Mini Review:

Uveitis in Juvenile Idiopathic Arthritis: recent therapeutic advances

Short title: Uveitis in Juvenile Idiopathic Arthritis

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Support: Australian Research Council (FT130101648)

Abstract

Uveitis is a common association of juvenile idiopathic arthritis (JIA) that previously has been characterized by poor vision 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 treatment of JIA-associated uveitis have recently expanded beyond conventional immunosuppressive drugs to the biologic agents. The biologic drugs that are most commonly employed for JIA-associated uveitis are the tumor necrosis factor alpha inhibitors. Other biologic 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 is one of the commonest autoimmune 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] Juvenile idiopathic arthritis-associated uveitis was designated "Disease of the Year" in 2013 by the journal, *Ocular Immunology and Inflammation*, enhancing awareness of the disease and prompting 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):[1] 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. The associated uveitis and the risk factors for 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 is variable in terms of the number of joints involved and the extra-ocular manifestations.[1] The subtypes also differ in age of onset, gender risk, ethnic predisposition, prognosis, as well as specific laboratory findings.[3] Uveitis that occurs in association with JIA presents as chronic anterior uveitis – typically presenting with an asymptomatic "white" eye – or less commonly as HLA-B27-associated acute anterior uveitis in enthesitis-related arthritis.[4] In the typical course, the uveitis lags behind the arthritis in onset; however some patients may present initially with uveitis and develop arthritis subsequently, usually within a period of months. Risk factors for the development of uveitis in JIA include early age of onset of disease, oligoarticular category, positive ANA and European ethnicity; uveitis also occurs more frequently in rheumatoid factor negative polyarthritis and psoriatic arthritis JIA subtypes.[2]

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 significant risk of morbidity in the pediatric population. Corticosteroid-sparing systemic immunosuppressive drugs are effective in controlling a 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 anti-metabolites 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 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 application of biologic drugs in cases resistant to conventional systemic immunosuppressive therapy or in situations in which conventional agents cannot be used. Juvenile idiopathic arthritis-associated uveitis is currently not an approved condition for the use of any biologic drug internationally, and thus presently such treatment is prescribed “off-label”. Biologic agents that have been used to treat JIA-associated uveitis include drugs that target: cytokines and cytokine receptors, i.e., tumor necrosis factor (TNF)-alpha, and the

interleukin (IL)-2 and IL-6 receptors; lymphocyte antigens, i.e., CD20; and lymphocyte co-stimulation signals, i.e., CD80 and CD86.

Tumor necrosis factor (TNF)-alpha inhibitors

The TNF-alpha inhibitors represent the major class of biologic 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-alpha blockers; the 29 patients with JIA-associated uveitis were significantly more likely to achieve quiescence irrespective of other systemic treatment. There are multiple TNF-alpha inhibitors in clinical use, including antibodies directed against the cytokine, i.e., infliximab and adalimumab, and decoy cytokine receptors, i.e., etanercept. In contrast to the antibodies, etanercept is generally considered to provide little therapeutic benefit for uveitis in patients with JIA. Unfortunately, however, recurrence of uveitis after discontinuation of 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 and colleagues[10] compared the clinical course for 16 children treated with infliximab with 12 children treated with adalimumab; a 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 and co-workers[11] used the National Italian Registry to show the same result. Interestingly, adalimumab appears to be more effective in inducing remission when used as primary biologic 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 to 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 United Kingdom-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, results of this study are likely to be important in determining the place of TNF-alpha 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 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 anterior chamber cell – in 4 of 6 patients. The investigators recommended larger randomized and masked trials. However, around the same time, production of daclizumab was discontinued, relating to decline in market demand as an immunosuppressive drug. Recently however, 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] that included patients with other uveitis subtypes. Thus, while it is too early to speculate about 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 and colleagues,[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 drug are given two weeks apart. Two recent retrospective case series have included a total of 18 patients with JIA-associated uveitis who failed TNF blockade.[19,20] These studies showed remission and/or drug sparing effects in over three quarters of patients, without occurrence of treatment-limiting complications. Re-treatment was effective when the intraocular inflammation recurred.

Abatacept

Cytotoxic T lymphocyte-associated antigen (CTLA)-4 prevents 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 Biologic Drugs

Drug safety assessments of biologic 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 number of patients and duration of follow-up. Allergic reactions may occur. As applies also to conventional systemic immunosuppressive drugs, the use of biologic drugs increases an individual's risk of incidental infection. For the TNF-alpha 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 ahead of initiating treatment. An unanswered question is whether there is an increased risk of malignancy in patients with JIA who are treated with biologic agents, and for younger patients the issue is particularly important; large, long-term studies will be necessary in order to address this question.[24] Unrelated to drug safety concerns, a major challenge to the access to the biologic 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, biologic treatments may have a major impact on 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 response 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 effectiveness and safety for the treatment of JIA-associated uveitis.

References

1. Petty RE, Southwood TR, Manners P, et al. International League of Associations for Rheumatology classification of juvenile idiopathic arthritis: second revision, Edmonton, 2001. *J Rheumatol.* 2004;31:390-392.

2. Heiligenhaus A, Heinz C, Edelsten C, et al. Review for disease of the year: epidemiology of juvenile idiopathic arthritis and its associated uveitis: the probable risk factors. *Ocul Immunol Inflamm.* 2013;21:180-191.

3. Prakken B, Albani S, Martini A. Juvenile idiopathic arthritis. *Lancet.* 2011;377:2138-2149.

4. Foeldvari I. Ocular involvement in juvenile idiopathic arthritis: classification and treatment. *Clin Rev Allergy Immunol* 2014 (in press).

5. Angeles-Han S, Yeh S. Prevention and management of cataracts in children with juvenile idiopathic arthritis-associated uveitis. *Curr Rheum Rep.* 2012;14:142-149.

6. Gregory AC, 2nd, Kempen JH, Daniel E, et al. Risk factors for loss of visual acuity among patients with uveitis associated with juvenile idiopathic arthritis. *Ophthalmology.* 2013;120:186-192.

7. Thorne JE, Woreta FA, Dunn JP, Jabs DA. Risk of cataract development among children with juvenile idiopathic arthritis-related uveitis treated with topical corticosteroids. *Ophthalmology.* 2010;117:1436-1441.

8. Kalinina Ayuso V, van de Winkel EL, Rothova A, de Boer JH. Relapse rate of uveitis post-methotrexate treatment in juvenile idiopathic arthritis. *Am J Ophthalmol.* 2011;151:217-222.

9. Shakoor A, Esterberg E, Acharya NR. Recurrence of uveitis after discontinuation of infliximab. *Ocul Immunol Inflamm.* 2014;22:96-101.

10. Simonini G, Taddio A, Cattalini M, et al. Prevention of flare recurrences in childhood-refractory chronic uveitis: an open-label comparative study of adalimumab versus infliximab. *Arthritis Care Res.* 2011;63:612-618.

11. Zannin ME, Birolo C, Gerloni VM, et al. Safety and efficacy of infliximab and adalimumab for refractory uveitis in juvenile idiopathic arthritis: 1-year followup data from the Italian Registry. *J Rheumatol.* 2013;40:74-79.

12. Simonini G, Taddio A, Cattalini M, et al. Superior efficacy of adalimumab in treating childhood refractory chronic uveitis when used as first biologic modifier drug: adalimumab as starting anti-TNF-alpha therapy in childhood chronic uveitis. *Pediatr Rheumatol Online J.* 2013;11:16.

13. Mansour AM. Adalimumab in the therapy of uveitis in childhood. *Br J Ophthalmol.* 2007;91:274-276.

14. Ramanan AV, Dick AD, Benton D, et al. A randomised controlled trial of the clinical effectiveness, safety and cost-effectiveness of adalimumab in combination with methotrexate for the treatment of juvenile idiopathic arthritis associated uveitis (SYCAMORE Trial). *Trials.* 2014;15:14.

15. Sen HN, Levy-Clarke G, Faia LJ, et al. High-dose daclizumab for the treatment of juvenile idiopathic arthritis-associated active anterior uveitis. *Am J Ophthalmol.* 2009;148:696-703 e691.

16. Adan A, Mesquida M, Llorenc V, et al. Tocilizumab treatment for refractory uveitis-related cystoid macular edema. *Graefes Arch Clin Exp Ophthalmol.* 2013;251:2627-2632.

17. Mesquida M, Molins B, Llorenc V, et al. Long-term effects of tocilizumab therapy for refractory uveitis-related macular edema. *Ophthalmology.* 2014;121:2380-2386.

18. Parikh JG, Tawansy KA, Rao NA. Immunohistochemical study of chronic nongranulomatous anterior uveitis in juvenile idiopathic arthritis. *Ophthalmology.* 2008;115:1833-1836.

19. Miserocchi E, Pontikaki I, Modorati G, et al. Rituximab for uveitis. *Ophthalmology.* 2011;118:223-224.

20. Heiligenhaus A, Miserocchi E, Heinz C, et al. Treatment of severe uveitis associated with juvenile idiopathic arthritis with anti-CD20 monoclonal antibody (rituximab). *Rheumatology.* 2011;50:1390-1394.

21. Ruperto N, Lovell DJ, Quartier P, et al. Abatacept in children with juvenile idiopathic arthritis: a randomised, double-blind, placebo-controlled withdrawal trial. *Lancet.* 2008;372:383-391.

22. Tappeiner C, Miserocchi E, Bodaghi B, et al. Abatacept in the treatment of severe, longstanding, and refractory uveitis associated with juvenile idiopathic arthritis. *J Rheumatol.* 2015;42:706-711.

23. Zulian F, Balzarin M, Falcini F, et al. Abatacept for severe anti-tumor necrosis factor alpha refractory juvenile idiopathic arthritis-related uveitis. *Arthritis Care Res.* 2010;62:821-825.

24. Mannion ML, Beukelman T. Risk of malignancy associated with biologic agents in pediatric rheumatic disease. *Curr Opin Rheumatol.* 2014;26:538-542.

25. Heiligenhaus A, Foeldvari I, Edelsten C, et al. Proposed outcome measures for prospective clinical trials in juvenile idiopathic arthritis-associated uveitis: a consensus effort from the multinational interdisciplinary working group for uveitis in childhood. *Arthritis Care Res.* 2012;64:1365-1372.