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A Publication for Rheumatology Nurse Practitioners and Physician Assistants

Juvenile Idiopathic Arthritis: Efficacy and Safety of Treatments

Martin J. Bergman, MD, Senior Editor

Juvenile idiopathic arthritis (JIA), an umbrella classification for chronic idiopathic arthritis in children, is the most common pediatric rheumatologic disease.^{1,2} JIA is a major cause of functional disability and eye disease leading to blindness in children.^{3,4} For an arthritis to be classified as JIA, the age at onset must be 16 years or less and the duration of arthritis must be at least 6 weeks, after exclusion of arthritis associated with other chronic illnesses.^{1,5} JIA was formerly referred to as juvenile rheumatoid arthritis (JRA). The new terminology was proposed by the International League Against Rheumatism (ILAR) and is currently widely adopted in Europe and the United States.⁵ (See Fast Facts: New Classification System for Pediatric Arthritis, page 3.)

Nonsteroidal anti-inflammatory drugs (NSAIDs), methotrexate (MTX), and corticosteroids have been the mainstays of medical therapy for JIA. The advent of anti-cytokine therapy directed against tumor necrosis factor- α (TNF- α), interleukin-1 (IL-1), and other targets promises improved efficacy for articular symptoms with fewer adverse effects.⁶

This issue of PCE Updates in Rheumatology reviews the clinical burden of JIA, the evolving therapies for JIA, and the management of uveitis in JIA. Rick Pope, MPAS, PA-C, presents a case study of a patient with JIA, with clinical commentary (page 8).

Needs Assessment

Juvenile idiopathic arthritis (JIA), the most common pediatric rheumatologic disease, can lead to lifelong symptoms and substantial disability; it is also the most common cause of pediatric uveitis, which can result in cataracts, glaucoma, and band keratopathy.^{1,2} Treatment goals include decreasing chronic joint pain and suppressing inflammation to improve function, allow normal growth and development, and prevent eye damage.^{1,3} Currently, there are no evidence-based management guidelines for JIA; treatment is based on disease subtype. Traditional therapies—nonsteroidal anti-inflammatory drugs, nonbiologic disease-modifying antirheumatic drugs, and corticosteroids—are associated with significant adverse effects in children.^{1,3} The advent of biologic therapies promises improved efficacy with fewer adverse effects.³ Clinicians in rheumatology practices need to be aware of current evidence on the efficacy and safety of nonbiologic and biologic treatments for JIA.

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Target Audience

Nurse practitioners (NPs), physician assistants (PAs), and physicians in the practice of rheumatology.

Learning Objectives

After completing this activity, participants should be better able to:

1. Define the revised criteria for classifying subtypes of JIA and explain the relevance to JIA management.
2. Formulate evidence-based treatment plans for patients with JIA.
3. Translate clinical evidence on anti-tumor necrosis factor- α agents into effective management plans for JIA-associated uveitis.

Practicing Clinicians EXCHANGE™

(continued on page 2)

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Clinical Burden of JIA

The reported prevalence rates of childhood arthritis vary widely, largely because of variations in disease classification criteria as well as misclassifications and misdiagnoses.^{2,7} Based on data on ICD-9-CM codes from the 2001 to 2004 National Ambulatory Medical Care

Survey and National Hospital Ambulatory Medical Care Survey, the average annualized estimate of the number of children with significant pediatric arthritis or other rheumatologic conditions in the United States is 294,000 (95% CI: 188,000-400,000).⁷ Pediatric arthritis contributes to an estimated 827,000

Perspectives From Rick Pope, MPAS, PA-C

What are the greatest challenges physician assistants (PAs) face in managing chronic arthritis in children?



From a clinician's perspective, education of the parents and patient is critical to the overall treatment plan. Success depends on the trust built over time among the practitioner, parents, and patient. One of the most important things I have learned is to offer the family an opportunity for a second opinion. This approach lends credence to you as a trusted healthcare provider and can enlist the help of other healthcare professionals in treating this difficult and potentially disabling disease.

Another part of the strategy is to contact the child's teachers, with the permission of the parents and the child, and inform them of the diagnosis and treatment plan. Enlisting the help of the physical education teacher can encourage the child to participate as fully as possible in the school's exercise programs with activities (eg, swimming) that will not jeopardize the joints, but still fulfill the child's goals and aspirations.

What strategies do you use to help parents weigh the benefits and risks of different treatments?

For female patients receiving MTX, counseling on pregnancy prevention is critical due to the teratogenicity of the drug. This discussion would be appropriate for

adolescent patients and should take place earlier rather than later. The parents need to be informed when the patient is younger than 18 years of age. Additionally, alcohol usage should be discussed because of the increased risk of liver toxicity with MTX. Although all adolescents should be given the sex and alcohol talk, it takes on extra importance for patients with JIA.

A substantial number of patients cannot tolerate NSAIDs. I warn parents and patients of the possible gastrointestinal (GI) and photosensitizing side effects of these agents. If the patient requires treatment with multiple medications, it also is important to warn of potential drug-drug interactions, especially for drugs that are hepatically metabolized. For example, interactions with systemic retinoids are of particular concern for patients being treated for acne. In addition, I recommend close monitoring of the patient's blood pressure at all visits, and I am careful to let parent and child know that elevated blood pressure is a potential side effect of treatment.

What is the PA's role in ongoing clinical assessment of JIA?

I enlist adolescent patients' help with keeping a dietary diary. I explain they are at increased risk of adult osteoporosis and need to maximize bone density with appropriate dietary intake. I then ask them to document their calcium and vitamin D intake, and I review the diary with them on their next visit. This gives patients a goal and the sense of having control over the disease. They often do quite well—taking pride in the activity.

(95% CI 609,000-1,044,000) ambulatory healthcare visits annually and imposes a substantial burden on the pediatric healthcare system.⁷

Substantial mortality and morbidity are associated with JIA. The estimated mortality rate among patients with JIA is 4- to 14-fold higher than in an age- and sex-matched healthy population.^{1,8} Amyloidosis and macrophage activation syndrome (MAS) are the main causes of mortality in JIA⁹; generalized growth failure, osteopenia, and uveitis are the major causes of morbidity.³

Although it is a rare complication of JIA, MAS but can be rapidly fatal. It occurs most often in patients with systemic-onset disease. Presenting features include nonremitting high fever, lymphadenopathy, hepatosplenomegaly, pancytopenia, liver dysfunction, hypertriglyceridemia, and hyperferritinemia. Because symptoms and signs of active systemic-onset JIA and MAS overlap, early recognition of MAS may be difficult.¹⁰

Generalized growth failure occurs secondary to prolonged severe disease and is aggravated by corticosteroid treatment. Active disease may cause premature epiphyseal closure resulting in short stature or localized growth defects, including micrognathia and shortening of the fingers, hands, forearms, toes, or feet.¹¹ Localized overgrowth also occurs classically at the knee, causing unequal leg lengths, with the involved leg growing longer. Puberty and the development of secondary sexual characteristics also are often delayed.³

Osteopenia in JIA is characterized by inadequate bone formation for age and low bone turnover.³ The decreased bone mass places children

with JIA at increased risk of fractures in adulthood and an earlier onset of more severe osteoporosis.¹²

The most common cause of pediatric uveitis is JIA, which can lead to cataracts, glaucoma, band keratopathy, and blindness.¹³ Chronic anterior uveitis is the type seen most often in JIA.¹⁴ Risk factors for uveitis include young age at diagnosis, female sex, antinuclear antibody (ANA) positivity, and the JIA subtype.^{13,14} Uveitis risk is highest in

oligoarticular JIA (12%) and lowest in systemic-onset JIA (1.8%).¹³ The relative contribution of specific risk factors to uveitis risk varies by JIA subtype. According to a long-term follow-up study of 1081 patients with JIA, female sex increases uveitis risk in patients with oligoarticular or persistent oligoarticular JIA; ANA positivity and young age at diagnosis each increase the risk in patients with rheumatoid factor (RF)-negative polyarticular JIA or

Fast Facts: New Classification System for Pediatric Arthritis

The American College of Rheumatology (ACR) criteria for JRA require arthritis in at least 1 joint for 6 weeks, onset prior to 16 years of age, and the exclusion of other causes of arthritis.⁴ These criteria are essentially identical to the ILAR criteria for JIA.^{1,5} The JRA classification is based on the clinical presentation of the disease (onset type). There are 3 major onset types that have been defined—systemic, oligoarticular (pauciarticular), and polyarticular—based on the systemic features of the illness and the number of joints with arthritis at

diagnosis.⁴ The JRA onset types are further subtyped based on the clinical course of the disease. The JIA classification system is based on growing data on clinical, immunologic, and genetic subtypes of chronic arthritis in children.⁵ Currently, there are 8 recognized subtypes of JIA.^{1,5} Although there are overlaps in the subtypes between the 2 classification systems, JIA differs from JRA in that it includes arthritis associated with juvenile psoriasis, inflammatory bowel disease, enthesitis, and undifferentiated arthritis.

JIA Nomenclature	JRA Nomenclature
Systemic arthritis (≥ 1 joint; starts with fever of at least 2 weeks' duration and documented as daily for at least 3 days; accompanied by ≥ 1 of the following: rash, lymph node enlargement, hepatomegaly, splenomegaly, and/or serositis)	Same
Oligoarthritis (≤ 4 joints in first 6 months of disease) ▶ Persistent oligoarthritis (≤ 4 joints throughout the disease course) ▶ Extended oligoarthritis (> 4 joints after first 6 months of disease)	Pauciarticular Pauciarticular onset, polyarticular course
Polyarthritis, RF-negative (≥ 5 joints in first 6 months of disease)	Same
Polyarthritis, RF-positive (≥ 5 joints in first 6 months of disease)	Same
Enthesitis-related arthritis (includes spondyloarthritis, IBD, presence of HLA-B27 antigen)	Not included
Psoriatic arthritis	Not included
Undifferentiated arthritis (fits none or ≥ 2 of above categories)	Not included

HLA = human leukocyte antigen; IBD = inflammatory bowel disease; RF = rheumatoid factor.

Lovell DJ1; Petty RE et al.⁵

persistent oligoarticular JIA (prior to uveitis); ANA positivity also increases uveitis risk in patients with enthesitis-related arthritis.¹⁴

If not present at JIA diagnosis, uveitis usually develops during the next 4 to 7 years. Hence, frequent ophthalmologic examinations are important in JIA. The recommended examination frequency for patients with JIA and unknown uveitis at diagnosis is shown in Table 1.⁴ Before uveitis is diagnosed, examination frequency depends on the patient's JIA subtype and risk category; after uveitis diagnosis, response to therapy and complications determine the frequency of ophthalmologic examinations. Early detection and treatment of uveitis can lead to a relatively good prognosis.⁴

The functional disability and growth retardation associated with JIA can markedly impact psychosocial functioning of afflicted children.¹⁵ Persistent inflammation of multiple joints with concomitant pain, stiffness, and fatigue can interfere with daily activities such as schoolwork and social life. The altered physical appearance due to generalized growth failure may affect self-image. Limping due to growth defects or the necessity to wear splints or braces may cause embarrassment. Therefore, the treatment of JIA should include the management of psychosocial functioning as well as management of arthritis.

The clinical outcome of JIA is variable, ranging from full recovery to lifelong symptoms and significant disability, and is dictated by the disease subtype. Recent data indicate that long-term remission in JIA is uncommon.¹⁶ Approximately 50% to 70% of children with polyarticular or systemic disease and 40% to 50% of

Table 1. Recommended Ophthalmologic Examination Frequency in Patients With JIA and Unknown Uveitis at Diagnosis^a

ANA Status	Age at Onset (y)	Disease Duration (y)	Risk Category	Ophthalmologic Examination Frequency (mo)
Oligoarthritis or polyarthritis				
+	≤6	≤4	High	3
+	≤6	>4	Moderate	6
+	≤6	>7	Low	12
+	>6	≤4	Moderate	6
+	>6	>4	Low	12
–	≤6	≤4	Moderate	6
–	≤6	>4	Low	12
–	>6	NA	Low	12
Systemic arthritis				
NA	NA	NA	Low	12

ANA = antinuclear antibodies; NA = not applicable.

^aRecommendations for follow-up continue through childhood and adolescence.

Cassidy J et al.⁴ Reproduced with permission from *Pediatrics* 117; 1843-1845, ©2006 by the AAP.

children with oligoarticular disease continue to have active disease in adulthood. Persistent active arthritis over prolonged periods increases the risk of joint destruction and functional disability and impairs quality of life in adulthood.^{11,17} Long-term outcome studies have shown that between 30% and 56% of patients with JIA have severe functional limitation (wheelchair bound or bedridden) and 13% to 75% need joint replacement in adulthood.¹¹

The substantial morbidity and mortality associated with JIA underscores the importance of early detection and early institution of treatments to prevent irreversible damage and improve functional outcomes.

Evolving Approach to Treatment

Treatment of JIA aims to decrease chronic joint pain and suppress inflammation to improve function, allow normal growth and development, and prevent eye damage.¹⁸ There are no evidence-

based treatment guidelines for the effective management of JIA. Treatment is tailored to the various subtypes of JIA. However, preliminary criteria for defining clinical remission in JIA have been formulated.¹⁹ (See Fast Facts: Clinical Remission Criteria, page 5.)

Traditional Approach

The traditional approach to treatment, based on the pyramid approach, uses NSAIDs and corticosteroids as initial therapy and gradually advances to more aggressive therapies (nonbiologic disease-modifying antirheumatic drugs [DMARDs]) during the disease course.^{9,20}

NSAIDs: Although NSAIDs, including aspirin, are effective for the management of symptoms associated with arthritis (such as pain, stiffness, and fever), they are only effective in a minority of patients, mainly those with oligoarthritis.⁹ Because of increased frequency of liver enzyme abnormalities and a possible

association with Reye syndrome, aspirin is no longer prescribed for JIA and has been replaced by NSAIDs.⁹ However, NSAIDs still carry the risk of gastroduodenal injury. Greater than 25% of children develop GI symptoms during NSAID therapy, including loss of appetite, duodenitis, and gastritis, although serious GI injuries are rare.⁹

Corticosteroids: Intra-articular corticosteroid injections are effective for oligoarthritis, producing rapid and sustained improvement of arthritic symptoms in the injected joint.⁹ They are also effective in controlling systemic symptoms, such as serositis, fever, and rashes in systemic-onset arthritis. However, steroid use is limited by its long-term adverse effects on bone and growth.⁹

Nonbiologic DMARDs: MTX is the most widely used nonbiologic DMARD in JIA and is the cornerstone of treatment for most patients with extended oligoarthritis and polyarthritis.⁹ Headache, abdominal pain, diarrhea, and nausea are common tolerability issues with the use of MTX.⁶ Transient hematologic and liver enzyme abnormalities may also occur with MTX, and persistent elevations of the latter are a risk factor for liver fibrosis and cirrhosis.²¹ Sulfasalazine and leflunomide (approved by the US Food and Drug Administration [FDA] only for adults with active RA) may be alternatives to MTX; however, these agents are not without safety concerns. Hypersensitivity reactions (eg, fever and skin rash, as in Stevens-Johnson syndrome) have been described with sulfasalazine. The potential cytotoxic and teratogenic effects of leflunomide are of concern in sexually-active adolescent patients.²¹

Fast Facts: Clinical Remission Criteria

Biologic therapies in JIA offer the potential to induce extended periods of complete disease inactivity in children with JIA. Standardized criteria for clinical remission are needed to enable clinicians and researchers to assess treatment effects and compare results across

studies. Preliminary criteria defining inactive disease, clinical remission on medication, and clinical remission off medication in certain subtypes of JIA have been developed based on consensus derived from international pediatric rheumatologists.¹⁹

Clinical Remission

On medication

- Criteria for inactive disease^a must be met for a minimum of 6 continuous months while the patient is on medication

Off medication

- Criteria for inactive disease^a must be met for a minimum of 12 continuous months while off all antiarthritis and antiuveitis medications

Inactive Disease^a

- No joints with active arthritis^b
- No fever, rash, serositis, splenomegaly, or generalized lymphadenopathy attributable to JIA
- No active uveitis (not yet defined)
- Normal ESR or CRP (if both are tested, both must be normal)
- Physician's global assessment of disease activity indicates no disease activity (ie, best score attainable on the scale used)

CRP = C-reactive protein; ESR = erythrocyte sedimentation rate.

^aOligoarticular (persistent and extended), RF-positive and RF-negative polyarticular, and systemic-onset JIA.

^bThe ACR defines a joint with active arthritis as a joint with swelling not due to bony enlargement or, if no swelling is present, with limitation of motion accompanied by pain on motion and/or tenderness. An isolated finding of pain on motion, tenderness, or limitation of motion on joint examination may be present only if explained by prior damage attributable to arthritis that is now considered inactive or nonrheumatological reasons such as trauma.

Adapted from Wallace CA et al.¹⁹

Efficacy and Safety of Biologic Agents in JIA

An increased understanding of the role of proinflammatory cytokines in the pathogenesis of JIA has led to the introduction of anti-cytokine therapy.⁶ TNF- α has been recognized as the major proinflammatory cytokine in polyarticular-course JIA.^{22,23} The efficacy and safety of the anti-TNF- α agents etanercept (ETN), adalimumab (ADA), and infliximab (INF) have been evaluated in placebo-controlled trials involving children 4 to 17 years of age with active polyarticular-course JIA. Responses to therapy in these trials were assessed using the 6 validated American College of

Rheumatology (ACR) response criteria for JIA (Table 2).²⁴ The definition of improvement for the ACR Pediatric 30 (Pedi 30) requires at least 30% improvement from baseline in at least 3 indicators of disease activity, with no more than 1 indicator worsening >30%. ACR Pedi 50, 70, 90, and 100 criteria are defined as an improvement from baseline of at least 50%, 70%, 90%, or 100%, respectively, in at least 3 of the 6 core set of variables, with no more than 1 of the remaining variables worsening >30%.

Etanercept: ETN is approved by the FDA for reducing the signs and symptoms of moderate-to-severe active polyarticular-course JIA. The

Table 2. ACR Validated Response Criteria in JIA: 6 Core Variables

1. Active joint count (joints with swelling or limitation of motion and tenderness/pain on motion)
2. Joints with limited range of motion
3. Parent/patient global assessment (on 0- to 10-cm VAS)
4. Physician global assessment (on 0- to 10-cm VAS)
5. Laboratory measure of inflammation (ESR or CRP)
6. Functional ability assessment (CHAQ)

ACR = American College of Rheumatology; CHAQ = Child Health Assessment Questionnaire; VAS = visual analogue scale.

Giannini EH et al.²⁴

efficacy of ETN for polyarticular-course JIA was established in a study of 69 children resistant to MTX that included an open-label lead-in phase, a double-blind placebo-controlled phase, and an open-label extension phase.²² Flare of disease, the primary efficacy end point, was significantly lower in ETN-treated patients compared with placebo-treated patients during the double-blind phase of the study (81% vs 28%, $P = .003$). The median days to disease flare after randomization was significantly longer with ETN (116 days vs

28 days, $P = .001$). At the end of the study, 80% of patients treated with ETN in the double-blind phase met the definition of 30% improvement compared with 35% of patients receiving placebo ($P < .01$). ETN therapy was well tolerated in this study; injection site reactions (39%), mild infections (35%), and headaches (20%) were the most common side effects. There were no significant differences in the frequency of adverse events (AEs) between the ETN and placebo study groups. The significant improvements achieved with ETN

in the double-blind phase were sustained for up to 8 years in the long-term extension phase (Figure 1).²⁵ The favorable safety profile of ETN also was maintained with continued exposure, with the overall rate of serious AEs (SAEs) (0.12 per patient-year) and the rate of medically important infections (0.03 per patient-year) remaining low.

Adalimumab: ADA is FDA approved as monotherapy or as combination therapy with MTX for reducing the signs and symptoms of moderate-to-severe active polyarticular-course JIA. The safety and efficacy of ADA monotherapy and ADA + MTX combination therapy were evaluated in 171 children with polyarticular-course JIA in a study that included a 16-week open-label lead-in phase, a 32-week double-blind placebo-controlled phase, and an open-label extension phase.²³ In the double-blind phase, disease flares occurred in significantly less patients on ADA monotherapy or ADA + MTX combination therapy versus placebo (43% vs 71%, $P = .03$; 37% vs 65%, $P = .02$). ACR Pedi 30, 50, or 70, responses were significantly greater with combination therapy versus placebo, while no significant differences in these parameters were seen between ADA monotherapy and placebo (Table 3). Response rates were sustained through 2 years of continued treatment with ADA in the extension phase of the study. The most common AEs reported with ADA throughout all phases of the study were minor infections and injection site reactions.²³

Infliximab: In contrast to ETN and ADA, the efficacy and safety of INF in polyarticular JIA has not been established. The only placebo-controlled, double-blind study was

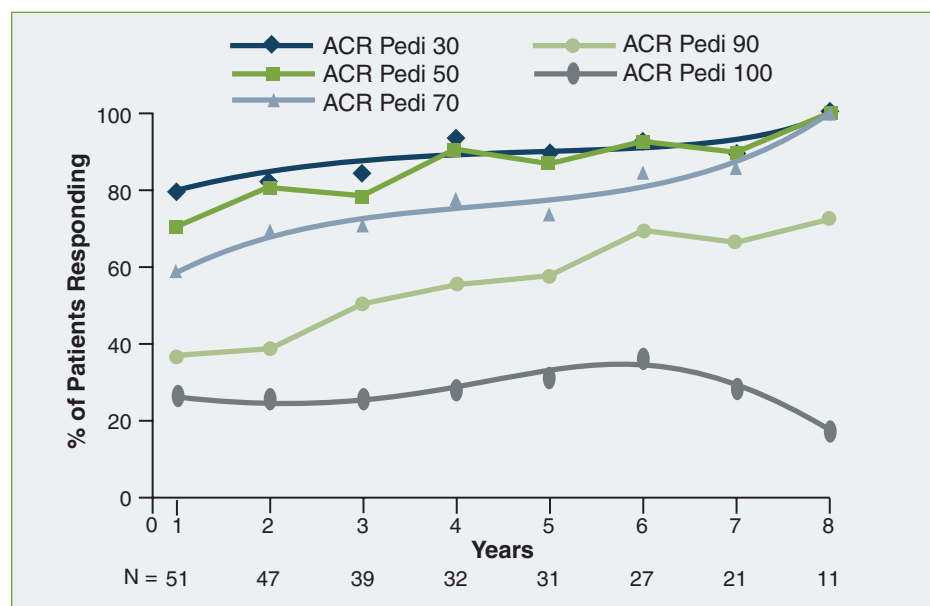


Figure 1. Patients receiving etanercept who met the ACR Pedi 30, 50, 70, 90, and 100 criteria for improvement, based on available data at each time point. Values were not available for all patients at years 2, 3, and 4. Lovell DJ et al.²⁵ Reproduced with permission of John Wiley & Sons, Inc. © 2008.

Table 3. ACR Pedi 30, 50, 70, and 90 Responses of Patients Receiving Placebo or ADA With or Without MTX for Active JIA at Week 48^a

ACR Pedi Response	No MTX			MTX		
	Placebo (N = 28)	ADA (N = 30)	P Value	Placebo (N = 37)	ADA (N = 38)	P Value
30	32%	57%	.06	38%	63%	.03
50	32%	53%	.10	38%	63%	.03
70	29%	47%	.16	27%	63%	.002
90	18%	30%	.28	27%	42%	.17

^aA patient who had a flare according to the protocol definition was classified as having no response from that point forward, regardless of the patient's American College of Rheumatology Pediatric (ACR Pedi) response at that time.

ACR Pedi 30, 50, 70, and 90 responses are defined as improvements of at least 30%, 50%, 70%, and 90%, respectively, in at least 3 of the 6 core variables (see Table 2), and a worsening of $\geq 30\%$ in no more than 1 variable.

Lovell DJ et al.²³ Reproduced with permission of Massachusetts Medical Society© 2008. All rights reserved.

not conclusive. This study was a crossover trial of 122 patients with persistent polyarticular JIA despite MTX therapy.²⁶ The primary efficacy end point, the ACR Pedi 30 response at 3 months, did not differ significantly between patients receiving INF (3 mg/kg or 6 mg/kg) and those receiving placebo. However, after crossover to INF, when all patients were taking INF 6 mg/kg, ACR Pedi 30 response was achieved in 73.2% of all patients. SAEs, infusion reactions, antibodies to INF, and newly induced ANAs and antibodies to double-stranded DNA were seen more frequently in patients taking INF 3 mg/kg than in those taking the 6 mg/kg dose.

Cases of lymphoma or other cancers have been reported in patients receiving anti-TNF- α therapy for JIA. The prescribing information for all anti-TNF- α agents warns of the possible cancer risk, and the FDA is conducting an ongoing safety review.²⁷

As knowledge of JIA pathogenesis has advanced, other potential therapeutic targets have emerged, including IL-1, activated T cells, and B cells.

Anakinra: The correlation of IL-1 with disease activity in JIA, particularly in systemic-onset JIA, has been confirmed in several studies.²⁸ Anakinra, a recombinant IL-1 receptor antagonist, is FDA approved for reducing signs and symptoms and slowing progression of structural damage in adults with moderately to severely active RA not responding to DMARD therapy. Its potential efficacy in systemic-onset JIA was first demonstrated in 2 patients with refractory disease.²⁹ Both patients experienced immediate and sustained resolution of symptoms (rash, fever, and arthritic symptoms) and normalization of laboratory markers of inflammation (ESR, hemoglobin level, white blood cells). A retrospective case series of 7 pediatric patients with treatment-resistant systemic-onset JIA also reported excellent responses to anakinra; 6 patients had resolution of systemic disease and joint disease and achieved remission.³⁰ These results support the use of anakinra as second-line therapy in children with systemic-onset JIA who have failed standard therapy. In contrast, another series of 20 patients with systemic-onset JIA reported marked

and sustained improvement (by ACR Pedi 50 criteria) in $< 50\%$ of patients.³¹ In all 3 case series, no significant adverse effects were recorded.²⁹⁻³¹ Placebo-controlled studies evaluating the efficacy and safety of anakinra in systemic-onset JIA are anticipated.

Abatacept: A selective T-cell costimulation modulator, abatacept is FDA approved for moderately to severely active polyarticular JIA in patients ≥ 6 years of age. It also may be effective in other JIA subtypes. In a double-blind, placebo-controlled trial, 190 children with active JIA (any of the 3 major subtypes) unresponsive to DMARD therapy received abatacept during a 4-month open-label phase; 122 responders were then randomized to abatacept (n = 60) or placebo (n = 62).³² Significantly fewer patients treated with abatacept experienced disease flares compared with patients treated with placebo (20% vs 53%, $P = .0003$). Frequency of AEs did not differ significantly between the 2 groups: 62% of abatacept recipients experienced AEs, compared with 55% of placebo recipients ($P = .47$). Only 2 serious AEs were reported, both in placebo recipients. Further studies are needed.

Rituximab: B cells are thought to play a major role in antigen presentation, autoantibody formation, and cytokine production in joint inflammation. Rituximab is a monoclonal antibody that selectively depletes mature CD20 B cells.³³ It is FDA approved for reducing signs and symptoms of RA and slowing progression of structural damage in adults with moderately to severely active RA inadequately responsive to TNF antagonist therapy. There are no controlled trials of rituximab in JIA. However, it was reported

Case Study: Managing JIA and Uveitis in a 7-Year-Old Girl

Rick Pope, MPAS, PA-C

Presentation

Rebecca is a 7-year-old girl who presents with an increasing effusion in her right knee. She was brought for the examination by her mother because school would be starting in 1 week. The mother had become increasingly concerned as Rebecca's condition had worsened during the past several weeks, and she now appeared nervous, unsure of what the next step for her daughter would entail.

Medical History

Rebecca had no history of knee trauma. She also had no history of joint swelling or stiffness, iritis, serositis, skin rashes, fever, weight loss, or other signs or symptoms of inflammatory arthritis.

Physical and Laboratory Findings

It was clear on examination that the effusion would require aspiration. In this case, knee aspiration would be diagnostic and therapeutic. Blood tests also were ordered.

- Gross appearance of the aspirate: cloudy, consistent with inflammatory arthritis
- ESR 23 mm/h (high) (normal value [child]: <10 mm/h)
- CR 1.4 mg/dL (elevated) (normal value: <0.8 mg/dL)
- RF 80 IU/mL (positive) (normal value: <14 IU/mL)
- ANA titer positive (negative value: titer <1:20)

Diagnosis

The physical and laboratory findings are consistent with a diagnosis of oligoarticular JIA.

Clinical Commentary

Rick Pope, MPAS, PA-C

The number of joints involved in JIA can dictate the disease subtype. Subtypes of JIA carry different risks of extra-articular manifestations. Patients with ANA-positive oligoarticular JIA should be referred for ophthalmologic examinations early in the course of their disease because they are at high risk of developing anterior uveitis.^{13,14} The inflammation can be subtle and requires slit lamp examination to reveal uveal inflammation. Slit lamp examinations at 3-month intervals are recommended for high-risk patients. Complications of uveitis include scleral redness, pupil irregularity, hypopyon, cataracts, and decreased visual acuity. Treatment with topical

corticosteroids can increase intraocular pressure and lead to glaucoma.³⁵

MTX, as a traditional DMARD, can be used with NSAIDs and intra-articular corticosteroid injections, if necessary, to control arthritis as well as iritis. The rationale for treatment of JIA in Rebecca is to maximize use of local therapies and minimize use of both corticosteroids and NSAIDs. There is a risk of premature closure of growth plates in JIA, resulting in short stature. Corticosteroids should be avoided, if possible, because of the increased risk of bone fragility in a population already at risk for adult premature osteoporosis. NSAIDs are helpful in 25% to 33% of patients, but can have adverse GI and photosensitizing effects.²⁰ A 4- to 6-week trial of NSAIDs can be used to determine whether they will be helpful. Liquid preparations are available for patients who cannot swallow pills. I warn about the possibility of GI side effects and photosensitivity and check the patient's blood pressure at every visit.

Treatment Decision

Rebecca's knee effusion was managed with joint aspiration and low-dose intra-articular corticosteroid injection. Therapy for JIA is started with MTX 10 mg/wk orally. Oral administration is preferred to parenteral administration in pediatric patients. As a young female patient with ANA-positive oligoarticular JIA, Rebecca is at high risk for uveitis. An ophthalmologic referral for uveitis screening is appropriate. Rebecca and her mother are also educated about JIA and its treatment and counseled about the risk of ophthalmologic complications.

Patient Follow-up

Rebecca eventually developed persistent oligoarticular JIA and would experience intermittent effusions in both knees. She also developed signs and symptoms of iritis; her first attack was treated with ophthalmologic corticosteroid preparations. Rebecca continued the low-dose MTX therapy. Her occasional joint flares were relatively easy to control with joint-specific injections of intra-articular corticosteroids.

that a woman with a 20-year history of refractory polyarticular JIA, was wheelchair-bound, and had a disease activity score (DAS28) of 8.32 was treated successfully with rituximab.³⁴ After failing ETN, INF, and ADA therapy, she was given 2 infusions of rituximab. Within 6 weeks, her DAS28 dropped to 4.22, and she had marked functional improvement, reflected by her renewed ability to walk and drive. Follow-up review at 3 months showed maintenance of disease remission with a DAS28 of 3.97. These results indicate a possible role for B-cell depletion in treatment-refractory polyarticular JIA. Additional investigation is needed.

Management of Uveitis

Corticosteroids have been the mainstay of initial treatment for severe uveitis. However, long-term corticosteroid therapy is associated with significant morbidity in children, including suppression of the hypothalamic-pituitary-adrenal axis, osteoporosis, aseptic necrosis of bone, growth retardation, secondary infection, and behavioral disturbance.^{35,36} Alternative therapies are needed for this devastating complication of JIA. TNF- α inhibitors appear to be effective against JIA-associated uveitis; however, INF and ADA may be more effective than ETN.^{36,37} These agents are not FDA-approved for treatment of JIA-associated uveitis.

Etanercept

The efficacy of ETN for uveitis in children with JIA has been evaluated in several small open-label studies with variable results. In a small prospective open-label trial in 10 children with treatment-resistant chronic uveitis, ocular inflammation

in 10 of 16 affected eyes was improved and remission achieved in 4 eyes within 3 months of ETN treatment initiation.³⁸ Among children with impaired vision, improvement was seen in 4 of 10 eyes. Improvements in ocular inflammation and vision were maintained during the 6-month study period. Exacerbation of uveitis during ETN treatment occurred in 1 eye. Active arthritis was present in 3 children at the beginning of ETN therapy and resolved in all 3 patients in ~6 weeks.³⁸ Continued follow-up of patients for another 6 months showed sustained benefit for up to 1 year in 4 patients.³⁹

In a multicenter, questionnaire-based study of 229 patients with JIA, ETN treatment was associated with relapses and the appearance of first courses of uveitis.⁴⁰ Relapses of uveitis flares occurred in 19 of 31 patients (61%). Patients with relapsing uveitis before institution of ETN treatment were at high risk of developing uveitis flares on ETN treatment. In addition, 2 patients developed uveitis for the first time during ETN treatment. This study did not find any significant difference in uveitis flares per year before and during ETN treatment. However, a high rate of improvement in joint symptoms was seen, with 87% of patients with uveitis flares achieving an ACR Pedi 30 response.⁴⁰

The differential efficacy of ETN in inflammatory eye disease and associated rheumatic disease seen in these 2 studies suggests mechanistic differences in the pathogenesis of ocular inflammation and joint inflammation.

Infliximab

INF has been shown to be more effective than ETN for the

treatment of JIA-associated uveitis in 2 retrospective studies. In 1 study of 45 patients with chronic uveitis associated with refractory JIA (24 receiving ETN and 21 receiving INF), ocular inflammation improved significantly more often in patients treated with INF compared with patients treated with ETN ($P = .047$).⁴¹ The number of uveitis flares per year also was significantly lower ($P = .015$) in patients receiving INF (mean 0.7, range 0-2) compared with patients receiving ETN (mean 1.4, range 0-3.2). In this study, uveitis developed for the first time in 4 patients taking ETN (2.2/100 patient-years) and in 1 patient taking INF (1.1/100 patient-years). Overall, uveitis improved in 14 of 45 patients (31%), did not change in 14 patients (31%), and increased in 17 patients (38%).⁴¹

The second study was a multinational survey that identified 47 patients with refractory JIA-associated uveitis treated with TNF- α inhibitors—34 patients with ETN and 13 with INF.⁴² In 12 patients, ETN was ineffective, and treatment was switched to INF; in 3 patients, INF was ineffective, and treatment was switched to ADA. In total, 34 cases of JIA-associated uveitis were treated with ETN, 25 cases with INF, and 3 cases with ADA. The final response to treatment was rated according to a composite index as good ($\geq 50\%$ reduction in local and systemic glucocorticoid dose), moderate ($\geq 50\%$ reduction in local or systemic glucocorticoid dose), or poor (no or $\leq 50\%$ reduction in both local and systemic glucocorticoid dose). On this composite scale, ETN achieved a good response in 53% of patients, moderate in 15%, and poor in 32%; INF was rated as good in 70%,

moderate in 30%, and poor in 0%. Physicians also rated treatment responses as good, moderate, or poor based on personal judgment. By physician rating, responses to ETN were good in 47%, moderate in 15%, and poor in 38%; the corresponding values for INF were 68%, 32%, and 0%. Based on the number of nonresponders (poor response), INF was significantly more effective than ETN (0% vs 38%, chi-square $P = .004$). Response to ADA was ranked as good by composite index and physician rating in all 3 patients treated.⁴²

Adalimumab

The efficacy of ADA for chronic refractory uveitis was evaluated in 2 small retrospective studies with variable results.^{43,44} In 1 study, response to ADA was analyzed in 18 patients, 17 with uveitis and JIA and 1 with uveitis of unknown origin; 7 patients had not responded to prior treatment with ETN, 3 of whom developed uveitis during ETN therapy.⁴³ ADA was effective (defined as no relapse or >2 fewer relapses than before treatment) in 16 patients

(88%). Response to ADA was mild (defined as 1 relapse fewer than before treatment) in 1 patient and absent in 1 patient. These results suggest that ADA is effective against uveitis and might be more effective than ETN. Additionally, in this study, ADA was effective or mildly effective for arthritic symptoms in 81% of patients with active arthritis.

The second retrospective study involved 20 patients with chronic refractory uveitis; 17 patients had active polyarticular JIA, and 19 patients had been treated with TNF- α inhibitors.⁴⁴ Mean duration of adalimumab therapy was 18.7 months (range, 4.5-35.6 months). Of the 20 patients, 7 (35%) showed improved activity of uveitis; 1 (5%) had worsening activity; and 12 (60%) had no significant change in uveitis activity. Those with improved uveitis activity were younger and had shorter disease duration. The mean number of uveitis flares per year decreased from 1.9 to 1.4 during ADA treatment. ADA was discontinued in 7 patients—6 because of inefficacy and 1 because of inactive uveitis.

Studies indicate a role for TNF- α inhibitors in the management of uveitis. However, further research is needed to define the patient population that best responds to each of the 3 agents, the effective dosages of these agents, and common response criteria to measure uveitis response so results from different studies can be compared.

PCE Takeaways

- JIA is associated with substantial mortality and morbidity.
- NSAIDs, MTX, and corticosteroids have been the mainstays of medical therapy for JIA, but are limited by adverse effects.
- TNF- α inhibitors are effective and safe for polyarticular-course JIA.
- Treatments for systemic-onset, enthesitis-related, and psoriasis-related arthritis have not been established.
- TNF- α inhibitors may also have a role in the management of JIA-associated uveitis; some agents may be more effective than others.

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About PCE Updates in Rheumatology...

Welcome to the second of 4 issues of 2008 *PCE Updates in Rheumatology*, Volume 2 developed for those NPs and PAs who serve patients in rheumatology practices throughout the country. "The demands for rheumatologic services are increasing exponentially with the aging population, while the number of physicians entering the rheumatology specialty is shrinking," according to the Society of Physician Assistants in Rheumatology (SPAR). Rheumatologists treating patients with rheumatoid diseases increasingly rely on specialist NPs and PAs to take an active management role in the frequent clinical contacts these patients require.

As healthcare professionals, NPs and PAs collectively provide a vital and increasing role in the diagnosis and management of acute and chronic illness. As clinicians, you spend more time with patients than most physicians, with your emphasis being patient disease state counseling and preventive care. Most importantly, NPs and PAs report that their roles have evolved from assisting physicians to treating and following their own patients. This increased role includes writing prescriptions,

monitoring patient progress, and seeing patients in your own examination rooms. As NPs and PAs, you are rapidly emerging as key providers of patient care. You practice with greater autonomy and prescribe more medication than ever before.

Approximately 286 NPs and 188 PAs see patients in rheumatology practices that provide ongoing care for patients with rheumatoid diseases. Therefore, you need to be thoroughly familiar with the latest therapeutic advances. This issue of *PCE Updates in Rheumatology* reviews the clinical burden of juvenile idiopathic arthritis (JIA), the traditional and evolving therapies for JIA, and the current evidence on management of JIA-associated uveitis.

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