically significant; however, after one year 73% of patients reported a significant improvement of ACR Pedi 30 [42]. Moreover, in JIA patients who remained in the study longer, IFX resulted to be safe and effective after 4 years of treatment [43]. These results led to the observation that the beneficial effects of IFX could require more than 16 weeks to develop.

IFX resulted to be an effective short-term treatment for JIA-associated uveitis but a subsequent ocular relapse has often been observed, even in patients who continued IFX therapy [44–46].

2.2.1.3.4. Safety and monitoring. Infliximab along with MTX was found to be safe and effective but associated with a high discontinuation rate. Infusion reactions were not uncommon (32%) and occurred more often in patients who were positive for antibodies to infliximab (58%) [43]. IFX must be administered under close clinical observation over a 2-h period and all children should be observed for at least 1–2-h post-infusion for acute infusion-related reactions. If previous reactions occurred, patients should be pre-treated with an antihistamine and/or hydrocortisone in order to decrease the risk of recurrence. The concomitant administration of IFX and MTX is recommended to prevent the development of anti–IFX antibodies, which seems to correlate with the infusion reaction and the clearance of IFX [47]. Infections remain the major concern with the use of IFX, with more cases of tuberculosis reactivation observed in IFX treated patients than those treated with ETN [29]. Essential laboratory monitoring should include complete blood count, transaminases, albumin, every 8–12 weeks.

2.2.1.4. Golimumab

2.2.1.4.1. Pharmacodynamic and pharmacokinetic properties. Golimumab (GOL) is a recombinant human monoclonal antibody against TNF that bind both soluble and membrane-bound human TNF preventing binding to its receptors. Half-life is estimated to be approximately 9 – 15 days. GOL is administered subcutaneously once a month. The recommended dose of GOL for children with a bodyweight less than 40 kg is 30 mg/m2 body surface area up to a maximum single dose of 40 mg administered. For children with a body weight of at least 40 kg, a dose of 50 mg is recommended.

2.2.1.4.2. Clinical indications. Recently EMA approved GOL for the treatment of pJIA in children from the age of 2 years, who have responded inadequately to previous therapy with MTX and in combination with it.

2.2.1.4.3. Clinical evidences of efficacy. The safety and efficacy of GOL were evaluated in the GO-KIDS study: a randomized, double-blind, placebo-controlled trial, involving 173 children (2 to 17 years old) with active pJIA, unresponsive to MTX. The primary endpoint was not met as, at week 48, treatment groups had comparable JIA flare rates (golimumab vs placebo: 32/78 = 41% vs 36/76 = 47%; p = 0.41), and rates of clinical remission were comparable (golimumab vs placebo: 10/78 = 12.8% vs 9/76 = 11.8%). Nonetheless, GOL resulted in rapid and clinically relevant improvement: 89% had a ACR Pedi 30 response and 79.2%/65.9%/36.4% demonstrated ACR Pedi 50/70/90 responses, with a tolerable safety profile [48].

2.2.1.4.4. Safety and monitoring. The most frequent adverse events observed in the GO-KIDS study were injection side reactions and infections, especially of the upper respiratory tract. More serious infections have been reported such as sepsis, pneumonia, tuberculosis, invasive fungal infections, and HBV reactivation. Antibodies to GOL were detected in 46.8% of the randomized patients, but were not significantly associated with decreased efficacy or injection site reactions [48]. Monitoring is similar to what has been described for the other anti-TNF agents.

2.2.1.5. Certolizumab-pegol

2.2.1.5.1. Pharmacodynamic and pharmacokinetic properties. Certolizumab-pegol (CTZ) is a humanized Fab fragment of a monoclonal antibody that binds TNF (soluble and trans-membrane form), which is conjugated with a molecule of polyethylene glycol (PEG). The lack of Fc region implicates that CTZ cannot fix complement inducing complement-dependent cytotoxicity, neither can cause antibody-dependent cell-mediated cytotoxicity, which are two of the main mechanisms of action of the other anti-TNF-α agents [40,49]. However, some recent evidences suggested that CTZ could directly induce non-apoptotic cell death in TNF-α expressing cells [50]. The attachment of PEG polymers to peptides delays the elimination of CTZ from the circulation, decreasing renal clearance, reducing proteolysis and immunogenicity. Moreover, the pegylation of the molecule avoids the transportation of the drug across the placenta during pregnancy. The estimated half-life is 14 days [40].

2.2.1.5.2. Clinical indications in JIA. Actually, no studies have been published regarding the use of CTZ in children; thus, CTZ is not approved by FDA or EMA for the treatment of JIA. A phase III, multicenter, open-label study to assess its safety and efficacy in children and adolescents with active pJIA is ongoing [51].

2.2.2. Anti IL-6

A few studies suggest the pivotal role of the proinflammatory cytokines IL-6 and IL-1 rather than TNF-α in active sJIA, and in pJIA [52,53]. Guidelines by ACR published this year confirm the 2013 update, which recognized the prototype IL-6 inhibitor Tocilizumab comparable to TNF-α inhibitors for treating JIA [9].

New biologic drugs targeting IL-6 are available but their use in JIA has not been approved yet (see text below).

2.2.2.1. Tocilizumab

2.2.2.1.1. Pharmacodynamic and pharmacokinetic properties. Tocilizumab (TCZ) is a recombinant humanized antibody against both soluble and membrane-bound IL-6 receptor.

In patients with sJIA it is administrated every 2 weeks by intravenous route according to weight: 8 mg/kg in patients weighing ≥30 kg or 12 mg/kg in patients weighing less than 30 kg. In patients with pJIA, the drug is monthly administrated at the dose of 8 mg/kg if the children's weight is more than 30 kg and 10 mg/kg if the weight is less than 30 kg. Recently, FDA approved also the subcutaneous formulation with prefilled siringe or autoinjector for use in children according to body weight: sJIA patient weighing <30 kg receive 162 mg every 2 weeks, and every week if the weight is ≥30 kg. In pJIA patients the dose is 162 mg every 3 weeks if the weight is <30 kg, and 2 weeks if the weight is ≥30 kg. This route of administration is not approved in Europe. The half-life of Tocilizumab is up to 16 days for the two bodyweight categories [54].

2.2.2.1.2. Clinical indications. According to EMA and FDA recommendation, TCZ is approved in patients 2 years of age and older with active sJIA refractory to previous therapy with NSAIDs and systemic corticosteroids and with pJIA (rheumatoid factor positive or negative and extended oligoarthritis) who have responded inadequately to MTX. It should be used as monotherapy, in case of intolerance to MTX or where treatment with MTX is inappropriate, or in combination with MTX.

A recent study suggested the efficacy of tocilizumab in treating severe and refractory uveitis associated with juvenile idiopathic arthritis [55].

2.2.2.1.3. Clinical evidences of efficacy. Tocilizumab was studied in a randomized, double-blind, phase III study in 56 children aged 2–19 years with sJIA refractory to conventional treatment. This drug was effective on 91% of patients by week 6 after 3 administrations of the open-label lead-in phase. These patients were randomly assigned to continue tocilizumab or to switch to placebo for a further 12 weeks. At this extension phase, 98% of patients receiving TCZ achieved ACR Pedi 30 [56].

These findings were confirmed in a multicenter double-blind placebo-controlled trial: at the end of the 12 weeks of study, 64 of 75 (85%) patients receiving tocilizumab versus 9 of 37 (24%) receiving placebo achieved the primary outcome including ACR Pedi 30 response and absence of fever [57].

2.2.2.1.4. Safety and monitoring. The most frequent adverse events observed in patients treated with Tocilizumab were infections, most frequently pneumonia and laboratory data anomalies such us a reduction in blood cell count [58]. The TENDER study enrolled children affected by sJIA and showed an infection rate of 3.4 per patient-year with tocilizumab versus 2.9 with placebo and the CHERISH trial for pJIA showed similar data [56,59]. Tocilizumab carries a higher infection risk when compared to adalimumab, abatacept, and etanercept [60]. The risk of serious infections was 11% per year of treatment [57]. Opportunistic infections are rare, tuberculosis has never been observed, while viral infections in particular influenza, EBV and VZV have been reported [61–64]. In additions, by reducing serum levels of C reactive protein, the use of TCZ could delay the diagnosis of infections, possibly leading to serious sequelae. The risk of lower intestinal perforation observed in adults with rheumatic diseases is extremely rare in children: only one case was reported in the literature in a patient affected by ERA HLA-B27+ [65]. Macrophage activation syndrome (MAS) is a rare and potentially fatal complication of sJIA. Events of MAS have also been described in patients under TCZ treatment presenting with similar clinical and laboratory features than those receiving conventional therapies. No correlation with TCZ and the occurrence of MAS have been reported [66].

Neutropenia and thrombocytopenia are dose-dependent adverse events, frequently observed for 12 mg/kg treatment [67]. Neutropenia (17%) is frequently mild and reversible and the occurrence of serious infection has not been demonstrated, while thrombocytopenia (4%) was not correlated with bleeding events [68]. Treatment with TCZ is also associated with increases in lipid parameters such as total cholesterol, LDL cholesterol and triglycerides, without raise of cardiovascular risk observed in RA patients [61,69].

Overall these side effects were more prevalent in sJIA than in pJIA suggesting an involvement of the disease itself and of the other drugs used, above all glucocorticoids [53].

Finally, hypersensitivity reactions have been observed, especially in the youngest patients [70]. The presence of anti-tocilizumab antibodies was frequent: 5 patients out of 56 in an sJIA open-label extension study at 144 weeks (the majority associated with infusion reactions) and in 1 out of 19 patients by week 48 in pJIA [59,71].

Overall, tocilizumab seems to be safe and patients should be monitored with complete blood counts, liver function tests, and lipid profile every 2– 3 months [61,67].

2.2.3. Anti IL-1

The first evidence of the efficacy of interleukin-1 inhibition was accidentally observed in two sJIA patients in 2004 [72]. Other studies confirmed the important role of this proinflammatory cytokine in the pathogenesis of sJIA. Indeed nowadays IL-1 blockers are the first choice of biologic drugs in patients resistant to conventional DMARDs, whereas anti-TNFα agents are less effective [73,74].

2.2.3.1. Anakinra

2.2.3.1.1. Pharmacodynamic and pharmacokinetic properties. Anakinra (ANR) is a recombinant interleukin-1 receptor which competitively inhibits the biologic activity of

interleukin-1α (IL-1α) and interleukin-1β (IL-1β) by blocking their binding to interleukin-1 type I receptor (IL-1RI).

ANR is administrated by subcutaneous injection once a day; the starting dose in children weighing less than 50 kg is 1–2 mg/kg/day, while patients weighing 50 kg or more are dosed with 100 mg/day. In patients with inadequate response, the dose can be escalated up to 4 mg/kg/day. The pharmacokinetic properties in sJIA are similar to what seen in RA patients: the maximum plasma concentrations occur at 3 to 7 h after administration and the drug elimination rate depends on kidney function, the clearance increased in line with creatinine clearance. In patients with mild renal impairment (CrCl 60 to 89 ml/min) dose adjustment is not needed [75].

2.2.3.1.2. Clinical indications. According to EMA recommendations ANR is indicated in adolescents, children, and infants aged 8 months and older with a bodyweight of 10 kg or above for the treatment of sJIA with active systemic features of moderate to high disease activity, or in patients with continued disease activity after treatment with non-steroidal anti–inflammatory drugs (NSAIDs) or glucocorticoids. It can be used in monotherapy or in associations with other DMARDs or anti–inflammatory drugs.

Other rheumatologic pediatric indications are Cryopyrin-Associated Periodic Syndromes (CAPS), a group of monogenic autoinflammatory diseases.

2.2.3.1.3. Clinical evidences of efficacy. Davies et al. in a systematic review analyzed 5 studies, included 2 RCT, regarding the efficacy of ANR in sJIA: in a prospective cohort study conducted on 20 new-onset patients, 80% of these reached ACR Pedi 90 response by 4 weeks, which was maintained at 12 months [7,76]. According to Gattorno et al. there were two subsets of sJIA patients: one characterized by a lower number of active joints and high neutrophil counts with a complete response, and the other with an incomplete or no response [77]. In a recent single-center prospective study which included 42 patients ANR monotherapy according to a treat-to-target strategy showed a rapid (33 days on average) and sustained attainment of inactive disease, 76–96% at 1 and 5 years, respectively. Similar to other studies, an increased absolute neutrophil count at baseline and a complete response after 1 month of ANR were highly associated with inactive disease at 1 year [78]. Further data suggested a short 'window of opportunity,' with a high risk of nonresponse in patients beginning the treatment after two months of disease onset [79].

2.2.3.1.4. Safety and monitoring. Available data suggest that skin reactions at the injection site are common minor adverse events, characterized by itching, rash, and erythema with a good response to ice packs and topical glucocorticoids. The risk of serious infections in a cohort of RA patients was increased compared with placebo, with an incidence of 1.8% versus 0.7% [75]. Patients should be monitored periodically with laboratory routine test including complete blood count, renal and liver function. Treatment must not be initiated in patients with neutropenia (ANC < $1.5x10^9$/L).

2.2.3.2. Canakinumab

2.2.3.2.1. Pharmacodynamic and pharmacokinetic properties. Canakinumab (CNK) is a human monoclonal antibody against interleukin-1β (IL-1β) of the IgG1/κ isotype subclass. It neutralizes the biological activity of this proinflammatory cytokine preventing IL-1β-induced gene activation and the production of inflammatory mediators.

The half-life ranges from 22 to 25 days justifies its subcutaneous administration every 4 weeks at a recommended dose of 4 mg/kg (up to a maximum of 300 mg) in patients with body weight ≥ 7.5 kg [80].

2.2.3.2.2. Clinical indications. CNK is indicated, according to EMA recommendations, for the treatment of active SJIA in patients aged 2 years and older who have responded inadequately to previous therapy with non-steroidal anti–inflammatory drugs (NSAIDs) and systemic corticosteroids. It can be given as monotherapy or in combination with MTX.

Other pediatric indications are the periodic fever syndromes: CAPS, TRAPS, HIDS/MKD, and FMF.

2.2.3.2.3. Clinical evidences of efficacy. In a phase II multicenter open-label study, ACR Pedi 50 was achieved in 60% of patients and, in line with the mentioned study by Gattorno et al., these patients had a fewer number of active joints and a higher white blood cell count at baseline compared to non-responders [77,81].

The efficacy of CNK in sJIA was demonstrated in two randomized double-blind placebo-controlled trials: in the first study 36 of 43 (84%) patients treated with CNK reached an ACR Pedi 30 response versus 4 of 41 (10%) of those receiving placebo; one-third of CNK group achieved the clinical remission within 15 days. In the second trial, 177 patients were randomized to receive treatment with CNK or to placebo: a sustained efficacy was observed in 82% of children in the CNK group after 2 years of treatment and a corticosteroid dose reduction was reached in about half of these patients [82]. Recently, Ruperto et al. published the open-label long-term extension study, where patients receiving canakinumab 4 mg/Kg/4 weeks, were followed for a minimum of 96 weeks. Glucocorticoid discontinuation was achieved in 44% of patients, suggesting a continuous glucocorticoid tapering effect of canakinumab. The response to the drug was sustained: at 2 years, ACR Pedi 50/70/90 response rates were 62%, 61% and 54%, respectively. A JADAS low disease activity score was obtained by 49% of patients at 2 years, and it was maintained up to 5 years. An early clinical response seemed to be a predictive factor of a long-term positive outcome, suggesting a timely shift therapy in no responders. In addition, the outcome of monotherapy versus the association CNK+MTX confirmed the limited therapeutic benefits of MTX to control sJIA [83].

Recent data suggested that CNK reduces innate immune gene expression and IL-6 levels in sJIA [84].

2.2.3.2.4. Safety and monitoring. CNK demonstrated a good safety profile: infections were the most common adverse events with similar rates than in placebo arms; neutropenia, thrombocytopenia, and elevations of transaminases have been reported. Antibodies against CNK were detected in 3% of patients, without a correlation with adverse events or clinical response [47].

MAS events were reported in seven patients with two associated deaths. The mortality rate was not increased compared to other studies on sJIA [85]. No new safety findings were observed with the long-term use of Canakinumab [83].

Patients treated with CNK should be monitored with complete blood counts and liver function at baseline, after 1

month and then every 3 months. Treatment should not be started in patients with leukopenia [47].

2.2.4. Biologics inhibiting cellular function and cell–cell interaction

2.2.4.1. Abatacept

2.2.4.1.1. Pharmacodynamic and pharmacokinetic properties. Abatacept (ABC) is a fusion protein composed of the Fc region of the immunoglobulin IgG1 fused to the extracellular domain of CTLA-4 (cytotoxic T-lymphocyte-associated protein 4), also known as CD152. CTLA-4 interacts with CD80 and CD86 expressed on the surface of antigen-presenting cells (APCs), preventing the co-stimulatory signal provided by CD28 when it binds to CD80 and CD86. Thus, ABC act as a negative regulator of T cell function [86]. ABC has also shown to decrease T-cell proliferation and to inhibit the production of TNF-α, interferon-γ and IL–2 [87]. The drug is administered as a 30-min intravenous infusion. The initial administration is followed by two infusions at 2 and 4 weeks, and then every 4 weeks. The recommended dose for patients from 6 to 17 years old, whose weight is lower than 75 kg is 10 mg/kg. Pediatric patients weighing more than 75 Kg should receive the adult dosing regimen with a maximum dose of 1000 mg. The estimated half-time is about 13 days. Recently, after a phase 3 open-label study, FDA approved subcutaneous ABC administration option for use in patients 2 years of age and older with moderately to severely active pJIA. ABC sc. should be initiated without an IV loading dose and administered once-weekly using weight-tiered dosing: 50 mg/0.4 mL syringe (for patients 10 to <25 kg), 87.5 mg/0.7 mL syringe (for patients 25 to <50 kg) and 125 mg/mL syringe (for patients ≥50 kg) [88].

2.2.4.1.2. Clinical indications. ABC, in pediatric patients, has been approved by EMA for the treatment of moderate to severe pJIA in children aged 2 years and older, who have had an insufficient response to other DMARDs, including at least one TNF inhibitor. ABC may be used as monotherapy or concomitantly with methotrexate.

2.2.4.1.3. Clinical evidences of efficacy. Abatacept was studied in a multicenter, randomized, double-blind, placebo-controlled withdrawal trial. One hundred and ninety children aged 6–17 years with a polyarticular course of JIA were enrolled, including patients with pJIA, extended oJIA, and sJIA without systemic manifestations for at least 6 months. In the first open-label phase, all patients received abatacept 10 mg/kg (maximum 1000 mg per dose) on days 1, 15, 29, 57, and 85. Of the 190 patients, 170 completed the first phase and 65% achieved an ACR Pedi 30 response. The 122 patients who were responders at the end of the first phase were subsequently randomized in a double-blind manner to receive either abatacept or placebo for 6 months or until they experienced a disease flare. The number of patients who developed a flare was significantly lower in the abatacept group compared with the placebo group [12 (20%) versus 33 (53%), respectively, P = 0.0003]; moreover, the time to disease flare for patients receiving placebo was significantly shorter than for ABC group. Significantly more patients in the abatacept group achieved an ACR Pedi 50, 70, and 90 response rates, as well as inactive disease status, than in the placebo group The AWAKEN trial was the first trial to include JIA patients who had failed TNF-α blockade. At the end of the open-label phase 76% of the TNF-α blockade-naïve group achieved an ACR Pedi 30 response, compared with 39% of patients who had failed TNF-α blocking agents in the past; inactive disease status was attained in 46% of the TNF-α blockade-naïve group, versus 20% in the latter group [89].

2.2.4.1.4. Safety and monitoring. During the double-blind period of the AWAKEN trial frequencies of adverse events did not differ in patients given abatacept and in controls. The most common system organ class reported was infections (36%), primarily upper respiratory tract infection, and nasopharyngitis. Other events that occurred with a prevalence of at least 5% were headache, nausea, diarrhea, cough, pyrexia, and abdominal pain. A total of six serious adverse events (acute lymphocytic leukemia, ovarian cyst, varicella infection, disease flare) were reported during the initial 4 months of treatment. One case of hypersensitivity reaction and one of multiple sclerosis were reported [89]. Treatment with abatacept continued to be generally safe and well-tolerated in the open-label long-term extension phase of the previously mentioned study, that involved 153 of the 190 enrolled patients [90]. The safety experience and immunogenicity for ABC administered subcutaneously were consistent with the intravenous study. Among the 173 enrolled patients, there were no reported cases of hypersensitivity reactions, and local injection site reactions occurred at a frequency of 4.4%. All the injection site reactions (including hematoma, pruritus, and erythema) were mild (83%) to moderate (17%) in severity, and none necessitated drug discontinuation.

The presence of anti-abatacept or anti–CTLA-4 antibodies was found in 11% of the patients for whom samples were available. The presence of these antibodies was generally transient and did not correlate with changes in abatacept pharmacokinetic, infusion reactions, AEs, SAEs, or loss of efficacy [90].

Patients should be monitored every 2–4 months, including essential laboratory monitoring such as complete blood count, transaminases, albumin levels.

2.2.4.2. Rituximab

2.2.4.2.1. Pharmacodynamic and pharmacokinetic properties. Rituximab (RTX) is a chimeric mouse/human monoclonal antibody directed against the CD20 antigen on the surface of B cells. CD20 is widely expressed on B cells, from early pre-B cells to later in differentiation, but it is absent on terminally differentiated plasma cells. RTX causes peripheral B cell depletion by both antibody-dependent cell-mediated cytotoxicity (ADCC) and complement-dependent cytotoxicity (CDC), and also by inducing cell death via apoptosis [91]. B cells have been proven to play a major role in the pathogenesis of JIA by producing autoantibodies, but they also can act as effector B-cells, antigen-presenting and cytokine-producing cells, and can regulate T-helper cell differentiation [92].

RTX is administered intravenously at a dose of 375 mg/m2 after premedication with methylprednisolone. The infusion of RTX should start slowly, at 50 mg/h; then, if no infusion

reactions occurs, the dose can be increased by 50 mg/h every 30 min to a maximum of 400 mg/h. Subsequent infusions can be given faster with an initial rate of 100 mg/h, followed by 50 mg/h increments every 30 min.

2.2.4.2.2. Clinical indications. There is no EMA or FDA indication for RTX use in the treatment of JIA. RTX can be used in combination with MTX for the treatment of adult patients with RA unresponsive to previous DMARDs or TNF-α inhibition. RTX has been used as an off-label treatment in JIA children with severe disease that failed to respond to conventional therapies.

2.2.4.2.3. Clinical evidences of efficacy. The evidence supporting RTX effectiveness in JIA patients mainly consists of case reports or small case series. One observational study tested the efficacy of RTX in 55 patients with severe JIA non responsive to anti-TNF-α. RTX, administered in courses of four weekly 375 mg/m2 i.v. infusions 24 weeks apart, was found to be effective, with more than 90% of patients achieving ACR Pedi 50 after 96 weeks. Remission was recorded in 25%, 52%, 75%, and 98% of patients following the first (24 weeks), second (48 weeks), third (72 weeks), and fourth (96 weeks) course of rituximab, respectively [93]. Another observational study assessed the efficacy and safety of RTX treatment in long-term follow-up of children with sJIA: disease remission was documented in 43%, 33%, 33% of patients after 2, 3, 4 years of follow up, respectively; improvement by ACR Pedi 30/50/70/90 was observed in 90%, 80%, 75%, 70%; 90%, 85%, 80%, and 75% and 98%, 95%, 95%, and 93% of patients. Within all period of observation remission of systemic manifestations was observed in 75% of patients [94]. RTX was found to be a promising effective treatment option even for refractory uveitis associated with JIA [95].

2.2.4.2.4. Safety and monitoring. The most frequent adverse events observed in patients treated with RTX are transfusion reactions: these include nausea, vomiting, allergic rash, abdominal pain, flu-like syndrome, rapid rise in body temperature to febrile levels, decreased, or increased blood pressure, headaches, dyspnea, and back pain, mostly during the first course of treatment. Infections are another common side effect the most common being those related to ear, nose, and throat, exacerbation of herpes infection, and skin infections [93].

As a consequence of B cell depletion, humoral responses are reduced in patients treated with RTX and recovery of immune cell function can take 6–10 months [96]. For these reasons it is recommended that inactivated vaccine schedules should be completed at least 1 week prior, and any live-attenuated vaccines should be completed a minimum of 4 weeks prior to commencing treatment. However, if a vaccine, such as influenza, needs to be administered during treatment with RTX, vaccination should be provided at least 6 months after the administration and 4 weeks before the next course of B cell-depleting therapy, although lower vaccine effectiveness is expected [97].

Concerning laboratory monitoring, in addition to routine blood tests (complete blood count, AST, ALT, creatinine), B-cell numbers and immunoglobulin levels should be checked every 3 months. In case of severe hypogammaglobulinemia, immunoglobulin replacement may be required.

2.3. Emerging biologic drugs

2.3.1. Rilonacept

Rilonacept (RLC) is a dimeric fusion protein consisting of the extracellular portions of the IL-1 receptor components required for IL-1 signaling, linked to the Fc portion of human IgG1. Rilonacept binds to and blocks both IL-1β and IL-1α, and with a lower affinity also binds the endogenous IL-1 receptor antagonist (IL-1ra) [98]. RLC is approved for children older than 12 years old affected by CAPS. It is not available in Europe.

The safety and efficacy of RLC have been shown during 23 months of open-label treatment, after a 4-week double-blind placebo-controlled phase, involving 24 children (4 to 20 years old) with sJIA. After 3 months ACR Pedi 30/50/70% response rate was 78.3/60.9/34.8%, respectively. Clinical improvements were maintained in 50% of patients at 2 years. A corticosteroid dose tapering was reached in 22 of 23 patients during the study, reducing the prednisone daily dose by half in 4 months and 58.8% of patients discontinued prednisone therapy.

In according with others trials RLC was generally well-tolerated: injection-site reactions and minor infections, in particular upper respiratory tract infections and viral gastroenteritis, were the most common adverse events. Overall, three patients discontinued: one due to depression, one to injection site reactions and one to pulmonary fibrosis/MAS, which was assessed as not related to the study drug [99,100].

2.3.2. Sarilumab

Sarilumab (SAR) is a human monoclonal antibody that binds to both soluble and membrane-bound IL-6 receptors (IL-6Rα), and inhibits IL-6 signaling pathway [101]. According to EMA SAR is recommended with MTX in adults with active RA who have responded inadequately to, or who are intolerant to one or more DMARDs. It can be given as monotherapy in case of intolerance to MTX or when treatment with MTX is inappropriate. Currently, SAR is under investigation in phase-II clinical trials for use in sJIA (NCT02991469) and pJIA (NCT02776735) in patients from 1 and 2 to 17 years old, respectively [102,103].

In a recent multinational open-label dose-finding study 42 children were evaluated during 12 weeks to identify an adjusted dose, efficacy, and safety of SAR. Patients were divided into two groups according to body weight (10–30 Kg and ≥30 Kg) and received three subcutaneous ascending doses of SAR from 2 mg/Kg to 4 mg/Kg. The exposure was similar among the subpopulations and comparable to equivalent doses in an adult with RA. A clinically relevant improvement was demonstrated by ACR Pedi 70 response achievement in 100% of patients with dose 3. The safety profile was tolerable: the most common adverse events were infections (66.7%) and transient neutropenia without infections (28.5%) [104]. Treatment with SAR is associated with laboratory changes such as decrease in absolute neutrophil count and elevation in lipid levels.

2.3.3. Ustekinumab

Ustekinumab (UST) is a fully human IgG1κ monoclonal antibody directed against the combined interleukin-12 and interleukin-23 p40 subunit. UST inhibits the bioactivity of human IL-12 and IL-23 by preventing p40 from binding to the IL-

12Rβ1 receptor protein expressed on the surface of immune cells. UST is indicated in adults for the treatment of active Crohn's disease or ulcerative colitis nonresponder or intolerant to conventional therapy or TNF-α antagonist [105]. Data in adults with psoriatic arthritis and case reports for pediatric psoriasis are promising [106]. In a monocentric retrospective review, Mannion et al. described five children with ERA who have failed one or more conventional DMARDs in addition to two different TNF-α inhibitors switched to ustekinumab. All patients had peripheral arthritis, enthesitis, and clinical or imaging evidence of sacroiliitis. During 8.2 months, a mean duration of exposure to ustekinumab, the physician global assessment of disease activity decreased in 4 of 5 patients, a reduction of a number of active joints and an improvement in enthesitis was achieved in 3 and 2 subjects, respectively, and a resolution of clinical sacroiliitis was observed in 3 children. One patient nonresponder to ustekinumab did discontinue after suffering minor adverse events [107].

A recent multicentre randomized, double-blind, placebo-controlled phase III trial (CADMUS) evaluated the safety and efficacy of ustekinumab in adolescents aged 12–17 years with moderate-to-severe plaque psoriasis for more than 6 months. In 110 patients ustekinumab was administered at a standard dose or reduced by 50% according to weight. After 12 weeks PASI75 was achieved in 80.6% and 78.4% of patients in full and half dosing, compared to 10.8% in the placebo group; PASI90 was attained by 54.1%, 61.1%, and 5.4% of half, full dosage and placebo group, respectively. Ustekinumab was generally well tolerated in adolescents: upper respiratory tract infections, especially nasopharyngitis were the most common adverse events. A worsening of psoriasis was reported in one patient with half-standard dosing by week 12 and by week 60 one transient leukopenia, one pyelonephritis, one ear infection, one allergic contact dermatitis from hair dye and one injection-site reaction were also reported [108].

2.3.4. Secukinumab

Secukinumab is a fully human IgG1/κ monoclonal antibody that selectively binds to and neutralizes the proinflammatory cytokine interleukin-17A (IL-17A), inhibiting its interaction with the IL-17 receptor. As a result, Secukinumab inhibits the release of proinflammatory cytokines, chemokines, and mediators of tissue damage and reduces IL-17A-mediated contributions to autoimmune and inflammatory diseases. Clinically relevant levels of Secukinumab can reach the skin and reduce local inflammation. Secukinumab is approved by EMA in adults for plaque psoriasis, psoriatic arthritis, alone or in association with MTX and for ankylosing spondylitis who have responded inadequately to conventional therapy. Data from adults suggest a possible use of this drug in JIA [109,110]. A multicenter, randomized, double-blind, placebo-controlled withdrawal study is ongoing to investigate the efficacy and safety of secukinumab in biologic-naïve children with active JPsA or ERA (NCT03031782) [111]. Eighty-six patients, aged from 2 to 17 years, have been enrolled in the first open-label phase. Time to flare is the primary efficacy endpoint [112].

A retrospective monocentric chart review was conducted in 14 patients with ERA resistant to TNF-α inhibitors switched to secukinumab, according to weight. In more than 50% of patients the dose had to be increased to 300 mg/dose to obtain a clinical improvement. Efficacy was evaluated with JADAS score: at months 3 in 14 patients JADAS 10 decreased from 8.07 to 6.35, 5.2 at months 6 in 10 patients and 6.0 at months 12 in 8 patients. The mean number of active enthesitis points was also assessed at 3 months/6 months/12 months with a reduction from 0.86 at timepoint 0 to 0.25/0.3/0.25. No discontinuations were observed due to adverse events [113].

2.3.5. Anti IL-18

IL-18 is a proinflammatory cytokine that belongs to IL-1 family and is naturally inhibited by IL-18 binding protein (IL-18BP). Tadekinig alfa is the recombinant human interleukin-18 binding protein (IL-18BP). High levels of IL-18 were detected in adult onset Still's disease compared with other inflammatory diseases, suggesting that IL-18 may represent a potential target for its treatment [114]. An open-label multicenter dose-escalating phase II clinical trial (NCT02398435) showed a favorable safety profile and a modest efficacy of Tadekinig alfa in adult onset Still's disease [115]. IL-18 levels are also elevated in patients with sJIA [116], may persist for at least a few months even in clinical remission, and substantially increased levels may be associated with risk of MAS [117,118]. Moreover, the presence of systemic features, the activation of the innate immune system and the absence of autoimmunity suggest that sJIA is an autoinflammatory rather than an autoimmune disease; therefore, Tadekinig alfa could be an effective drug in sJIA.

2.3.6. Small molecules

Although the purpose of this manuscript is to discuss exclusively biological drugs, there are interesting emerging data on Janus kinase (JAK) inhibitors. These small molecules provide a novel mechanism of action by affecting intracellular signaling pathways and their efficacy has been demonstrated in multiple successful clinical trials in adults with RA and PsA [119]. Limited data are available for the use of these drugs in JIA, as Kerrigan et al., described in a recent review [120], but there are several ongoing trials evaluating the safety, efficacy, and pharmacokinetics of tofacitinib, baricitinib, and upadacitinib in patients with pJIA and sJIA [121–127].

3. Biosimilars

With the term biosimilar EMA and FDA define a biologic product that is similar to an already approved reference biologic drug in terms of safety, efficacy/potency, and purity/quality [128].

To date, only a few reports exist about the experience with biosimilars in the treatment of JIA. In a real-word setting, UK authors described the characteristics of patients with JIA starting infliximab and etanercept biosimilars, including biological naïve, patients switched from a non-originator, and few others switched directly from an originator product [129]. Among the 14 patients followed from 6 months to 2 years, 4 of them switched to another biologic; two serious adverse events were reported, both cases of recurrent uveitis in patients switching from a non-originator biologic to infliximab biosimilar [129].

By extrapolating data from adult comparative studies, biosimilars can potentially be marketed quicker and with reduced costs, thereby increasing access to biologic drugs for children with JIA. Table 1 includes the originators and biosimilars of TNF-α inhibitors that have been approved for JIA and that are currently in use. Concerning the other biologic drugs, they only have been approved or under evaluation for adult patients: two Rituximab biosimilars have been approved by EMA (Truxima and Rixaton), at least two Tocilizumab biosimilars are undergoing comparative clinical development (LusiNEX and BAT 1806), and a considerable number more are in various stages of development.

4. Risk of malignancies under biologic treatment

Large observational-studies from different national databases, have shown a twofold to fourfold increase in malignancies in children with JIA who were naïve to biologics, compared with the general population [130–133]. A Taiwanese cohort-study of 2892 children reported an Hazard Ratio of 3.14 (95% CI 1.98 to 4.98) for the risk of malignancy in patients with juvenile arthritis who were naïve to methotrexate and biologics. The relative risk (RR) in patients treated with MTX was 2.02 (95% CI 0.67 to 6.04), and in patients treated with anti-TNF-α agents, the RR was 2.07 (95% CI 0.36 to 11.49) [130]. More recently, a cohort-study identified 28,005 patients with JIA, 26% of them treated with anti-TNF-α. The standardized incidence ratios (SIRs) were 0.97 (0.91– 1.05), 2.1 (1.1– 3.5) and 3.1 (1.3–6.1) respectively, for the matched control population, JIA children treated with anti-TNF-α and JIA children not in treatment with anti-TNF-α. The adjusted HR for cancer (all sites) was 1.58 (0.88– 2.85) for TNF- α users versus no TNF- α users, HR for lymphoma between these groups was 2.64 (0.93– 7.51). Authors conclude that anti-TNF-α do not substantially increase the overall risk of malignancy, nonetheless a possible association between the use of these biologic drugs and lymphoma cannot be excluded [134]. No specific data about the incidence of cancer among JIA patients treated with others biologic drugs are available.

5. Conclusions

Since biologic drugs have been introduced in the clinical practice in the management of JIA, the prognosis for children with this disease has dramatically improved. Further efforts are required in genetic and pathological research in order to implement targeted therapies and personalized therapeutic interventions, improving remission rates and minimizing treatment-related side effects.

6. Expert opinion

Biologic therapies for juvenile idiopathic arthritis and other pediatric conditions have revolutionized the outcome of these disorders. Approval of these drugs has followed what had been achieved in adult rheumatology, mainly thanks to regulatory agencies. There is now a plethora of therapies that are directed against variable targets, and the clinician has the choice of several drugs for the same conditions. Research is advancing very fast, and it is likely that in the next future more drugs will be approved. Oral ways of administration are already available for small molecules, and this is certainly an advantage when dealing with young children. The compliance is, in fact, one of the major obstacles for correct long-term treatment. Studies on disease pathogenesis will hopefully shed light on the complexity of these disorders, and the hope is the discovery of new targets, in order to be more and more specific in suppressing inflammatory pathways without harming natural defenses. In the pediatric age, it is it critical to consider the immaturity of the immune system, and the long life expectancy. Reports of neoplastic disorders and infectious risk carry a substantial burden for the families, but current data are relatively reassuring. Finally, pharmacoeconomics considerations will also be very important to deal with, considering the high cost of most of these molecules. Availability of drugs in a large part of the word is limited, and industries should work with governments in order to plan activities which may benefit young patients also in underserved areas.

With regard to new drugs, biotechnology has advanced so fast that it is not likely to bring any new molecule which is really different from the current ones in the next future. There will be certainly new data regarding the use of already approved molecules for different indications, as well as the approval for JIA of drugs currently tested for RA. On top of the discovery of new targets, research should focus on finding the right time to start the right therapy, the correct dosage and schedule in order to bring the disease under control, and the proper way of tapering or stopping the drugs. This is likely to be very difficult, since the rarity of these diseases makes such studies quite hard to perform in a very large number of patients. Biologic drugs are in fact very potent and effective, and finding differences between schedules is not easy. However, this could save public money and make possible to treat larger number of patients. The introduction of biosimilars will also be useful in this regard, and research should also focus on comparative trials and proof of equivalence between these drugs and their originators. Head-to-head trials for molecules of different categories will also be welcome, since we yet do not know exactly which one to choose in case of a common indication.

Of course, going back to the basis of treating these disorders, it is important and even fundamental to precisely define the characteristics of each clinical situation, since what is called JIA refers not to a single disease but is an umbrella term. We probably treat different kinds of diseases with the same drugs, and a better categorization based on biological parameters in addition to the currently used clinical ones is currently explored.

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