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EDITORIAL

Evolution of treatment options for juvenile idiopathic arthritis

Tao Ren, Jia-Hui Guan, Yu Li, Nan-Nan Li, Zheng Li

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Abstract

A recent study published in *World J Clin Cases* addressed the optimal non-steroidal anti-inflammatory drugs (NSAIDs) for juvenile idiopathic arthritis (JIA). Herein, we outline the progress in drug therapy of JIA. NSAIDs have traditionally been the primary treatment for all forms of JIA. NSAIDs are symptom-relief medications, and well tolerated by patients. Additionally, the availability of selective NSAIDs further lower the gastrointestinal adverse reactions compared with traditional NSAIDs. Glucocorticoid is another kind of symptom-relief medications with potent anti-inflammatory effect. However, the frequent adverse events limit the clinical use. Both NSAIDs and glucocorticoid fail to ease or prevent joint damage, and the breakthrough comes along with the disease-modifying antirheumatic drugs (DMARDs). DMARDs can prevent disease progression and reduce joint destruction. Particularly, the emergence of biologic DMARDs (bDMARDs) has truly revolutionized the therapeutics of JIA, compared with conventional synthetic DMARDs. As a newly developed class of drugs, the places of most bDMARDs in the management of JIA remain to be well established. Nevertheless, the continuous evolution of bDMARDs raises hopes of improving long-term disease outcomes for JIA.

Key Words: Juvenile idiopathic arthritis; Treatment; Non-steroidal anti-inflammatory drug; Disease-modifying antirheumatic drug; Evolution

Core Tip: In past decades, the pharmacological treatments for juvenile idiopathic arthritis (JIA) have undergone a dramatic evolution from non-steroidal anti-inflammatory drugs to disease-modifying antirheumatic drugs (DMARDs), especially the emergence of biologic DMARDs enable patients with refractory JIA to achieve disease remission. This editorial focuses on the progress in treatment options for JIA. We hope that this editorial could provide valuable information for use of anti-JIA drugs.

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INTRODUCTION

Juvenile idiopathic arthritis (JIA) refers to a broad term characterizing all forms of arthritis occurred in children before 16 years of age. JIA is a common autoimmune disease and a leading cause of childhood disability[1]. As a heterogeneous group of arthritis, JIA may subside with age, or, often extend chronic disease and inflammation of the joints throughout middle age in a significant proportion of patients[2,3]. Clinical manifestations of JIA include joint pain, swelling and stiffness. Moreover, it usually accompanies other systemic symptoms of flaccid fever, rash, and enlargement of liver, spleen and lymph nodes[4,5].

The goal of treatment is to control disease activity and prevent complications. Current treatment options include non-pharmacological and pharmacological interventions. Non-pharmacological interventions, such as psychological rehabilitation and exercise, are indispensable and helpful to foster the normal psychosocial and social development of the child and to keep or restore joint function and normal mobility[6,7]. Pharmacological interventions are the mainstay in the management of JIA. The therapeutic strategies have evolved markedly, owing to the availability of a growing number of specific and potent medications. Herein, we specifically discuss the progress of pharmacological treatments for JIA.

NONSTEROIDAL ANTI-INFLAMMATORY DRUGS

Non-steroidal anti-inflammatory drugs (NSAIDs) have traditionally been the mainstay treatment for all forms of JIA. Although the era of biological targeted therapy comes, NSAIDs are still suggested as first-line therapy[8]. NSAIDs work by blocking cyclooxygenase (COX) synthesis to exert analgesic and anti-inflammatory effects[9]. They can alleviate joint pain, swelling, stiffness and fever, but have no effects on joint damage. NSAIDs are well tolerated by children with few side-effects. Moreover, the availability of COX-2 selective inhibitors further lowers the adverse reactions compared with traditional NSAIDs[10]. The most common traditional NSAIDs for JIA include naproxen and ibuprofen, while celecoxib and rofecoxib are frequently used selective NSAIDs[11]. However, the comparative effectiveness and safety between different NSAIDs remains inconclusive. Although two studies suggested the superiority of celecoxib in effectiveness and rofecoxib in safety over other NSAIDs[12,13], these findings still need to be confirmed by solid evidence. Noticeably, the duration of NSAID monotherapy for more than 2 months is discouraged if arthritis is still active[14].

GLUCOCORTICOID

Glucocorticoid is another kind of symptom-relief medication that can exert rapid and potent anti-inflammatory effect. Glucocorticoid is necessary when NSAIDs fail to provide desired efficacy. Intra-articular injection of glucocorticoid is the main treatment for monoarticular or oligoarticular JIA without systemic symptoms[15]. This topical therapy is very helpful for preventing deformities that occur after chronic arthritis. Triamcinolone hexacetonide is preferred for intra-articular injection, since it offers a more durable clinical response than the other available glucocorticoids[16]. Systemic glucocorticoid is usually restricted to systemic JIA with extra-articular manifestations[7]. Prednisone is often the drug of choice for oral administration. However, the adverse events (*e.g.*, growth retardation, infection, and osteoporosis) limit the prolonged use of glucocorticoid at large dose[17].

DISEASE-MODIFYING ANTIRHEUMATIC DRUGS

Conventional synthetic disease-modifying antirheumatic drugs

Conventional synthetic disease-modifying antirheumatic drugs (csDMARDs) are usually used in the initial therapy of polyarthritis, and in the case of inadequate efficacy from first-line treatment for oligo-arthritis[16]. The introduction of methotrexate (MTX) was a significant milestone in csDMARDs[18]. MTX exerts long-acting anti-inflammatory effects mainly through inhibition of interleukin (IL)-1 production[19]. Owing to its sustained effectiveness and acceptable toxicity, MTX remains the first choice second-line drug for JIA that is not controlled by NSAIDs or intra-articular corticosteroid injection[20,21]. Noticeably, prolonging MTX administration for 12 months did not yield additional benefit after the achievement of disease remission by 6 months treatment[22]. The other commonly used csDMARDs include sulfasalazine, lefunomide and cyclophosphamide, and they produce anti-inflammatory effects through different mechanisms. Leflunomide is less effective than MTX[23], but it is still an effective treatment for patients with MTX intolerance[24]. In addition, sulfasalazine is often the csDMARD of choice in patients with enthesitis-related arthritis[25].

Biologic DMARDs

The pharmacological therapeutics for JIA are still evolving, in which biologic DMARDs (bDMARDs) represent the most active and revolutionary field. bDMARDs are mainly selective inhibitors targeting one of three major pro-inflammatory cytokines (TNF, IL-1β, and IL-6). The other newly developed agents include anti-T cell-specific inhibitors, CD20 monoclonal antibodies, and Janus kinase (JAK) inhibitors. They are usually given along with MTX to patients who have an inadequate response to MXT alone.

The first bDMARD introduced to the treatment of JIA is etanercept, a recombinant human TNF-α receptor antagonist. Subsequently, other anti-TNF drugs were developed, such as infliximab, adalimumab, golimumab and certolizumab. Etanercept has been demonstrated the sustained benefits in growth velocity, bone status, and quality of life, and achieving complete disease quiescence in half of the patients[26-28]. Adalimumab is found to be highly effective in patients with or without previous treatment by other biologic agents[29]. Moreover, adalimumab achieves higher response rate than infiximab which is not approved for use in JIA[30]. Golimumab fails to exert superior efficacy over placebo in a trial and it has not yet been approved for use in JIA[31]. Certolizumab is still being evaluated by an ongoing trial. Of these drugs, only etanercept and adalimumab are authorized for use in JIA by both the United States Food and Drug Administration (FDA) and the European Medicines Agency (EMA).

Other bDMARDs that have been approved to be effective in MTX-resistant JIA include IL-1 inhibitors and IL-6 inhibitors. Canakinumab, an IL-1 inhibitor, has been approved by FDA and EMA for use in systemic JIA[32], while Tocilizumab, a monoclonal antibody against IL-6 receptor, has been approved for use in both polyarticular and systemic JIA[33,34]. Unlike the key role of TNF-α in polyarticular JIA, increasing evidence suggests that the major pathogenic cytokines in active systemic JIA are IL-1 and IL-6[35,36]. Patients with the systemic subtype of JIA generally respond well to an IL-1 inhibitor or IL-6 inhibitor, whereas an anti-TNF agent could be less effective in this subtype.

Abatacept is a selective T-cell activation blocker by targeting cytotoxic T-lymphocyte-associated antigen-4. The efficacy and safety of abatacept in JIA have been evidenced by a double-blind randomized controlled withdrawal trial, and then it is approved in the United States and Europe for JIA[37]. Rituximab is a human mouse chimeric monoclonal antibody targeting B lymphocyte (CD20). It is recommended for children with JIA who remain highly or moderately active with poor prognostic factors after sequential treatment with anti-TNF drugs and abatacept[38]. Besides, some newer drugs have been developed for the treatment of JIA, mainly JAK inhibitors, *e.g.*, tofacitinib[39], baricitinib[40] and ruxolitinib [41]. Their efficacy and safety have been established in randomized controlled trials, and some of them have already been approved for use in JIA.

CONCLUSION

Huge progress has been achieved in available medications and treatment recommendations. The pharmacological treatments have undergone a dramatic evolution from NSAIDs to DMARDs, especially bDMARDs. Although treatment of JIA remains difficult, new treatments offer valuable opportunities for some patients with refractory JIA.

FOOTNOTES

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