Juvenile Idiopathic Arthritis
Therapies in the 21st Century

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Abstract

Juvenile idiopathic arthritis (JIA) is an umbrella term for seven or more clinical patterns of arthritis of unknown cause in children. Until the mid-1980s, therapy for children, with what was then called juvenile rheumatoid arthritis in the United States and juvenile chronic arthritis (JRA) elsewhere, consisted primarily of a small repertoire of antiinflammatory drugs and corticosteroids. However, only a small percentage of children respond to NSAIDs (nonsteroidal antiinflammatory drugs) alone; almost all will respond to corticosteroids, but with the cost of unacceptable toxicities. Juvenile arthritis was often a crippling disease. The controlled trial that demonstrated methotrexate therapy was safe and effective in children was the major advance of that decade. With the burgeoning understanding of the immune system and the advent of biologic agents in the 21st century, pediatric rheumatologists now have many more therapies to offer patients, with the expectation that their disease will be controlled. This review will discuss current therapy and the approach to treatment of JIA.

Over the years, rheumatologists have struggled with, and continue to struggle with, identification and classification of “their” diseases. In the past, this may have merely sprung from a desire for neatness and order in our clinical thinking, as our pharmaceutical armamentarium was sorely limited. Today, with the ever increasing number of biologic agents available, it is a necessity to have a clear scheme of disease definition to evaluate the utility of these agents in rheumatologic diseases, among them juvenile arthritis. To this end, the International League of Associations for Rheumatology (ILAR) has been revising the definition(s) of the diseases called juvenile rheumatoid arthritis (JRA) in the U.S. and juvenile chronic arthritis (JCR) in the international theater. This classification system, which has recently undergone its second revision, has advanced the term “juvenile idiopathic arthritis” (JIA) to refer to these idiopathic disorders.1

The term juvenile idiopathic arthritis, like its predecessors, juvenile rheumatoid arthritis and juvenile chronic arthritis, is a collective term for clinical patterns of arthritis in children. All of them are defined as a chronic arthritis in a child 16 years of age or younger, lasting for 6 or more weeks in the absence of any known cause. The underlying assumption of the ILAR classification is that these disorders can, on a clinical basis, be defined and there will be no overlap among them. Included in JIA are eight clinical patterns that include the five classic disorders of JRA as well as juvenile psoriatic arthritis and the spondyloarthropathies associated with inflammatory bowel disease, ankylosing spondylitis, and Reiter’s syndrome (Table 1). Moreover, this nomenclature also contains exclusion criteria for each subtype to assist in the specificity of the classification system (Table 2).

Although the categorization has not undergone formal validation, several preliminary studies have demonstrated its utility, even though the distinction among the oligoarthritides and psoriatic arthritis has been the most problematic.2,4 As the terms JRA, JCA, and JIA are not wholly interchangeable, this review will defer to the classification used by each published study discussed, and will use the ILAR classification of Juvenile Idiopathic Arthritis as appropriate.
Nonsteroidal Antiinflammatory Drugs (NSAIDS) in JIA

NSAIDS have been a mainstay for decades in treating the juvenile arthritides. NSAIDs inhibit the cyclooxygenase pathway of arachidonate metabolism, preventing formation of the proinflammatory prostaglandins. It is stated that for one-third of children with arthritis, NSAID therapy is successful in achieving control. In oligoarticular arthritis, NSAIDs are still frequently used as monotherapy. A recent survey of 129 pediatric rheumatologists found that 72% would use an NSAID as first-line therapy for persistent oligoarthritis for at least two months, and 21% would con-
continue until 6 months of persistence of disease. This initial approach does not appear to have significantly changed since 1996 when pediatric rheumatologists, in a similar survey with 175 responders, reported they would “usually” (defined as more than 75% of the time) use an NSAID in pauciarticular JRA.

The efficacy of NSAIDs, however, is not high. In a recent double-blind study, comparing rofecoxib and naproxen in pauciarticular and polyarticular JRA, between 50 and 60% of patients achieved an ACR (American College of Rheumatology) Pedi 30, using the core set criteria (Table 3) for improvement in juvenile arthritis. Moreover, side effects of NSAIDs in children are not infrequent. In this study, over 10% of children reported abdominal pain with naproxen therapy. Similar results for both efficacy and side effects were recently published in a study comparing naproxen with celecoxib.

The number of NSAIDs with FDA (Food and Drug Administration) approval for use in children with JRA is limited (Table 4) and the inability of children to swallow whole pills limits their use even further. Finally, if joint contractures or muscle atrophy are apparent at diagnosis, rapid initiation of more aggressive therapy is indicated.

**Intraarticular (IA) Corticosteroids in JIA**

Steroid injections have been used in rheumatoid arthritis (RA) for decades. However, its use in children was limited for many years due to concerns about steroid effects on cartilage and local suppression of limb growth from high concentrations of corticosteroids in the joint space. However, this has not proved to be the case. Gadolinium contrast-enhanced MRI performed before, at 7 weeks and at 13 months after 1 mg/kg IA injection of triamcinolone hexacetonide, demonstrated marked improvement in synovitis, with no structural damage. Moreover, patients with pauciarticular JRA who received intraarticular steroids within the first two months of diagnosis demonstrated no leg-length discrepancies as compared to a group of children who had been treated primarily with NSAIDs for several years. Recognition that IA steroids are safe and well tolerated has increased their use in children. In the 1996 survey, IA steroid was used to treat pauciarticular JRA between 25% to 50% of the time. In the more recent survey, 73% of pediatric rheumatologists administered IA steroids to patients with extended oligoarthritis after two months of NSAIDs and 99% did so at 6 months if NSAIDs did not achieve control. The long-acting preparation, triamcinolone hexacetonide, remains the preferred compound for pediatric rheumatologists.

**Methotrexate and JIA**

As in adult RA, methotrexate has become the second-line drug of choice for children with JIA for whom NSAIDs or IA steroids or both together are ineffective or inappropriate. Evidence for the effectiveness of methotrexate, confirming earlier case reports, was demonstrated in 1993 when the Pediatric Rheumatology Collaborative Study Group (PRCSG) published a metaanalysis of three clinical trials comparing treatment of children with JRA with oral gold, d-penicillamine, hydroxychloroquine, and methotrexate at 5 mg/m² and 10 mg/m². Only methotrexate at 10 mg/m²/week proved to show efficacy, with approximately 50% of children having a 50% or greater improvement using a composite index (a predecessor of the ACR Pediatric 30/50/70 indices, vide
In a retrospective chart review of 101 patients with JRA (all subtypes), found methotrexate therapy resulted in a complete response, defined as “the absence of synovitis and normalization of laboratory parameters while on medication,” in 48 patients. However, subsequent withdrawal of methotrexate therapy in these responders led to a relapse of disease in approximately 50% of those who had achieved a complete response. In summary, methotrexate has been shown to be both efficacious and safe.\textsuperscript{5,14} However, over the years there has been some “dose creep” in that the maximum doses prescribed have gotten larger—1 mg/kg/dose up to 40 mg weekly—without any proof of increasing efficacy. Rupert and coworkers\textsuperscript{15} addressed this issue, comparing 6 months treatment of 15 mg/m\textsuperscript{2}/week (intermediate dose) to 30 mg/m\textsuperscript{2}/week (high dose) of parenteral methotrexate in 80 children with polyarticular JIA who had not responded to 6 months of standard dose methotrexate at 8 to 12.5 mg/m\textsuperscript{2}/week. At the conclusion of the trial, 25/40 children in the intermediate group versus 23/40 children in the high dose group achieved ACR Pedi 30, demonstrating no superiority of the higher dose. Of interest, side effects were equivalent in both doses.

**TNF-α Inhibitors and JIA**

The inflammatory synovitis in JIA is maintained by a panoply of cytokines, among which TNF-α is a major contributor. Hence, inhibitors of TNF-α were rapidly evaluated for efficacy in controlling JIA shortly after their development. Etanercept is, at present, the only TNF-inhibitor approved for use in JIA. Etanercept is a chimeric molecule of a soluble TNF receptor coupled to the Fc fragment of IgG1. It is given by subcutaneous injection. Etanercept lowers the quantity of free TNF-α available for maintenance of the inflammatory synovitis of JIA. The design of the study to evaluate etanercept’s effectiveness as therapy for JIA, published by Lovell and associates\textsuperscript{16} has become the model for subsequent studies of biologic agents in children. In this study, 69 children with active JIA, despite 10 mg/m\textsuperscript{2}/week of methotrexate, were given etanercept at 0.4 mg/kg, twice weekly in an open-label fashion after discontinuation of other therapy. After three months, 51 patients (74%) responded to etanercept as defined by the ACR Pedi 30 core set criteria\textsuperscript{17} and were entered into a double blind phase of the trial, in which half received placebo injections and half continued on etanercept. By 4 months after randomization, 21/26 patients receiving placebo had flared, whereas only 7/25 patients on etanercept had flared. Those patients who flared restarted etanercept in an open label extension. Reinstating etanercept therapy proved efficacious in achieving a response that was equivalent to that in the initial open-label phase of this trial.\textsuperscript{18} Of the initial cohort of 58 patients, 32 of these children have been followed for more than 4 years and have maintained their responses with minimal adverse events. Lovell and colleagues\textsuperscript{16} noted in their study that etanercept appeared to be less effective in patients with systemic JIA. Kimura and coworkers\textsuperscript{19} confirmed this observation in a survey of pediatric rheumatologists. Data was obtained on 82 patients with systemic onset JIA; only 46% had a good to excellent response, while 54% were considered to have a fair to poor response.

Infliximab is a chimeric human/mouse monoclonal antibody directed against TNF-α, administered by intravenous infusion on a monthly to every eight week timetable. Like etanercept, it lowers the quantity of TNF-α available to maintain an inflammatory response. Unlike etanercept, in the presence of complement, it can trigger killing of cells bearing surface TNF-α. Infliximab is currently approved for use in adult RA and Crohn’s disease, but not in JIA. Anecdotal reports have shown good results and an open-label study showed similar results with infliximab and etanercept in achieving ACR Pedi 50 by 12 months of treatment.\textsuperscript{20} However, a multicenter controlled trial in the use of infliximab in JIA had technical difficulties, resulting in an under-powered study that did not achieve statistical significance for primary outcome measures.

One of the complications of JIA is a chronic, non-granulomatous uveitis, reported in approximately 15% of patients with persistent oligoarthritis and 5% of patients with polyarticular disease. Richards and associates\textsuperscript{21} and Rajaraman and colleagues\textsuperscript{22} each reported six cases of JIA-associated uveitis, poorly responsive to other therapies; patients were then treated with infliximab and had marked improvement at doses ranging between 5 to 10 mg/kg. Other investigators have had similar success with infliximab. Interestingly, etanercept does not seem to be as effective in controlling uveitis.\textsuperscript{23}

Adalimumab is a tumor necrosis factor (TNF) antagonist, a human antibody against TNF-α that is administered by subcutaneous injection on a weekly to alternate week schedule. As concomitant use of methotrexate has been demonstrated to prolong the half-life of adalimumab in patients with rheumatoid arthritis, the trial in children was designed with two groups: one with adalimumab on a background of methotrexate and one on adalimumab alone. In a manner similar to the etanercept trial, responders to open-label treatment were assigned, in a double blind manner, to either continue on adalimumab or be switched to placebo. Results were reported at the 2006 meeting of the American College of Rheumatology.\textsuperscript{24} In either group (with or without background methotrexate) adalimumab therapy proved superior to placebo. Fewer patients receiving adalimumab experienced an arthritis flare and those who did flare took longer to do so. The median time to flare for patients on adalimumab, either with or without methotrexate was more than 32 weeks. The median time to flare for those receiving placebo with or without methotrexate was 20 weeks or 14 weeks, respectively. Both of these values achieved statistical
The trial design was again similar to the etanercept trial, including those who have failed other biologic therapies. Other Therapies

Abatacept is the most recent biologic agent approved for use in RA. It has a unique mechanism of action, in that it blocks a cell activation signal from the antigen-presenting cell to the T-cell, rather than acting as a cytokine inhibitor. Abatacept has been studied in children with polyarticular course JIA, including those who have failed other biologic therapies. The trial design was again similar to the etanercept trial, beginning with an open-label phase before responders went on to a double-blind, placebo-controlled randomization. The results of the open-label phase were recently presented at the 2006 meeting of the American College of Rheumatology. Sixty-five percent (123/170) of patients had at least an ACR Pedi 30 response, 49% demonstrated an ACR Pedi 50 response, and 28% demonstrated an ACR Pedi 70 response.

Autologous stem cell transplant has been used in patients with JIA who have been resistant to treatment. Data published in 2004 demonstrated 18/34 patients had a complete response; six showed a partial response, and seven did not respond. Five children died—three of transplant-related mortality and two of disease-related mortality. Although this procedure has helped some number of children whose disease was intractable, the authors recognize the risk involved. It is hoped that with better understanding of immune activation and control, such high-risk procedures will not be necessary in future.

Anti-IL-6 Therapy and JIA

IL-6 is another proinflammatory cytokine that is markedly elevated in SOJIA. Its production is stimulated by IL-1 and its presence subsequently causes generation of acute phase reactants by the liver, maturation of B-cells, and activation of T-cells. IL-6 levels have correlated with fever, disease activity, and platelet counts. Hence, inhibition of IL-6 is currently being examined as therapy for SOJIA. Effects of treatment with a humanized, monoclonal anti-IL-6 receptor antibody, tocilizumab, has been reported in two small studies in SOJIA and more recently in poly- and oligoarticular onset disease. All of these studies showed a promising response but were short-term safety studies rather than long-term efficacy studies.

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Outcome of JIA

Despite the advances in therapy for JIA, no treatment has been demonstrated to be curative. Wallace and colleagues have reported a review of 437 patients with JIA who had 4 to 21 years of follow-up between 1980 and 2000. Eighty-nine percent of children had at least one period of inactive disease (ID), defined as no arthritis, normal serum inflammatory markers, no systemic features, and a physician’s global assessment indicating no active disease. ID was further divided into two categories: clinical remission off medication (CRM) and clinical remission off medication (CR). To be classified as “clinical remission off medication” required 12 months of inactive disease while remaining off medication. Disappointingly, only 26% of patients achieved CR and, of those, only 6% remained in CR more than 5 years. The investigators note that their study has limitations in that it is retrospective and may be biased toward poorer outcome. In addition, the patients were limited to those seen before 2000, hence, whether biologic agents may change outcome is unknown. Gottlieb and coworkers have prospectively collected data on two cohorts of patients with JRA—both before and after the availability of biologic agents. Patients who received biologic therapies early in the course of the disease (median, 3.8 mos) had significantly fewer swollen joints (1.1 joints) than those who received biologic therapy late (median 38.1 mos, 7.2 swollen joints). Whether early use of intensive therapy, including biologic agents, will elicit long-term remissions is the subject of a trial to begin in 2007.

Treatment of JIA

There is no treatment algorithm uniformly agreed upon in JIA although there is a single publication of a metaanalysis of evidence-based use of methotrexate. Thus, the following recommendations reflect the current practice of the author. NSAIDs can be used in all types of JIA to control pain and...
help diminish inflammation. They are also used during that period of evaluation for other causes of arthritis, particularly when a patient presents before 6 weeks of disease. Intrarticular corticosteroid (triamcinolone hexacetonide at 1 to 2 mg/kg) should be used in persistent oligoarticular JIA and in joint(s) resistant to therapy in polyarticular disease. Methotrexate at 15 mg/m²/week should be instituted on confirmation of diagnosis of polyarticular course JIA. If the oral route is chosen and inadequate response is achieved after several months, the subcutaneous route should be utilized. A short course of oral prednisone (0.5 to 2 mg/kg) may be required for very active disease. A biologic agent should be added if the response to methotrexate is inadequate; as of this writing, among the biologic agents, only etanercept is approved for use in JIA, or JRA.

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References


