Juvenile Idiopathic Arthritis: A Review for the Pediatrician

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Introduction

Juvenile idiopathic arthritis (JIA) is the most common rheumatic disease of childhood. It also is one of the more common chronic diseases of childhood, occurring as frequently as juvenile diabetes mellitus, four times more frequently than cystic fibrosis and sickle cell anemia, and 10 times more frequently than acute lymphoblastic leukemia, hemophilia, or muscular dystrophy. JIA is a new classification of juvenile arthritis developed by the International League Against Rheumatism (ILAR) that is used worldwide; it is replacing the previous American classification of juvenile rheumatoid arthritis (JRA). The cause of JIA is unknown, but substantial evidence suggests that the pathogenesis is autoimmune. The diagnosis of JIA is one of exclusion and is made by using a combination of historical, clinical, and laboratory data. The disease course is highly variable, and in the past, JIA had been viewed as a more benign illness than is recognized currently. Recent data reveal that a substantial number of children diagnosed with JIA have active disease that persists into adulthood and results in functional limitation. Thus, the management of JIA has become more aggressive earlier in the course of disease to limit permanent disability.

Definitions

JIA is defined as the presence of objective signs of arthritis in at least one joint for more than 6 weeks in a child younger than age 16 years after other types of childhood arthritis have been excluded. Arthritis is defined as the presence of swelling of the joint or two or more of the following: limitation of motion, tenderness, pain with motion, or joint warmth. Many causes of arthritis must be excluded before JIA can be diagnosed definitively (Table 1). These causes include, but are not limited to, infectious and postinfectious etiologies (septic arthritis, acute rheumatic fever, Lyme disease), hematologic and neoplastic disease, connective tissue diseases (systemic lupus erythematosus, juvenile dermatomyositis), vasculitis (Henoch-Schönlein purpura), and other inflammatory conditions (sarcoidosis, familial Mediterranean fever). The clinical features define disease-onset types in the first 6 months of disease. JIA is divided into eight categories; this new JIA classification is compared with the old JRA classification in Table 2.

Epidemiology

The incidence and prevalence of JIA vary significantly among different ethnic and geographically separate populations. The overall prevalence of JIA is estimated to be from 0.07 to 4.01 per 1,000 children, with an incidence of 0.008 to 0.226 cases of JIA per 1,000 children. In urban African-American children, the prevalence of JIA appears to be lower (26/100,000) than in the Caucasian population. In particular, oligoarticular JIA, which accounts for approximately 40% of newly diagnosed cases of JIA in the Caucasian population, appears much less frequently in African and Asian populations. In populations other than those of Northern European descent, such as African, East Indian, and the Canadian aboriginal group, polyarticular JIA is the predominant type of JIA.

Pathogenesis

The pathogenesis of JIA is not understood well. Substantial evidence suggests that JIA is an autoimmune process, and several aspects of the immune response may be involved. Many data have been generated demonstrating human leukocyte antigen (HLA) associations in JIA. The class I gene, HLA B27, long has been associated with enthesitis-related JIA patients, who may develop a spondyloarthropathy. The class II genes, HLA DR1 and

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Table 1. Differential Diagnosis of Juvenile Idiopathic Arthritis

Monoarthritis

- Infection: especially Lyme disease
- Mechanical: hypermobility, Legg–Calvé–Perthes disease, osteochondritis dissecans, fracture
- Malignancy: leukemia; bone and synovial membrane tumors

Polyarthritis

- Infections: viral, bacterial, fungal
- Reactive arthritis: rheumatic fever, poststreptococcal, *Yersinia*, postvaccination, serum sickness
- Malignancy: leukemia, neuroblastoma
- Connective tissue disease: systemic lupus erythematosus, sarcoidosis, dermatomyositis, vasculitis, scleroderma, inflammatory bowel disease, psoriasis, periodic fever syndromes
- Inherited: Fabry disease, Farber disease

HLA DR4, are seen in children who are seropositive for rheumatoid factor and who develop severe erosive adult-like RA. HLA DQA 0101 is associated with a polyarticular, erosive joint disease. Independently, the haplotype DRB1104 is strongly associated with uveitis.

In addition to immunogenetic data, evidence suggests that JIA may be caused by abnormal autoimmune responses. In polyarticular JIA, macrophage-derived tumor necrosis factor (TNF)-alpha has an important role, and in systemic-onset JIA, high levels of interleukin (IL)-6 are found. One theory suggests that JIA is antigen-driven and T-cell-mediated. The data supporting this hypothesis include: the presence of activated T cells in the synovial tissue of children who have JIA, the presence of specific oligoclonally expanded T-cell populations in the synovium, and the predominance of the Th1 cytokines in the synovium of the inflamed joints.

Other theories propose that rather than being mediated solely by T-cell responses, JIA may be caused by innate immunity and the inflammatory response. Immune complexes in children who have JIA differ in size, composition, and biologic activity. Immune complexes activate the inflammatory cascade. In vitro, the immune complexes found in children who have JIA produce a cytokine profile similar to that seen in an inflamed joint. Furthermore, it is possible that the immune complexes trigger the process of endothelial activation and leukocyte recruitment to the joint in JIA. Clearly, the immunopathogenesis of JIA is complex and probably is multifactorial, involving both T- and B-cell responses as well as the inflammatory response.

Clinical Features

JIA is divided into eight categories based on clinical symptoms in the first 6 months of the disease (Table 2): 1) systemic, 2), oligoarthritis persistent, 3) oligoarthritis extended, 4) polyarthritis rheumatoid factor (RF)-negative, 5) polyarthritis RF-positive, 6) enthesitis-related arthritis (the enthesis is the area where tendon attaches to bone), 7) psoriatic arthritis, and 8) other. This scheme is used worldwide and is being validated for clinical homogeneity, immunogenetic stability, and homogeneity. Each category exhibits distinct clinical presentations, immunogenetic associations, and outcomes, supporting the concept that JIA actually represents a mixture of diseases that have different pathogenetic bases, resulting in the common clinical expression of chronic arthritis.

Systemic JIA

Children who have systemic JIA (soJIA) account for 10% of all cases of JIA. The disease may develop in a child at any age, but the peak onset is between ages 1 and 6 years, and soJIA affects boys and girls equally. The defining characteristic of soJIA is daily or twice-daily high, spiking fevers. Classically, children experience temperatures reaching greater than 102.2°F (39°C) in the evening or early in the morning. The temperature rises rapidly and returns to normal or below normal rapidly. Early in the course, children may appear very ill when they are febrile but appear healthy at other times, and this quotidian fever pattern may not be observed. The classic transient, faint pink, blanching macular or maculopapular rash of soJIA frequently accompanies the fever. Other systemic features include lymphadenopathy, hepatosplenomegaly, and pericarditis. With persistent disease, osteoporosis and growth abnormalities such as short stature occur from active disease and steroid treatment; brachydactyly (30%) and micrognathia (40%) also are seen.

The systemic features of soJIA may precede the development of overt arthritis by weeks to months. The extra-articular features are self-limiting and resolve in 50% of cases within 5 years of diagnosis. However, children who have soJIA may develop rare, life-threatening complications such as pericardial tamponade, systemic vasculitis, and macrophage activation syndrome (MAS). MAS is characterized by persistent high fever, pancytopenia, abnormal liver function, encephalopathy, disseminated intravascular coagulation, and a low erythrocyte sedimentation rate. A late but diagnostic finding, when found,

Table 2. The New Classification of JIA, Clinical Criteria, and Comparison to JRA*

JIA (ILAR) Classification	Clinical Features of JIA as Defined by ILAR Classification	JRA (ACR) Classification	General Comments
Systemic arthritis	Arthritis with/preceded by daily fever for at least 2 weeks and one/more of: evanescent nonfixed erythematous rash, generalized lymphadenopathy, hepato/splenomegaly and serositis.	Systemic-onset JRA	• 50% remit in year 1 • 25% have severe destructive joint disease • General growth abnormalities • Macrophage activation syndrome
Oligoarthritis	Arthritis of one to four joints during the first 6 months of disease.	Pauciarticular (JRA) Type I	• Young age onset • Uveitis, especially ANA+ • Leg length discrepancy
• Persistent	Affects no more than four joints throughout the disease course.		
• Extended	Affects more than four joints after the first 6 months.		• Destructive joint disease • Therapy as for poly JIA
Polyarthritis (RF-negative)	Affects five or more joints in the first 6 months of disease. Tests for RF are negative.	Polyarticular JRA (RF does not alter classification)	• 10% destructive joint disease
Polyarthritis (RF-positive)	Affects five or more joints in the first 6 months of disease. Tests for RF are positive on two occasions at least 2 months apart.	Polyarticular JRA (RF does not alter classification)	• Like adult RA • Seen in late childhood • Severe destructive joint disease
Enthesitis-related arthritis	Arthritis and enthesitis or arthritis or enthesitis with at least two of: sacroiliac tenderness and/or inflammatory spinal pain, human leukocyte antigen (HLA) B27-positive, family history in a first- or second-degree relative of medically confirmed HLA B27-associated disease.	Excluded in JRA classification, but some youth in this group at onset may be similar to late-onset pauciarticular JRA type II in JRA classification	• Develops into juvenile spondyloarthropathies (including juvenile ankylosing spondylitis, juvenile psoriatic arthritis, Reiter syndrome, and arthropathies of inflammatory bowel disease) • Acute uveitis seen
Psoriatic arthritis	Arthritis and psoriasis or arthritis and at least two of: dactylitis, nail abnormalities, family history of psoriasis in at least one first-degree relative.	Excluded in JRA classification	• Develops into juvenile spondyloarthropathies (including juvenile ankylosing spondylitis, juvenile psoriatic arthritis, Reiter syndrome, and arthropathies of inflammatory bowel disease) • Acute uveitis seen
Other	Arthritis of unknown cause persisting for at least 6 weeks that either does not fulfill criteria for any categories or fulfills criteria for more than one category		

RF=rheumatoid factor, ANA=antinuclear antibody
*Adapted from Gardner-Medwin J, Southwood T. Current developments in juvenile arthritis. *Rheumatic Disease Topical Reviews.* 2001(5).

Table 3. Comparison of JIA, Acute Rheumatic Fever (ARF), and Poststreptococcal Arthritis (PSRA)*

Symptoms	JIA	ARF	PSRA
Antecedent streptococcal infection	No	Yes	Yes
Latency period from infection to arthritis	NA	2 to 3 wk	<2 wk
Arthritis			
Symmetry	Yes	No	Yes
Migratory	No	Yes	No
Axial skeleton	Yes	No	Yes
Response to NSAIDs/ASA	Slow	Prompt	Slow
Duration of arthritis	Prolonged	Short	Prolonged
Pericarditis	Yes	Rare	Rare
Myocarditis/valvulitis	Up to 6%	50%	Rare
ASO titers	30%	Yes	Yes
Anti-DNAse B	No	Yes	Yes
Prophylaxis with antibiotics	NA	American Heart Association	1 year

NSAID=nonsteroidal anti-inflammatory drug, ASA=acetylsalicylic acid, ASO=antistreptolysin O
*Adapted from Shulman ST, Ayoub EM. Post-streptococcal reactive arthritis. *Curr Opin Rheum*. 2002;14:564.

is active phagocytosis by macrophages and histiocytes in the bone marrow. Treatment is aggressive and involves steroids and immunosuppression with cyclosporin and anti-TNF-alpha drugs. A number of triggers have been implicated in the cause of MAS in soJIA, including viral infections such as mononucleosis, nonsteroidal anti-inflammatory drugs (NSAIDs), sulfasalazine, methotrexate, and etanercept, an anti-TNF-alpha biologic drug. Ultimately, in most cases, the long-term prognosis for children who have soJIA depends on the severity of the arthritis.

Laboratory findings in children who have soJIA include leukocytosis, thrombocytosis, anemia, and elevated acute-phase reactants. Antinuclear antibodies (ANAs) are found in only 5% to 10% of children. RF rarely is seen (<2%). High levels of ferritin also can assist with the diagnosis of soJIA.

Diagnosing soJIA can be particularly difficult at the onset of disease if the arthritis is absent. The possibilities of systemic infection of bacterial or viral origin, malignancy, inflammatory bowel disease (IBD), acute rheumatic fever (ARF), systemic vasculitides such as polyarteritis nodosa, or other collagen vascular disease such as systemic lupus erythematosus need to be considered and excluded. Knowledge of the subtle clinical differences between soJIA and these other illnesses aids in rapid diagnosis. Sepsis tends to result in a hectic fever pattern, and the temperature tends not to return to normal. Children who have ARF have persistent fevers that respond dramatically to salicylates (Table 3). Although children who have JIA have pericarditis, ARF should be suspected if a patient exhibits endocarditis and a diastolic murmur in addition to pericarditis. In ARF, the arthritis is extremely painful, unlike the arthritis of soJIA, and it is migratory and asymmetric. The arthritis of ARF is transient and resolves without any sequelae, unlike the arthritis of soJIA. The rash of ARF is erythema marginatum, and the edge of the rash expands with passing time. In contrast, the rash of soJIA is nonmigrating and appears with the fever or if the skin becomes warm, such as after a bath. In both illnesses, the antistreptolysin O (ASO) titer may be elevated. For children who have soJIA, the ASO titer may be a manifestation of the generalized inflammatory state rather than an indicator of recent streptococcal infection. More specific antistreptococcal antibody assays, such as antihyaluronidase, antistreptokinase, or antiDNase B, may be useful in distinguishing JIA from ARF. Leukemia also can imitate soJRA; 15% of children who have leukemia can present with arthritis, and the rash can be indistinguishable (Table 4). Key findings in leukemia that are not seen in soJIA are low white blood cell (WBC) and platelet counts and an elevated lactate dehydrogenase concentration. Distinguishing between soJIA and leukemia is particularly important because treating leukemia with steroids can delay the diagnosis and, thus, worsen the prognosis.

Oligoarthritis JIA

Children who have oligoarthritis JIA (oligo JIA) experience arthritis in four or fewer joints in the first 6 months of disease. Oligo JIA accounts for 40% of all cases of JIA.

Table 4 Comparison of soJIA With Leukemia

Symptom	soJIA	Leukemia
Arthritis	Less painful, morning stiffness	Severe pain, bone pain, night pain
Rash	90%	10%
Fever	High, spiking	Low-grade
White blood cell counts	High	Normal, low, or high with blasts
Platelet counts	High	Normal or low

Children who have oligo JIA are divided into two additional groups that are characterized by the course of the joint disease after the first 6 months: persistent (affecting no more than four joints throughout the disease) and extended (affecting more than four joints throughout the disease). Children who have oligo JIA typically experience disease onset between the ages of 1 and 5 years. Girls are affected more frequently than boys (4:1) and are ANA-positive 75% to 85% of the time. Children who are ANA-positive are at the greatest risk for developing uveitis. Overall, 30% to 50% of children who have oligo JIA develop uveitis. The eye disease tends to be a nongranulomatous chronic inflammatory process in the anterior chamber of the eye that is asymptomatic in 80% of affected children. Among children who have JIA, those who have oligo JIA experience the best outcome in terms of joint function, but chronic uveitis may result in significant morbidity, including corneal clouding, cataracts, glaucoma, and visual loss. Appropriate, frequent evaluations of all children who have JIA, but particularly those who have ANA-positive oligo JIA, may prevent serious ocular complications. The American Academy of Pediatrics has a suggested plan for the frequency of eye examinations according to the type of arthritis (Table 5). (Table 5 uses the American classification of JRA, so refer to Table 2 for the equivalent ILAR classification.)

Oligo JIA most frequently affects the large lower extremity joints, especially the knees and ankles. Most children present with a swollen, warm joint and a limp that is often worse in the morning and after a nap. Over- and undergrowth of the long bones is common, resulting in leg length discrepancy. This is most often due to a sustained increase in blood flow to the growth plate following chronic inflammation that causes increased growth or early epiphyseal closure. Constitutional symptoms are rare. The differential diagnosis includes infections, Lyme disease, postviral arthritis, trauma, and neoplasm. In older children, mechanical causes of oligoarticular arthritis, such as structural abnormalities (eg, discoid meniscus, Legg-Calvé-Perthes disease, slipped capital femoral epiphysis, and osteoid osteoma) should be considered. Joint aspiration and examination of the joint fluid is especially important to rule out infection. If the joint WBC count is higher than 100×10^3/mcL (100×10^9/L) and 90% are polys, infection is likely. Joint fluid cultures always should be obtained if the joint fluid is aspirated.

The group of children who have oligo JIA and do not have a good outcome are those whose arthritis becomes polyarticular and erosive. This disease subset is termed extended oligoarticular JIA, and affected children often require treatment with the immunosuppressive drugs used for those who have polyarthritis JIA.

Table 5. American Academy of Pediatrics Guidelines for Screening Eye Examinations in JIA*

JRA Onset Subtype	Age of Onset <7 y	Age of Onset >7 y
Systemic	Annual	Annual
Polyarticular		Every 6 months for 4 years, then annually
ANA-positive	Every 3 to 4 months for 4 years, then every 6 months for 3 years, then annually	
ANA-negative	Every 6 months for 4 years, then annually	
Pauciarticular		Every 6 months for 4 years, then annually
ANA-positive	Every 3 to 4 months for 4 years, then every 6 months for 3 years, then annually	
ANA-negative	Every 6 months for 4 years, then annually	

*Reproduced from Lovell DJ. Pediatric rheumatic diseases. In: Klippel JH, ed. *Primer on the Rheumatic Diseases.* 12th ed. Atlanta, Ga: Arthritis Foundation; 2000:538

Polyarthritis JIA

Polyarthritis JIA (poly JIA) is defined as JIA involving five or more joints within the first 6 months of disease. Approximately 25% of children who have JIA have the polyarthritis form. Poly JIA is more common in girls and may occur at any time during childhood. Children who have poly JIA may be categorized further into those who have a positive serum RF finding and those who are RF-negative. RF-positive youth are usually girls whose disease onset occurs in later childhood (at least age 8 y) and are HLA DR4-positive. The arthritis of RF-positive poly JIA is usually symmetric, small joint arthritis. Children who have positive RF are at greater risk for developing severe erosive joint disease, rheumatoid nodules, and a poorer functional outcome than are children who have RF-negative poly JIA. RF-negative poly JIA often causes an arthritis that involves fewer joints and may not demonstrate symmetric joint involvement. In addition, 40% to 50% of children who have poly JIA have a positive ANA finding.

Children who have poly JIA present with morning stiffness, limited joint mobility, and joint swelling. The systemic manifestations of poly JIA are less dramatic than those of soJIA. Children may experience fatigue, protein-calorie malnutrition, delayed growth, anemia, and osteopenia. Chronic anterior uveitis develops in 5% of children. Micrognathia is found in 15% of children who have poly JIA as well as other growth abnormalities, such as leg length discrepancies (30%) and brachydactyly (20%).

The differential diagnosis of poly JIA is considerably different from that of soJIA. Infectious processes such as Lyme disease, gonorrhea, or viral infections may cause polyarthritis. Other collagen vascular diseases, such as systemic lupus erythematosus, scleroderma, dermatomyositis, and the spondyloarthropathies, must be excluded. Finally, malignancy may present with joint pain and swelling due to malignant infiltration of bone or synovium.

Enthesitis-related JIA

Enthesitis-related arthritis is characterized by inflammation of the enthesis, where tendon attaches to bone, and arthritis. In addition, affected children tend to have any two of the following: sacroiliac joint tenderness, inflammatory spinal pain, the presence of HLA B27, a positive family history, acute anterior uveitis, and onset of oligoarthritis or polyarthritis in a boy older than 8 years of age. Ultimately, many such children develop one of the identifiable spondyloarthropathies that include juvenile ankylosing spondylitis (AS), reactive arthritis, and IBD-associated arthritis.

The diagnosis of AS requires radiographic evidence of sacroiliitis that may not be evident for many years. Computed tomography scans of the sacroiliac joint may reveal changes consistent with inflammation earlier than plain radiography. AS may occur prior to the age of 16 years. The disease is much more common in boys (male to female ratio, 6:1), and a large percentage (82% to 95%) of children who have AS are HLA B27-positive. Arthritis occurring after a genitourinary or gastrointestinal infection is termed reactive arthritis and may be associated with acute conjunctivitis and asymptomatic urethritis. In children, the most common antecedent infection is gastrointestinal. The arthritis is acute, asymmetric, and usually involves large joints. Children may develop oral ulcers and keratoderma blennorrhagicum, a rash that begins as a papular eruption on the soles and palms but evolves initially into a pustular rash and finally becomes scaly.

Several patterns of arthritis are associated with IBD. Overall, 7% to 20% of children who have IBD develop arthritis. Occasionally, the arthritis precedes the development of gastrointestinal symptoms. Usually, children who have IBD develop asymmetric arthritis of the lower extremities. Girls and boys develop this pattern of arthritis equally, and there is no obvious association with HLA B27. However, a subset of children who have IBD develops axial arthritis as well as peripheral arthritis. This pattern of arthritis is more common in boys than in girls (4:1), and 80% of affected children are HLA B27-positive.

Psoriatic JIA

Psoriatic arthritis is diagnosed in children who have chronic arthritis and definite psoriasis or two of the following criteria: dactylitis, nail pitting or onycholysis, and a family history of psoriasis. Children may develop peripheral arthritis only or peripheral arthritis and axial arthritis. HLA B27 is seen in children who have the axial arthritis and psoriasis. The arthritis can be chronic and destructive, requiring immunosuppressive treatment used for children who have polyarthritis JIA.

Treatment

JIA is a chronic illness, and the treatment should involve a multidisciplinary team to address all areas of normal growth, social development, and physical functioning as well as pharmacologic treatment to limit chronic joint pain, inflammation, and damage. Physical and occupational therapy are absolutely necessary aspects of treat-

ment that help maintain strength and mobility and teach children adaptive mechanisms for the performance of activities of daily living independently. Splints are fashioned to maintain good joint position and limit the development of joint contractures. Social workers, rheumatology nurses, and the children's families are essential to the maintenance of normal social interactions and academic performance. The youth and family should keep in contact with their primary physician to have the appropriate age-related health supervision visits and health prevention counseling. When a multidisciplinary approach is used to meet all of the needs of children who have JIA, the affected young adults have been shown to function more effectively and surpass their peers in levels of postsecondary schooling and degree attainment.

With the understanding that JIA is a chronic illness that has the potential for significant morbidity, the pharmacologic treatment of the articular and extra-articular manifestations has become more aggressive and initiated earlier in the course of disease. NSAIDs are the first-line treatment for relief of joint symptoms, but are not considered disease-modifying. Most NSAIDs inhibit both the constitutive form of cyclo-oxygenase (COX-1) as well as the inducible form of the enzyme (COX-2) that are involved in the inflammatory response. Only ibuprofen, naproxen, tolmetin, choline magnesium trisalicylate, and aspirin, all nonspecific COX inhibitors, have been approved by the United States Food and Drug Administration (FDA) for use in children. Aspirin no longer is the first choice for treatment of JIA due to the dosing frequency and increased toxicity. In cases of mild arthritis, NSAID therapy alone may be sufficient. The average time to symptomatic improvement with a particular NSAID is 1 month, but up to 25% of children do not demonstrate clinical improvement until 8 to 12 weeks. Approximately 50% of children have symptomatic improvement to the first NSAID tried, but of those who do not respond to the first NSAID, 50% obtain symptomatic relief with the next NSAID used.

Most children tolerate NSAIDs well. The most common adverse effects are abdominal pain and anorexia. The true prevalence of gastritis or gastric ulceration in JIA is unknown but appears to be less than in adults. Taking NSAIDs with food and using antacids, histamine-2 blockers, or proton pump inhibitors can minimize the gastrointestinal toxicity in children who have JIA. NSAIDs also may have hematologic, renal, dermatologic, hepatic, and neurologic adverse effects. Increased bruising is common, although significant bleeding is rare. Liver enzyme concentrations may increase in 3% to 5% of children treated with nonsalicylate NSAIDs and 15% to 20% of children treated with salicylates. Only rarely does functional hepatic damage occur. Less than 5% of children develop hematuria or proteinuria from NSAIDs. Central nervous system symptoms develop in a small number of children receiving NSAIDs and include mood changes, headaches, and tinnitus. Naproxen may induce pseudoporphyria, a rash characterized by small blister formation that leaves a hypopigmented scar on healing. It is seen most commonly in fair-skinned children in sun-exposed areas. Reye syndrome has been reported in children taking aspirin when they contract varicella or influenza. We recommend children stop their NSAIDs if they develop either varicella or influenza.

At least two thirds of children who have persistently active joint disease require disease-modifying antirheumatic drugs (DMARDS), agents that retard the radiologic progression of disease. The child who is taking immunosuppressive drugs such as methotrexate (a DMARD), steroids, and biologics is considered immunocompromised and should not receive live vaccines. Before starting immunocompromising drugs, varicella and measles-mumps-rubella titers (if none or only the first dose has been given) should be obtained. If the titers are negative, vaccines should be offered before starting therapy. Similarly, immunocompromised children should be evaluated for exposure to tuberculosis (TB) before starting immunosuppressive drugs because TB has reactivated after starting the immunosuppressive drugs.

Methotrexate is the most commonly prescribed DMARD for JIA and has been used for more than 10 years, resulting in better clinical outcomes. It is used most frequently in children who have a polyarticular onset or course of JIA or soJIA. Approximately 70% of children demonstrate a favorable clinical response. Children who have soJIA and continue to exhibit systemic features respond somewhat less frequently. The clinical response to methotrexate may not be apparent for 4 to 6 weeks after therapy has been initiated and may not be maximal until 3 to 6 months of treatment. If oral methotrexate therapy is not successful, subcutaneous dosing has been shown to improve markers of active JIA with no significant increase in toxicity.

In general, methotrexate is tolerated well by children. Folic acid (1 mg daily) is administered to decrease the frequency and severity of adverse effects. Gastrointestinal adverse effects, including oral ulcers, decreased appetite, and abdominal pain, are the most common toxicities seen with methotrexate and occur in 13% of children. Hepatic toxicity has not been a major problem in children, and significant liver damage is rare. Most pediatric

rheumatologists monitor blood counts and liver enzymes, as recommended by the American College of Rheumatology for adult patients receiving methotrexate. This guideline suggests monitoring the complete blood count, platelet count, aspartate aminotransferase, albumin, and creatinine every 4 to 8 weeks. Pulmonary toxicity from methotrexate is very rare in children who have JIA. Although methotrexate has been used for more than 10 years for JIA, long-term data on the teratogenic, carcinogenic, or immunosuppressive risks in JIA are unavailable. Methotrexate is the mainstay of therapy, but recently, combination DMARD therapy such as methotrexate and leflunomide has been shown to have better clinical outcomes when methotrexate monotherapy fails.

Understanding that TNF and other cytokines play a major role in the pathogenesis of JIA, scientists have developed TNF-alpha antagonists and other cytokine inhibitors to treat JIA. Therapies that have been tested prospectively in adults who have rheumatoid arthritis often are used in children before their safety and efficacy have been evaluated fully. At this time, only methotrexate and etanercept have FDA approval for use in JIA, but many others are being studied.

Etanercept, a TNF receptor antagonist, is the first biologic to be approved by the FDA for use in JIA. In a randomized, prospective, placebo-controlled trial in children who had severe JIA not controlled by methotrexate, etanercept induced a rapid, significant improvement in the clinical and laboratory features of JIA. The median improvements ranged from 40% to 95%. Etanercept is well tolerated in children, with headache, upper respiratory tract infections, and injection site reactions being the toxicities reported most commonly. Rare but serious infections such as sepsis and varicella meningitis have been reported. Unvaccinated susceptible children taking etanercept who are exposed to varicella should be given varicella-zoster immune globulin after exposure and acyclovir at the earliest sign of infection. Other infections, such as TB, histoplasmosis, and listeriosis, have been reported in people taking anti-TNF-alpha drugs. Neurologic disorders, retrobulbar optic neuropathy, cutaneous vasculitis, and pancytopenia have been reported. Data on the long-term toxicity of etanercept are not available. Other anti-TNF-alpha biologics such as infliximab and adalimumab have been given to children who have JIA, with improved response. In addition, anti-IL-6R, termed MRA, has been tried in two children with some success who had soJIA, as has thalidomide. A few anecdotal reports indicate good responses to the use of anakinra or IL-1 receptor antagonist in JIA.

Other, more traditional DMARDS also are used to control JIA. In a placebo-controlled trial, sulfasalazine was significantly more effective in controlling disease activity than was placebo in children who had JIA. Those who have enthesitis-related JIA respond better to sulfasalazine. Toxicities can be significant, including gastrointestinal complaints, leukopenia, and liver transaminase elevation. Prospective controlled trials of penicillamine, hydroxychloroquine, and auranofin have been performed in children who have JIA. These medications did not demonstrate any greater efficacy than placebo. Injectable gold results in clinical improvement in 50% to 60% of children, but gold is not used much today because its efficacy is not as good as that of methotrexate and the biologics, and the toxicity of injectable gold is significant.

Systemic oral or intravenous pulse corticosteroids are used for the serious systemic manifestations of soJIA, including pleuritis, pericarditis, fever, anemia, and MAS. Because long-term use of corticosteroids results in significant morbidity, these agents are not used for long-term treatment of JIA joint disease. Low-dose steroids are used for short periods of time for children who have severe polyarthritis and functional impairment to provide symptomatic relief while other agents are initiated. The toxicities of corticosteroids are well known and include immunosuppression, adrenal suppression, hypertension, diabetes, cataracts, osteoporosis, avascular necrosis, mood swings, cushingoid features, and obesity. On the other hand, intra-articular corticosteroids may be indicated for children whose joint involvement is limited, such as those who have oligoarticular JIA. Triamcinolone hexacetonide is the drug of choice; its use has resulted in a significant improvement in joint swelling and function at 6 months in a number of children who have JIA. Furthermore, magnetic resonance imaging of the joints injected with corticosteroids has not revealed cartilage damage.

For those whose joint cartilage is destroyed, surgery is a viable option. Total joint replacements are being performed with great success for young people who have JIA. The longevity of the replaced joint must be considered when embarking on such surgery. In addition, when intubation is being considered for a surgical procedure, atlantoaxial instability and limited mouth excursion should be considered. Reconstructive surgery, such as for micrognathia, has been successful in older youth.

If all therapies fail, an autologous stem cell transplant (ASCT) can be considered. These have been performed on a small number of patients. As of 2003, 29 patients are registered in the European database, with a follow-up of 3 years. Of these, 16 are in drug-free remission, 8 are in partial remission or relapse, 1 was a nonresponder, and 4

died. The early deaths that were related to MAS while the patients were receiving ASCT have not recurred since the protocol was changed.

Treatment of the anterior uveitis associated with JIA is the responsibility of the ophthalmologist. Children need to be seen frequently so ocular inflammation can be recognized early. The initial therapeutic agents are dilating agents and topical corticosteroids. Local subtenon injections of corticosteroids also are used to control the ocular inflammation if topical agents are not effective. On occasion, systemic steroids may be used. For children who have chronic steroid-dependent uveitis, methotrexate has shown efficacy. Trials evaluating the use of etanercept in the uveitis associated with JIA have been disappointing, although infliximab seems to be more promising.

Outcome

The outcome of JIA is difficult to assess. All outcome studies describe results of treatment begun several years ago, when the newer regimens were not being used. Therefore, the data may not reflect outcomes using current practices. The reported mortality rates from JIA have ranged from 0.29% to 1.1% of children in the United States. These rates, while appearing low, are much higher than the standardized rate of 0.08% for healthy people between the ages of 1 and 24 years. Mortality in children clearly is related to the onset type, with soJIA accounting for approximately 60% of all deaths in children who have JIA. Many of these deaths were related to infection.

Disability also is related to disease type. A study published in 2000 examining adults who had JIA an average of 26.4 years after diagnosis revealed that 37% had active arthritis, with 11% of these adults in Steinbroker functional classes III and IV, indicating that they had considerable difficulty with self-care. Most of them (80%) had poly JIA or a polyarthritis course such as oligoarthritis-extended JIA. In a study published in 1984, 8.7% of children followed for 10 years or more were in Steinbroker functional classes III or IV. These children had either poly or soJIA. Persistent active arthritis is seen in JIA of all categories: in 22% to 41% of children who have oligo JIA, 45% to 50% of children who have poly JIA, and 27% to 48% of children who have soJIA.

In addition to disability from the arthritis, significant disability from uveitis still occurs despite improvements in therapy. Recent studies suggest that as many as 15% of children who have uveitis develop significant visual impairment, and 10% are blind in at least one eye.

Conclusion

JIA is a common and potentially devastating chronic disease of childhood. Our understanding of the pathogenesis is far from complete. Although steadily improving, the current clinical treatment regimens do not always halt disease progression. With improved understanding of the etiology of JIA, new therapeutic modalities will become available. The ability to predict outcome for an individual patient can help determine which therapies are appropriate and which toxicities are worth tolerating. It is hoped that in the near future, JIA will be recognized earlier in its course, treatment will be more effective, and disability will be much more limited.

Suggested Reading

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