Pediatr Drugs (2016) 18:101–108
DOI 10.1007/s40272-016-0164-6

THERAPY IN PRACTICE

Difficult-To-Treat Juvenile Idiopathic Arthritis: Current and Future Options

Ilaria Pagnini[1] · Federico Bertini[1] · Rolando Cimaz[1]

Published online: 3 March 2016

Abstract Juvenile idiopathic arthritis (JIA) is the most common chronic rheumatic disease in childhood and is usually treated with non-steroidal anti-inflammatory drugs or disease-modifying anti-rheumatic drugs (DMARDs) such as methotrexate or sulfasalazine. However, not all patients respond to these treatments, and toxicities may limit long-term use or diminish compliance. With advances in pharmacotherapy and the development of new therapeutic agents, there have been improvements in treatment of both systemic and non-systemic JIA, particularly with biologic agents such as anti-tumor necrosis factor (TNF)-α, anti-interleukin (IL)-1, and anti-IL6. Anti-cell therapies, such as co-stimulator blockers or anti-CD20, small molecules, and biosimilars represent new areas of interest, and, while many are not yet currently commercially available for use in children, preliminary studies appear to be promising. In the present article, the authors review therapeutic strategies for the different JIA subtypes, mainly according to guidelines and recommendations. Newer and possible future treatments for arthritis, already approved in adults but currently under study in children, are also discussed. Drugs currently in development plans for rheumatoid arthritis, which hopefully will also be useful for JIA patients in the future, are also mentioned in this paper.

Key Points

Non-steroidal anti-inflammatory drugs and disease-modifying anti-rheumatic drugs still represent the first line of treatment, but in moderate or severe disease activity or cases with poor prognosis, initiation of tumor necrosis factor (TNF)-α inhibitors is recommended, especially for patients with polyarticular course juvenile idiopathic arthritis (JIA).

Systemic JIA seems to benefit from interleukin (IL)-1 and IL-6 inhibition more than other JIA categories.

Biosimilars have been studied in adults but not yet in children. These drugs offer a considerable cost saving, but concerns remain regarding their immunogenicity, efficacy, and toxicity.

New molecules, such as JAK and phosphodiesterase inhibitors, have been studied in adults, and trials in children are warranted or already ongoing.

1 Introduction

Juvenile idiopathic arthritis (JIA), an heterogeneous group of arthritides of unknown etiology, is the most common chronic rheumatic disease in childhood, with a global prevalence of 16–150 per 100,000 [1]. According to the International League of Associations for Rheumatology (ILAR), JIA is defined as arthritis of unknown origin that begins before the 16th birthday and is persistent for at least

✉ Rolando Cimaz
r.cimaz@meyer.it

[1] AOU Meyer, Viale Pieraccini 24, 50139 Florence, Italy

Table 1 Biologic therapies mainly used in the treatment of juvenile idiopathic arthritis

Drug	Dose and dose interval	Recommended monitoring	Approved indications
Abatacept	IV 10 mg/kg/dose (max. 1000 mg) q4w	CBC with differential, ESR, liver function tests q12w	Poly JIA from 6 years of age
Adalimumab	SC 24 mg/m^2/dose (max. 40 mg) q2w	CBC with differential, ESR, liver function tests q12w	Poly JIA from 2 years of age; ERA from 6 years of age
Etanercept	SC 0.4 mg/kg/dose (max. 25 mg) twice weekly OR 0.8 mg/kg/dose weekly	CBC with differential, ESR, liver function tests q12w	Poly and extended oligo JIA from 2 years of age, psoriatic arthritis from 12 years, ERA from 12 years of age
Tocilizumab	IV 8–12 mg/kg/dose q2w	CBC with differential, ESR, liver function tests q12w	Systemic JIA from 2 years of age, poly JIA from 2 years of age
Anakinra	SC 2 mg/kg (max. 100 mg) daily	CBC with differential, ESR, liver function tests q12w	Not approved for JIA
Canakinumab	SC 4 mg/kg/dose q4w	CBC with differential, ESR, liver function tests q12w	Systemic JIA in patients ≥2 years of age

CBC complete blood count, *ESR* erythrocyte sedimentation rate, *ERA* enthesitis-related arthritis, *IV* intravenous, *JIA* juvenile idiopathic arthritis, *qXw* every x weeks, *SC* subcutaneous

6 weeks, with other known conditions excluded [2]. There are seven subtypes of JIA, defined by clinical signs present during the first 6 months of illness.

JIA is typically treated with disease-modifying anti-rheumatic drugs (DMARDs) such as methotrexate, sulfasalazine, and leflunomide, or with biologic agents [3–10]. However, not all patients respond to these treatments, and some DMARDs or anti-inflammatory agents are associated with toxicities that limit long-term use or diminish compliance [9, 10]. 'Difficult-to-treat JIA' refers to a group of patients who have not responded to standard anti-rheumatic drugs, for whom treatment with biologics is indicated. Here, the authors review the newer and possible future treatments for the arthritis and systemic features in children with JIA, including evidence supporting efficacy and safety of these therapies. Treatment for cases resistant to standard therapies are described considering the different JIA categories, and the main characteristics of biotherapies are summarized in Table 1.

2 Oligoarticular Juvenile Idiopathic Arthritis (JIA)

Oligoarthritis JIA (oligo-JIA) is characterized by arthritis in four or fewer joints during the first 6 months of disease. There are two types of oligo-JIA: (1) persistent oligoarthritis, characterized by never more than four joints affected during disease course, and (2) extended oligoarthritis, characterized by more than four joints affected after the first 6 months of disease. According to the American College of Rheumatology (ACR) 2011 Recommendations for the treatment of JIA [11], the first line of treatment is non-steroidal anti-inflammatory drugs (NSAIDs) or glucocorticoid joint injections, as needed. If the patient has a poor response, defined by the persistence of the arthritis and/or onset of uveitis, methotrexate may be considered (especially in extended oligo-JIA). After a few months of unsuccessful therapy, especially in cases of moderate or severe disease or poor prognostic features (e.g., arthritis of the hip or cervical spine, or persistent increase of inflammatory markers), a tumor necrosis factor (TNF)-α inhibitor may be needed.

Etanercept and adalimumab are currently the only TNF inhibitors that the US FDA and the European Medicines Agency (EMA) have approved for use in JIA. The first is a dimeric protein consisting of the human p75 TNF receptor fused with the Fc region of human immunoglobulin (Ig)-G. It binds to circulating TNFα, preventing its interaction with the cell surface receptor and subsequent activation of the inflammatory cascade. In 1999, it became the first biologic agent to be FDA approved for use in children older than 2 years with moderate to severe polyarticular course JIA [12]. Adalimumab is a fully humanized monoclonal IgG antibody that binds both soluble and membrane-bound TNFα. In 2008, it became FDA approved for use in children aged >4 years with oligo-extended JIA and polyarticular JIA [13].

3 Polyarticular JIA

In up to 50 % of patients, the disease course may be polyarticular (pJIA), rheumatoid factor positive or negative, and both are at risk for profound disability. First line of treatment, according to the 2011 ACR recommendations for the treatment of JIA [11], may include NSAIDs therapy, but continuation of NSAIDs monotherapy for longer than 2 months is considered inappropriate for patients with active arthritis. In patients with high disease activity or

moderate disease activity but features of poor prognosis (see above), initiation of methotrexate is recommended as initial treatment.

In a recent study, an early response to methotrexate predicted good long-term outcome, and achieving inactive disease at least once within 5 years from onset also predicted less joint damage [14].

Initiation of TNFα inhibitor, classically etanercept or adalimumab, has been recommended for patients who have received methotrexate for 3 months at the maximum tolerated dose and have moderate or high disease activity, or after 6 months of methotrexate with low disease activity [11].

Abatacept, the first in a class of agents that selectively modulates the CD80/CD86:CD28 co-stimulatory signal for T-cell activation, has been recommended as a treatment approach for patients who have received a TNFα inhibitor for 4 months, or more than one TNFα inhibitor sequentially, and have moderate or high disease activity. In a randomized, double-blind, placebo-controlled withdrawal trial in 190 patients with pJIA (aged 6–17), 20 % of patients with abatacept experienced arthritis flares compared with 53 % of patients who switched to placebo [15]. In the long-term extension study, Ruperto et al. [9] showed that patients treated with intravenous abatacept every 4 weeks had a significant and durable clinical response. The drug is now approved as first biologic treatment in patients aged ≥6 years.

In patients with pJIA despite treatment with DMARDs or approved biological agents, up to 30 % continue to have active disease. Tocilizumab is a humanized, monoclonal, anti-human interleukin (IL)-6 receptor (IL-6R). In a phase III randomized trial, 188 patients received tocilizumab, and 163 of those patients were then randomized to either continue tocilizumab or switch to placebo. JIA flare occurred in 25.6 % of patients who continued tocilizumab versus 48.1 % of patients who received placebo, demonstrating that intravenous tocilizumab every 4 weeks is safe and efficacious for the management of pJIA [16]. The drug is now approved for pJIA.

There may be a window of opportunity to most effectively treat chronic arthritis, and some papers support the benefits of early and aggressive therapy. A study on early pJIA, targeting to achieve minimally active or inactive disease in 59 DMARD-naïve patients, demonstrated that infliximab plus methotrexate was superior to DMARDs in combination (methotrexate, sulfasalazine, and hydroxychloroquine) and superior to methotrexate alone. The study authors were able to commence aggressive disease-modifying therapy very early and demonstrated a clinically significant short-term outcome [17]. However, other authors have not confirmed these results, and more experience is needed to draw firm conclusions.

4 Systemic JIA

Systemic JIA (sJIA) is characterized by fever and other systemic manifestations, while arthritis may manifest later, sometimes after weeks or months from the onset of fever.

It is now becoming increasingly clear that the markedly distinct clinical presentation of sJIA is associated with unique immunologic abnormalities. Several lines of evidence suggest that the role of the adaptive immune system in JIA may be rather limited compared with the other JIA types, while the contribution of innate immunity may be much more prominent. Clinical and translational studies suggest the pivotal role for two potent pro-inflammatory cytokines: IL-1 and IL-6. In these cases, therapeutic experience has taught us a lot about disease pathogenesis, and the importance of these two cytokines has been confirmed by proving the clinical efficacy of blocking their activity. This effect does not seem to be as important in other types of JIA. Current therapeutic options based on 2013 ACR recommendations [18] suggest the following.

The use of NSAIDs as first line of treatment is uncertain, especially for patients with severe disease. Initiation of systemic glucocorticoids (with or without additional concurrent therapy) has been recommended as initial therapy for patients with fever and physician global assessment of overall disease activity of ≥7. Initiation of systemic glucocorticoids following up to 2 weeks of NSAIDs has been recommended for patients with persistent fever [11].

The use of methotrexate is recommended for patients with active arthritis following monotherapy, while this is inappropriate for the initial management of patients with active fever and without active arthritis [19]. Intravenous glucocorticoid pulse therapy is sometimes used to treat the refractory systemic features of systemic JIA. The rationale of this approach is to achieve an immediate, profound anti-inflammatory effect and to minimize toxicity related to long-term continuous therapy in moderate to high daily doses. Methylprednisolone is the drug of choice, at a dose of 10–30 mg/kg/pulse up to a maximum of 1 g, administered according to various protocols. A single administration may be repeated as clinically needed (e.g., daily for 3–5 days, or as alternate day pulses for three doses). Adverse events include headaches, abdominal pain, vomiting, hives, hypotension, tachycardia, and hyperglycemia.

As specified above, the underlying inflammatory process in sJIA is distinct from that in other JIA subtypes, with a central role for both IL-1 and IL-6. As such, the main therapies are targeted against these cytokines. The 2013 update of the 2011 ACR recommendations for the treatment of JIA, focusing on therapy for sJIA, outlines the indications for use of IL-1 and IL-6 inhibitors, including

anakinra, canakinumab, and tocilizumab [18]. The first is not FDA approved while the other two are.

However, anakinra, a human recombinant IL-1 receptor antagonist is recommended as a possible initial therapy for patients with active systemic features and/or varying degrees of synovitis. A placebo-controlled study [20] showed that anakinra treatment is effective in sJIA, at least in the short term, and is also associated with normalization of blood gene expression profiles in clinical responders.

In 2011, an international, multi-center study in 46 sJIA patients using anakinra as first-line therapy (either as monotherapy or in conjunction with steroids and/or methotrexate), showed that rapid resolution of systemic symptoms and refractory arthritis occurred in almost 90 % of patients. Those who partially responded were noted to be significantly younger at onset [21]. However, this was an uncontrolled retrospective study and lacked proper controls. The use of anakinra as first-line treatment is therefore still debated.

Another treatment option for patients with JIA is canakinumab, a fully humanized monoclonal antibody against IL-1. In 2012, two phase III parallel studies showed the efficacy of monthly subcutaneous canakinumab (4 mg/kg) in sJIA with active systemic features. In trial 1, a single injection of canakinumab resulted in inactive disease within 15 days in 33 % of patients. The results of trial 1 were corroborated by those of trial 2, which showed that 31 (62 %) of 50 patients continuously treated with canakinumab had inactive disease status. These controlled studies [22] led to FDA and EMA approval.

Tocilizumab, a humanized monoclonal antibody against IL-6 receptor, is also approved and recommended in patients with persistently active sJIA. In a randomized, double-blind, phase III study, 56 children with refractory disease were treated with three doses of tocilizumab 8 mg/kg every 2 weeks during a 6-week open-label lead-in phase. A total of 91 % of the patients responded and were randomized to continue tocilizumab or switched to placebo for 12 weeks. By week 48 of the extension phase, 98 % of the patients achieved an ACR Pediatric 30 response. Laboratory indicators of acute-phase reactants changed rapidly within 2 weeks after the first infusion of tocilizumab. IL-6-R inhibition rapidly returned body temperature to normal and increased the median hemoglobin concentration [23].

Positive results were also demonstrated in another multicenter controlled trial in which 112 children with active sJIA were randomized to receive tocilizumab or placebo every 2 weeks for 12 weeks. The primary outcome (JIA ACR 30 response and absence of fever) occurred in 85 % of patients who received tocilizumab compared with 24 % who received placebo [24].

5 Enthesitis-Related Arthritis

Enthesitis-related arthritis (ERA) is a subset of JIA that preferentially affects boys, most frequently in the pre-adolescent and adolescent age group. Human leukocyte antigen (HLA)-B27 is associated with this subset, although it is not required for diagnosis. Extra-articular manifestations (gastrointestinal, ocular, mucosal, and cutaneous) occur in a variable portion of patients. Unlike adult ankylosing spondylitis (AS), inflammatory back pain is rarely present at onset, even though sacroiliac and spinal involvement may occur in up to two-thirds of patients during the first 10 years of disease [25].

Initiation of a TNF inhibitor is recommended for patients who have received an adequate trial of standard therapy (NSAIDs, methotrexate, sulfasalazine) and have high disease activity and/or features of poor prognosis such as radiographic joint damage. Adalimumab has been recently shown to be effective in this JIA category [26].

6 Psoriatic Arthritis

Juvenile psoriatic arthritis (JPsA) is defined as arthritis associated either with psoriasis or with two of the following features: dactylitis, nail pitting or onycholysis, psoriasis in a first-degree relative [2].

While treatment for adult psoriatic arthritis includes four FDA-approved TNF inhibitors (infliximab, etanercept, adalimumab, and golimumab) [27–30], recommendations in JPsA are extrapolated from pJIA and include NSAIDs, DMARDs, and anti-TNF agents. NSAIDs are often employed initially but typically do not induce remission. Large joints can be treated with glucocorticoid joint injections. In patients with involvement of multiple joints, DMARDs, such as sulfasalazine or methotrexate, are indicated. An inadequate response is addressed by the addition of a second DMARD or, increasingly, the addition of or substitution with a TNFα inhibitor.

7 Newer And Future Treatments

Despite the established practice with NSAIDs and DMARDs and the availability of biologic drugs for patients with JIA, the need for the development of more treatment options remains. For patients who have not responded to classic anti-rheumatic therapy, new drugs will revolutionize treatment and outcome. We discuss here the possible future treatments for arthritis currently under study in children, focusing on biologic and targeted synthetic therapies, and including evidence supporting efficacy and

safety of these therapies. Finally, we mention products that are in the pipeline and may prove useful in the near future for rheumatoid arthritis and JIA.

7.1 Anti-Tumor Necrosis Factor

A trial of golimumab, another TNF inhibitor, has been completed for pJIA. This randomized, double-blind, placebo-controlled study evaluated the efficacy and safety of golimumab in patients with active JIA and at least five joints with active arthritis with poor response to methotrexate. It was a phase III study, 173 patients were enrolled, and outcomes were percentages of participants with ACR 30 response at week 16 and week 48, who did not experience a flare of disease through week 48 (NCT01230827). However, the trial has failed to meet primary and major secondary endpoints.

A new trial of golimumab in pJIA, started December 2014, is currently recruiting participants (NCT02277444). This is a phase III, multicenter, open-label trial, with the purpose of evaluating the pharmacokinetics of golimumab administered intravenously to pediatric participants with pJIA. The study is currently ongoing, and results have not yet been published.

Another TNF inhibitor under study in pJIA is certolizumab pegol, in the trial Pediatric Arthritis Study of Certolizumab Pegol (NCT01550003). This is a phase III, multi-center, open-label study to assess the pharmacokinetics, safety, and efficacy of certolizumab pegol in children and adolescents with moderately to severely active pJIA. The study is currently ongoing, and no study results have been posted. Obviously, these last two drugs have not yet been approved.

7.2 Anti Interleukin (IL)-1

Rilonacept is an anti-IL1, acting as a soluble decoy receptor for IL-1. In 2013, Lovell et al. [31] studied 23 sJIA patients who first received rilonacept or placebo then 23 months of open-label treatment. No significant differences in efficacy were observed between the rilonacept- or placebo-treated patients during the double-blind phase, but fever and rash completely resolved by month 3 in all patients during the open-label treatment period and did not recur. The drug is neither FDA approved nor available in Europe.

7.3 Anti IL-6

IL-6 is a pro-inflammatory cytokine that plays a key role in the pathogenesis of sJIA [32]. Antagonists of IL-6 also include sarilumab, which has been used in adults with RA. There are currently no ongoing trials in children with sJIA, but in adults fewer adverse events have been reported than with tocilizumab [33]. In the SARIL-RA-MOBILITY trial [34], a favorable response to therapy was seen over 12 weeks.

Sirukumab and clazakizumab are two humanized monoclonal antibodies against IL-6. Neither is currently in use for children with sJIA, but some studies have been undertaken in adults. Sirukumab is undergoing phase III clinical studies in RA [33]. In the phase II study (SIROUND-D) in patients with active RA, improvements in the signs/symptoms of RA were seen, but one patient died of a brain aneurysm [35]. Clazakizumab is also used in adults with RA, and a phase II study in patients with active RA despite methotrexate demonstrated efficacy at various doses (80, 160, 320 mg, with two administrations at day 1 and week 8) compared with placebo, with rapid and significant improvements in disease activity [36].

7.4 Janus (JAK) Kinase Inhibitors

Another important group of new treatments for RA targets Janus (JAK) kinases. The JAK are a family of four tyrosine-receptor kinases (JAK1, JAK2, JAK3, JAK4) that play a pivotal role in cytokine receptor signaling pathway via their interaction with signal transducers and activators of transcription proteins. These proteins are very important in regulating inflammatory pathways [37]. Different trials are now investigating the efficacy (NCT02592434), long-term safety (NCT 015500551), and pharmacokinetics (NCT01513902) of tofacitinib, the first kinase inhibitor approved for inflammatory diseases [38–42]. The drug is approved for RA in the USA but not in Europe, and a pediatric trial is ongoing.

7.5 Anti IL-12/IL-23

Ustekinumab, a monoclonal antibody directed against the p40 subunit of IL-12 and IL-23, received FDA approval to treat PsA in September 2013, supported by findings from two phase III, multicenter, randomized controlled trials [44, 45]. The drug is approved for the treatment of children aged >12 years with resistant psoriasis.

7.6 Phosphodiesterase Inhibitors

Apremilast is a small molecule that specifically inhibits phosphodiesterase 4, resulting in increased cyclic adenosine monophosphate (AMP) in immune cells, which can down-regulate the inflammatory responses by inhibiting expression of inflammatory cytokines and increasing expression of anti-inflammatory mediators [46]. The FDA approved apremilast for the treatment of adult PsA in March 2014, based on the results of the PALACE 1, 2, 3, and 4 studies that included approximately 1500 patients with active disease treated with

DMARDs and/or biological agents [47]. Apremilast seems to be more effective on skin involvement, with less efficacy on arthritis and enthesitis.

7.7 Others

Infliximab, a chimeric monoclonal antibody to TNFα, was shown to be efficacious in adult AS, which is considered the adult equivalent of pediatric ERA. With current biologic therapeutics approaching patent expiration, there has been considerable interest in developing biosimilar products, which are similar but not identical to approved 'reference' agents [48]. In this study, patients affected by AS were randomized to receive 5 mg/kg of CT-P13 ($n = 125$) or infliximab ($n = 125$), and the results showed that the pharmacokinetic profiles of biosimilar and 'reference' agents were equivalent. CT-P13 was well tolerated, with an efficacy and safety profile comparable to that of infliximab up to week 30. As yet, no studies about biosimilars in pediatric populations have been undertaken.

Rituximab is a chimeric monoclonal antibody to the B-cell antigen CD20 that has been approved for adult-onset RA refractory to anti-TNF therapy [49–51]. Most reports in children are studies in sJIA [52, 53]. Despite this lack of evidence, there is a recommendation from the ACR for the use of rituximab for severe, unresponsive pJIA [11]. UK NHS guidelines recommend rituximab use in pJIA with rheumatoid factor (RF)-positive patients in whom two TNFα inhibitors have failed [54].

Agents targeting IL-6, such as sarilumab, ALX-0061, sirukumab, MEDI5117, clazakizumab, and olokizumab [33], are all in different study plans and stages for the treatment of RA. Of these, sarilumab and ALX-0061 differ from tocilizumab in structure and affinity. Sarilumab is the first human monoclonal antibody against IL-6Rα, and a phase III clinical trial is underway. According to the results from a clinical trial, the number of patients who achieved an ACR20 improvement was higher in the group that received sarilumab 150 mg weekly than in the group that received placebo [34]. Clinical trials comparing the efficacy of sarilumab versus tocilizumab, and sarilumab versus etanercept plus methotrexate, are currently underway [33]. Sirukumab is also not currently commercially available in the USA, but has been used in RA and is undergoing phase III clinical studies [33]. The clinical efficacy of sirukumab has been suggested in a phase II clinical study (SIROUND-D) that showed significant improvement in most evaluation criteria, including ACR50, Disease Activity Score (DAS), and clinical disease activity index [35].

Although some 30 kinase inhibitors have been approved for therapeutic use, it was only in November 2012 that the first kinase inhibitor (tofacitinib) was approved for the treatment of an inflammatory disease [38–42]. The other JAK inhibitors currently in clinical development include JAK1 and JAK2 (baricitinib), JAK1 and JAK3 (peficitinib), JAK3 (decernotinib), JAK1 (filgotinib, INCB-039110, ABT-494, and INCB-047986), or JAK2 (AC-410). Baricitinib inhibits JAK1/2. In a phase II study, 301 patients with moderate to severe RA despite methotrexate were treated with baricitinib (1, 2, 4, or 8 mg) once daily on background methotrexate therapy. Baricitinib produced a highly significant improvement in the ACR20 response at the two highest doses. The combined data from these doses showed a 76 % response, highly significant compared with the 40 % response of the placebo group, with effects evident after 2 weeks of treatment. The two highest doses also produced significant improvements in the ACR50 and ACR70 response rates [37]. Vertex decernotinib (VX-509) is a selective JAK3 inhibitor in clinical development. A phase IIb study used both once- and twice-daily dosing in 350 RA patients poorly responsive to methotrexate. Results showed an improvement of ACR20, ACR50, ACR70, and DAS28 values with the higher doses [43].

Secukinumab, an anti-IL17A monoclonal antibody, is FDA approved for psoriasis, and studies have demonstrated its efficacy in PsA [55–58].

8 Conclusions

Advances in the understanding the mechanisms of inflammation and autoimmunity have translated into drug development. Biologic treatments have modified the natural history of JIA, improving the long-term outcome. Fortunately, images of children with destructive arthritis, severe joint deformities, growth retardation, or disability are quickly becoming history and reminders of just how far we have come.

In previous decades, high-quality research studies in children were scanty, and data largely came via extrapolation from adult studies. The creation of pediatric rheumatology research groups (e.g., PRINTO [Paediatric Rheumatology International Trials Organisation] and CARRA [Childhood Arthritis & Rheumatology Research Alliance]) has enabled the development of larger, multicenter and international studies to be conducted, providing more accurate efficacy and safety evidence. Anti-cytokine drugs have revolutionized the treatment of JIA. Small molecules and biosimilars represent new areas of interest and, while the majority are not yet commercially available for use in children, preliminary studies appear promising.

The achievements obtained in physical and functional outcomes of children with JIA not only positively impact their quality of life, but also the lives of their families, resulting in fewer missed days from school and work. Hopefully, with research in basic mechanisms of the

disease and predictors of outcome, we will be able to tailor treatment to individual patients, with the aim of obtaining rapid remission while avoiding unnecessary treatments.

Compliance with Ethical Standards

Conflict of interest I Pagnini, F Bertini, and R Cimaz declare no conflicts of interest.

Funding No sources of funding were used to support the writing of this manuscript.

References

1. Ravelli A, Martini A. Juvenile idiopathic arthritis. Lancet. 2007;369:767–8.
2. Petty RE, Soutwood TR, Manners OP, Baum J, Glass DN, Goldenberg H, et al. International League of Association for Rheumatology classification of juvenile idiopathic arthritis: second version, Edmonton, 2001. J Rheumatol. 2004;31:390–2.
3. Lovell DJ, Giannini EH, Reiff A, Cawkell GD, Silverman ED, Norton JJ, et al. Etanercept in children with polyarticular juvenile rheumatoid arthritis. N Engl J Med. 2000;342:763–9.
4. Ruperto N, Lovell DJ, Cuttica R, Wilkinson N, Woo P, Espada G, et al. A randomized, placebo-controlled trial of infliximab plus methotrexate for the treatment of polyarticular-course juvenile rheumatoid arthritis. Arthritis Rheum. 2007;56:3096–106.
5. Silverman E, Mouy R, Spiegel L, Jung LK, Sautermann RK, Lahdenne P, et al. Leflunomide or methotrexate for juvenile rheumatoid arthritis. N Engl J Med. 2005;352:1655–66.
6. Lovell DJ, Ruperto N, Goodman S, Reiff A, Jung L, Jarosova K, et al. Adalimumab with or without methotrexate in juvenile rheumatoid arthritis. N Engl J Med. 2008;359:810–20.
7. Giannini EH, Brewer EJ, Kuzmina N, Shaikov A, Maximov A, Vorontsov I, et al. Methotrexate in resistant juvenile idiopathic arthritis: results of the U.S.A.-U.R.S.S. double blind, placebo-controlled trial. N Engl J Med. 1992;326:1043–9.
8. Ruperto N, Murray KJ, Gerona V, Wulffrat N, de Oliveira SK, Falcini F, et al. A randomized trial of parenteral methotrexate comparing an intermediate dose with a higher draw in children with juvenile idiopathic arthritis who failed to response to standard doses of methotrexate. Arthritis Rheum. 2004;50:2191–201.
9. Ruperto N, Lovell DJ, Quartier P, Paz E, Rubio-Pérez N, Silva CA, et al. Long-term safety and efficacy of abatacept in children with juvenile idiopathic arthritis. Arthritis Rheum. 2010;62:1792–802.
10. Hashkes PJ, Laxer RM. Medical treatment of juvenile idiopathic arthritis. JAMA. 2005;294:1671–84.
11. Beukelman T, Patkar NM, Saag KG, Tolleson-Rinehart S, Cron RQ, DeWitt EM, et al. 2011 American College of Rheumatology recommendations for the treatment of juvenile idiopathic arthritis: initiation and safety monitoring of therapeutic agents for the treatment of arthritis and systemic features. Arthritis Care Res. 2011;63:465–82.
12. Lovell DJ, Reiff A, Illowite NT, Wallace CA, Chon Y, Lin SL, et al. Safety and efficacy of up to eight years of continuous etanercept therapy in patients with juvenile idiopathic arthritis. Arthritis Rheum. 2008;58:1496–504.
13. Hayward K, Wallace CA. Recent development in anti-rheumatic drugs in pediatrics: treatment of juvenile idiopathic arthritis. Arthritis Res Ther. 2009;11:216.
14. Bartoli M, Tarò M, Magni-Manzoni S, Pistorio A, Traverso F, Viola S, et al. The magnitude of early response to methotrexate therapy predicts long-term outcome of patients with juvenile idiopathic arthritis. Ann Rheum Dis. 2008;67:370–4.
15. Ruperto N, Lovell DJ, Quartier P, Paz E, Rubio-Pèrez N, Silva CA, et al. Abatacept in children with juvenile idiopathic arthritis: a randomized, double-blind, placebo-controlled withdrawal trial. Lancet. 2008;372:383–91.
16. Brunner HI, Ruperto N, Zuber Z, Keane C, Harari O, Kenwright A, et al. Efficacy and safety of tocilizumab in patients with polyarticular-course juvenile idiopathic arthritis: results from a phase 3, randomized, double-blind withdrawal trial. Ann Rheum Dis. 2015;74:1110–7.
17. Tynjälä P, Vähäsalo P, Tarkiainen M, Kröger L, Aalto K, Malin M, et al. Aggressive combination drug therapy in very early polyarticular juvenile idiopathic arthritis (ACUTE-JIA): a multicenter randomized open-label clinical trial. Ann Rheum Dis. 2011;70:1605–12.
18. Ringold S, Weiss PF, Beukelman T, DeWitt EM, Illowite NT, Kimura Y, et al. 2013 update of the 2011 American College of Rheumatology recommendations for the treatment of juvenile idiopathic arthritis: recommendations for the medical therapy of children with systemic juvenile idiopathic arthritis and tuberculosis screening among children receiving biologic medications. Arthritis Rheum. 2013;65:2499–512.
19. Woo P, Southwood TR, Prieur AM, Doré CJ, Grainger J, David J, et al. Randomized, placebo-controlled, crossover trial of low-dose oral methotrexate in children with extended oligoarticular or systemic arthritis. Arthritis Rheum. 2000;43:1849–57.
20. Quartier P, Allantaz F, Cimaz R, Pillet P, Messiaen C, Bardin C, et al. A multicenter, randomized, double-blind, placebo-controlled trial with the interleukin-1 receptor antagonist anakinra in patients with systemic-onset juvenile idiopathic arthritis (ANAJIS trial). Ann Rheum Dis. 2011;70:747–54.
21. Nigrovic PA, Mannion M, Prince FH, Zeft A, Rabinovich CE, van Possum MA, et al. Anakinra as first-line disease modifying therapy in systemic juvenile idiopathic arthritis: report of forty-six patients from an international multicenter series. Arthritis Rheum. 2011;63:545–55.
22. Ruperto N, Brunner HI, Quartier P, Constantin T, Wulffraat N, Hoffer G, et al. Two randomized trials of canakinumab in systemic juvenile idiopathic arthritis. N Engl J Med. 2012;367:2396–406.
23. Yokota S, Imagawa T, Mori M, Miyamae T, Amhara Y, Takei S, et al. Efficacy and safety of tocilizumab in patients with systemic-onset juvenile idiopathic arthritis: a randomized, double-blind, placebo-controlled, withdrawal phase III trial. Lancet. 2008;371:998–1006.
24. De Benedetti F, Brunner HI, Ruperto N, Kenwright A, Wright S, Calvo I, et al. Randomized trial of tocilizumab in systemic juvenile idiopathic arthritis. N Engl J Med. 2012;367:2385–95.
25. Pagnini I, Savelli S, Matucci-Cerinic M, Fonda C, Cimaz R, Simonini G. Early predictors of juvenile sacroiliitis in enthesitis-related Arthritis. J Rheumatol. 2010;37:2395–401.
26. Bugos-Vargas R, Tse SM, Horneff G, Pangan AL, Kalabic J, Goss S. A randomized, double-blind, placebo-controlled multicenter study of adalimumab in pediatric patients with enthesitis-related arthritis. Arthitis Res Care (Hoboken). 2015;67:1503–12.
27. Mease PJ, Goffe BS, Metz J, VanderStoep A, Finck B, Burge DJ. Etanercept in the treatment of psoriasis arthritis: a randomized trial. Lancet. 2000;356:385–90.
28. Mease PJ, Gladman DD, Ritchlin CT, Ruderman EM, Steinfeld SD, Choy EH, et al. Adalimumab for the treatment of patients with moderately to severely active psoriasis arthritis: results of a double-blind, randomized, placebo-controlled trial. Arthritis Rheum. 2005;52:3279–89.
29. Antoni CE, Kavanaugh A, van der Hejide D, Beutler A, Keenan G, Zhou B, et al. Two-year efficacy and safety of infliximab

treatment in patients with active psoriasis arthritis: finding of the Infliximab Multinational Psoriatic Arthritis Controlled Trial (IMPACT). J Rheumatol. 2008;35:869–76.
30. Kavanaugh A, McInnes I, Mease P, Krueger GG, Gladden D, Gomez-Reino J, et al. Golimumab, a new human tumor necrosis factor alpha antibody, administered every four weeks as a subcutaneous injection in psoriasis arthritis: twenty-four-week efficacy and safety results of a randomized, placebo-controlled study. Arthritis Rheum. 2009;60:976–86.
31. Lovell DJ, Giannini EH, Reiff AO, Kimura Y, Li S, Hashkes PJ. Long-term safety and efficacy of rilonacept in patient with systemic juvenile arthritis. Arthritis Rheum. 2013;65:2486–96.
32. De Benedetti F, Martini A. Is systemic juvenile rheumatoid arthritis an interleukin 6 mediated disease? J Rheumatol. 1998;25:203–7.
33. Kim GW, Lee NR, Pi RH, Lim YS, Lee YM, Lee JM, et al. IL-6 inhibitors for treatment of rheumatoid arthritis: past, present, and future. Arch Pharm Res. 2015;38:575–84.
34. Huizinga TW, Fleischmann RM, Jasson M, Radin AR, van Adelsberg J, Fiore S, et al. Sarilumab, a fully human monoclonal antibody against IL-6R in patients with rheumatoid arthritis and an inadequate response to methotrexate: efficacy and safety results from the randomized SARIL-RA-MOBILITY Part A trial. Ann Rheum Dis. 2014;73:1626–34.
35. Smolen JS, Weinblatt ME, Sheng S, Zhuang Y, Hsu B. Sirukumab, a human anti-interleukin-6 monoclonal antibody: a randomized, 2-part (proof-of-concept and dose- finding), phase II study in patients with active rheumatoid arthritis despite methotrexate therapy. Ann Rheum Dis. 2014;73:1616–25.
36. Mease P, Strand V, Shalamberidze L, Dimic A, Raskina T, Xu LA, et al. A phase II, double-blind, randomized, placebo-controlled study of BMS945429 (ALD518) in patients with rheumatoid arthritis with an inadequate response to methotrexate. Ann Rheum Dis. 2012;71:1183–9.
37. Norman P. Selective JAK inhibitors in development for rheumatoid arthritis. Expert Opin Invest Drugs. 2014;23:1067–77.
38. O'Sullivam LA, Lioungue C, Lewis RS, Stephenson SE, Ward AC. Cytokine receptor signaling through the Jak-Stat-Socs pathway in disease. Mol Immunol. 2007;44:2497–506.
39. LaBranche TP, Jesson MI, Radi ZA, Storer CE, Guzova JA, Bonar SL, et al. JAK inhibition with tofacitinib suppresses arthritis joint structural damage through decreased RANKL production. Arthritis Rheum. 2012;64:3531–42.
40. Fleischmann R, Kremer J, Cush J, Schulze-Koops H, Connel CA, Bradley JD, et al. Placebo-controlled trial of tofacitinib monotherapy in rheumatoid arthritis. N Engl J Med. 2012;367:495–507.
41. van Vollenhoven RF, Fleischmann R, Cohen S, Lee EB, Garcìa Meijide JA, Wagner S, et al. Tofacitinib or adalimuamb versus placebo in rheumatoid arthritis. N Engl J Med. 2012;367:508–19.
42. Berhan A. Efficacy, safety and tolerability of tofacitinib in patients with an inadequate response to disease modifying antirheumatic drugs: a meta-analysis of randomized double blind controlled studies. BMC Muscoloskelet Disord. 2013;14:332.
43. Fleishmann RM, Damjanov NS, Kibitz AJ, Legedza A, Hoock T, Kinnman N. A randomized double-blind placebo-controlled, twelve-week, dose-ranging study on decernotinib, an oral selective JAK3 inhibitor, as monotherapy in patient with active rheumatoid arthritis. Arthritis Rheum. 2015;67:334–43.
44. McInnes IB, Kavanaugh A, Gottlieb AB, Puig L, Rahman P, Ritchlin C, et al. Efficacy and safety of ustekinumab in patients with active psoriasis arthritis: 1 year results of the phase 3, multicenter, double-blind, placebo-controlled PSUMMIT 1 trial. Lancet. 2013;382:780–9.
45. Ritchlin C, Rahman P, Kavanaugh A, McInnes IB, Puig L, Li S, et al. Efficacy and safety of the anti-IL12/23 p40 monoclonal antibody, ustekinumab, in patient with active psoriatic arthritis despite conventional nonbiological and biological anti tumor necrosis factor therapy; 6-month and 1-year results of the phase 3, multicenter, double-blind, placebo-controlled PSUMMIT 2 trial. Ann Rheum Dis. 2014;73:990–9.
46. Schafer P. Apremilast mechanism of action and application to psoriasis arthritis. Biochem Pharmacol. 2012;83:1583–90.
47. Kavanaugh A, Mease P, Gomez-Reino JJ, Adebajo AO, Wollenhaupt J, Gladden DD, et al. Treatment of psoriatic arthritis in a phase 3 randomized, placebo-controlled trail with apremilast, an oral phosphodiesterase 4 inhibitor. Ann Rheum Dis. 2014;73:1020–6.
48. Park W, Hrycaj P, Jeka S, Kovalenko V, Lysenko G, Miranda P, et al. A randomized, double-blind, multi center, parallel-group, prospective study comparing the pharmacokinetics, safety, and efficacy of CT-P13 and innovator infliximab (INX) in patient with ankylosing spondylitis: the PLANETAS study. Ann Rheum Dis. 2013;72:1605–12.
49. Mease PJ, Cohen S, Gaylis NB, Chubick A, Kaell AT, Greenwald M, et al. Efficacy and safety of retreatment in patients with rheumatoid arthritis with previous inadequate response to tumor necrosis factor inhibitors: result from the SUNRISE trial. J Rheumatol. 2010;37:917–37.
50. Lopez-Olivo MA, Amezaga Urruela M, McGahan L, et al. Rituximab for rheumatoid arthritis. Cochrane Database Syst Rev. 2015;(1):CD007356.
51. Cohen SB, Emery P, Greenwald MW, Dougados M, Furie RA, Genovese MC, et al. Rituximab for rheumatoid arthritis refractory to antitumor necrosis factor therapy: results of a multicenter, randomized, double-blind, placebo controlled, phase III trial evaluating primary efficacy and safety at twenty-four weeks. Arthritis Rheum. 2006;54:2793–806.
52. Narvàez J, Diaz-Tornè C, Juanola X, Geli C, Llobet JM, Nolla JM, et al. Rituximab therapy for refractory systemic onset juvenile idiopathic arthritis. Ann Rheum Dis. 2009;68:607–8.
53. Feito JG, Pereda CA. Rituximab therapy produced rapid and sustained clinical improvement in a patient with systemic onset juvenile idiopathic arthritis refractory to TNF alpha antagonist. J Clin Rheumatol. 2009;15:363–5.
54. NHS England clinical reference group for paediatric medicine. Interim clinical commissioning policy statement: biologic therapies for the treatment of juvenile idiopathic arthritis (JIA). 2015. https://www.engage.england.nhs.uk/consultation/specialised-services-policies/user_uploads/biolgcs-juvenl-idiop-arthrs-pol.pdf.
55. Felquer ML, Soriano ER. New treatment paradigms in psoriatic arthritis: an update on new therapeutics approved by the U.S. Food and Drug Administration. Curr Opin Rheumatol. 2015;27:99–106.
56. McInnes IB, Sieper J, Braun J, Emery P, van der Heijde D, Isaacs JD, et al. Efficacy and safety of secukinumab a fully human anti-interleukin-17A monoclonal antibody, in patients with moderate-to-severe psoriatic arthritis: a 24 week, randomized, double blind, placebo controlled, phase II proof-of-concept trial. Ann Rheum Dis. 2014;73:349–56.
57. McInnes IB, Mease PJ, Kirkham B, Kavanaugh A, Ritchlin CT, Rahman P, et al. Secukinumab, a human anti-interleukin-17A monoclonal antibody, in patients with psoriatic arthritis (FUTURE 2): a randomized, double blind, placebo controlled, phase3 trial. Lancet. 2015;386:1137–46.
58. Mease PJ, McInnes IB, Kirkham B, Kavanaugh A, Rahman P, van der Heijde D, et al. Secukinumab inhibition of interleukin-17A in patients with psoriatic arthritis. N Engl J Med. 2015;373:1329–39.