ABSTRACT

The treatment of juvenile idiopathic arthritis (JIA) is largely based on multicenter pharmaceutical studies, individual patient responses, and physician experience, although consensus guidelines are lacking for patients not responsive to conventional treatment. Pharmacologic treatment is driven by the subtype of JIA and disease severity. Nonsteroidal anti-inflammatory drugs, disease-modifying antirheumatic drugs, and biologic agents are important components of pharmacotherapy. Patient adherence and a multidisciplinary healthcare team approach are essential to optimal clinical outcomes.


Recent and planned pharmaceutical studies have focused on patients whose disease has remained active despite conventional treatment. These studies have been facilitated by the development of core outcome measures, developed by investigators leading the Pediatric Rheumatology Collaborative Study Group (PRCSG) and Pediatric Rheumatology International Trials Organization (PRINTO). These measures are currently accepted by the US Food and Drug Administration (FDA) for use in clinical studies of drugs for juvenile idiopathic arthritis (JIA). The core set of outcome variables are:

- Physician global assessment of disease activity
- Parent/patient assessment of overall well-being
- Functional ability
- Number of joints with active disease
- Number of joints with limited range of motion
- Erythrocyte sedimentation rate (ESR)

The Juvenile Arthritis 30% Core Set Criteria defines improvement as improvement from baseline of at least 30% in any 3 of the variables, with no more than 1 of the remaining variables worsening greater than 30%.

Similarly, Wallace et al have developed the following definition of JIA remission, accepted by the PRCSG and PRINTO, which includes:

- No active synovitis
- No fever, rash, serositis, splenomegaly, or generalized lymphadenopathy attributable to JIA
- No active uveitis
- Normal ESR and/or C-reactive protein
- Physician’s global assessment of no active disease

Inactive disease has been defined as the condition of meeting all of the above criteria. Patients reach clinical remission on medication (CRM) when they have inactive disease for 6 continuous months while taking medication. Clinical remission off medication (CR) is attained when patients have 12 continuous months of inactive disease off all anti-arthritis and anti-uveitis medications.

PHARMAOCOLOGIC TREATMENT OF ARTHRITIS IN CHILDREN

Michael L. Miller, MD

*Based on a presentation by Dr Miller at a roundtable held in San Antonio, Texas, on May 16, 2008.

†Professor of Pediatrics, Feinberg School of Medicine, Northwestern University, Director of Clinical Service, Clinical Practice Director, Department of Pediatrics, Medical Director of Informatics, Division of Immunology/Rheumatology, Children’s Memorial Hospital, Chicago, Illinois.

Address correspondence to: Michael L. Miller, MD, Children’s Memorial Hospital, Box 50, 2300 Children’s Plaza, Chicago IL 60614. Email: mmiller@childrensmemorial.org.
The remission patterns of JIA were characterized in a study by Wallace et al that examined criteria for CRM and CR (Figure 1). The study concluded that only 25% of patients achieved CR during the 4 or less years of follow-up, and an even smaller proportion sustained CR for more than 5 years. Patients with rheumatoid factor (RF)-positive polyarticular JIA were least likely to achieve CR, whereas those with pauciarticular JIA (persistent oligoarthritis) were more likely to achieve CR. Very few patients with polyarthritis achieved remission off medication.

**Pharmacotherapy Classes for JIA**

**Nonsteroidal Anti-Inflammatory Drugs and Other Analgesics**

Nonsteroidal anti-inflammatory drugs (NSAIDs), effective analgesics with weak anti-inflammatory actions, are often sufficient treatment for children with pauciarticular JIA. NSAIDs are nonselective inhibitors of the cyclooxygenase (COX) isoenzymes that promote conversion of arachidonic acid to prostaglandins, thromboxanes, and prostacyclins. COX-1 may be induced by inflammation and is constitutively expressed in the gastric mucosa, platelets, and vasculature, accounting for some NSAID-associated adverse events (AEs). AEs tend to be similar among all agents and include abdominal pain, peptic ulcer, hepatotoxicity, hematuria, other renal toxicity, tinnitus, worsening of asthma, and central nervous system effects. Adding a proton pump inhibitor (PPI) or H₂ antagonist may improve abdominal pain; holding therapy may alleviate other AEs.

Cyclooxygenase-2 inhibitors may be useful for children who fail or are intolerant of NSAIDs; however, lack of activity against COX-1–mediated inflammation may limit their effectiveness. Cardiovascular AEs related to COX-2 inhibitors have been found in adults but not definitively in children.

Some patients require additional medication to control pain. Ketorolac, an NSAID with strong analgesic properties, may be used as an oral agent for up to 5 days as needed for breakthrough pain while patients continue on oral NSAID treatment. Tramadol may be used for analgesia in JIA but will not reduce inflammation. Muscle relaxants (ie, amitriptyline, methocarbamol, or metaxalone) may be effective in selected patients with axial muscle pain. When any analgesic is used excessively, other diagnoses (eg, musculoskeletal pain syndrome, malignancy, or infection) should be considered.

**Corticosteroids**

Intravenous and oral corticosteroids have a limited role in JIA, because of the potential for tachyphylaxis, in the face of persisting risk of AEs. Additionally, potential danger exists when corticosteroids are used in patients before a diagnosis is made because of the risk of partial treatment of malignancy or untreated infection. High-dose intravenous pulse therapy with methylprednisolone may be effective in some children with acute severe polyarticular arthritis. Intraarticular corticosteroids can be effective in children with persisting inflammation in a single joint, particularly in the knees, and has been associated with decreased risk of developing leg length discrepancy. Joint injections have also been useful in children with polyarticular arthritis.

**Disease-Modifying Antirheumatic Drugs**

The most commonly used disease-modifying antirheumatic drugs (DMARDs) for JIA are sulfasalazine, methotrexate (MTX), and leflunomide. Gold salts and penicillamine are seldom used. Although antimalarial drugs were found to be no better than placebo as primary DMARD treatment, they...
may be useful as adjunctive treatment in some patients, as has been found in adults with rheumatoid arthritis (RA). MTX can be associated with nausea and vomiting, which may respond to ondansetron. Injectable MTX may avoid gastrointestinal (GI) intolerance and may achieve better serum concentrations in some children.

Immunosuppressive agents, such as azathioprine and chlorambucil, are rarely used. The association of chlorambucil with malignancy and sterility has restricted its use to amyloidosis. In addition to MTX, other immunosuppressive agents, however, have been used for uveitis, particularly cyclosporine. Cyclosporine has also been an important addition to corticosteroid treatment of macrophage activation syndrome (MAS). MAS (also referred to as hemophagocytic lymphohistiocytosis) can be a complication of systemic JIA, but more often develops after viral infections (particularly Epstein-Barr virus) or occurs sporadically or as familial lymphohistiocytic syndrome. MAS is potentially life threatening; manifestations include fever, hepatosplenomegaly, adenopathy, and bone marrow suppression. Other characteristic laboratory findings include elevated lactic acid dehydrogenase and triglyceride levels, as well as striking elevations in ferritin levels. Sedimentation rates may be normal, perhaps as a result of hepatic involvement.

Biologic agents, such as tumor necrosis factor (TNF)-α inhibitors, may be more specific for synovial inflammation and less toxic than immunosuppressive agents. Etanercept, the first US FDA-approved biologic for JIA, mimics the activity of naturally occurring soluble TNF receptors, thereby preventing TNF from binding to cell surface receptors. Etanercept is well tolerated and has shown significant efficacy for children with active polyarticular JIA. In practice, it has been used in children as young as 2 years of age. Although infliximab, a monoclonal antibody directed against TNF, was not more effective than placebo in a randomized study, the authors pointed out reasons (including sample size and brevity of the placebo phase) why the study may not have detected efficacy. Furthermore, anecdotal experience suggests that increasing the dose up to 10 mg/kg may be effective in some patients who do not respond to typical doses of 3 to 6 mg/kg. However, unapproved dosing regimens may not always be covered by insurance carriers, and it is important to document the reason for their recommendation, including failure of other agents or lower doses. Another example concerns adalimumab, recently approved for JIA as a subcutaneous (SQ) injection given every other week. Some patients only respond when the medication is given weekly.

Other biologics have also been found effective in clinical studies. Anakinra, an interleukin (IL)-1 inhibitor, and tocilizumab, an IL-6 inhibitor, may play an expanding role in treatment of children with systemic JIA. Abatacept binds to the costimulatory molecules CD80 and CD86 on antigen-presenting cells to prevent T-cell activation. T cells require at least 2 signals (ie, CD28 and cytotoxic T-lymphocyte antigen 4) to become fully activated, which is prevented by abatacept. Plans for multicenter studies of additional biologic agents are in progress.

Biologics can be associated with injection site and infusion reactions. Infliximab should be given with ongoing monitoring, such as in a tertiary center or infusion center. More serious AEs associated with biologics include the potential to develop serious infections and demyelinating disease. Screening for tuberculosis should be performed, and biologics should be held when patients have infections requiring antibiotics. TNF inhibitors may induce anti-DNA antibodies, which could result in autoimmune disease, such as lupus-like syndrome. Biologics should not be administered in combination with each other.

**Dr Rich:** Assuming childhood infections are common in patients with JIA, is therapy held relatively frequently?

**Dr Miller:** Patient assessment determines if therapy should be held, which is not necessary for minor or viral infections. Parents are well informed to communicate any infection symptoms to healthcare providers. In practice, therapy is not withheld frequently.

**Dr Myers:** Because symptoms improve while on therapy, patients and parents are often reluctant to hold therapy.

**Dr Rich:** To avoid antibiotic overuse, antibiotics are no longer recommended for certain cases of childhood illness, such as non-streptococcal pharyngitis, which are often viral in etiology. In these cases, rheumatologists may not need to hold JIA therapy, depending on physician assessment.

Based on response to therapy, a brief treatment
algorithm is shown in Figure 2. Biologics, MTX, and other second-line agents may be initiated early if severe joint involvement is present, particularly if the patient is RF positive. For many years, when patients showed resolution of active synovitis, MTX had been discontinued before stopping NSAID treatment. However, because of NSAID-associated AEs, most centers currently discontinue NSAIDs followed by MTX and finally biologics in patients whose synovitis has become inactive.

**Dr Myers:** Insurance coverage may be problematic with initiating biologics early.

**Dr Miller:** Recently, obtaining insurance approval has been easier if documentation supports treatment decisions.

**Dr Rich:** What percentage of patients requires initial treatment with biologics?

**Dr Miller:** Very few patients require biologics initially, perhaps 5% or less of all patients with arthritis followed at tertiary centers. Nevertheless, early introduction of DMARDs and biologic agents may be important in decreasing long-term morbidity associated with chronic arthritis in children.

**Multidisciplinary Treatment Approach**

Children with arthritis are best cared for when a multidisciplinary team communicates flexibly with each other as equal participants in coordinating their services. In addition to pediatric rheumatologists, other healthcare professionals play important roles. Nurses and nurse practitioners offer assistance with direct care and education. Social workers assist with coping and school issues. Pharmacists provide medication information and education. Physical and occupational therapists treat the sequelae of inflammation, such as fibrosis or muscle atrophy, using pain modalities and range-of-motion exercises. All of these professionals can help with adherence problems, because they often learn of these problems directly from patients and their families. Other healthcare professionals often involved in the care of children with arthritis include nutritionists, psychologists/psychiatrists, physiatrists, and orthotists. In addition, patients and parents must themselves be active members of the treatment team.

**Medication Adherence**

In a study of 48 newly diagnosed children with JIA, medication adherence to NSAIDs was monitored over 28 days using an electronic monitoring device. It was found that only 52% of patients were adherent (≥80% of prescribed doses). Children with higher active joint counts showed higher adherence, perhaps because more disease activity was associated with more pain and other morbidity. Adherence was also associated with higher socioeconomic status. Rapoff has recently reviewed this issue and offers the following strategies to improve adherence:

- Educate early and often
- Ensure patients and families have behavioral skills to implement regimens
- Anticipate and address barriers
- Keep regimens as simple as possible
- Teach older patients self-management strategies
- Refer if needed for serious problems

**Future Treatment Approach**

Biologics show promise for the treatment of chil-
Dren with JIA. Future research for JIA should focus on improving therapy outcomes. It may be possible in the future to stratify patients by genotyping, permitting identification of appropriate candidates for biologic therapies at the onset of disease. Long-term studies should assess sustained improvement in quality of life. New targets of treatment may be identified, such as osteoprotegrin, cell adhesion molecules, angiogenesis promoters, and chemotactic factors. Partial stem cell replacement and gene therapy may also be promising in some patients unresponsive to other treatment.

**DISCUSSION**

**Dr Rich:** What is typical follow-up in stable patients in whom therapy has been discontinued?

**Dr Miller:** Follow-up data have been difficult to collect. Electronic medical records could allow better data collection that may provide useful information in the future. However, most pediatric rheumatology centers like to see patients at least yearly, once they meet criteria for remission, to monitor for possible recurrence of disease. Parents are asked to notify the child’s pediatric rheumatologist of any return of symptoms prior to return visits.

**Dr Myers:** Complete NSAID discontinuation may not be possible in some stable patients who continue to experience morning stiffness.

Although early aggressive therapy is optimal, managed care requirements may prevent initiating biologics. State Medicaid programs may require failure to 2 NSAIDs and 6 months of MTX therapy before approving biologics. Additionally, these programs may check patient compliance through pharmacy dispensing records. Without these cost control mechanisms, managed care treatment expense would be staggering.

**Dr Miller:** As further clinical studies become available, evidence-based medicine will likely support not only our anecdotal observations but also managed care decisions. Data from comprehensive electronic medical records, including pharmacy medication profiles and laboratory results, could facilitate this process.

**Dr Penna:** Is Figure 2 widely accepted as standard of practice? Is the evidence for biologics so robust that they would be first-line agents if cost were not a factor?

**Dr Myers:** The algorithm reflects typical standard of practice. NSAIDs are first-line agents and some are easily accessible, being available over-the-counter (OTC). MTX is typically second-line therapy whereas biologics tend to be reserved for patients with MTX failure. In polyarticular JIA, biologic treatment would be initiated very early if cost were not a factor.

**Dr Miller:** In one clinical study of adult RA, combination therapy of etanercept plus MTX was shown to be well tolerated and more effective than MTX alone. Cost constraints of biologics also impede the early initiation of combination therapy.

**Dr Swims:** Is long-term risk of malignancy a concern, particularly since this patient population is pediatric?

**Dr Miller:** Biologics and MTX are associated with a risk of malignancy, which requires appropriate patient and caregiver counseling. The benefits of therapy may outweigh surgical and disabling risks associated with untreated disease. Evidence seems to suggest that some children with arthritis may be willing to take more risk than parents in treating their disease.

**Dr Swims:** Because biologics can be discontinued in patients with JIA, perhaps the risk of malignancy is somewhat lower as compared to adult patients with RA, who often require lifelong therapy.

In patients with JIA, is it appropriate to increase MTX doses to maximum doses before therapy failure is declared? Are MTX side effects a concern? How long should MTX be administered before switching to biologics?

**Dr Miller:** MTX doses are typically maximized in children unresponsive to lower doses, and doses used in children are higher than those used in adults. Typical doses are 1 mg/kg to a maximum of 25 mg.

**Dr Myers:** Doses are titrated up to the highest tolerated dose. Administering maximum doses does not improve effectiveness but could increase toxicity and potentially decrease adherence due to lack of tolerability.

Methotrexate is typically administered for 6 months before failure is declared, which may be the duration required by managed care providers. Once the optimal dose is reached, MTX may be effective in as many as 60% of patients, and these patients will not require switching to biologics. Conversely, 30% of patients may fail to MTX and require biologics.

**Dr Saleh:** In a recently published study in *Arthritis & Rheumatism*, there were no reported cases of malignancy in a small group of children taking etanercept for up to 8 years.
In adult RA, combination therapy of TNF-α inhibitors with MTX seems to increase efficacy and reduce antichimeric antibody formation. In patients with JIA, are TNF-α inhibitors administered in combination with MTX or as monotherapy?

**Dr Miller:** Although the original etanercept study for JIA used monotherapy, studies in adults have demonstrated the synergistic effect of combination therapy with MTX. Consequently, combination therapy is typically used in patients with JIA. However, combination therapy is dependent on prescriber practice habits and institutional protocols. In adult RA, is oral or SQ MTX preferred? When is oral switched to SQ MTX?

**Dr Saleh:** Initial MTX therapy is typically oral. However, the threshold for switching to SQ MTX has been lowered in recent practice because SQ MTX seems to be better tolerated and more efficacious. Patients with RA can receive injectable MTX and biologics.

**Dr Rich:** Are there any difficulties in terms of insurance coverage for SQ MTX?

**Dr Myers:** The injectable is available as generic whereas the oral is available as brand name only. Therefore, drug cost is less expensive for injectable MTX.

**Dr Swims:** Although MTX prescribing information recommends intramuscular (IM) injection, the literature supports SQ injection in adults, which is less painful than IM and more effective than oral due to improved bioavailability. Therefore, injectable and oral doses can be interchanged milligram for milligram.

**Dr Myers:** Injectable MTX is given once weekly for JIA. Pediatric rheumatologists occasionally initiate therapy with injectable dosing because of improved tolerability and supporting literature.

**Dr Saleh:** Injectable MTX is typically well tolerated in adults and is associated with minimal injection site reactions. In contrast, biologics are associated with injection site reactions in up to 20% of patients, making drug nonadherence a significant problem.

**Dr Rich:** Are patients able to fill prescriptions for injectable MTX at retail pharmacies, or are they required to use specialty pharmacies?

**Dr Miller:** Patients in managed care plans typically require prescriptions for a 3-month supply that must be filled at a specialty pharmacy. Other patients can receive prescriptions at local pharmacies.

**Dr Penna:** Is it appropriate for managed care providers to require 6 months of MTX therapy before switching to biologic therapy?

**Dr Miller:** It is patient-specific, dependent on the number of joints involved, RF status, and the extent of joint damage. Evidence-based medicine in the form of multicenter long-term follow-up may help define consensus regarding these types of issues.

**Dr Myers:** Overall, a trial with MTX is appropriate because patients will often respond, and therapy costs can be controlled. However, patients with rapidly advancing JIA in multiple joints should have the option to start biologics early.

**Dr Busbey:** At the Veterans Affairs Medical Center (VAMC), the MTX trial is 3 months not 6 months.

**Dr Swims:** Because MTX dosing is generally titrated, several months may be required before the optimal dose is reached. This titration could potentially lengthen MTX therapy to 6 months or longer.

**Dr Myers:** Optimal dose titration will also allow patients time to learn their disease and treatment, which should be considered before deciding to change therapies.

**Dr Rich:** Should managed care providers require an injectable MTX trial before switching to biologic therapy?

**Dr Myers:** This requirement is reasonable so long as the total MTX trial is 6 months, including oral and injectable dosing.

**Dr Miller:** Initiating therapy with injectable MTX would be more appropriate for children with severe disease or uveitis.

**Dr Saleh:** Etanercept and adalimumab are approved for children as young as 2 and 4 years respectively. Is therapy used in children younger than these ages?

**Dr Myers:** Therapy has been used in children younger than these ages. However, managed care provisions may guide treatment decisions because payment could be denied.

**Dr Miller:** Etanercept would possibly be preferred because adalimumab has not been studied in children aged younger than 4 years and has limited data in children less than 15 kg.

**Dr Penna:** How often is nonadherence suspected as the reason for a suboptimal response?

**Dr Miller:** Studies indicate that nonadherence is most prevalent with NSAIDs. Severity scores seem to improve when adherence improves. Because biologics and MTX are used in children with more severe disease, adherence seems less problematic.

**Dr Myers:** Patients may stop taking medications
when symptoms improve and resume medications when symptoms return, causing the disease to wax and wane. Nonadherence should be ruled out whenever treatment failure occurs. Pharmacy refill histories could provide physicians with nonadherence information. Additionally, adherence to refills could suggest which medications seem to control symptoms more effectively.

**Dr Miller:** Streamlining adherence through formal programs could improve clinical outcomes while potentially controlling therapy costs.

**Dr Busbey:** Would managed care providers require a PPI added to NSAID therapy to prevent GI intolerance, as required at the VAMC?

**Dr Rich:** PPIs would not be required except if the possibility of GI erosion was anticipated.

**Dr Penna:** Because OTC NSAIDs and PPIs are available, insurance may not cover these medications. Pharmacy medication profiles would be incomplete unless patients reported taking OTC medications.

**Dr Rich:** Insurance may cover OTC medications with written prescriptions because OTC medications are typically less expensive than branded prescription alternatives.

**Dr Saleh:** Because studies support that MTX effectiveness does not improve significantly at doses higher than 20 mg weekly, would adding a biologic be preferred over using higher MTX doses?

**Dr Miller:** MTX approval for JIA was largely based on an international study that compared placebo, 5 mg/m² and 10 mg/m². Although the study showed the low-dose group did respond, the investigators were unable to clarify the effect of dose escalation because a high dose, such as 15 mg/m², was not included. Since then, a dose escalation effect seems to be suggested in the literature, and it is not uncommon to start doses between 15 mg/m² to 20 mg/m².

**Dr Myers:** Although I prefer conservative dose titration to avoid toxicities, I tend to titrate more aggressively in children with uveitis, in which many biologics may be ineffective.

**Dr Swims:** How are corticosteroids used in patients with JIA?

**Dr Miller:** Intraarticular corticosteroids seem to be useful in pauciarticular arthritis, potentially more effective than NSAIDs. Triamcinolone hexacetonide seems more effective than the acetamide derivative. Large joints may require doses of 40 to 80 mg. JIA and spondyloarthropy patients with systemic inflammatory disease may respond to pulse therapy with high-dose IV methylprednisolone. Prednisone and methylprednisolone should be used judiciously in children with arthritis.

### REFERENCES


