Juvenile idiopathic arthritis: management and therapeutic options

Ther Adv Musculoskel Dis
(2012) 4(2) 99–110
DOI: 10.1177/1759720X11413630

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***Abstract*:** The goals of treatment for juvenile idiopathic arthritis (JIA) include: suppression of inflammation, achievement of remission, relief of pain, maintenance of function and doing so with minimal toxicity. Important discoveries over the past 10–15 years have led to more targeted treatments for children with JIA. The International League of Associations for Rheumatology (ILAR) classification system for childhood arthritides, better assessment tools for clinical response, improved definitions of remission, new imaging techniques and evidence in gene expression profiling have all contributed to the development of more targeted treatments. Nonsteroidal anti-inflammatory agents still have a role in mild disease and intra-articular steroid injections continue to be used most commonly in patients with oligoarticular JIA. Disease-modifying agents such as methotrexate have demonstrated efficacy and safety; however, in many patients, the disease remains active despite this treatment. These children now receive more targeted treatment including the tumor necrosis factor alpha (TNFα) inhibitors, interleukin-1 blockade, interleukin-6 blockade, selective costimulation modulators and selective B-cell blockade. The biologic targeted therapies have changed the strategy in which we treat our children with JIA; however, there remains much to be learned about the long-term effects and safety of these medicines.

***Keywords*:** juvenile idiopathic arthritis, non-steroidal anti-inflammatory drugs, disease-modifying agents, tumor necrosis factor alpha inhibitors, interleukin-1 blockade, interleukin-6 blockade, selective costimulation modulators, selective B-cell blockade

Introduction

The goals of treatment of juvenile idiopathic arthritis (JIA) include suppression of inflammation with achievement of remission, relief of pain, maintenance of function, and minimizing toxicity. Advances in classification of JIA, definition of remission, improved imaging techniques, gene expression research, and biomarkers have improved our understanding of childhood arthritis and facilitated better treatments and outcomes. A multidisciplinary team approach to the management of the patients is important. The role of allied health professionals in the management of JIA has evolved in importance. Physical and occupational therapy, nurse practitioners and advanced practice nurses, clinic nurses, nutritionists, and social workers have significantly improved the care of children with arthritis; however, their specific roles will not be discussed in the scope of this paper.

In the early 1990s, the global growth of the pediatric rheumatology community spawned the need for improved communication. In 1994, a committee of ILAR (International League of Associations for Rheumatology) was convened to develop criteria for the types of chronic idiopathic childhood arthritides in order to have more homogeneous groups. In the ILAR classification system, the term JIA replaced both juvenile chronic arthritis (JCA) and juvenile rheumatoid arthritis (JRA). The onset of arthritis was defined as occurring before 16 years old and duration of a minimum of 6 weeks. JIA was then divided into seven subgroups each with a specific clinical phenotype [Krumrey-Langkammerer and Hafner, 2001]. These ILAR classification criteria facilitated communication and research analysis which will lead to improved international collaboration and advance use of improved treatments and better understanding of outcomes.

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Also in the mid-1990s, the assessment of clinical response in JIA was not standardized and multiple outcome measures were utilized. Thus, a standardized core set of measures and a definition of improvement for the evaluation of response to therapy in JIA was developed. This definition has been adopted by the Food and Drug Administration (FDA) and the American College of Rheumatology (ACR) as the primary outcome for all clinical trials involving children with JIA [Giannini *et al.* 1997]. Criteria for inactive disease and clinical remission on and off medication for oligoarticular and polyarticular JIA was developed by Wallace and colleagues [Wallace *et al.* 2004]. Inactive disease was defined as: no joints with active arthritis, no fever, rash, serositis, splenomegaly or generalized lymphadenopathy attributable to JIA, no active uveitis, normal erythrocyte sedimentation rate (ESR) and C-reactive protein (CRP) and a physician's global assessment of disease activity indicating no disease activity. Clinical remission was divided into two types: clinical remission on medication and clinical remission off medication. In the 'on medication' group, the criteria for inactive disease are required for a minimum of 6 continuous months and in the 'off medication' group, the criteria for inactive disease are required for 12 continuous months.

New therapeutic strategies have created a growing need for a reproducible radiographic assessment standard for evaluation of structural joint damage in JIA [Damasio *et al.* 2010]. Assessment of structural damage is a clinical trials key outcome endpoint in efficacy studies and is now required by the FDA as a measure of disease progression in disease-modifying antirheumatic drugs (DMARDs) in patients with rheumatoid arthritis (RA) [Center for Drug Evaluation and Research, 1999]. New imaging techniques such a diffusion-weighted and perfusion imaging, delayed gadolinium-enhanced cartilage imaging, T2 relaxation time mapping and quantitative computer-assisted tools for MRI are under evaluation for better and earlier assessment of synovial, cartilaginous or osseous abnormalities [Damasio *et al.* 2010].

Genetic and molecular markers are also emerging as important in the classification of patients and determining which patients will remain in remission or will flare from their disease. Gene expression profiling is the method most commonly used thus far to enrich our understanding of the molecular basis of RA and JIA [Jarvis and Frank, 2010]. The feasibility of this approach for patient classification (for example, active *versus* inactive disease, disease subsets) and assessment of response to therapy has been demonstrated over the past 7 years [Jarvis and Frank, 2010]. Myeloid related proteins (MRPs) 8 and 14 are specifically secreted during interaction of phagocytes and activated endothelium and have been shown to be useful biomarkers for monitoring disease activity [Frosch *et al.* 2000].

Treatment of JIA

The treatment of JIA has changed over the past 20 years both in the armamentarium of medications used and the approach to therapy [Hashkes *et al.* 2010]. In the past, JIA was treated with nonsteroidal anti-inflammatory drugs (NSAIDs) with delayed addition of advanced therapy; often after cartilage damage had occurred. Cohort studies have demonstrated increased evidence for earlier, more aggressive approach to treatment [Albers *et al.* 2009; Minden, 2009; van Rossum *et al.* 2007]. Clinical trials research has been directed at more targeted therapies based on what has been learned about the pathophysiology of disease.

Intra-articular steroid injections

Intra-articular corticosteroid injections (IACIs) are utilized for active arthritis, usually with a small number of active joints [Ilowite, 2002]. It is used most commonly in oligoarticular JIA but may also be used in other subtypes of JIA when a few joints remained inflamed despite systemic therapy or as a bridge therapy in patients with polyarticular disease as advanced drug therapy is beginning to gain control. Many studies have focused on the duration of sustained benefit after IACI which appears to vary widely [Ravelli *et al.* 2001; Breit *et al.* 2000; Padeh and Passwell, 1998]. Investigators have found that concomitant use of methotrexate effects longer periods of remission [Marti *et al.* 2008]. Additional studies have demonstrated a superior efficacy of triamcinolone hexacetonide compared to triamcinolone acetonide [Eberhard *et al.* 2004; Zulian *et al.* 2004]. In 2008, Unsal and Makay studied thirty seven children with JIA who were treated with one or more IACI; 95 joints were injected with a total number of 125 injections [Unsal and Makay, 2008]. Complete remission of the joint inflammation lasting at least 6 months was obtained in 62 of 95 injections (65%). Treatment of the joint contractures was

successful in 35 of 51 joints (69%). In patients with oligoarticular arthritis, 21 of 26 injected joints (81%) were in full remission at 6 months. The 6-month remission was significantly lower in the other subtypes of JIA. These authors concluded that IACIs are an effective and safe treatment for inflammatory joints in JIA, particularly in the oligoarticular form. Padeh and colleagues studied 71 patients with JIA and also concluded that IACI was a safe and effective mode of therapy especially for patients with oligoarticular JIA and was effective in correcting joint contractures and deformities [Padeh and Passwell, 1998]. There is considerable variability in the treatment strategy for monoarthritis in JIA; NSAID *versus* IACI [Beukelman *et al.* 2007]. Utilizing a decision analysis model Beukelman and colleagues concluded that IACI appears to be the optimal treatment strategy in monoarthritis in JIA [Beukelman *et al.* 2008].

Nonsteroidal anti-inflammatory drugs

NSAIDs have been recommended as one treatment approach for patients with low disease activity and without evidence of joint contracture; however, the 2010 American College of Rheumatology guidelines for the treatment of JIA suggests that continuing NSAID monotherapy (without additional therapy) for longer than 2 months was inappropriate for patients with active arthritis irrespective of poor prognostic features; defined as arthritis of hip or cervical spine, ankle or wrist; and marked or prolonged inflammatory marker elevation; or evidence of radiographic damage [Beukelman *et al.* 2011; Giannini *et al.* 1990; Bhettay, 1986].

Disease-modifying antirheumatic drugs

Methotrexate has been used in the treatment of JIA for nearly 20 years and has been the cornerstone of treatment for many patients with JIA. A new era of treatment started in 1992 with a randomized controlled trial showing methotrexate administered weekly at 10 mg/m^2 was superior to placebo or 5 mg/m^2 [Giannini *et al.* 1992]. In 2004 Ruperto and colleagues showed that by increasing the dose of methotrexate to 15 mg/m^2 per week and giving methotrexate parenterally was effective for most patients not responsive to 10 mg/m^2 per week. He also reported that there was no additional advantage to giving the higher doses of up to 30 mg/m^2 per week [Ruperto *et al.* 2004]. The greatest efficacy of methotrexate was seen in patients with extended oligoarthritis, while in a randomized study no significant effect was found in patients with systemic arthritis [Woo *et al.* 2000; Ravelli *et al.* 1999b, 1994; Halle and Prieur, 1991]. Two small uncontrolled series have demonstrated that methotrexate may decrease the rate of progression of radiographic joint damage [Ravelli *et al.* 1998; Harel *et al.* 1993].

Foell and colleagues investigated whether longer methotrexate treatment during remission of JIA prevents flares after withdrawal of medication and whether MRP 8/14 biomarkers identify patients at risk for flares [Foell *et al.* 2010]. The study was a prospective, open, medication withdrawal randomized clinical trial including 364 patients with JIA. The primary outcome was relapse rate and the secondary outcome was time to relapse. In patients with JIA in remission, a 12-month *versus* 6-month withdrawal of methotrexate did not reduce the relapse rate [Foell *et al.* 2010]. Higher MRP8/14 concentrations were associated with risk of relapse after discontinuing methotrexate, suggesting subclinical activity which was not apparent when the methotrexate was discontinued [Foell *et al.* 2010].

Side effects of methotrexate include oral ulcerations, nausea and rarely significant liver enzyme abnormalities. Tests to monitor complete blood cell counts, liver-related enzymes and renal function are recommended although it is unclear how often this testing should be done. Folic acid 1 mg taken daily has been shown to decrease occurrences of nausea, oral ulcerations and perhaps liver-related enzyme abnormalities without decreasing the efficacy of methotrexate [Ravelli *et al.* 1999a; Hunt *et al.* 1997]. Prey and Paul found that supplementation with folic acid is effective to reduce adverse hepatic effects associated with methotrexate treatment as well. They also found that there is no difference in benefit between folinic acid and folic acid, but the lower cost of the folic acid encourages its use [Prey and Paul, 2009]. Nausea and gastrointestinal complaints are common in children taking methotrexate. Some patients may develop a psychological aversion to the methotrexate and may benefit from cognitive behavioral therapy and relaxation techniques [van der Meer *et al.* 2007]. Very few serious infections have been reported with the use of methotrexate. Patients should avoid live vaccinations while on methotrexate. Rare cases of Hodgkin's and non-Hodgkin's lymphoma have been reported in children on methotrexate [Hashkes and

Laxer, 2005]. Other DMARDs such as leflunomide and sulfasalazine have been successfully employed in patients with JIA [Silverman *et al.* 2005].

Foeldvari and Wierk evaluated the effectiveness of leflunomide in JIA by undertaking a retrospective review of medical records of patients with JIA who initiated treatment between April 2001 and October 2006. A total of 58 patients were included in the study and the mean duration of leflunomide was 1.45 years. The mean swollen joint count decreased from 1.40 to 0.60 and the mean tender joint count decreased from 1.83 to 0.29. Improvements were observed in childhood health assessment questionnaire (CHAQ), pain, and well-being scores [Foeldvari and Wierk, 2010]. Sulfasalzine has also been used successfully in the treatment of patients with oligoarticular and polyarticular onset JIA and that sulfasalazine treatment early in the active phase of the disease has beneficial effects that persist for many years [van Rossum *et al.* 2007, 1998].

Biologics

In many patients, the disease remains active despite treatment with IACI, NSAID and DMARDs; necessitating treatment with biologic therapies. Biologics that are currently being used include the anti-tumor necrosis factor alpha (anti-TNFα) agents (etanercept, adalimumab, infliximab), agents that target interleukin (IL)-1 (anakinra, rilonacept, canakinumab), inhibitors of T-cell costimulation (abatacept), agents that target the IL-6 receptor (tocilizumab) and agents that inhibit CD20 B cells (rituximab) (See Table 1).

TNF*a* inhibitors

Etanercept

The TNFα inhibitor etanercept is a genetically engineered fusion protein consisting of two identical chains of the recombinant extracellular human TNF-receptor p75 monomer fused with the Fc domain of a human IgG1. Etanercept binds both TNFα and lymphotoxin alpha and inhibits their activity [Danila *et al.* 2008]. It is licensed by the FDA in the United States for children over 2 years of age at a dose of 0.4 mg/kg twice weekly or 0.8 mg/kg once weekly by subcutaneous injection. Lovell and colleagues evaluated the efficacy and safety of etanercept in patients with polyarticular-course JIA who were refractory or intolerant to methotrexate. In the open-label 3 month study 69 patients received 0.4 mg/kg of etanercept twice weekly. A total of 51 (74%) responded and were then randomized in a double-blinded, placebo-controlled withdrawal study for 4 months [Lovell *et al.* 2000]. The withdrawal rate was significantly higher in the placebo group (81%) compared with the etanercept group (28%), $p < 0.003$; and the median time to flare was 28 days in the placebo group compared with 116 days in the etanercept group, $p < 0.001$. Among the 69 patients included in this study, only two severe adverse events (SAEs) were reported: one case of depression and gastroenteritis, and one treatment discontinuation owing to urticaria. Continued use of etanercept for 8 years was found to have a good safety profile and no increase in the rate of SAEs [Lovell *et al.* 2008a]. Etanercept has been shown to be affective in juvenile spondyloarthropathy, enthesitis-related arthritis (ERA), psoriatic arthritis, and extended oligoarthritis [Breda *et al.* 2011]. Etanercept has also been studied for the treatment of uveitis but no differences were found between the placebo and treatment groups [Smith *et al.* 2005].

Infliximab

Infliximab is a chimeric human/murine monoclonal antibody which possesses a human IgG1 C region and murine V regions effective in binding TNFα [Haines, 2007]. Owing to the murine fragment, infliximab retains immunogenicity and can cause anaphylaxis, lack of efficacy, and infusion reactions [Isaacs, 2009]. Infliximab is given by intravenous infusion; with frequency ranging from every 2–8 weeks, at a dose of 3–6 mg/kg [Ruperto *et al.* 2010, 2007]. Infliximab has been shown to be efficacious in juvenile ERS and in the management of refractory JIA associated uveitis. It appears more effective than etanercept for JIA-associated uveitis [McCann and Woo, 2007]. Infliximab is not FDA approved for treatment of JIA but it is approved for the use in inflammatory bowel disease (IBD), specifically in Crohn's disease (CD), where it has been demonstrated to induce clinical remission in patients with active luminal inflammatory disease [Cucchiara and Morley-Fletcher, 2007]. In the randomized, placebo-controlled trial of infliximab plus methotrexate for the treatment of polyarticular course JIA, there was a higher proportion of patients in the 3 mg/kg infliximab group than in the placebo group that achieved pediatric 30 responses; however, the between-group difference in this primary efficacy endpoint

was not statistically significant. By week 16, after the crossover from placebo to infliximab 6 mg/kg when all patients were receiving infliximab, an pediatric 30 response was achieved in 73.2% of patients and by week 52, the pediatric 50 and 70 responses had been reached in 69.6% and 51.8% of patients, respectively. Interestingly, the safety data indicated that the 3 mg/kg dose appeared less favorable than that of the 6 mg/kg dose with more frequent occurrences of adverse events. Authors concluded that these results warranted further investigation. It is possible that the infliximab study probably was a negative study because the dose of infliximab studied (3 mg/kg) was too low [Ruperto *et al.* 2007].

Adalimumab

Adalimumab is a humanized monoclonal anti-TNF antibody that offers a higher binding activity and a less immunogenic effect based on its fully humanized structure. The FDA-approved adalimumab for the treatment of active polyarticular JIA in children above the age of 4 in 2008 [Hayward and Wallace, 2009]. Adalimumab is also licensed for use in RA, ankylosing spondylitis, psoriatic arthritis, and severe CD [Shirota *et al.* 2008]. The efficacy of adalimumab was studied in a trial of 171 patients with polyarticular-course JIA [Lovell *et al.* 2008b]. The dose of adalimumab is 24 mg/m^2 with a maximum dose of 40 mg given as a subcutaneous injection every other week. Lovell and colleagues showed that adalimumab, with or without methotrexate, improved signs and symptoms of disease in children with polyarticular course JIA, and the higher responses were among children receiving adalimumab in combination with methotrexate [Lovell *et al.* 2008b]. At 48 weeks, the patients treated with methotrexate and adalimumab had significantly better responses than those receiving placebo; the differences between patients who received adalimumab alone and those who received placebo were not significant [Lovell *et al*. 2006]. Lovell and colleagues have shown a good safety profile over a 1-year period [Lovell *et al*. 2006]. Adalimumab has also been used for the treatment of JIA-associated uveitis [Vazquez-Cobian *et al.* 2006]. Tynjala and colleagues retrospectively reviewed 20 JIA children with chronic uveitis on adalimumab treatment. Improvements of ocular inflammation were noted in 35% of the patients during the period of observation, especially in those with shorter disease duration and of a younger age [Tynjala *et al.* 2008].

Safety of TNF*a* inhibitors

Infection

The long-term safety of these new therapies is still unclear. The compelling concerns are the increased risks for infections, induction of autoimmunity, and possible malignancies [Diak *et al.* 2010; Hashkes *et al.* 2010]. Rates of infections vary considerably between studies. The vast majority of reported infections were mild, common childhood illnesses and, in most cases, the rate of a serious infection was approximately 1–3 cases per 100 patient-years of treatment [Hashkes *et al.* 2010]. The serious infections included severe bacterial infections and varicella-zoster infections. All patients must be screened for tuberculosis before starting treatment with an anti-TNF agent. Rare cases of mycobacterium infections have been reported in children with JIA treated with anti-TNF agents [Hashkes *et al.* 2010], and cases of invasive fungal infections especially in areas endemic to these diseases such as histoplasmosis [Smith and Kauffman, 2009].

Autoimmune phenomenon

Autoimmune phenomena including the development of autoantibodies, drug-induced lupus, deymyelinating disease, uveitis, psoriasis, and IBD have been reported [Hashkes *et al.* 2010]. A prospective study of 26 patients with JIA, treated with either infliximab or etanercept for >2 years, showed that 6 patients (23%) had persistently raised levels of autoantibodies, five patients had asymptomatic antinuclear antibodies (ANAs) and one patient had antithyroid antibodies with Hashimoto disease [Kanakoudi-Tsakalidou *et al.* 2008]. Lovell and colleagues found that none of the 43 patients originally treated with etanercept had developed persistently elevated autoantibodies. In the open-labeled infliximab extension study, 15 of 78 (19%) developed new-onset ANAs and 4 of 61 (7%) of patients developed antibodies to double-stranded DNA but no cases of clinical autoimmune disease were observed [Ruperto *et al.* 2010]. In general, the development of overt autoimmune disease in children with JIA treated with anti-TNF agents is rare; however, if such autoantibodies lead to overt signs of autoimmune disease or if a patient develops an infusion reaction, most pediatric rheumatologists choose to discontinue the drug.

Malignancy

In postmarketing surveillance data on anti-TNF agents collected by the FDA in 1998–2008, 48 malignancies were reported in pediatric patients, of which 20 occurred in rheumatic conditions (15 in JIA, 3 in ankylosing spondylitis, 1 in psoriatic arthritis, and 1 in sarcoidosis), and the remainder in patients with IBD [Diak *et al.* 2010; Hashkes *et al.* 2010]. The majority of the cases (88%) occurred in patients who were using other concomitant immunosuppressive agents, including corticosteroids, azathioprine, methotrexate, and mercaptopurine (6-MP) [Diak *et al.* 2010; Hashkes *et al.* 2010]. About 50% of the malignancies reported to the FDA were lymphomas, with leukemia, melanoma, and other solid tumors also reported [Hashkes *et al.* 2010]. Ten patients were reported with hepatosplenic T-cell lymphoma, all with IBD, nine of whom died. Nine of these patients were treated with infliximab and one adalimumab [Hashkes *et al.* 2010]. All of the children were on concomitant immunosuppressive agents, particularly 6-MP and azathioprine. Recorded malignancy rates across all infliximab-treated patients were higher than the expected background levels for lymphoma and all malignancies [Hashkes *et al.* 2010]. Malignancy rates associated with etanercept were higher than expected only for lymphoma [Hashkes *et al.* 2010].

Bernatsky and colleagues examined cancer occurrence within JIA registries at three Canadian pediatric rheumatology centers; 1834 subjects were linked to regional tumor registries to determine the occurrence of invasive cancers from 1974 to 2006. The total number of cancers expected was calculated by multiplying the person years in the cohort by age, sex, and calendar specific cancer rates. Investigators found that only one invasive cancer was identified in this large sample of patients with JIA suggesting that in the initial years after diagnosis with JIA, the risk of invasive cancers is not markedly increased [Bernatsky *et al.* 2011].

Onel states that autoimmune diseases are likely to be associated with an increased risk for malignancy but goes on to state that a child or adult with a severely disabling or even fatal inflammatory disorder has only a rare chance of developing a malignancy and that the disease should not preclude treatment with anti-TNF agents. She explains that even in those individuals noted to have cancer-associated genetic variants, there will be many more individuals who do not develop malignancy than there will be individuals who do [Onel and Onel, 2010].

Systemic JIA

Systemic JIA (SJIA) is associated with distinct immunologic abnormalities. Several lines of evidence suggest that the role of the adaptive immune system in SJIA is limited compared with the other JIA subtypes, while the contribution of the innate immunity is more prominent [Barnes *et al.* 2009; Frosch and Roth, 2008; Fall *et al.* 2007; Ogilvie *et al.* 2007; Pascual *et al.* 2005; Ramanan and Grom, 2005]. Many of the clinical features of SJIA are similarly seen in the auto-inflammatory syndromes including: fever, multisystem involvement, a polycyclic course in some patients, and the laboratory markers of inflammation [Vastert *et al.* 2009]. New data supports neutrophils and monocytes as the effector cells as opposed to lymphocytes. There is a strikingly high level of neutrophil and monocyte derived S100 proteins that appear to distinguish SJIA from many other febrile illnesses [Wittkowski *et al.* 2008]. Two pro-inflammatory cytokines: IL-1 and IL-6 appear to perpetuate the inflammation in systemic JIA. These are the two cytokine pathways that have been directly targeted in the newest treatments for SJIA.

Interleukin-1 blockade

IL-1 is a pro-inflammatory cytokine secreted by monocytes and macrophages. It activates antigen-presenting cells and CD4+ lymphocytes and promotes lymphocyte differentiation; and it increases prostaglandin E2, collagenases, and neutral proteinases production [Breda *et al.* 2011]. Sera from patients with SJIA stimulated IL-1 gene expression and production in mononuclear blood cells from healthy individuals, providing rationale for the use of this medication in patients with SJIA [Pascual *et al.* 2005]. Initial studies looking at IL-1 blockade were done in patients with cryopyrin-associated periodic syndromes (CAPSs) such as Muckle–Wells syndrome (MWS), familial cold-induced autoinflammatory syndrome (FCAS), and neonatal onset multisystem inflammatory disease, where there is evidence for the role of IL-1β in the pathogenesis of the disease [Hoffman *et al.* 2008]. Anakinra, rilonacept and canakinumab block IL-1β.

Anakinra

Anakinra, licensed in 2001 by the FDA for the treatment of adults affected by RA, is a fully human IL-1 receptor antagonist. It competitively binds to the IL-1 receptor and blocks endogenous IL-1 signaling. It is a short-acting agent that requires daily subcutaneous injections with a starting dose of 1–2 mg/kg with a maximum dose of 100 mg/dose. Recent studies have demonstrated promising results using anakinra for both the systemic and articular components of SJIA; including patients that were unresponsive to anti-TNF agents [Nigrovic *et al.* 2011; Quartier *et al.* 2011]. The largest study on the safety and efficacy of anakinra for JIA was a controlled trial that included 86 patients with polyarticular JIA who were treated for up to 40 weeks with a daily dose of 1 mg/kg, maximum 100 mg daily [Ilowite *et al.* 2009]. Patients with SJIA at onset showed a more favorable response than those with polyarthritis or oligoarticular onset. A total of 126 AEs were recorded, of which six were considered serious [Ilowite *et al.* 2009]. The most common AE was injection-site reactions. Such reactions usually decreased in intensity over time. Sharma and colleagues report other potential side effects including serious infections, neutropenia, nausea, diarrhea, cardiopulmonary arrest, influenza-like symptoms and production of anti-anakinra antibodies [Sharma *et al.* 2008]. Many pediatric rheumatologists are now using anakinra as primary therapy for patients with systemic symptoms.

Rilonacept

Rilonacept is a recombinant fusion protein of IL-1 receptor protein components and the Fc portion of a human immunoglobulin. Preliminary data on 21 children treated with rilonacept at 2.2–4.4 mg/kg administered by subcutaneous injection once weekly showed 10/21 (47%) patients achieving an ACR 70 response at 42 weeks [Hayward and Wallace, 2009]. In February 2008, rilonacept was approved by the FDA for the treatment of the two CAPS, FCAS, and MWS, in patients aged 12 years and older [Hoffman *et al.* 2008].

Canakinumab

Canakinumab is a fully human anti-ILβ monoclonal antibody that selectively blocks IL-1β and is administered by subcutaneous injection or intravenous infusion at a dose of 2 mg/kg every 8 weeks [Lachmann *et al.* 2009]. This new agent is in several international trials for the treatment of CAPS and is in a clinical trial for SJA.

Interleukin-6 blockade: tocilizumab

IL-6 is also a pro-inflammatory cytokine produced by mononuclear cells, vascular endothelial cells, and fibroblasts in response to stimulation by IL-1 and TNFα [Breda *et al.* 2011]. It stimulates B-cell growth, osteoclast activation, and hepatocyte synthesis of acute phase reactants [De Benedetti and Martini, 1998]. IL-6 plays an important role in the pathogenesis of anemia and growth failure of children with SJIA [De Benedetti and Martini, 1998]. Tocilizumab is a recombinant, humanized monoclonal antibody that binds to the IL-6 receptor, blocking the IL-6 signal transmission. Tocilizumab showed an excellent and rapid effect in children with SJIA in a double-blind, placebo-controlled trial with intravenous administration of 8 mg/kg every 2 weeks [Yokota *et al.* 2008]. Further studies are currently underway to evaluate the use of tocilizumab in the treatment of polyarticular and SJIA. Tocilizumab was approved for the use in SJIA in April 2011; for patients 2 years of age and older, 12 mg/kg for patients <30 kg and 8 mg/kg for patients >30 kg.

Selective costimulation modulators

Abatacept is a fully human soluble fusion protein consisting of the extracellular domain of the CTLA4 antigen and a fragment of Fc domain of IgG. It is the first of a class of biologics that targets the activation signal from antigen-presenting cells (APCs) to T cells [Breda *et al.* 2011]. It results in the depletion of T cells, inhibition of their function, and activation of naïve T cells and memory T cells. The signal is mediated by CD80 and CD86, expressed on APCs, and by CD28 of T cells [Breda *et al.* 2011]. Ruperto and colleagues reported clinical benefit in a randomized double-blind, placebo-controlled trial for JIA patients irrespective of the clinical subtype. As in other trials with biologics, SJIA patients were excluded from the study if they had systemic manifestations [Ruperto *et al.* 2008]. Following this trial in April of 2008, abatacept received FDA approval for treatment of severe polyarticular JIA in children aged 6 years or older. Dosing in patients 6–17 years is 10 mg/kg based on body weight at each visit and not to exceed 1000 mg. Children aged 6 years and older weighing >75 kg should follow the adult dosing schedule. Abatacept is given as an infusion with three loading doses every other week in the first month then

Table 1. Biologic Agents used in the treatment of JIA.

Biologic	Route of administration	Therapeutic target	Structure and mechanism of action
Etanercept (Enbrel)	Subcutaneous injection	TNF-α	Fusion protein of TNF-receptor p75 monomer fused with Fc portion of human immunoglobulin
Infliximab (Remicade)	Intravenous infusion	TNF-α	Chimeric human/murine monoclonal antibody
Adalimumab (Humira)	Subcutaneous injection	TNF-α	Humanized monoclonal antibody
Anakinra (Kineret)	Subcutaneous injection	IL-1	Humanized IL-1 receptor antagonist
Rilonacept (IL-1 TRAP)	Subcutaneous injection	IL-1	Fusion protein of IL-1 receptor protein components with Fc portion of human immunoglobulin
Canakinumab (Ilaris)	Subcutaneous injection or intravenous infusion	IL-1	Humanized monoclonal antibody
Tocilizumab (Actemra)	Intravenous infusion	IL-6	Humanized monoclonal antibody
Abatacept (Orencia)	Intravenous infusion	Activation signal from APCs to T cells	Fusion protein of CTLA4 Ag with Fc portion of human immunoglobulin
Rituximab (Rituxan)	Intravenous infusion	B cells	Chimeric human/murine monoclonal antibody

IL, interleukin; TNF, tumor necrosis factor; APC, antigen-presenting cell.

given every 4 weeks. Infusion reactions occur but are generally mild [Zulian *et al.* 2010].

Selective B-cell blockade

Rituximab is a chimeric murine–human monoclonal antibody directed against CD20+ B cells. It selectively depletes CD20+ B lymphocytes, inhibits cell growth, and induces apoptosis [Rubbert-Roth and Finckh, 2009; Shirota *et al.* 2008]. It was initially approved for the treatment of non-Hodgkin's B-cell lymphoma. Rituximab has been effective in many autoimmune disorders and is mostly used in severe adult RA and systemic lupus erythematosus. There are no trials assessing the use of rituximab in JIA but there are several case reports of B-cell depletion for autoimmune disease, including JIA in pediatric patients [Jansson *et al.* 2011; El-Hallak *et al.* 2007]. Progressive multifocal leukoencephalopathy (PML) is a rare demyelinating disease of the brain due to polyoma virus or JC virus. PML is rare and almost always seen in association with an underlying immunosuppressive condition. An increased risk has been suggested for rituximab, although most of the patients developing PML have been treated for B-cell disorders that predispose to the development of PML [Berger *et al.* 2009].

The biologic targeted therapies have changed the strategy in which we treat patients with JIA; however, there is much to be learned about these medications. We are alerted to the possible increased malignancy risks associated with the use of the anti-TNF agents in JIA and in IBD, particularly in patients treated for longer than 2 years. The future of safe treatment for our children with JIA is going to depend on the continued vigilance and cooperative interdisciplinary relationships with physicians and pharmaceutical companies. They would be able to better monitor patients on these new agents through an international registry. Work is ongoing with the FDA and pharmaceutical companies to explore this possibility. Gene expression studies and disease biomarker research will expand and provide clinicians evidence for patient selection and improved methods to monitor active inflammation. The next decade in pediatric rheumatology will show promise of significantly improved outcomes for the patients with JIA.

Funding

This research received no specific grant from any funding agency in the public, commercial, or not-for-profit sectors.

Conflict of interest statement

Ruth – NIH Rilonacept clinical Trial (Site PI) and Pfizer-SINCERE NSAID Study (Site PI). Passo – Pfizer, consultant Celicoxib Safety.

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