Juvenile Idiopathic Arthritis
What the Clinician Needs to Know

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Abstract

Juvenile idiopathic arthritis (JIA) includes several forms of chronic arthritis in childhood with no apparent cause. JIA is the most common rheumatic disease in children, and may result in pain, joint deformity, and growth impairment, with possible persistent active arthritis into adulthood. Prior treatment involved non-specific agents, several with significant adverse effects. The recent use of biologics now provides target-specific therapy, which may be better tolerated. Through continued translational research and clinical trials, one better understands the biology mediating disease, with the hope of offering safer, more effective medicine, and potential cure. This review will outline the clinical features of JIA, as well as provide the latest updates in treatment.

The subtypes formerly outlined in the older juvenile rheumatoid arthritis (JRA) classification are included within the newer juvenile idiopathic arthritis (JIA) classification and are based on predominant clinical manifestations and laboratory features within the first 6 months of disease. JIA includes eight heterogeneous subgroups of arthritis with no apparent cause, lasting more than 6 weeks, with disease onset prior to age 16 (Table 1). The diagnosis of JIA is one of exclusion, ruling out other rheumatic or infectious causes of arthritis. JIA also includes additional sub-classifications, such as extended-oligoarticular JIA, psoriatic arthritis, enthesitis-related arthritis, and undifferentiated arthritis as defined in Table 1. This review will focus on the subsets initially included in the JRA classification, including oligoarticular JIA, polyarticular JIA, and systemic-onset JIA.

JIA is the most common rheumatic disease in children with “over 300,000” children with JIA in the USA, with an estimated incidence of 2 to 20 cases per 100,000 children, and no clear racial predelection. Twice as many girls may develop JIA, mainly reflecting the female predominance of the oligoarticular subset, the largest subgroup. Certain subsets have an age-specific peak incidence; however, it is unusual for children to develop JIA before 6 months of age. It is not uncommon to discover a family history of autoimmune disease.

Standard, placebo-controlled trials are difficult in children with JIA, largely due to the inherent ethical and emotional strain for placing a child into a placebo group, rather than the study drug with demonstrable benefit in RA. JIA outcome measures have been validated and are now widely used in clinical trials, including the ACR Pedi 30/50/70. The majority of the recent trials largely pertain to recalcitrant, methotrexate non-responder polyarticular JIA, which may not be applicable to the individual patient.

The 2011 ACR JIA treatment guidelines were published as the result of consensus conferences and critical appraisal of the literature. The overall objective is to eliminate all signs and symptoms of active disease, preserve normal joint function, and maintain growth. Children are exposed to prolonged inflammation and adverse effects of long-term medications.

Children with JIA have less comorbidity than adults, and may therefore better tolerate medications. This may explain the superior tolerability of medications, such as methotrexate, though there are limited safety studies. The availability of liquid preparations of medications, as well as the palatability of these medications, is also important. The lack of oral preparations for newer biologic agents also may be difficult for the child.
The treatment of JIA requires a multidisciplinary, holistic approach with every effort for the child to avoid the “sick role.” All healthcare professionals, including physiatrists, physical therapists, psychologists, and others, play key roles. It is essential that all children resume normal activities, with the utmost importance placed on regular school attendance. Physical rehabilitation is helpful in early disease, with a focus on pain management, splinting, assistive device evaluation, aerobic conditioning, and other treatment modalities. One should avoid prolonged casting or immobilization.

Nonadherence is a potential barrier, especially during adolescence. Early establishment of non-judgmental and open communication, as well as incorporating the patient in making age-appropriate decisions, may help avoid this situation, so as to engender a sense of control and self-advocacy. Appropriate transition of the pediatric patient to the adult rheumatologist is also an important process over months to years, though it can also be a period of potential drop out from the healthcare system.

Localized growth impairment is not uncommon, and may result in significant leg length discrepancy. Permanent growth impairment may result in premature closure of the growth plate. The temporomandibular joint may also be affected and result in micrognathia or other jaw dysfunction. Generalized growth impairment may be seen in polyarticular and systemic JIA, secondary to prolonged inflammation, glucocorticoid toxicity, and other factors.

Much data regarding long-term outcome of JIA are limited because of retrospective data collection, lack of or inadequate sub-typing of JIA onset, and an underrepresentation of the persistent oligoarthritis subtype, which tends to have a better long-term prognosis. Furthermore, the majority of the prior longer-term outcome data pertains to patients with JIA before the “age” of biologics. JIA does not “burn out” as previously believed, with 25% of adults JIA still requiring methotrexate for arthritis, in addition to reporting growth impairment, disability, lower quality of life, and unemployment.

### Oligoarticular JIA

Oligoarticular JIA (Oligo-JIA) is the most common subset of JIA, accounting for almost 60% of patients. Eighty percent are girls, with a peak age of onset between 1 and 3 years of age. The patient presents with arthritis of four or fewer joints during the first 6 months of disease. Oligo-JIA commonly has an indolent presentation, making prompt diagnosis more challenging. Atypical features for oligo-JIA include erythema, severe pain, and hip involvement. It is common for children with oligo-JIA to avoid stressful positions that aggravate their arthritis, which may result in disuse atrophy or joint contracture.

A positive ANA is present in up to 85% of patients with oligo-JIA. Rheumatoid factor is not seen in this subset. Although patients with oligo-JIA may have mild anemia, inflammatory markers are often normal in the setting of active arthritis or uveitis. Up to 50% of patients with initial oligoarthritis in the first 6 months may later develop polyarthritis, involving five or more joints, and are therefore re-classified as extended-oligoarticular JIA, with lower disease activity scores.
likelihood of adult remission. Predictors of patients evolving into extended-oligoarticular JIA include ankle, wrist or hand arthritis, symmetric arthritis, arthritis in two to four joints, and the presence of an elevated ANA titer or ESR.6 Up to 50% of oligoarthritis patients with a positive ANA may develop uveitis.7 Other factors associated with increased risk include female gender, under 6 years of age, and less than 4 years of disease duration. Such patients require slit lamp examinations every 3 months. Chronic anterior uveitis in JIA is often asymptomatic and inconsistently correlates with the presence of arthritis. Most children respond to topical steroids, yet some patients may be refractory or develop complications, including glaucoma, cataracts, synechiae, band keratopathy, macular edema, and blindness.5,7 Though lacking FDA-approval, systemic therapy may be required, including methotrexate, mycophenolate mofetil, and infliximab as well as others.

Non-Steroidal Anti-Inflammatory Drugs (NSAIDs)

NSAIDs are the cornerstone medication and are commonly used as monotherapy. More than six NSAIDs are FDA-approved for use in JIA, with liquid formulations available. Although mild adverse effects are not infrequent, NSAIDs are very well tolerated in children. The withdrawal of rofecoxib, a selective COX II inhibitor, from the market in 2004, has resulted in COX II inhibitors being less commonly used.

Intra-Articular Glucocorticoid Injections

Intra-articular (IA) glucocorticoid injections are often the treatment of choice for persistent arthritis of one or two joints after a trial of NSAIDs. The clinician may elect to perform a joint injection earlier in the course, should there be significant leg length discrepancy, muscle atrophy, or joint contracture. IA steroids provide immediate, effective, long-lasting, local treatment often resulting in a sustained response.

Polyarticular JIA

Polyarticular JIA (poly-JIA), with symmetric arthritis of five or more joints within the first 6 months, accounts for 25% to 40% of JIA and is subclassified into rheumatoid factor (RF) positive and RF negative patients. Constitutional features may be present, including fatigue, anorexia, weight loss, anemia, and low grade fever. Anterior uveitis is uncommon. Rheumatoid factor positive poly-JIA accounts for less than 10% of JIA and is essentially childhood onset of (adult) rheumatoid arthritis, with characteristic erosive arthritis, classic deformities, and variable presence of rheumatoid nodules. Arthritis may also involve the cervical spine and temporomandibular joint. Seropositive disease onset is typically seen in children older than 8, with a 90% female predominance. RF positive poly-JIA has a poor prognosis without appropriately aggressive treatment. Seronegative poly-JIA patients have a variable prognosis and account for approximately 30% of JIA. Ninety percent of patients are girls, with peak age of onset between 1 to 3 years, although it may occur at any time. All children with polyarthritis ultimately require disease modifying anti-rheumatic drug (DMARD) therapy or a biologic agent. Low-dose corticosteroids are used sparingly as a bridging drug for their immediate anti-inflammatory properties, as many DMARDs may require several weeks to reach full therapeutic effect.

Disease Modifying Anti-Rheumatic Drugs (DMARDs)

Methotrexate is Still the Gold Standard

For over 30 years, low-dose weekly methotrexate has been used as an affordable, well-tolerated DMARD, which is effective in over 75% of patients with JIA. A study examining methotrexate and leflunomide reported an unprecedented ACR Pedi 70 response in 86% of poly-JIA patients taking methotrexate after 2 years of open-label medication.8 Although transient liver enzyme elevation is not uncommon, there have been no reported cases of severe irreversible liver fibrosis, and pulmonary toxicity including nodulosis is rare.

Sulfasalazine and Leflunomide May be Considered

Sulfasalazine received FDA approval in 1998 after a trial demonstrated efficacy in JIA versus placebo.9 Still, adverse events are not uncommon, including anorexia, abdominal pain, and rash. When cost, availability, or concerns regarding lack of longer term outcome data with biologics are raised, sulfasalazine may be considered as alternative or additional therapy. As mentioned, a trial of methotrexate versus leflunomide in 94 DMARD-naïve poly-JIA patients demonstrated ACR Pedi 50 of 73%, with most responders maintaining this response in the 2-year open-label extension study at week 48, suggesting its utility in the treatment of JIA.8

General Principles of Biologics

The efficacy and long-term safety data for methotrexate, which is effective for the majority of JIA patients, cannot be overemphasized. Furthermore, the majority of studies evaluating the efficacy of newer biologic therapy include a relative minority of JIA patients, who have polyarthritis refractory to methotrexate. The relatively high cost, parental administration, and lack of “longer” term data are also barriers. As risk of infection and response to vaccination is of concern, it is advisable to update all vaccinations prior to the initiation of therapy and avoid live vaccinations during DMARD or biologic therapy. In response to the 2009 FDA issued black-box warning pertaining to the potential association of malignancy, a recent review of the USA Medicaid database of over 7,800 children with JIA revealed that children with JIA appear to have a higher standardized incidence ratio (SIR) of 4.4 for malignancy compared to those without JIA, and the addition of methotrexate or anti-TNF agents did not appear to change the likelihood of malignancy.10

Etanercept

In 1999, etanercept was the first biologic to receive FDA approval for poly-JIA, based on 74% of patients achieving at
least an ACR Pedi 30 at 3 months in 69 patients with poly-JIA despite NSAIDs and methotrexate. Eight-year safety and efficacy data demonstrated that the long-term safety profile was maintained and exposure-adjusted rates of serious adverse events (SAEs) did not increase over time, with no reported cases of malignancies, lupus, or demyelinating disorders.

**Adalimumab**

Adalimumab was FDA-approved in 2008 for use in poly-JIA after a withdrawal-study of 190 active poly-JIA patients, who had previously received NSAIDs with or without methotrexate. After 100 weeks of the open-label extension ACR Pedi 50, 70, and 90 responses were achieved in an impressive 86%, 77%, and 40% of patients, respectively, with a sustained response up to 170 weeks. Serious adverse events perhaps related to adalimumab included viral infections, pharyngitis, and pneumonia.

**Infliximab**

In 2007, a study of 122 poly-JIA patients with persistent disease despite methotrexate therapy was conducted with patients randomized to receive infliximab or placebo infusions for 14 weeks, after which all patients received infliximab through week 44. After the 1 year open-label treatment with infliximab, ACR Pedi 50 and 70 responses were achieved in 70% and 52% of patients, respectively. Although generally well tolerated, there were serious adverse events, including infusions reactions, human anti-chimeric antibodies (HACAs), and newly induced antinuclear antibodies. As infliximab did not achieve a statistically significant difference in its primary endpoint of an ACR Pedi 30 at week 14 versus placebo, it did not receive FDA approval for JIA, though still commonly used “off-label.”

**Combination Therapy**

In view of the data which suggests early, aggressive combination therapy may improve outcome in RA, this question was investigated contemporaneously in two multi-center studies in the USA and Europe, utilizing etanercept and infliximab, respectively. The USA trial in 85 biologic naïve poly-JIA randomized patients to receive methotrexate monotherapy versus combination therapy of methotrexate, etanercept, and prednisone. Though not statistically significant, 40% of patients in the aggressive arm achieved clinically inactive disease in contrast to 23% of patients who received methotrexate alone. In Europe, 60 biologic and DMARD naïve patients were randomized to receive one of three treatments: 1. Methotrexate plus infliximab, 2. methotrexate alone, 3. methotrexate, sulfasalazine, and hydroxychloroquine with an ACR Pedi75 of 100%, 50%, and 65%, respectively.

**Abatacept**

A phase III, multicenter, double-blind, randomized, controlled withdrawal study was conducted with abatacept in 190 patients with active poly-JIA despite at least one DMARD. All children initially received intravenous abatacept (10mg/kg) during the 4 month open-label period, in addition to their prior stable dose of methotrexate if applicable. Patients who achieved an ACR Pedi 30 were randomized to abatacept or placebo for the following 6 months or until disease flare. At 4 months, ACR Pedi 50 and 70 were achieved in 50% and 28% of patients. Almost one third of patients had previously discontinued anti-TNF therapy, and 25% of these patients were able to achieve an ACR Pedi 50 at 4 months; abatacept received FDA-approval for JIA in 2008. Adverse events included headache, nausea, diarrhea, cough, and upper respiratory infection.

**Systemic-Onset JIA**

Systemic-onset JIA (SJIA) comprises only 10% of JIA, though it accounts for a significant percentage of the morbidity and mortality in JIA. It is characterized by daily high-spiking fever for at least 2 weeks and the classic salmon-colored evanescent rash, found most commonly on the trunk, axilla, and inguinal areas, with exacerbation by fever. Arthritis may be absent at diagnosis, making the diagnosis more challenging, as the extra-articular features, such as serositis, fever, anemia, or hepatosplenomegaly, often predominate. Laboratory evaluation may reveal leukocytosis, thrombocytosis, anemia, hepatitis, and hyperferritinemia. Unlike other subsets of JIA, there is no gender disparity, and SJIA may occur at any age. Further distinguishing this subset is the very rare presence of uveitis, rare ANA positivity, and absent rheumatoid factor.

Almost 40% of SJIA patients develop chronic, erosive polyarthritis, requiring therapy with DMARDs or biologics. Predictors of poor prognosis in SJIA include onset at less than 6 years of age, disease duration for greater than 5 years, or persistent systemic features at 6 months of disease including fever, the need for corticosteroids, and thrombocytosis. After the systemic features subside, it is the chronic arthritis which predominates. Mortality is less than 0.3% for patients with SJIA, secondary to macrophage activation syndrome (MAS), infection, or cardiac complications. Although an uncommon complication, the amyloidosis can rarely be seen.

**Macrophage Activation Syndrome**

Macrophage activation syndrome is an uncommon but potentially life-threatening complication in SJIA, and is considered a reactive, secondary hemophagocytic lymphohistiocytosis syndrome, with the diagnostic hallmark of the presence of well-differentiated, activated macrophages phagocytosing hematopoietic cells within the bone marrow. Inconsistent and debatable triggers of MAS include viral infections and alteration of medication regimen. Clinical features of MAS may include liver failure, coagulopathy with hemorrhage or thrombophilia, encephalopathy, and risk of death in up to a 22% of patients. Laboratory features include markedly elevated ferritin, pancytopenia, prolonged PT and PTT, hypofibrinogenemia, elevated fibrin split products, and hypertriglyceridemia. Patients often require ICU...
management for hemodynamic instability, hemorrhage, and seizure, with the majority of patients requiring high-dose pulse steroids and other immunosuppressive agents, such as cyclosporine A, etoposide, thalidomide, cyclophosphamide, or infliximab.

**Anakinra and Other Anti-IL Therapeutics**

Interleukin-1 Beta (IL-1β) has been implicated in the pathogenesis of SJIA. Most recently, a randomized double-blind placebo-controlled trial in patients with active SJIA demonstrated efficacy of anakinra versus placebo in children who continued to have active disease despite prior treatment, including glucocorticoids, methotrexate, and etanercept. Adverse effects of this agent include injection site reaction, hepatitis, and possible increased susceptibility to infection. An open-label, phase 2 trial of canakinumab, a fully humanized monoclonal antibody binding IL-1β, followed by a withdrawal phase in over 100 active SJIA patients, 2/3 who had previously taken biologics including anakinra, demonstrated that 73% of patients were able to achieve an ACR Pedi50, though seven patients developed MAS. A current phase II/III trial of anakinra in refractory SJIA is underway, as well a trial using rilonacept, an IL-1 Trap.

**Tocilizumab**

Plasma levels of interleukin-6 (IL-6) may also be very elevated in patients with SJIA and have been shown to correlate with arthritis, fever, and thrombocytosis. The use of tocilizumab, a humanized, monoclonal antibody against the IL-6 receptor, has demonstrated efficacy in open-label trials of SJIA, and in 2008 a trial of 56 SJIA patients with persistent disease despite DMARD or biologic therapy was conducted in which tocilizumab was administered as monotherapy to all patients during the 6 week open-label, lead-in phase followed by randomization to placebo for patients who achieved at least an ACR Pedi 30 response for the following 12 weeks or until disease flare. At the end of the open-label extension period, 90% of patients achieved an ACR Pedi 70 response by week 48. Adverse events included infusions reactions, gastrointestinal hemorrhage, bronchitis, and gastroenteritis. A recent study of 112 active SJIA patients randomized to tocilizumab or placebo with non-responders offered open label drug demonstrated that 80% of patients had at least an ACR Pedi70, with 52% of patients discontinuing glucocorticoids by week 52.

**Summary**

Juvenile idiopathic arthritis is the most common rheumatic disease of childhood, and may result in disability with persistent arthritis into adulthood. The majority of JIA consists of the oligo-JIA subtype, with a risk of asymptomatic anterior uveitis. DMARD or biologic therapy may be required in patients with recalcitrant arthritis or uveitis. Systemic-onset JIA is an impressive, inflammatory disease that may be complicated by MAS, requiring high dose steroids and the addition of DMARD or biologic therapy, most recently with successful use of anti-IL-1 therapy. It is essential that the clinician focus on the elimination of disease activity, with the return to normal functioning, including school, and the prevention of disability.

**Disclosure Statement**

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**References**