Juvenile Idiopathic Arthritis: A Focus on Pharmacologic Management CE

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ABSTRACT

Juvenile idiopathic arthritis is a chronic condition that affects many pediatric patients. It is a prevalent disease and has become the most common rheumatologic disease of childhood. The condition encompasses multiple different forms of chronic arthritides classified based on the location and number of joints affected as well as the presence or lack of a number of different inflammatory markers. The exact etiology is unknown but is thought to be multifactorial with genetic, humoral, and environmental factors playing a key role. Many pharmacologic agents are available for use in the treatment of juvenile idiopathic arthritis, with management involving the use of symptom-reducing agents and disease-modifying antirheumatic drugs. Treatment is not without adverse events, with many of the agents require monitoring regimens and patient education. Without treatment, the progression and chronicity of the disease can result in significant morbidity, with the potential for devastating consequences on the child's quality of life. J Pediatr Health Care. (2018) *32*, 515-528.

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KEY WORDS

Juvenile idiopathic arthritis, pediatrics, pharmacotherapy

OBJECTIVES

1. Describe the pathophysiology, clinical presentation and diagnosis of juvenile idiopathic arthritis (JIA).
2. Discuss the use of nonsteroidal anti-inflammatory drugs, glucocorticoids, and non-biologic disease modifying antirheumatic drugs in the management of JIA.
3. Explain the role of biologic disease modifying antirheumatic drugs in the management of JIA.
4. Recommend a treatment plan based on classification of JIA and disease activity.
5. Identify monitoring parameters and adverse effects associated with pharmacologic treatment.

INTRODUCTION

Juvenile idiopathic arthritis (JIA) is the most common rheumatologic disease and has the potential to cause long-term morbidity and physical disability. Older terms, including *juvenile rheumatoid arthritis,* which is used more commonly in the United States, and *juvenile chronic arthritis,* which is preferred in Europe, were replaced by the term *JIA* at the meeting of the International League of Association for Rheumatology (ILAR) in the late 1990s (European League Against Rheumatism, 1977). The ILAR highlighted the onset of JIA that begins during childhood and provided a clear distinction from adult-onset rheumatoid arthritis. JIA in itself is not a disease but rather a term that encompasses all forms of arthritides. It is defined as arthritis of unknown etiology that begins before the 16th birthday and persists for at least 6 weeks.

JIA is a diagnosis of exclusion, so other conditions that present with similar clinical manifestations need to be ruled out, including connective tissue diseases (e.g., systemic lupus erythematosus), trauma, infection (e.g., septic joints, osteomyelitis, viral illnesses, Lyme disease), and malignancies. Therefore, the diagnosis of JIA is usually prolonged, which can delay the initiation of treatment, resulting in devastating consequences such as permanent joint destruction, joint contractures, leg-length discrepancies, and blindness secondary to chronic uveitis. Recent advances in pharmacologic treatment have significantly improved the outcome of JIA in children.

EPIDEMIOLOGY

JIA is the most common pediatric autoimmune musculoskeletal condition. Although the exact incidence of JIA in the United States is unknown, the incidence is estimated to be about 2 to 20 per 100,000 children; the prevalence is about 16 to 150 per 100,000 children in Europe and North America (Giancane et al., 2016). Oligoarthritis is the most common subtype of JIA in North America, with rheumatoid factor–positive (Rf+) polyarthritis being the least common subtype (Giancane et al., 2016). The disease more commonly affects females than males (> 2:1); however, sex distribution varies with disease subtype (Giancane et al., 2016; Minden et al., 2002). Age at onset of disease also differs among subtypes, with a median age of onset of 4 years in oligoarthritis, 11 years in enthesitis-related arthritis (ERA), and 12 years in Rf+ polyarthritis (Minden et al., 2002). In addition, ethnicity can affect the prevalence of disease subtype, highlighting the potential for involvement of genetic predisposition (Schwarz, Simpson, Kerr, & Jarvis, 1997). For example, African Americans are more likely to develop polyarticular and Rf+ disease (Espinosa & Gottlieb, 2012), oligoarthritis is the most common JIA subtype in White children of European descent, and enthesitis-related arthritis tends to be more prevalent in children of Mexican and Asian descent (Woo & Colbert, 2009).

PATHOPHYSIOLOGY

The exact etiology and pathogenesis of JIA are unknown, although genetic, environmental, and autoimmune factors are thought to play a role in the development of this disease. A genetic predisposition for JIA has been suggested through concordance rates of 25% to 40% in monozygotic twins and siblings having a 15- to 30-fold higher prevalence of JIA compared with the normative population (Woo & Colbert, 2009). The *IL2RA/CD25* and *VTCN1* genes have been proposed to confer susceptibility toward the development of JIA (Hinks et al., 2009). In patients with ERA, test results for human leukocyte antigen (HLA)-B27 are commonly positive, and HLA-B27 has been correlated with the development of inflammation of the axial skeleton, specifically involving the hip (Woo & Colbert, 2009). Several environmental factors, including breastfeeding and vitamin D and sun exposure, have been identified as having a protective effect against the development of JIA. In contrast, environmental factors such as infection and maternal smoking may increase the risk of developing or worsening the disease (Ellis, Munro, & Ponsonby, 2010). Further studies are needed to comprehensively examine these environmental hypotheses.

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Humoral and cell-mediated immunity are involved in the pathogenesis of JIA. Cell-mediated release of proinflammatory cytokines, such as tumor necrosis factor–alpha (TNF-α), interleukin (IL)-6, and IL-1 secondary to T-cell activation, continues to be the best described pathogenesis of JIA and is the focus of many newer pharmacologic agents. Radiographic models have confirmed this etiology by evidence of a higher percentage of activated T cells in the synovium of patients with JIA. In addition, diagnostic tests show that patients with polyarticular and systemic JIA (SJIA) have higher levels of TNF-α, IL-6, and IL-1 compared with other JIA subtypes (Borchers et al., 2006; Espinosa & Gottlieb, 2012). Activation of the humoral immune response is evident through the production of autoantibodies such as antinuclear antibodies (ANA), as well as complement activation and an increase in serum immunoglobulins (Igs), such as IgM rheumatoid factor. It is estimated that ANAs are detected in 30% to 50% of patients with JIA, and detection has a positive correlation with development of uveitis, a complication of JIA (Borchers et al., 2006).

CLINICAL PRESENTATION AND DIAGNOSIS

The clinical manifestation and treatment algorithms of JIA depend on the subtype of arthritis that is present. Arthritis must be present for 6 weeks before the diagnosis of JIA can be made. Morning stiffness or gelling phenomenon (i.e., stiffness after long periods of sitting or inactivity) are common complaints. Arthralgia often occurs during the morning, with improvements throughout the day. Different classifications of JIA have been developed by organizations including the American College of Rheumatology (ACR), EULAR, and ILAR (Beukelman et al., 2011; EULAR, 1977; Petty et al., 2004; Ringold et al., 2013). The progression of the disease nomenclature and their differing classifications are summarized in Table 1. The ILAR 2001 classification was developed in response to a need for a more consis-