Uveitis in Juvenile Idiopathic Arthritis: Recent Therapeutic Advances

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Abstract
Uveitis is a common association of juvenile idiopathic arthritis (JIA) that has previously been characterized by poor visual prognosis with limited options for effective treatment. Since corticosteroid treatment is not a preferred long-term option for most patients with this condition, systemic immunosuppressive therapy is frequently employed. The medical options for the treatment of JIA-associated uveitis have recently expanded beyond conventional immunosuppressive drugs to the biological agents. The biological drugs that are most commonly employed for JIA-associated uveitis are the tumor necrosis factor-α inhibitors. Other biological agents that have been used to treat the disease include drugs that target cytokine receptors, lymphocyte antigens and lymphocyte co-stimulation signals. This Mini Review highlights recent developments in the medical treatment of JIA-associated uveitis.

Introduction
Juvenile idiopathic arthritis (JIA) is one of the commonest immune-mediated diseases with an onset in childhood. It is recognized as arthritis of unknown etiology with an onset before the age of 16 and of at least 6 weeks duration, for which other potential medical causes have been ruled out [1]. Anterior uveitis is an important association of JIA, with potentially sight-threatening course and complications, that occurs in 10–20% of all cases [2]. JIA-associated uveitis was designated 'Disease of the Year' in 2013 by the journal Ocular Immunology and Inflammation, enhancing awareness of the disease and prompting a review of the current state of understanding of the disease and its management. This Mini Review focuses on recent developments in the medical treatment of JIA-associated uveitis.

Disease Classification
Seven mutually exclusive categories of JIA are defined by the International League of Associations for Rheumatology (ILAR) as follows: systemic arthritis, oligoarthritis (divided into persistent and extended subcategories), polyarthritis (divided into rheumatoid factor negative and positive subcategories), psoriatic arthritis, enthesitis-related arthritis, and undifferentiated arthritis [1]. The associated uveitis and the risk factors for the development of ocular inflammation do not form part of the ILAR classification of JIA.

Disease Manifestations
As recognized by the ILAR classification, the systemic presentation and course of JIA are variable in terms of the number of joints involved and the extraocular manifesta-
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Management of JIA-Associated Uveitis

The management of JIA-associated uveitis involves both medical control of the inflammation and surgical approaches to its complications, particularly cataract. Intraocular surgery is outside the scope of this review, but readers are referred to an excellent recent review of cataract management in patients with JIA-related uveitis [5]. Control of inflammation and the use of systemic immunosuppressive medications have been clearly associated with better visual acuity in patients with JIA-associated uveitis by the Systemic Immunosuppressive Therapy for Eye Disease (SITE) Cohort Study [6]. In mild disease, treatment may be limited to corticosteroid eye drops with or without a topical cycloplegic agent. When a topical corticosteroid is used no more than twice daily, the risk of drug-induced cataract formation is probably negligible [7]. However, when such treatment is used more frequently, the risk of cataract and the difficulty in compliance often indicate the need for systemic treatment.

Oral corticosteroid may be used to gain rapid control of active uveitis, but long-term treatment carries a significant risk of morbidity in the pediatric population. Corticosteroid-sparing systemic immunosuppressive drugs are effective in controlling the majority of cases of both joint and ocular disease in patients with JIA [4]. The conventional immunosuppressive drug that is most commonly employed is methotrexate. Other antimetabolites are alternatives to treat JIA-associated uveitis, including azathioprine, mycophenolate mofetil and leflunomide. Despite the absence of randomized controlled trials evaluating the efficacy of these agents in JIA uveitis, multiple case reports and case series have provided evidence of efficacy. Unfortunately, these drugs do not appear to change the course of disease; in one study conducted at the University Medical Center Utrecht, 69% of patients experienced a relapse of uveitis following the cessation of methotrexate, which had controlled their disease for a median of 1.5 years [8].

In the past 5 years, the most exciting development in the medical treatment of JIA-associated uveitis has been the application of biological drugs in cases resistant to conventional systemic immunosuppressive therapy or in situations in which conventional agents cannot be used. JIA-associated uveitis is currently not an approved condition for the use of any biological drug internationally, and thus presently such treatment is prescribed ‘off-label’. Biological agents that have been used to treat JIA-associated uveitis include drugs that target cytokines and cytokine receptors (tumor necrosis factor-α, TNF-α, and the interleukin receptors for IL-2 and IL-6), lymphocyte antigens (CD20) and lymphocyte co-stimulation signals (CD80 and CD86).

TNF-α Inhibitors

The TNF-α inhibitors represent the major class of biological drug used today for JIA-associated uveitis that is resistant to treatment with conventional immunosuppressive medications. The SITE Cohort Study described treatment success within 12 months in 75% of 56 children with various forms of uveitis who were treated with TNF-α blockers; the 29 patients with JIA-associated uveitis were significantly more likely to achieve quiescence irrespective of other systemic treatment. There are multiple TNF-α inhibitors in clinical use, including antibodies directed against the cytokine (infliximab and adalimumab) and decoy cytokine receptors (etanercept). In contrast to the antibodies, etanercept is generally considered to provide little therapeutic benefit for uveitis in patients with JIA. Unfortunately, however, the recurrence of uveitis after discontinuation of the TNF blockade appears to be relatively common [9].

The effectiveness of infliximab and adalimumab for JIA-associated uveitis has been compared in studies from clinical centers in Italy. Simonini et al. [10] compared the clinical course for 16 children treated with infliximab with 12 children treated with adalimumab; the majority of these children had JIA-associated uveitis. There was a higher probability of remission over a 3-year period in the adalimumab-treated group. Zannin et al. [11] used the National Italian Registry to show the same result. Inter-
estingly, adalimumab appears to be more effective in inducing remission when used as the primary biological therapy [12]. As highlighted by Mansour [13], other advantages of adalimumab may be superior tolerability, lower immunogenicity and the option of home administration, being delivered by subcutaneous injection, in comparison with infliximab, which requires intravenous infusion.

The SYCAMORE trial is 'the first randomized controlled trial … (to) … assess the clinical effectiveness, safety and cost effectiveness of … (a TNF-alpha inhibitor) … in combination with methotrexate for the treatment of JIA-associated uveitis' [14]. This UK-based study is randomizing 154 patients with uveitis that is active despite treatment with methotrexate to receive additional treatment with adalimumab or placebo for a period of 18 months. As a controlled clinical trial, the results of this study are likely to be important in determining the place of TNF-α blockade in the treatment of JIA-associated uveitis.

Daclizumab

Daclizumab is a humanized monoclonal antibody that targets the alpha subunit of the IL-2 receptor. Clinical investigators at the National Eye Institute conducted a small open-label prospective phase II study of a 52-week treatment of daclizumab for JIA-associated uveitis approximately 5 years ago [15]. They reported treatment success – determined as a 2-grade reduction in the anterior chamber cell – in 4 of 6 patients. The investigators recommended larger randomized and masked trials. However, around the same time, the production of daclizumab was discontinued, relating to a decline in market demand as an immunosuppressive drug. Recently, the drug has been under intensive study for the treatment of multiple sclerosis. Thus, the recommended clinical trials in JIA-associated uveitis may now be possible.

Tocilizumab

Tocilizumab is a fully humanized monoclonal antibody that recognizes the IL-6 receptor. A handful of cases of recalcitrant JIA-associated uveitis treated with tocilizumab have been described as part of two small case series collected at the University of Barcelona [16, 17], which included patients with other uveitis subtypes. Thus, while it is too early to speculate about the usefulness of the drug for this disease in particular, tocilizumab certainly is a potential addition to the biological armamentarium that is used to treat JIA-associated uveitis.

Rituximab

Extensive histopathological evaluation of the eye of a child with JIA-associated uveitis was recently undertaken by Parikh et al. [18], revealing many B cells and their progeny, plasma cells, within the eye. This research provides strong rationale for targeting the B cells in patients with the disease. Rituximab is a chimeric mouse-human monoclonal antibody that is directed against the CD20 surface marker of B cells and results in the death of these cells. Typically, two infusions of the drug are given 2 weeks apart. Two recent retrospective case series have included a total of 18 patients with JIA-associated uveitis who failed the TNF blockade [19, 20]. These studies showed remission and/or drug-sparing effects in over 75% of patients, without the occurrence of treatment-limiting complications. Retreatment was effective when the intraocular inflammation recurred.

Abatacept

Cytotoxic T-lymphocyte-associated antigen (CTLA)-4 prevents the co-stimulation of T cells by preventing CD28 binding to CD80 or CD86. Abatacept is a chimeric protein of immunoglobulin Fc and the extracellular portion of the CTLA-4 molecule. Abatacept has been found to control joint inflammation in JIA in a large, randomized, double-blind, placebo-controlled withdrawal trial [21]. In contrast, uncontrolled retrospective and prospective trials of abatacept for JIA-associated uveitis have been contradictory in terms of showing benefit for the intraocular inflammation [22, 23].

Use of Biological Drugs

Drug safety assessments of biological drugs in the treatment of children with JIA-associated uveitis have not identified a high incidence of serious adverse events, but clearly the body of literature is limited in terms of both the number of patients and the duration of follow-up. Allergic reactions may occur. As applies also to conventional systemic immunosuppressive drugs, the use of biological drugs increases an individual’s risk of incidental infection. For the TNF-α inhibitors in particular, treatment carries the risk of reactivation of tuberculosis. Thus, children must be thoroughly investigated to exclude existing infectious disease, including tuberculosis, and immunizations should be up to date before initiating treatment. An unanswered question is whether there is an increased risk of malignancy in patients with JIA who are treated with biological agents, and for younger patients the issue is particularly important; large, long-term studies will be necessary in order to address this question [24]. Unre-
lated to drug safety concerns, a major challenge to gaining access to the biological drugs for JIA-associated uveitis is their considerable cost.

**Outcomes of Disease**

The visual prognosis of JIA-associated uveitis has been considered guarded, with incidence of vision loss reported at 0.18 per eye-year in the SITE Cohort Study [6]. However, biological treatments may have a major impact on the course of disease. The Multinational Interdisciplinary Working Group for Uveitis in Childhood [25] has developed outcome measures specifically for JIA-associated uveitis to aid in standardizing and categorizing responses to treatment for future therapeutic clinical trials. Conformity of description and grading of ocular disease should allow better comparison between immunosuppressive drugs in relation to their effectiveness and safety for the treatment of JIA-associated uveitis.

**References**