Juvenile idiopathic arthritis (JIA), the most common form of arthritis in children, is an idiopathic autoimmune disease that affects children worldwide. Early and accurate diagnosis is necessary to effectively treat and minimize the potentially crippling effects of JIA. Recognizing the clinical syndromes of the various types of JIA is essential to achieving the goals of therapy, which include relieving pain and inflammation, reducing joint destruction, restoring physical function and normal growth, and alleviating psychosocial burden on children. (Adv Stud Pharm. 2008;5(6):170-175)

The September 3, 2001, cover story of Newsweek highlighted arthritis, its 21 million American sufferers, its potentially crippling effects, and its complicated treatment.1 Arthritis, or inflammation of the joint, refers to over 100 rheumatic conditions that may also have systemic effects. The disease is distributed worldwide. Due to physical, economic, and emotional impairment, arthritis should not be minimized, and proper treatment is vital to optimal patient care.

Juvenile idiopathic arthritis (JIA) has been described worldwide in many races and geographic areas and is not a rare disease. Epidemiology data have defined JIA incidence as 9.2 to 13.9 cases per 100,000 individuals per year and prevalence as 65 to 113.4 cases per 100,000 individuals. JIA is the most common form of chronic arthritis in children and one of the most common chronic childhood illnesses, with prevalence numbers rivaling those of diabetes and cystic fibrosis. Its physical impact can cause emotional and financial trauma in both patients and parents.

**Characteristics of JIA**

Juvenile idiopathic arthritis, along with adult rheumatoid arthritis (RA), seems to be a relatively modern disease whose exact etiology is unknown. In 1864, the French physician Cornil provided the first detailed description of JIA in a 29-year-old female with chronic arthritis since the age of 12.2 The English physician Still presented the classic description of childhood arthritis in 1897 with his description of lymphadenopathy, splenomegaly, fever, and joint swelling in 12 patients.3 The term juvenile RA was coined by Coss and Boots in 1946.4 This term was later changed to juvenile arthritis or JIA to reflect its differences from adult RA.

Unlike RA, JIA comprises a group of diseases, and it differs from RA in its diagnosis and clinical course. JIA can be difficult to diagnose, because typical RA tests may be unreliable in children. The clinical course of JIA differs from RA, in that the former affects normal growth and development, may have a slower rate of joint damage, and the pauciarticular form may more readily enter into spontaneous remission.

Juvenile idiopathic arthritis causes joint pain, stiffness, swelling, and decreased motility. All joints may be affected. Left untreated, JIA can eventually cause joint destruction and deformity, which may cripple physical function and disrupt normal physiological growth (eg, asymmetrical leg bone or toe growth).

**Classification Criteria**

Juvenile idiopathic arthritis classification criteria define the age of onset to be less than 16 years.
Arthritis must be present in 1 or more joints and is defined as swelling or effusion, or the presence of 2 or more of the following signs: limitation in range of motion, tenderness or pain on motion, and increased heat. Diagnosis is confirmed when the duration of the disease is 6 weeks or longer and when other forms of arthritis are excluded. The highest incidence of JIA occurs between the ages of 1 and 3 years, with the early onset occurring more commonly in girls, but the onset can occur at any age.

The 3 types of JIA are classified as polyarticular, pauciarticular, and systemic disease (Table). Polyarticular arthritis tends to be more severe and potentially destructive, particularly if rheumatoid factor is positive. Patients with systemic disease are often hospitalized due to severe symptoms and may receive their initial diagnosis upon hospitalization. In terms of ancillary manifestations (Table), morning stiffness may be present with all types of JIA, whereas rash, fever, and pericarditis tend to occur with systemic arthritis.

### Table. Classification and Ancillary Manifestations of Juvenile Rheumatoid Arthritis

<table>
<thead>
<tr>
<th>Polyarticular Arthritis (≥5 joints)</th>
<th>Pauciarticular Arthritis</th>
<th>Systemic Disease</th>
<th>Ancillary Manifestations</th>
</tr>
</thead>
<tbody>
<tr>
<td>• 5 joints</td>
<td>• ≤4 joints</td>
<td>• Arthritis with intermittent fever</td>
<td>• Morning stiffness</td>
</tr>
<tr>
<td>• 2 subtypes: rheumatoid factor positive or negative</td>
<td>• Typically early childhood onset (peak between ages 1 and 3)</td>
<td>• Rash (maculopapular, salmon-pink, or blanching eruption)</td>
<td>• Rheumatoid rash</td>
</tr>
<tr>
<td>• Generally symmetric involvement of any joints</td>
<td>• Late-onset group (approximately age 9)</td>
<td>• Enlarged lymph nodes</td>
<td>• Intermittent fever</td>
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<tr>
<td>• Typically more severe, destructive form</td>
<td></td>
<td></td>
<td>• Pericarditis</td>
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<td></td>
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<td>• Chronic uveitis</td>
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### Chronic Uveitis

Chronic uveitis, or intraocular inflammation of the uvea, is an ancillary manifestation associated with all types of JIA, but is most common with pauciarticular arthritis. Typical ophthalmoscopic features include inflammatory cell migration, asymptomatic bilateral synchiae (scarring), cataracts, and band keratopathy (calcium deposition). High-risk factors for development of this complication include being female, age younger than 6 years, diagnosed with JIA for less than 2 years, and positive for antinuclear antibodies. If chronic uveitis is not treated aggressively, chronic keratitis may occur and lead to blindness.

### Pathophysiology

Synovial fluid analysis of swollen joints is often used to rule out other causes of arthritis. A fluid that appears cloudy and has leukocyte counts greater than 2000 with greater than 50% neutrophils is consistent with an inflammatory-type picture. Additionally, poor mucin clot formation due to partial hyaluronic acid degradation is observed. Cultures and Gram stains should be done to exclude infectious etiologies.

The presence of specific human leukocyte antigens (HLA) appears to be associated with JIA. The HLA system resides on chromosome 6 and is essential to immune function. Specifically, the class II antigens (HLA-DR, -DP, and -DQ) appear to be associated with inflammatory diseases, including JIA. The major histocompatibility complex polymorphisms appear to alter the peptide binding sites of the arthritogenic peptides that T cells recognize and, thereby, predispose these individuals to the development of autoimmune disease. The HLA type may also alter the development of pathogenic T-cell repertoires. The HLA-peptide relationship is heterogeneous and varies with the JIA type.

Antigen-activated T cells release cytokines that play key roles in pathophysiology (Figure 1). Tumor necrosis factor (TNF)-α is produced by monocytes, macrophages, B cells, T cells, and fibroblasts and is an important cytokine mediator of the inflammatory cascade. TNF-α stimulates macrophages to produce additional TNF-α and the interleukins IL-1 and IL-6. TNF-α is also a potent stimulator of IL-1, IL-6, and IL-8, which stimulate chondrocytes, osteoclasts, and fibroblasts to release metalloproteinases and, ultimately, lead to the erosion of bone and cartilage.

In RA and JIA, joint pathogenesis involves inflammation of the synovial lining, with resulting pannus
formation due to inflammatory cell migration (Figure 2). The pannus is comprised primarily of invasive lining cells with attributes of transformed cells (open nuclei, high expression of oncogenes, and increased metalloproteinases). Simultaneously, destruction of the bone and cartilage occurs as a result of antibody deposition. One feature of JIA that distinguishes it from other inflammatory arthropathies is the propensity of the synovium to become hyperplastic and locally invasive at the synovial interface with cartilage and bone (pannus interface). Antirheumatic medications for JIA often target the rapidly dividing cells of the pannus.

**RATIONALE OF PHARMACOLOGIC TREATMENT**

A primary pharmacologic goal is the prevention of joint inflammation and further destruction of the bone and cartilage. Nonsteroidal anti-inflammatory drugs (NSAIDs) inhibit prostaglandin synthesis, prevent the inflammatory response, and are typically used as first-line agents for JIA. Cyclooxygenase-2 specific NSAIDs may be preferred in patients who have a tendency to bleed or have gastrointestinal intolerance, although side effects must be monitored.

Disease-modifying antirheumatic drugs (DMARDs) are typically used as second-line agents in the treatment of JIA to prevent radiographic changes associated with joint destruction. DMARDs consist of medications (e.g., immunosuppressive, antimalarial, and biologic) that alter immune function. Current biologics target cytokines in the inflammatory cascade. The most common biologics currently used in JIA inhibit the cytokine TNF-α. These biologic agents have demonstrated favorable efficacy in children with JIA and have become widely used, either as US Food and Drug Administration (FDA)-approved agents or in clinical studies.

**FUTURE DIRECTIONS**

Historically, determining individual patient response to specific JIA therapies has been difficult. Treatment plans are a series of trial and error strategies that attempt to decrease joint pain and destruction, suppress the inflammatory response, improve physical function, and preserve normal growth and development. With the recent completion of human genome sequencing, new tools are available to study the phenotypes of patients with arthritis. Through profiles determined by microarray analysis and genome-wide association studies, researchers hope to be able to better categorize patients and subsequently tailor treatments to suit the needs of individuals.
DISCUSSION

**Dr Rich:** Managed care providers often assume that drug therapy and disease management have been appropriately established by specialists, such as rheumatologists. Are patients typically referred to specialists by their primary care physicians (PCPs)?

**Dr Myers:** In tertiary care centers, most patients are referred by PCPs, or other specialists such as allergists or orthopedists, who refer to pediatric rheumatologists to confirm diagnosis and select appropriate treatment. PCPs often vary in their level of comfort with proper differential diagnosis, initial workup, and selection of candidates for rheumatology referral.

**Dr Rich:** Because the cost of biologic therapy is relatively high, is it appropriate for managed care providers to require diagnosis verification by a rheumatology specialist?

**Dr Miller:** Pediatric rheumatology centers (PRCs), if available, should initiate biologic treatment, a decision with which many PCPs seem to agree.

However, pediatric rheumatologists are not available in some geographic areas, and the timeliness of referral to pediatric rheumatologists can vary, particularly in children with long-standing diagnosis. Studies of practice patterns seem to show not only late referral but also late diagnosis of children with JIA.

**Dr Myers:** Rather than using a stepwise approach to treatment, physicians in more rural communities without PRCs or extensive training may be more apt to choose more costly treatments or corticosteroids based on pharmaceutical marketing or perceived ease of use. Referral to PRCs may be more cost effective because specialists methodically confirm diagnosis and choose optimal drug therapy.

**Dr Rich:** Until clinical studies demonstrate significant disease modification with biologics, cost considerations in addition to appropriate therapy choices drive managed care decisions. When PRCs are confirming diagnoses and prescribing therapies, managed care providers are more willing to accept therapy choices.

**Dr Saleh:** It seems that patient access to pediatric rheumatologists is impeded and may not occur until after failure to many therapies and in advanced stages of disease, which may warrant biologics and aggressive therapy. If pediatric patients were treated earlier, as with adult RA, would disease management and remission achievement be easier?

**Dr Myers:** Early diagnosis and early treatment is unquestionably optimal for disease management. Generally, untreated patients in later stages of disease and with existing joint damage are the most difficult to manage.

**Dr Miller:** In the adult population, patients with RA may experience exacerbation after biologic agents are discontinued. More data are needed to determine if this increase also occurs in the pediatric population. Subjectively, it seems that biologic agents may be stopped in some pediatric patients without rebound flares occurring, which suggests that biologic therapy may not be required for excessive periods in some children.

**Dr Myers:** Pediatric rheumatologists often attempt to wean patients from biologic therapies when patients enter remission to avoid excessive time on medications. However, a significant number of children may experience rebound exacerbation of JIA symptoms.

Education of PCPs and other related specialists, such as orthopedists, is optimal to JIA management. Rheumatologists should educate other physicians about JIA differential diagnosis and initial treatment so that patients are diagnosed early and treated appropriately.

**Dr Bushey:** At the Veterans Affairs Medical Center (VAMC), the use of biologics is restricted to rheumatologists. This restriction avoids inappropriate use by PCPs and ensures rheumatology referral.

**Dr Miller:** Biologics should be initiated in PRCs; however, patients can return to their referral centers, or even home healthcare agencies, for future therapies provided that periodic review and coordination exists with the PRCs. One exception may be infliximab, which is possibly more suited to the day hospital setting due to stringent monitoring requirements for serious systemic adverse reactions.

**Dr Penna:** Are there any promising diagnostic tests that may some day help determine the precise drug for individual patients? Managed care concerns include not only drug costs but also corresponding diagnostic test costs, as well as the availability of tools that help identify best therapies for individual patients.

**Dr Myers:** Although unavailable presently, research seems to be heading toward developing such tests, which could dramatically improve patient care.

**Dr Miller:** Although research may be investigating these tests, particularly in adults, I believe that research is heading more toward understanding the basic biology of rheumatoid conditions. Genetic phenotyping in conjunction with treatment stratification would be valuable to patient care. However, ethical and political
questions could arise with this approach because patient privacy could be breached and insurance coverage refused.

**Dr Swims:** As observed in adult RA, is there a window of opportunity in JIA for treatment to be most effective in preventing joint destruction?

**Dr Myers:** Early treatment definitely results in better patient outcomes. This window of opportunity emphasizes the need to educate PCPs.

**Dr Saleh:** Are the polyarticular and pauciarticular types of JIA considered the same disease process or different phenotypes? Are these types of JIA investigated together as one disease state in clinical trials, or are they differentiated? Is there any difference between the 2 types in terms of response to therapy?

**Dr Myers:** The joint pathophysiology of these types appears to be the same, featuring pannus formation and invasion into the cartilage and bone. However, the types differ phenotypically, which is mostly expressed as differences in disease aggression. The polyarticular form tends to be more aggressive, as seen in rheumatoid factor-positive disease. Investigators often use animal models to investigate joint pathophysiology, because they allow the investigator to simplify the variables involved in disease. Until phenotypic differences are more fully understood, treatment is typically the same for both JIA types, except that the use of aggressive therapies varies with the degree of arthritis.

**Dr Miller:** Some gene expression studies have shown preliminary differences between systemic JIA and other febrile illnesses.

**Dr Penna:** One managed care perspective is that early aggressive treatment conflicts with the need to control cost through drug utilization review. The VAMC approach of requiring specialists to prescribe biologics is an effective method to overcome this conflict. However, in areas without readily available pediatric rheumatologists, this requirement could delay treatment inappropriately. Additionally, local PCPs may not easily accept this provision by managed care providers.

**Dr Myers:** Unfortunately, our most effective treatments are currently the most expensive. Until therapy costs decrease, deciding when to use biologics in lieu of less expensive therapies for JIA will continue to remain challenging. The cost tier for JIA treatment is much higher since the advent of biologic therapies in the past 10 years.

**Dr Rich:** Another issue is lifetime maximum benefits associated with health insurance. In adult patients with RA, biologic therapy discontinuation is rare because joint destruction tends to continue throughout life. Do patients with JIA require long-term biologic therapy, or are biologics able to slow disease progression to the point of therapy discontinuation?

**Dr Myers:** A significant number of patients will go into remission, sometimes spontaneously. In children, I prefer to attempt to wean them from biologic therapy, particularly to determine remission durability. However, it is difficult to predict who will remain disease-free and who will need to restart therapy. Because therapies change as newer agents become available, predicting therapy response becomes even more complicated.

**Dr Miller:** One issue to consider with cost of therapy is that socioeconomic consequences may result from untreated or undertreated disease. Data have shown that prior to the advent of biologic therapies, some children with polyarticular disease had difficulties entering the workforce as adults.

**Dr Busbey:** One review article reported that approximately 30% of patients with JIA did not graduate from high school.

**Dr Myers:** A large prospective observational study continues to recruit patients with JIA and other related conditions to learn more about the causes and course of these diseases.

**Dr Rich:** Although long-term studies may provide valuable information about future therapy benefits, managed care providers generally focus on studies that examine short-term therapy benefits. A primary goal of managed care is immediate or short-term cost containment.

Managed care typically covers the cost of high-priced therapies, including for some patients who have reached lifetime maximums. This blanket coverage impedes an important incentive to drive down the price of biologics and other costly therapies. Managed care providers are conflicted because denying benefits or requiring patient cost sharing for high-priced therapies could be disparaging.

**Dr Miller:** When evaluating clinical studies, therapy success with biologics should be carefully defined. Before the first clinical trials of biologics started in adults with RA, the US FDA required a quality-of-life (QOL) component to be incorporated into assessment of responsiveness before treatment approval would be granted. Completing high school and maintaining employment may also be effective ways to measure
success of treatment. Clinical trial results that only report clinical and biologic changes after treatment do not provide QOL information.

REFERENCES