

Juvenile Idiopathic Arthritis

An Update for the Clinician

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Abstract

Juvenile idiopathic arthritis (JIA) comprises a collection of all forms of chronic arthritis in childhood with no apparent cause. JIA is the most common rheumatic disease in children, and may result in significant pain, joint deformity, and growth impairment, with persistence of active arthritis into adulthood. Prior to the mid 1990s, the therapeutic armamentarium for JIA was more limited, utilizing non-specific agents, many with significant adverse effects. With the relatively recent use of biologics, one can provide more 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 current and future pharmacotherapy.

According to the International League of Associations for Rheumatology (ILAR), Juvenile Idiopathic Arthritis (JIA) includes all forms of arthritis with no apparent cause, lasting more than 6 weeks, and with disease onset prior to age 16.¹⁻³ JIA is the most common rheumatic disease in children^{4,5} and consists of eight heterogeneous subgroups (Table 1). JIA has replaced former classification nomenclature, including juvenile rheumatoid arthritis (JRA) and juvenile chronic arthritis (JCA) internationally. The primary aim for the reclassification of JIA was to define relatively homogeneous, mutually exclusive subsets of arthritis, for both prognostic and research purposes. Furthermore,

the majority of JIA is not “rheumatoid” in appearance as one understands the clinical phenotype of adult rheumatoid arthritis (RA).

The subtypes formerly outlined in the JRA classification are included within the newer JIA classification and are based on predominant clinical manifestations and laboratory features within the first 6 months of disease, categorizing patients as oligoarticular (formerly pauciarticular), polyarticular, or systemic-onset JIA. These subsets represent the focus of this manuscript. The newer JIA classification has further expanded the former JRA classification to include other sub-classifications, such as extended-oligoarticular JIA, psoriatic arthritis, enthesitis-related arthritis, and undifferentiated arthritis. The extended-oligoarticular JIA pertains to the patient who develops polyarthritis, despite only a few joints during the first 6 months of disease onset. Though previously (and appropriately) recognized as a separate disease entity, psoriatic arthritis as defined in table 1 is also included in the new classification. Enthesitis-related arthritis was formerly known as spondyloarthropathy or spondyloarthritis and includes patients with varying presence of arthritis and enthesitis as well as ankylosing spondylitis. Undifferentiated arthritis pertains to patients who do not fulfill criteria for other sub-classifications or fulfill more than one. This review will focus on the subsets initially included in the JRA classification, including oligoarticular JIA, polyarticular JIA, and systemic-onset JIA.

As with most classification criteria in rheumatology, the diagnosis of JIA is one of exclusion, obligating the clinician to rule out other causes of chronic arthritis including rheumatic, infectious, and other potential causes of chronic synovitis. The original classification of JIA has been revised several times, most recently in 2004 resulting in further clarification of the various subsets, correcting prior incongruence, and improving its clinical utility to the rheumatologist.⁶

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Table 1 Classification of Subtypes of Juvenile Idiopathic Arthritis

Systemic Onset

Arthritis with or preceded by at least 2 weeks of daily fever, with at least 3 days of documented "quotidian" fever

Plus one or more of the following

1. Evanescent, non-fixed erythematous rash
2. Generalized lymph node enlargement
3. Hepatomegaly, splenomegaly, or both

Exclusions 1 to 4

Oligoarthritis Onset

Persistent Oligoarthritis

Arthritis of 4 or fewer joints throughout disease course

Exclusions 1 to 5

Extended oligoarthritis

Arthritis of 5 or more joints after initial 6 months of oligoarticular diseases

Exclusions 1 to 5

Polyarthritis Onset

Rheumatoid Factor negative

Arthritis of 5 or more joints during initial 6 months of disease

Rheumatoid factor negative

Exclusions 1 to 5

Rheumatoid Factor positive

Arthritis of 5 or more joints during initial 6 months of disease

Rheumatoid factor positive for two or more occasions, at least 3 months apart

Exclusions 1, 2, 3, 5

Psoriatic Arthritis

Arthritis and psoriasis

Or

Arthritis and two of the following

1. Dactylitis
2. Nail pitting or onycholysis
3. Psoriasis in a first-degree relative

Enthesitis Related Arthritis

Arthritis and enthesitis

Or

Arthritis OR enthesitis and two of the following:

1. Sacroiliac joint tenderness or inflammatory lumbosacral pain
2. HLA B27 positive
3. Arthritis in a male over 6 years of age
4. Acute anterior uveitis
5. History of ankylosing spondylitis, enthesitis-related arthritis, sacroiliitis with inflammatory bowel disease, reactive arthritis (Reiter's syndrome), or acute anterior uveitis in a first-degree relative

Exclusions 1, 4, 5

Undifferentiated Arthritis

Fulfills none of the above subsets

Or

Fulfills more than one of the above subsets

Exclusion Criteria for JIA

1. Psoriasis or a history of psoriasis in a first-degree relative
2. Arthritis in an HLA B27 positive male beginning after his 6th birthday
3. History of ankylosing spondylitis, enthesitis-related arthritis, sacroiliitis with inflammatory bowel disease, reactive arthritis (Reiter's syndrome), or acute anterior uveitis in a first-degree relative
4. IgM rheumatoid factor on 2 or more occasions at least 3 months apart
5. Diagnosis of systemic juvenile idiopathic arthritis

(From: Petty RE, et al. Revision of the proposed classification criteria for juvenile idiopathic arthritis: Durban, 1997. *J Rheumatol*, 1998;25(10):1991-4.)

As with most rheumatic disease, classification should be seen as a work in progress, and there is evidence to suggest that subdividing JIA based on arbitrary joint counts may not be appropriate. Recent data suggest that the presence of anti-nuclear antibody (ANA) positivity and the age of onset correlate better with clinically relevant phenotypes, risk of uveitis, expression of genes related to humoral immunity, and the presence of synovial lymphoid neogenesis.⁷⁻¹⁰ It is the hope of this investigator that this biology will be incorporated or even replace the next revision of the JIA classification.

Epidemiology

JIA is the most common form of rheumatic disease in children. The incidence of JIA is estimated at 2 to 20 cases per 100,000 children, with a prevalence of 16 to 150 cases per 100,000 children worldwide, with no clear racial predilection.¹¹ There are “over 300,000” children with JIA in the United States, though exact data are unknown, largely due to the lack of awareness and aptitude in diagnosing this arthritis in those who may be the first point of contact in the evaluation of a child with musculoskeletal disease, such as the pediatrician, family practitioner, or emergency room physician, many who never had any formal training in pediatric musculoskeletal exam. Furthermore, there is a relative shortage of pediatric rheumatologists, with less than 300 specialists in the United States, and several states lacking even a single pediatric rheumatologist, furthering the limitations in medical education, as well as lack of adequate clinical care. Similar to most rheumatic disease, twice as many girls may develop JIA, mainly reflecting the female predominance of the oligoarticular subset, which is 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, similar to the epidemiology of most other childhood rheumatic disease. It is not uncommon to discover a family history of autoimmune disease,

and patients with JIA have a sibling recurrence risk of approximately 15%.^{12,13}

Research Approaches

Conducting the standard, placebo-controlled pharmacotherapy trials in children with JIA is challenging, especially when involving medication with demonstrable benefit in RA. There is an inherent ethical and emotional strain for the child, family, and physician in placing a patient into a placebo group. Today, the majority of clinical drug trials in JIA utilize the withdrawal study design, exemplified by the etanercept trial in JIA in 1999.¹⁴ This study was the result of the successful collaboration of the Pediatric Rheumatology Collaborative Study Group (PRCSG), consisting of a national research group of pediatric rheumatologists, who have unified to study uncommon rheumatic diseases of childhood. Additional national and international research consortiums that have made other clinical trials possible include the Childhood Arthritis and Rheumatology Research Alliance (CARRA) and the Pediatric Rheumatology International Trials Organization (PRINTO).

Prior to the etanercept withdrawal trial design, much of the “evidence” regarding treatment of JIA was based on extrapolation from the adult RA literature, as well as a few placebo-controlled trials, case series, open-label trials, or anecdotal studies by “experts” in pediatric rheumatology. JIA outcome measures have been validated and are now widely used in clinical trials, including the ACR Pedi 30/50/70 (Table 2), as well as a clinical definition of disease remission (Table 3).^{15,16} As a result of the successful collaborative efforts of the pediatric rheumatology community, newer biologic therapy has been studied and ultimately approved by the U.S. Food and Drug Administration (FDA), though other commonly used medications are still used off-label, lacking FDA-approval. It is important to be aware that the majority of the recent clinical trials involving newer biologics pertain to polyarticular JIA and

Table 2 Criterial for Improvement in Juvenile Idiopathic Arthritis

Core Set Criteria

1. Number of active joints (0-75)
2. Number of joints with loss of motion (0-67)
3. Physician’s global assessment of disease activity by VAS (0-100)
4. Parent/Patient global assessment of overall well being by VAS (0-100)
5. Functional assessment via Childhood Health Assessment Questionnaire (0-3)
6. ESR

Patient must have at least a 30% improvement in 3/6 items and a worsening of 30% in no more than one item to achieve an ACR Pedi 30 response.

ACR Pedi 50 and 70 response require 50% or 70% improvement in 3/6 criteria, and worsening of 30% in no more than one item

Additional Measures

1. Parent’s global assessment of pain by VAS (0-100)
2. Parent’s global assessment of arthritis by VAS (0-100)
3. Child’s assessment of discomfort by facial affective scale (1-9)

(From: Giannini EH, Ruperto N, Ravelli A, et al. Preliminary definition of improvement in juvenile arthritis. *Arthritis Rheum.* 1997 Jul;40(7):1202-9.)

Table 3 Preliminary criteria for inactive disease and clinical remission of JIA

Inactive Disease
1. No joints with active arthritis.*†
2. No fever, rash, serositis, splenomegaly, or generalized lymphadenopathy attributable to JIA
3. No active uveitis (to be defined)
4. Normal ESR or CRP (if both are tested, both must be normal)
5. Physician's global assessment of disease activity indicates no disease activity (i.e. best score attainable on the scale used)
Clinical Remission
Two types of clinical remission are proposed:
1. Clinical remission on medication. The criteria for inactive disease must be met for a minimum of 6 consecutive months while the patient is on medication.
2. Clinical remission off medication. The criteria for inactive disease must be met for a minimum of 12 consecutive months while off all antiarthritis medications

*As defined by ACR: A joint with swelling not due to bony enlargement or, if no swelling is present, limitations of motion accompanied by either pain on motion or tenderness; †Isolated finding of pain on motion, tenderness, or limitation of motion on joint examination may be present only if explained by either prior damage attributable to arthritis that is now considered inactive or nonrheumatologic reason such as trauma. (From: Wallace CA, Ravelli A, Huang B, Giannini EH. Preliminary validation of clinical remission criteria using the OMERACT filter for select categories of juvenile idiopathic arthritis. *J Rheumatol.* 2006; Apr33(4):789-95.)

often recalcitrant disease, which may not be applicable to the individual patient.

General Treatment Aspects

Treatment Algorithms

Various therapeutic algorithms have been published regarding the treatment of children with chronic arthritis, although there are no widely accepted protocols.^{17,18} Beukelman and colleagues proposed the 2011 American College of Rheumatology treatment guidelines for JIA as the result of consensus conference and critical appraisal of the literature with the purpose of providing sufficient evidence for safe, effective treatment of the various subgroups of JIA.¹⁹ The clinician seeks to eliminate all signs and symptoms of active disease, in order to preserve normal joint function and prevent deformity and disability. As JIA is a chronic, potentially lifelong disease, many children are exposed to periods of prolonged inflammation with immediate as well as potential long-term potential consequences, as well as the potential adverse effects of long-term medications.

Growth Disturbance

Unlike RA, the clinician is treating a growing patient with JIA. Localized growth impairment is not uncommon, and may result in significant leg length discrepancy, as knees are commonly involved joints.²⁰ Although catch-up growth is possible, one may develop permanent growth impairment if the growth plate closes prematurely secondary to arthritis. The temporomandibular joint may also be affected in children with systemic or polyarticular JIA and result in micrognathia, irregular growth of the jaw, or other jaw dysfunction.²¹ Generalized growth impairment is not uncommonly seen in polyarticular and systemic JIA and is often multi-factorial, secondary to periods of prolonged inflammation as well as medication toxicity and other factors. Every attempt is made to preserve normal growth as well as the healthy psychosocial development of children

with arthritis. Fortunately, the growing skeleton of a child with JIA may be an advantage, potentially enabling the child to recover from lesions deemed permanent in adult RA, such as bone erosion or avascular necrosis.²²

Medication Tolerability, Palatability and Availability

In contrast to a typical RA patient with other co-existing disease, children with JIA have less co-morbidity, and may, therefore, better tolerate medications. This may explain the superior tolerability of medications in JIA, such as methotrexate, although there are limited safety studies. Furthermore, there are limited safe studies regarding commonly used NSAIDs. The availability of liquid preparations of medications, as well as the palatability of these medications is also important. In regards to newer biologic agents that are being developed, the lack of availability of oral preparations may make administration challenging as many children and families may be anxious with parenteral administration.

Multidisciplinary Approach

The treatment of JIA requires a multidisciplinary, holistic approach with every effort for the child and family to avoid the "sick role." All healthcare professionals, including physiatrists, physical therapists, psychologists, and others, play key roles in the chronic care of the child with JIA. It is essential that all children resume normal activities, with the utmost importance placed on regular attendance in school with their peers. Prolonged home schooling should be avoided. Physical rehabilitation is especially invaluable at diagnosis and in early disease, with a focus of pain management, splinting, assistive device evaluation, aerobic conditioning, and other treatment modalities tailored to the individual patient at various time points throughout their illness in order to preserve, maintain, or improve physical functioning, thereby helping prevent deformity and dis-

ability. It is of the utmost importance that the therapist is familiar with both children and arthritis, and one should avoid prolonged casting or immobilization.

Noncompliance is a potential barrier in the care of children and adolescents with chronic disease. Early establishment of non-judgmental and open communication, as well as incorporating the patient in making age-appropriate therapeutic decisions, may help avoid this situation, so as to engender a sense of control and self-advocacy in the child. For example, a child may be offered the choice of which arm to receive a subcutaneous injection. A related psychosocial dynamic is appropriate transition of the pediatric patient to the adult rheumatologist. Transition should be a smooth process over a period of months to years depending on the patient, as it is often is a period of potential drop out from the healthcare system. Similar to adolescence, transition is a sensitive period of time, with mixed emotions for the patient, family, and physician, all of whom may unknowingly contribute a less than ideal evolution from pediatric to adult care.

Clinical Presentation

Clinical Vignette

A 2-year-old girl is noted to have a swollen right knee after minor trauma. Upon further history, it is discovered that she has been frequently limping after very active days, for the past several months. On physical exam, she has a relatively painless, warm, effusion with a 10° flexion contraction of her right knee. Arthritis of the right ankle is also discovered on complete musculoskeletal examination.

Oligoarticular JIA

Oligoarticular JIA (Oligo-JIA) is the most common subset of JIA, accounting for 50 to 60% of most cohorts of JIA. Eighty percent of patients are girls, with a peak age of onset between 1 and 3 years of age. By definition, the patient presents with arthritis of four or fewer joints during the first 6 months of disease. Knees and ankles are most commonly affected, and at presentation 50% of patients have a monoarthritis.²³ As illustrated by the clinical vignette, oligo-JIA commonly has an indolent presentation, often making the prompt diagnosis more challenging, as children are always well appearing and only rarely have moderate joint pain. Furthermore, the lack of formal training in pediatric musculoskeletal exam among clinicians who would commonly be the first point of contact, including family medicine physicians, pediatricians, and emergency medicine physicians, may result in a delay in diagnosis for many months. Features that are atypical for oligo-JIA include joint erythema, acute onset of severe pain resulting in an inability to bear weight, and hip involvement. It is common for children with oligo-JIA to modify their behavior to accommodate their arthritis, avoiding stressful positions that aggravate their affected joints, which may ultimately result in disuse atrophy or joint contracture over

time. A classic example is of the right-handed oligo-JIA patient who switches to use their left hand after developing right wrist arthritis.

A positive ANA may be present in up to 85% of patients with oligo-JIA and uveitis.²⁰⁻²⁴ Rheumatoid factor, although arguably the most common “autoimmune lab” sent on children presenting with non-traumatic musculoskeletal pain, should not be sent on the patient with oligo-JIA, as it is not seen in this JIA subset. Rheumatoid factor is not infrequently falsely positive, likely more related due to non-specific immune complex formation in the setting of viral disease, for example. Although patients with oligo-JIA may have mild anemia, inflammatory markers, such as ESR or CRP, are commonly normal in the setting of active arthritis or uveitis, and the clinician should not be reassured that the patient does not have active disease in the setting of normal laboratory data.

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.^{20,25} This subset of oligo-JIA is associated with poorer outcome, and lower likelihood of adult remission. Predictors of patients evolving into extended-oligoarticular JIA include: ankle, wrist, or hand arthritis; symmetric arthritis; arthritis in 2 to 4 joints; and the presence of an elevated ANA titer or ESR.²⁶

Depending on the JIA subtype and other factors, uveitis may be seen not uncommonly in JIA.¹⁰ The uveitis is typically bilateral and may be seen at diagnosis or later in the disease course, not consistently correlating with the activity of the arthritis. Much like the arthritis, the chronic anterior uveitis of JIA is often asymptomatic, as children rarely report complaints such as erythema, pain, or change in vision. Patients at highest risk for uveitis include ANA positive oligo-JIA patients; 20% to 30% developing eye disease and almost 50% in children less than 2.¹⁰ Other factors associated with increased risk include: female gender, age less than 6 years at diagnosis, and less than 4 years of disease duration.²⁷ Such patients are deemed high risk and require frequent screening slit lamp examinations every 3 to 4 months.²⁸ Most children with anterior uveitis respond to topical steroids, yet some patients may be refractory to topical therapy or develop iatrogenic complications from topical steroids, including glaucoma and cataracts, which are seen in up to 15% and 25% of patients, respectively.^{27,29}

Without appropriately aggressive treatment and close ophthalmologic follow-up, uveitis may result in further complications, such as synechiae (23%), band keratopathy (14%), macular edema (5%), and blindness (5% to 10%).²⁷ Systemic immunomodulatory therapy may, therefore, be required, including methotrexate, mycophenolate mofetil, and infliximab as well as others.³⁰⁻³² Although anti-tumor necrosis factor (TNF) therapy may be helpful in select patients with uveitis, etanercept does not appear to be effective and may even exacerbate uveitis.^{33,34} Though many systemic

immunomodulatory therapeutics are effective in pediatric uveitis, they are all used off-label, lacking FDA-approval.

Treatment

Non-Steroidal Anti-Inflammatory Drugs (NSAIDs)

NSAIDs are the cornerstone pharmacotherapeutics for the majority of patients. They are commonly used as monotherapy in patients with oligoarticular JIA. Through inhibition of the cyclooxygenase (COX) pathway of arachidonate metabolism, NSAIDs prevent the production of the proinflammatory prostaglandins. More than six NSAIDs are FDA-approved for use in JIA, with liquid formulations available of naproxen, ibuprofen, meloxicam, and indomethacin. Although adverse effects are not infrequent, NSAIDs are very well tolerated in children. There are limited safety studies regarding NSAIDs in JIA, though two recent studies demonstrated safe use of NSAIDs in children with abdominal pain and headache as the more common adverse reports, up to 30% and 15% respectively.^{35,36} Non-selective NSAIDs, such as naproxen, are effective agents that are available in palatable liquid formulations and reasonable dosing regimens, which are important considerations when prescribing medication for children. The withdrawal of rofecoxib, a selective COX II inhibitor, from the market in 2004, due to concerns regarding increased risk of thromboembolic phenomenon in adults, has resulted in COX II inhibitors being less commonly used in JIA. As there are few safety studies regarding the use of NSAIDs in JIA, a 5-year registry has just been completed that is seeking to collect further safety data of nonselective NSAIDs and celecoxib, a COX II inhibitor (<http://clinicaltrials.gov/ct2/show/NCT00688545>).

Intra-Articular Glucocorticoid Injections

After a trial of NSAIDs, intra-articular (IA) glucocorticoid injections are often the treatment of choice in oligoarthritis with persistent arthritis of one or two joints. 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. Sherry and colleagues demonstrated that children with oligo-JIA who received early administration of IA steroids within the first 2 months of disease onset had significantly less leg length discrepancy than patients who had received primarily NSAIDs.³⁷ In addition to the potential adverse effects and difficulties administering daily systemic medicine to small children, IA steroids provide immediate, effective, long-lasting, local treatment. Intra-articular injections often result in a sustained response, with no recurrence of arthritis in up to 70% of patients at 1 year and 40% at 2 years of follow-up.³⁸ One year follow-up gadolinium-enhanced MRI of joints injected with triamcinolone hexacetonide demonstrated markedly improved synovitis, and no evidence of joint damage in all examined joints.³⁹ Should a patient have a recurrence of arthritis, the clinician may inject the same joint up to 3 times in a year. Longer-acting triamcinolone

hexacetonide (*Kenalog or Aristospan*) is the preferred preparation among rheumatologists.

Polyarticular JIA

Clinical Vignette

A 15-year-old girl is evaluated for diffuse musculoskeletal pain for the past 4 months. She has missed several days of school due to fatigue, morning stiffness, and has quit the basketball team. She has lost weight but denies the presence of any fever or rash. On physical exam, she has swollen, tender, symmetric polyarthritis of multiple finger joints, bilateral wrists, elbows, and ankles. She is rheumatoid factor positive and has multiple carpal bone erosions on hand x-rays.

Polyarticular JIA (poly-JIA) accounts for 25 to 40% of JIA and is subdivided into rheumatoid factor (RF) positive and RF negative patients.⁶ The patient presents with painful, symmetric arthritis of five or more joints within the first 6 months of disease onset, almost always involving the finger joints. Although patients with poly-JIA not uncommonly have extra-articular constitutional features, such as fatigue, anorexia, weight loss, anemia, elevated inflammatory markers, morning stiffness, and low grade fever, they do not have consistently high spiking fever or rash, differentiating this from systemic-onset JIA. Also, unlike oligo-JIA, anterior uveitis is uncommon.

Rheumatoid factor positive poly-JIA accounts for only 5 to 10% of JIA. Clinicians should, therefore, be more selective when ordering this test, as there is a high false-RF positive rate in children, as stated previously. Unlike RA, anti-cyclic citrullinated peptide is not as consistent, informative, or reliable in JIA overall, though it is not infrequently checked. Seropositive poly-JIA patients have the identical clinical phenotype as adult rheumatoid arthritis, with early-onset, aggressive, erosive, symmetric polyarthritis, and the potential for classic Boutonnière and swan neck joint deformities with variable presence of rheumatoid nodules. Understandably, many pediatric rheumatologists consider this JIA subtype to be earlier-onset RA, rather than a unique “pediatric” arthritis, due to onset of arthritis prior to the age of 16, a not uncommon critique of the current JIA nomenclature. In addition to peripheral joint disease, patients also have propensity to develop arthritis of their cervical spine and temporomandibular joint, the latter which is often relatively clinically asymptomatic, though potentially resulting in disturbances of growth and function.^{20,21} Disease onset is typically seen in children older than 8, though more common in adolescence, with a 90% female predominance. RF positive poly-JIA has a lifelong prognosis that is poor, without appropriately aggressive treatment. Seronegative poly-JIA patients have a more 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 poly-JIA ultimately require a disease modifying anti-rheumatic drug (DMARD) therapy, a

biologic agent, such as anti-TNF- α therapy, or both. As a bridging drug, low-dose corticosteroids are used sparingly, for their immediate anti-inflammatory properties, which is important as many DMARDs such as methotrexate require several weeks to reach full therapeutic effect. As poly-JIA patients are at high risk for lifelong disease, their ability to be weaned off medication is questionable.

Disease Modifying Anti-Rheumatic Drugs (Dmards)

Methotrexate (Rheumatrex)

For over 30 years, low-dose (less than 30 mg), weekly methotrexate has been used as an effective DMARD in the majority of patients with JIA. Methotrexate was demonstrated to be significantly more effective than placebo in one of the few randomized, double-blind, placebo-controlled trials involving 127 children.⁴⁰ In a 1993 meta-analysis of three prior clinical trials investigating oral gold, d-penicillamine, hydroxychloroquine and methotrexate, the latter demonstrated a 50% or greater improvement in 50% of the children given methotrexate at 10 mg/m²/week.⁴¹ A 2005 study by Silverman and associates 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.⁴²

Methotrexate is well-tolerated in children when given with folic acid, with many children safely tolerating oral or subcutaneous doses up to 30 mg with anecdotal efficacy. Ruperto and colleagues investigated the use of higher doses of parenteral methotrexate (intermediate dose: 15 mg/m²/week; and high dose: 30 mg/m²/week) in children with poly-JIA who had not responded to 6 months of standard methotrexate doses of 8 to 12.5 mg/m²/week. Patients who received the higher dose of methotrexate did not have a therapeutic response greater than those who received the intermediate dose of 15 mg/m²/week.⁴³ Despite these results, some pediatric rheumatologists may still increase the dose of methotrexate to 1 mg/kg, up to 30 mg weekly, though less commonly than in the past with the introduction of biologics. After methotrexate is initiated and clinical response is obtained, it is unclear when, if ever, one should stop methotrexate, as up to 60% of patients with poly-JIA may flare with arthritis.⁴⁴

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.⁴⁵ Transient transaminitis is often managed by withholding methotrexate until normalization of liver enzymes, with successful resumption of methotrexate thereafter. With its affordability, proven efficacy, safety, and tolerability, methotrexate is the DMARD of choice against which all other DMARDs or biologics are judged.

Sulfasalazine (Azulfidine)

Sulfasalazine has been used extensively in the treatment of arthritis for over 30 years. In Europe, prior anecdotal reports

and open-labeled studies suggested efficacy of sulfasalazine in the treatment of JIA.^{46,47} A 24 week randomized, double-blind, placebo-controlled, multicenter study of 70 patients with early-onset oligoarticular or polyarticular JIA demonstrated decreased joint pain or swelling and inflammatory markers in patients on sulfasalazine vs. placebo, ultimately leading to its FDA approval in 1998.⁴⁸ Of note, nearly a third of patients on sulfasalazine ultimately discontinued the medication due to adverse events, which were most commonly anorexia, abdominal pain, and rash. These side effects as well as the proven efficacy of methotrexate and the discovery of biologics may partly explain the less common use of sulfasalazine in the United States. Still, when cost, availability, or parental concerns regarding lack of longer term outcome data with biologics in JIA are raised, sulfasalazine may be considered as alternative or add-on combination therapy with other agents.

Leflunomide (Arava)

Leflunomide has been shown to be a safe, well-tolerated, and effective DMARD for RA.^{49,50} Silverman and colleagues conducted a 16 week study of methotrexate versus leflunomide in 94 DMARD-naïve poly-JIA patients, in a double-dummy, blinded fashion followed by a 32 week blinded extension.⁴² Response rates were unprecedented for both leflunomide and methotrexate with patients achieving an ACR Pedi 50 of 73% and 86%, respectively at 16 weeks. Furthermore, most responders were able to maintain this response in the 2 year open-label extension study, with 70 to 86% of patients receiving either medication achieving an ACR Pedi 50 or 70 at week 48. Most common adverse events included elevated liver enzymes, headache, abdominal pain, nausea or vomiting, diarrhea, alopecia, and viral infections. Serious adverse event possibly related to treatment included suspected salmonellosis, abnormal liver function tests, and parapsoriasis. Despite these impressive results, leflunomide did not receive FDA approval for JIA, due to concerns regarding inadequate plasma concentrations of its M1 active metabolite in children less than 40 kg. This may contribute to its lack of popularity among pediatric rheumatologists in the United States.

Biologic Therapy

General Principles

The efficacy and long term safety data for methotrexate, which is effective for the majority of JIA patients, cannot be overemphasized. Furthermore, it is important for the clinician to be aware that the majority of studies evaluating the efficacy of newer biologic therapy include a relative minority of JIA patients, who are predominantly poly-JIA patients with recalcitrant disease despite methotrexate. The impressive promotional campaigns of these new biologics educate our patients, many who come requesting the initiation of these medications prematurely. The relatively high cost of biologics, which can easily reach \$15,000 a year, as well as the lack of

current available oral preparations, may also make administration more challenging. Furthermore, as these medications have only been used since the late 90s, “longer” term data are not available. Nevertheless, anti-TNF biologic therapy has clearly transformed the therapeutic armamentarium of JIA, providing elegant, target-specific agents. Anti-TNF biologics are the most likely reason that fewer children are in wheelchairs or in need of other assistive devices, demonstrating the critical role of TNF- α in the pathogenesis of a significant fraction of patients with JIA. Still, anti-TNF therapy is not effective in a subset of JIA patients, demonstrating that other pathogenic factors may play a key role.

Though anti-TNF therapy was studied for use in the treatment of sepsis, infection risk as well as response to vaccination is of concern. In general, it is advisable to update all vaccinations prior to the initiation of therapy and avoid live vaccinations during DMARD or biologic therapy. Demonstrating a negative purified protein derivative (PPD) or serum quantiferon prior to initiation of an anti-TNF agent is mandatory as there is a clear risk for tuberculosis reactivation with the use of these medications. Regarding other serious concerns related to anti-TNF therapy, in 2009 the FDA issued a black-box warning pertaining to the potential association of malignancy in children who received anti-TNF therapy.⁵¹ Forty-eight children receiving anti-TNF therapy (infliximab, N = 31; etanercept, N = 15; adalimumab, N = 2) developed cancer, half of which were lymphomas, as well as other forms including leukemia, melanoma, thyroid cancer, and a rare intestinal T-cell lymphoma in patients with Crohn’s disease. Only 19 patients had JIA, though the background rate of malignancy in JIA was unknown, unlike RA. Furthermore, the majority of patients were on concomitant immunosuppressives, which carry potential risk of malignancy.

In response to the black-box warning, Beukelman and colleagues conducted a review of the U.S. Medicaid database from 2000 to 2005 in over 7,800 children with JIA ever versus never exposed to methotrexate or anti-TNF medications compared to controls, which included patients with either asthma or attention deficit hyperactivity disorder.⁵² Children with JIA appear to have a higher standardized incidence ratio (SIR) of 4.4 for malignancy compared to those without JIA. The addition of methotrexate, anti-TNF agents, or both did not appear to change the likelihood of malignancy. It is not unreasonable to speculate a link between TNF blockade and malignancy; however, the irrational fear of rare complications, however unfortunate, may result in the return of wheelchairs in the pediatric rheumatology clinic. More investigation in this matter is warranted.

Anti TNF- α therapy

Etanercept (Enbrel)

Etanercept is a soluble, dimeric, fusion protein consisting of the human p75 TNF receptor fused to the Fc region of human IgG1. Etanercept is a well-tolerated, effective bio-

logic for RA.^{53,54} In 1999, etanercept was the first biologic to receive FDA-approval for poly-JIA, as a result of efficacy data from a randomized study in JIA, which was the sentinel withdrawal study design in JIA, used in many subsequent JIA trials.¹⁴ Sixty-nine patients with active poly-JIA, despite NSAIDs and methotrexate, were enrolled in a multicenter, randomized, double-blind withdrawal study. After an initial 14-day methotrexate washout period, all patients received etanercept (0.4 mg/kg, max 25 mg) twice weekly for the first 3 months, as part of the open-label part of the trial. Stable doses of NSAIDs and low dose prednisone (≤ 0.2 mg/kg, max 10 mg/day) were allowed. Seventy-four percent of patients deemed responders, having achieved at least an ACR Pedi 30 after the first 3 months of etanercept monotherapy, were then randomized to etanercept withdrawal for months 4 through 7 until either disease flare occurred or 4 months elapsed. Patients randomized to continue etanercept for 4 months had a significantly longer median time to disease flare than the placebo group. Patients who flared re-started etanercept in the open-label extension. Correlating with etanercept trials in adult RA, a German registry suggested improved efficacy of etanercept in combination therapy with methotrexate.⁵⁵

Eight-year safety and efficacy data from a total of 318 patient-years, including 26 of the initial 69 patients who entered the eighth year of continuous treatment with etanercept, demonstrated that the long-term safety profile was maintained and exposure-adjusted rates of serious adverse events (SAEs) did not increase over time. The most common new SAE beyond 4 years consisted of arthritis flare, and there were no reported cases of malignancies, lupus, or demyelinating disorders.⁵⁶ Other follow-up studies have also supported improvement in growth and quality of life, as well as a sustained response with etanercept.⁵⁷⁻⁵⁹ An Italian registry of 40 poly-JIA patients on etanercept demonstrated apparent radiologic resolution of prior erosions on follow-up x-rays, although future prospective studies are necessary to validate this outcome.²² Another 3 year study of children with polyarticular or systemic onset JIA demonstrated up to 13% increase in growth from baseline in children who received etanercept.⁵⁹

Adalimumab (Humira)

Adalimumab is a humanized IgG monoclonal anti-TNF-antibody that is effective in reducing the pain, swelling, and joint destruction of adult RA.^{60,61} 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.⁶² All patients received open-label 24 mg/m² (maximum 40 mg) of adalimumab subcutaneously every other week for 16 weeks. Responders, who achieved at least an ACR Pedi 30 response, were randomized to continue adalimumab or subcutaneous placebo for up to 32 weeks or until disease flare. After 100 weeks of the open-label extension ACR Pedi 50 and 70 responses were achieved in an impressive

86% and 77% of patients, respectively, surpassing any clinical response data in RA. Furthermore, 40% of patients achieved an ACR Pedi 90 (equivalent of clinical remission) at 16 weeks, with a sustained response at up to 170 weeks of follow-up. Although 16% of patients demonstrated at least one positive test for an anti-adalimumab antibody, the presence of these antibodies did not lead to a greater incidence of adverse events or drug discontinuation. Counter intuitively, these antibodies developed in 5 of 85 (6%) patients receiving methotrexate, in contrast to 22 of 86 (26%) of patients not receiving methotrexate. Unlike etanercept, the addition of methotrexate did not appear to provide any additional benefit in these patients. Adverse events were not common and usually considered mild, such as infection and injection site reactions. Serious adverse events perhaps related to adalimumab were present in 14 patients, including viral infections, pharyngitis, and pneumonia.

Infliximab (Remicade)

Infliximab is an intravenous chimeric (mouse-human) IgG1 monoclonal antibody that binds both membrane-bound and soluble TNF- α . Infliximab has been shown to be an effective agent in adult RA.^{63,64} In 2007, a phase III, multi-center, randomized, double-blind, placebo-controlled study of 122 poly-JIA patients with persistent disease despite methotrexate therapy was conducted.⁶⁵ Patients were randomized to receive infliximab (3 or 6 mg/kg) or intravenous placebo infusions for 14 weeks, after which all patients received infliximab through week 44. Patients were randomized to either one of two groups. Patients in Group 1 received methotrexate plus infliximab through week 44. Patients in Group 2 received methotrexate plus placebo for 14 weeks, followed by methotrexate plus infliximab (6 mg/kg) through week 44. Although the difference in ACR Pedi 30 at week 14 between placebo and 3 mg/kg infliximab was not statistically significant (63.8% and 49.2%, respectively), 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 more serious adverse events, including infusions reactions, human anti-chimeric antibodies (HACAs) to infliximab, and newly induced antinuclear antibodies in the 3 mg/kg group than the 6 mg/kg group, for unclear reasons. Decreased efficacy over time is perhaps attributed to the development of HACAs. 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. Nevertheless, it is still commonly used "off-label" by rheumatologists, as infliximab is effective in JIA based on the open-label study, as well as anecdotal reports, case series, and personal experience.

Combination Therapy

In view of the clinical data which suggests early, aggressive combination therapy may improve outcome in RA, this ques-

tion was investigated contemporaneously in two multi-center studies in the United States and Europe, utilizing etanercept and infliximab, respectively. In the United States, the Trial of Early Aggressive Therapy (TREAT) in poly-JIA trial enrolled 85 biologic naïve poly-JIA patients with mean disease duration of 5 months. Patients were randomized to receive methotrexate monotherapy versus combination therapy of methotrexate (up to 40 mg) and etanercept and prednisone (0.5 mg/kg, up to 60 mg tapered off by week 16). Though not statistically significant, 40% of patients in the aggressive arm achieved the formal definition of clinically inactive disease in contrast to 23% of patients who received methotrexate alone. In Europe, the Aggressive Combination Drug Therapy in very early polyarticular JIA (ACuTE-JIA) trial enrolled 60 biologic and DMARD naïve patients with mean disease duration of 1.9 months to be randomized to receive one of three treatments: methotrexate versus methotrexate plus infliximab versus methotrexate, sulfasalazine, and hydroxychloroquine. At 6 months, an ACR Pedi75 was achieved in 100% of patients who received methotrexate plus infliximab, in contrast to 50% of patients who received methotrexate and 65% of patients who received methotrexate, sulfasalazine, and hydroxychloroquine. Though these data are suggestive of the benefits of early and aggressive therapy, longer term outcome data are necessary.

Co-stimulatory Blockade

Abatacept (Orencia)

More than 75% of patients respond to methotrexate as a first line DMARD for JIA. Of those who fail to have an adequate response to methotrexate, the majority will respond to an anti-TNF agent. Still, as in adult RA, a fraction of JIA patients may not respond to anti-TNF therapy, suggesting that other factors beyond this cytokine may play a pivotal role in certain patients. Rather than targeting cytokines specifically, one may target T cell activation via blockade of CD80/86-CD28 costimulatory signaling between the antigen presenting cell and T cell that is essential for proper T cell activation and proliferation. Abatacept is an intravenous, soluble, fully human fusion protein consisting of the extracellular domain of CTLA-4 linked to a modified Fc portion of human IgG. Abatacept competitively binds to CD80 or CD86 on antigen presenting cells, which therefore cannot bind to CD28 on T cells, inhibiting successful T cell activation. Abatacept has been successfully used in adult RA.^{66,67} 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.⁶⁸ All children initially received intravenous abatacept (10 mg/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. Patients on other DMARDs or biologics required a washout period of at least 4 weeks prior to abatacept.

Twenty-five percent (47/190) of patients did not respond to abatacept after the initial 4 month open-label period and were excluded from further randomization to placebo. Patients on abatacept had fewer flares of arthritis than placebo, 20% and 53%, respectively. At 4 months, ACR Pedi 50 and 70 were achieved in 50% and 28% of patients. Almost 1/3 of patients had previously discontinued anti-TNF therapy, and 25% of these patients were able to achieve an ACR Pedi 50 at 4 months, suggesting its efficacy in patients deemed "TNF failures." Adverse events were seen in 70% of abatacept patients and 55% of placebo, most commonly headache, nausea, diarrhea, cough, and upper respiratory infection. Serious adverse events were seen in six patients (3%), including arthritis flare, varicella, ovarian cyst, and acute lymphocytic leukemia, although retrospective review of the clinical data suggested that the leukemia preceded treatment with abatacept. As a result of this trial, abatacept received FDA-approval for JIA in 2008.

Systemic-onset JIA

Clinical Vignette

A five-year-old boy is admitted for further evaluation of his 3 week history of fever of unknown origin, malaise, and intermittent rash. He is discovered to have pericarditis, hepatosplenomegaly, lymphadenopathy, elevated inflammatory markers, and pancytopenia, leading to further evaluation by infectious disease and oncology. Polyarthritis is discovered on subsequent physical exam.

Systemic-onset JIA (S-JIA) comprises only 10% of JIA, though it accounts for a significant percentage of the morbidity and mortality in JIA. Identical to adult Still's disease, S-JIA is characterized by daily high-spiking fever for at least 2 weeks. The classic salmon-colored evanescent rash consists of discrete circumscribed macules that may be surrounded by a ring of pallor or develop central clearing. This rash is found most commonly on the trunk, axilla, and inguinal areas, and may be exacerbated by fever, stress, or a hot bath, emphasizing the importance of a full skin exam when the patient is febrile. The arthritis of S-JIA is commonly polyarticular, and usually presents within the first 3 months of onset, though it may be absent or unrecognized at diagnosis. The clinician may, therefore, be false reassured, not considering this diagnosis, though patients with S-JIA almost never have a chief complaint of "joint pain." Since arthritis may not be present early, diagnosing S-JIA is 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 S-JIA may occur at any age. Further distinguishing this subset is the very rare presence of uveitis, rare ANA positivity, and absent rheumatoid factor.

Although 60 to 85% of patients with S-JIA may experience a quiescent phase, up to 37% of patients develop chronic,

erosive polyarthritis, requiring therapy with DMARDs and biologics.²⁰ Predictors of poor prognosis in S-JIA include: age of onset less than 6 years, disease duration for greater than 5 years, or persistent systemic features at 6 months of disease including fever, the need for corticosteroids, and thrombocytosis.⁶⁹ After the systemic features subside, it is the chronic arthritis which predominates, often resulting in misclassification as poly-JIA, though the patient had clear systemic-onset disease. Mortality is less than 0.3% for patients with S-JIA in North America, with the vast majority of patients dying from macrophage activation syndrome (MAS), infection, or cardiac complications. Although an uncommon complication, the prevalence of amyloidosis is 1.4% to 9% in patients with S-JIA.²⁴

Macrophage Activation Syndrome

Macrophage activation syndrome (a.k.a. reactive or secondary hemophagocytic lymphohistiocytosis syndrome) is an uncommon, but potentially life-threatening syndrome seen in S-JIA. There is debate among rheumatologists regarding whether Macrophage activation syndrome (MAS) is a separate entity from S-JIA or rather an extreme variant within the spectrum of S-JIA. Pathogenesis is likely related to impaired cytotoxicity of NK cells and CD8 positive T cells, low perforin levels, and endothelial activation ultimately culminating in an overwhelming cytokine storm with activated macrophages infiltrating organs, such as the bone marrow and liver. The diagnostic hallmark of MAS is the presence of well-differentiated, activated macrophages actively phagocytosing hematopoietic cells within the bone marrow. Inconsistent and debatable triggers of MAS include viral infections and alteration of medication regimen.^{70,71}

Clinical features of MAS include fever, liver failure, coagulopathy with hemorrhage and thrombophilia, encephalopathy, and seizures. A diagnosis of MAS carries up to a 22% risk of mortality.⁷² Laboratory features include markedly elevated ferritin, pancytopenia, prolonged PT and PTT, hypofibrinogenemia, elevated fibrin split products, and hypertriglyceridemia. A clinical pearl regarding MAS is the normalization of an ESR in the setting of clinical deterioration, which likely signifies a worsening consumptive process with hypofibrinogenemia, thus resulting in a normal ESR. 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, based on anecdotal evidence and small case series.⁷³

Targeting IL-1 and IL-6

Anakinra (Kineret)

Although anti-TNF therapy is widely used in patients with JIA, it appears to be less effective in S-JIA. A survey of pediatric rheumatologists demonstrated that 54% of patients with S-JIA had a fair or poor response to etanercept.⁷⁴ Interleu-

kin-1 Beta (IL-1 β) is another proinflammatory cytokine that has been implicated in the pathogenesis of JIA.^{75,76} Anakinra is a recombinant, human, injectable IL-1 receptor antagonist that is FDA-approved for RA and has been investigated as a therapeutic option in JIA. An open-label trial of anakinra in nine S-JIA patients demonstrated dramatic resolution of fever in 7/9 patients, arthritis in 6/8 patients, and laboratory parameters (ESR, leukocytosis, anemia, thrombocytosis), within the first week of therapy.⁷⁷ In a study by Pascual and coworkers, nine patients with prolonged, steroid-dependent, medically refractory sJIA who received anakinra had resolution of fever, leukocytosis, chronic, persistent anemia, and thrombocytosis within 1 week of starting treatment.⁷⁷ A retrospective study by Zeff and colleagues demonstrated successful treatment of 33 patients with sJIA, resulting in less steroid dependence and rapid improvement in anemia and thrombocytopenia.⁷⁸ Recently, a multi-center report documented the effectiveness of anakinra, either alone, or in conjunction with corticosteroids or methotrexate, in treating 46 sJIA patients from the time of diagnosis.⁷⁹ Most recently, a randomized double-blind placebo-controlled trial in patients with active sJIA demonstrated efficacy of anakinra vs. placebo in children who continued to have active disease, despite prior treatment, including glucocorticoids, methotrexate, and etanercept.⁸⁰ Not unexpectedly, IL-1 may not be the absolute defining factor in all patients with S-JIA, and a recent study by Gattorno and colleagues suggested two clinical S-JIA subsets, including IL-1 blockade “responders” (10/22, 45%) with a lower number of active joints and an increased absolute neutrophil count, in contrast to the “non-responders” group.⁸¹ Adverse effects of this agent include injection site reaction, hepatitis, and possible increased susceptibility to serious infection and secondary malignancy.^{82,83} An open-label, phase 2, dose escalation trial of Canakinumab, a fully humanized monoclonal antibody binding IL-1 β , in 23 patients, 70% of whom had previously taken anakinra, demonstrated that 60% of patients were able to achieve an ACR Pedi50 at Day 15, suggesting alternative agents in patients deemed anakinra failures.⁸⁴ A current phase II/III trial of anakinra in refractory S-JIA is underway, as well a trial using riloncept, an IL-1 Trap.

Tocilizumab (Actemra)

Plasma levels of interleukin-6 (IL-6) may also be very elevated in patients with S-JIA and have been shown to correlate with arthritis, fever, and thrombocytosis.⁸⁵ Transgenic mice over-expressing human IL-6 demonstrate impaired growth, commonly found in patients with S-JIA, resulting from chronic inflammation.⁸⁶ The use of tocilizumab, a humanized, monoclonal antibody against the IL-6 receptor has demonstrated efficacy in open-label trials of S-JIA.⁸⁷ In 2008, Yokota and colleagues published the results of their Phase III trial of 56 S-JIA patients with persistent disease despite DMARD and biologic therapy.⁸⁸ Eighty-eight percent (49/56) of patients had persistent fever, with a mean ESR

of 44.5 mm/hr at baseline. After an appropriate DMARD/biologic washout period, tocilizumab infusion (8 mg/kg) was administered as monotherapy every 2 weeks for three doses to all patients during the 6 week open-label, lead-in phase. Subsequently, randomization to placebo occurred in the group of patients who achieved an ACR Pedi 30 response for the following 12 weeks, or until disease flare-up.

Patients who responded to tocilizumab were allowed to enroll in the open-label extension phase for at least 48 weeks. At week 6, ACR Pedi 50 and 70 responses were achieved in 86% and 68% of patients, respectively, including improvement in fever, thrombocytosis, and ESR. At the end of the open-label extension period, 90% of patients achieved an ACR Pedi 70 response by week 48, and corticosteroids were reduced by at least 50% in the majority of patients. Sub-analysis regarding patients previously taking anti-TNF therapy were not presented for unclear reasons. Adverse events included infusions reactions, gastrointestinal hemorrhage, bronchitis, and gastroenteritis. Three patients developed anti-tocilizumab IgE antibodies. An ongoing international phase III trial seeks to determine the ideal dosing regimen and continues to evaluate the efficacy of tocilizumab.

Outcome

Much of the prior data regarding long-term outcome of JIA into adulthood 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. Despite these biases, JIA does not “burn out” as previously believed, with a significant fraction of adults having deformity, functional limitation, growth disturbance, or active arthritis as a consequence of their JIA. Zak and Pedersen retrospectively reviewed the charts of 65 patients with an average of 26.4 years of disease, discovering that 11% of patients had severe disability, and 22% had undergone JIA-related surgery.⁸⁹ Packham and Hall investigated functional outcome in 246 adults with JIA with average disease duration of 28.3 years, including 50% oligoarticular-onset JIA, demonstrating shorter stature in contrast to the general population, and micrognathia in 32.7%, especially in patients with S-JIA and RF negative poly-JIA. Twenty-three percent of these patients were still taking methotrexate.²⁹ In addition to functional impairment and active arthritis, adults with JIA may also have significant impairment of their quality of life with a higher unemployment rate (24.6%), despite excellent educational achievement compared to control populations.⁹⁰

Summary

Juvenile idiopathic arthritis is the most common rheumatic disease of childhood, and may result in both short and long-term disability with persistent arthritis into adulthood. The

prior juvenile rheumatoid arthritis (JRA) nomenclature is now included within the JIA classification, which also includes extended oligoarthritis, psoriatic arthritis, enthesitis related arthritis, and undifferentiated arthritis. The majority of JIA consists of the oligo-JIA subtype, with a relatively high risk of asymptomatic anterior uveitis. Although this subtype of arthritis is often not very painful, significant deformity and growth disturbance may occur without appropriate therapy. DMARD or biologic therapy may be required in extended oligo-JIA or uveitis. All poly-JIA patients will likely require aggressive DMARD, biologic therapy, or both with RF positive patients carrying a worse prognosis for lifelong disease. Systemic-onset JIA is an impressive, inflammatory disease that may be complicated by MAS, requiring high dose steroids, and the addition of DMARD, biologic therapy, or both, most recently with successful use of anti-IL-1 therapy.

Currently, there are less than 300 pediatric rheumatologists in the United States. A large fraction of these physicians are active members of the various pediatric rheumatology research collaborative study groups, including CARRA and PRCSG. If a pediatric rheumatologist is unavailable, many of children with JIA may be cared for by adult rheumatologists, generalists, clinical immunologists, and other physicians. With continued collaborative research efforts, we hope to gain a better understanding of the biology and epidemiology of childhood arthritis, and thereby offer better therapies for our patients with the hope of a future cure. In the meantime, 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 in children with JIA.

Disclosure Statement

The author has no financial or proprietary interest in the subject matter or materials discussed, including, but not limited to, employment, consultancies, stock ownership, honoraria, and paid expert testimony.

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