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PEDIATRIC RHEUMATOLOGY (S OZEN, SECTION EDITOR)

Treatment of Uveitis Associated with Juvenile Idiopathic Arthritis

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Abstract Chronic anterior uveitis affects 10–30 % of patients with juvenile idiopathic arthritis (JIA) and is still a cause of blindness in childhood. In most patients it is asymptomatic, bilateral, and recurrent, so careful screening and early diagnosis are important to obtain the best long-term prognosis. The treatment of chronic uveitis associated with JIA is challenging. Initial treatment is based on topical steroids and mydriatic drops. Methotrexate is the most common first-line immunomodulatory drug used. For refractory patients, biologicals, mainly the anti-tumor-necrosis-factor (TNF) drugs adalimumab and infliximab, have been revealed to be effective and have changed the outcome for these patients. Collaboration between pediatric rheumatologists and ophthalmologists is important for the successful diagnosis and treatment of patients with uveitis associated with JIA.

Keywords Uveitis · Juvenile idiopathic arthritis · Corticosteroids · Methotrexate · Biologicals · Adalimumab · Infliximab · Abatacept

Introduction

Uveitis is one of the major extra-articular manifestations of juvenile idiopathic arthritis (JIA), affecting 10–30 % of JIA patients [1, 2]. It is typically a chronic anterior uveitis, and in most patients is asymptomatic, bilateral, and recurrent [3]. It usually appears during the first four years after diagnosis of JIA, but may develop years later or even before the onset of arthritis [4]. Early diagnosis is highly important to obtain the best long-term prognosis and, therefore, careful screening should be performed after diagnosis of JIA. Screening intervals should be adapted on the basis of JIA subtype, the presence of antinuclear antibodies (ANA), and duration of arthritis [4, 5].

Treating chronic uveitis associated with JIA is a challenge for ophthalmologists and pediatric rheumatologists because of its aggressiveness and frequent complications; it is still a cause of blindness in childhood [6]. Initial treatment with topical drops is often not enough to control ocular inflammation, requiring a second line of treatment. In recent years, reports on treating uveitis in patients with JIA with a variety of immunomodulators and biological drugs have been published. Most of the studies are retrospective or include few patients, which makes it difficult to draw evidence-based conclusions.

It is well known that specific clinical variables, including the presence of complications at first presentation, are prognostic factors for visual acuity in uveitis associated with JIA. However, there is a lack of biomarkers that can be used in clinical practice to predict uveitis outcomes [7–10]. Moreover, the broad variety of outcome measures used makes it difficult to compare the disease course, risk of structural complications, level of impairment to visual function, and response to treatment. With the objective of standardizing outcome measures for future interventional studies, an international interdisciplinary working group for uveitis in childhood, consisting of ophthalmologists and pediatric rheumatologists, was formed and is currently validating a proposed preliminary core set of outcome measures for JIA-associated uveitis [11••].

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Corticosteroids

Topical corticosteroids are usually the initial treatment option for chronic anterior uveitis. High-potency corticosteroids, for example prednisolone acetate 1 % or dexamethasone 0.1 %, are preferred to low-potency alternatives. Mydriatics association is recommended to dilate the eye and prevent the formation of synechiae. The number of topical drops should be adapted to the degree of inflammation and should be gradually reduced as the inflammation is brought under control, to minimize side effects including ocular hypertension and cataracts. Topical treatment should be maintained until there are no cells in the anterior chamber. Thorne et al. [12] investigated the risk of cataract development and topical corticosteroid use in a retrospective cohort of 75 children with JIA-associated uveitis. No cataracts were seen in those treated with ≤2 drops daily, and eyes receiving ≤3 drops daily had an 87 % reduced risk of developing a new cataract during follow up compared with eyes treated with higher daily doses. Therefore, all effort should be made to limit use of topical steroids to fewer than three drops daily, and preferably to fewer than two drops daily.

If uveitis is not controlled with standard treatment, systemic corticosteroids can be used, preferably in short courses to reduce the known side effects of prolonged corticosteroid treatment. Subtenon steroid injections carry a risk of severe complications, including glaucoma, cataracts, subconjunctival hemorrhage, and infections, and they are considered for cases of uveitis with a high degree of inflammation that have not improved when treated with topical corticosteroids.

Immunomodulatory Drugs

Methotrexate

Methotrexate (MTX) is a folic-acid analogue that inhibits the dihydrofolate reductase enzyme and DNA replication. Although the effect of MTX in JIA-associated uveitis has not been assessed in prospective randomized studies, a positive effect has been reported in numerous case series [13–15] and it is still the first-line steroid-sparing agent for chronic uveitis [16•]. In a recent meta-analysis of the efficacy of MTX for treating chronic childhood uveitis, it was estimated that the overall probability of improvement to intraocular inflammation was 73 %. MTX doses ranged from 7.5 to 30 mg m^{-2}. Approximately 20 % of patients experienced adverse events caused by MTX administration, mostly gastrointestinal discomfort and nausea, and less frequently elevation of liver enzymes [16•].

Azathioprine

Azathioprine is a purine-synthesis inhibitor that interferes with DNA replication. In a retrospective multicenter study including 41 patients with JIA and chronic uveitis treated with azathioprine, Goebel et al. [17] reported that uveitis inactivity was obtained in 61.5 % of patients receiving monotherapy and 66.7 % of patients to whom azathioprine was administered with other immunosuppressives. Although there are few reports on the effect of azathioprine on JIA-associated uveitis, it is included in the German Guidelines algorithm of treatment for uveitis associated with JIA [18••].

Mycophenolate Mofetil

Mycophenolate mofetil (MMF) inhibits the inosine monophosphate dehydrogenase enzyme, which is essential to RNA and DNA synthesis and is used by T and B lymphocytes. There are several reports on efficacy of MMF from large series of patients with chronic uveitis [19–21], but fewer for pediatric patients with JIA-associated uveitis. In a retrospective analysis of 17 children with chronic uveitis of a mixture of different etiology, Doycheva et al. [22] reported that a steroid-sparing effect was obtained for 88 % of the patients and that MMF was effective for 64 % of the patients (although only one patient had uveitis associated with JIA). A few years later, Chang et al. [23], in a retrospective review of 52 pediatric patients who had uveitis treated with MMF, revealed that 15 of the 25 patients with JIA-associated uveitis (60 %) achieved long-term disease control (quiescence for at least two years on MMF monotherapy and no more than two flare-ups, which were treated with an increase of MMF dose).

Leflunomide

Leflunomide inhibits the enzyme dihydro-orotate dehydrogenase, attenuating the cellular and humoral immune response. It has proved safe and effective for the joint component of JIA [24]. In a recent small case series, eight of 13 cases of chronic uveitis associated with JIA (61.5 %) responded to leflunomide [25].

Biological Treatment

Tumor-Necrosis-Factor Inhibitors

Infliximab

Infliximab (INF) is a chimeric monoclonal antibody that blocks tumor necrosis factor alpha (TNF-α), a proinflammatory cytokine involved in the pathogenesis of JIA. Although

not approved for treating JIA it was the first anti-TNF drug available, and there are many reports of its efficacy for JIA-associated uveitis [26–29].

In the Italian National Registry, which included 108 JIA patients with anterior uveitis, 88 were treated with INF and reported a remission rate of 42.8 % (clinical remission was defined as the absence of active uveitis for more than six months with no or less than one daily topical treatment) [30•]. In a more recent study of 88 patients with non-infectious uveitis of a mixture of different etiology treated with infliximab, 81.8 % achieved clinical remission (including 15 of the 16 patients with JIA-associated uveitis included in the study) [31].

It has been suggested that pediatric patients with JIA-associated uveitis may require higher dose by weight of INF compared with pediatric patients with only arthritis, pediatric patients with other forms of uveitis, or adult patients. Dose escalation may be necessary to achieve disease control in patients with uveitis [32]. These doses have found to be safe for and well-tolerated by pediatric patients [33]. However, a loss of efficacy over time has been documented for INF, probably resulting from the production of anti-INF antibodies [34]. Monitoring serum levels of INF and antidrug antibodies may be helpful for evaluating and optimizing efficacy and safety of INF [35]. The use of other immunosuppressants with INF may also help to reduce the risk of developing neutralizing anti-drug antibodies.

Adalimumab

Adalimumab (ADA) is a fully human monoclonal antibody against TNF-α, and is approved for the treatment of polyarticular JIA in children over two years old. A recent retrospective analysis of 15 children with uveitis, including 10 with JIA-associated uveitis, revealed that clinically significant improvement in intraocular inflammation was achieved for 85.7 % of patients. After treatment with ADA, nine of the 15 patients (60 %) experienced a decrease in annual recurrence of at least one episode per year, including four patients (25 %) who remained recurrence free for periods ranging from four to 18 months [36]. In a large retrospective cohort of children with JIA and refractory chronic uveitis, treatment with ADA for a mean of two years was associated with an overall improvement of disease activity in 57 % of cases [37]. Dobner et al. reported efficacy of ADA for 80 % of a cohort of adult and pediatric patients with different forms of non-infectious uveitis [38]. Similar treatment efficacy for children with uveitis treated with ADA has been reported in other retrospective studies [39–41]. Garcia de Vicuña et al. [42•] reported a multicenter prospective case series to assess efficacy and safety of ADA for uveitis associated with JIA. Thirty-nine children with uveitis, who either were not responsive to standard immunosuppressive therapy or were intolerant of it, were enrolled. A significant reduction in inflammation of the anterior chamber and posterior segment, macular thickness, and immunosuppression load was observed, without significant side effects requiring discontinuation of therapy. Similarly, in another prospective case series enrolling patients with JIA-associated uveitis, after a mean follow-up of 18.2±7.7 months resolution of anterior chamber inflammation was obtained in 29/38 eyes (76 %) [43]. The first randomized controlled trial (multicenter, double-blind, placebo-controlled) to assess the clinical effectiveness, safety, and cost effectiveness of ADA in combination with MTX for the treatment of JIA-associated uveitis (SYCAMORE trial) is taking place. It will randomize 154 patients who have active uveitis despite receiving MTX treatment for at least 12 weeks, and all participants will be treated for 18 months, with follow-up of three years from randomization. The primary end point of the study will be time to treatment failure [44].

As well as having a greater ease of subcutaneous administration, ADA has become the first anti-TNF of choice as a result of at least two studies that have indicated somewhat better control of JIA-associated uveitis with ADA than with INF [30•, 45]. In the article of Simonini et al. [45] it was reported that ADA was as efficacious as INF during the first year of treatment, but maintained remission for a longer period and performed better in the long-term survival analysis. Moreover, in a recent long-term retrospective analysis of the efficacy and tolerability of TNF inhibitors for treating children with refractory antinuclear antibody (ANA)-associated chronic anterior uveitis (most of them JIA patients), control of ocular inflammation was achieved in 71 % of patients after one year and 72 % of patients after two years of treatment [46]. When analyzing the efficacy of each TNF inhibitor for controlling the activity of uveitis, the authors of the study found that ADA was superior to INF; none of the three patients treated with etanercept responded.

Data on immunogenicity of ADA has revealed an association between the development of antidrug antibodies, diminished serum drug levels, and poorer treatment response. Moreover, the incidence of ADA antibodies was found to be lower for ADA given concomitantly with MTX than for ADA monotherapy [47]. Monitoring serum levels and antidrug antibodies may be helpful for evaluating efficacy and for making decisions about and possible changes to the therapeutic strategy.

Etanercept

Etanercept is a recombinant TNF receptor that binds and blocks free TNF, and is effectively used in the treatment of children with JIA. However, on the basis of several reports of poor response to etanercept in controlling ocular inflammation [29, 46, 48, 49], it is believed to be less effective than INF and ADA for treating uveitis. Therefore, in the absence of

prospective studies directly comparing the effectiveness of different anti-TNF agents, etanercept is not currently recommended in the treatment algorithm of uveitis.

Other Anti-TNF

Golimumab is a newer anti-TNF drug that is given subcutaneously every four weeks and, although its use for JIA is off-label [50, 51], several case reports have been published including adults and pediatric patients with JIA-associated uveitis [52–55]. Certolizumab is another new TNF antagonist, which is pegylated to prolong its half-life, but there are not yet any reports of its use for treating uveitis associated with JIA.

Anti-IL 6

Tocilizumab is a humanized recombinant antibody that binds to the IL-6 receptor and inhibits the downstream signaling of IL-6 and thus its proinflammatory effects. Although it is already approved for treating polyarticular and systemic JIA in patients two years of age and older, little has been published on the treatment of uveitis associated with JIA. In 2012, Tappeiner et al. [56] published a Letter to the Editor regarding three patients treated with tocilizumab for JIA-associated severe chronic anterior uveitis, which was refractory to high doses of topical corticosteroids, disease-modifying antirheumatic drugs (DMARD), and at least one TNF-α inhibitor. Within a mean follow-up period of nine months (range 6–12 months), inactivity of uveitis was achieved in two of the patients. Adan et al., in a series of five patients with cystoid macular edema secondary to different etiologies, included one patient with JIA-associated uveitis for whom treatment with tocilizumab resulted in reduced macular edema, improved visual acuity, and sustained uveitis remission. Similarly, an adult patient with a retinal vasoproliferative tumor secondary to a long history of JIA-associated uveitis was treated with tocilizumab, and after 12 injections an ophthalmic examination revealed a partial regression of the lesion, reduced macular edema, and improved visual acuity [57]. Tocilizumab may become a treatment option for patients with JIA-associated uveitis which is refractory to conventional immunosuppressive and anti-TNF drugs. A phase I–II open-label trial, to assess the efficacy and safety of tocilizumab in the management of JIA-associated vision-threatening uveitis that is refractory to other systemic immunosuppression, is currently recruiting patients [58].

Anti-lymphocytes

Abatacept

Abatacept is a fusion protein that inhibits the co-stimulation and activation of T lymphocytes, and is approved for treating polyarticular JIA in children over six years old. Its efficacy against JIA-associated uveitis refractory to conventional immunosuppression and other biologicals has been reported in several case studies [59–61]. Zulian et al. [62] reported a series of seven patients with oligo-JIA and chronic longstanding uveitis. All already had ocular complications and had not responded to previous immunosuppressive therapy, nor to two or more anti-TNF. All patients responded to abatacept, although only one patient went into complete remission. The frequency of uveitis flares decreased from a mean of 3.7 episodes to a mean of 0.7 episodes (during the six-month period before and after abatacept initiation). One patient discontinued treatment because of oral mycosis and arthritic flare. A later, updated report, with a mean follow-up of 21 months, revealed that five of the six patients who were on abatacept maintained good control of both uveitis and arthritis, although one relapsed after 12 months of treatment, with flares of both arthritis and uveitis [60].

A phase I–II dose-ranging, randomized clinical trial of abatacept for treating refractory non-infectious uveitis is in progress [63].

Rituximab

Rituximab is a monoclonal antibody against the CD20 cell-surface antigen of B cells. It is not commonly used for treating JIA, and it is not approved for this indication. However, it has been reported to be effective for treating scleritis and other ocular inflammation. On the basis of the histopathology of uveitis associated with JIA, in which a cell infiltrate dominated by plasma cells and B cells (predominantly $CD20^{+}$) is found, efficacy of rituximab treatment for JIA-associated uveitis has been evaluated in two retrospective case series [64, 65]. Around the 4th–5th month, after a cycle of two infusions of rituximab at two-week intervals, seven of the eight patients in one series [65] and seven of the 10 patients in the other [64] achieved inactivity of the uveitis. However, half the patients in both series underwent a recall infusion 6–12 months after the first one because of recurrence of uveitis.

Our Experience

Motivated by the lack of standardized treatment for uveitis associated with JIA, over the past few years the uveitis working group of the Spanish Society of Pediatric Rheumatology (SERPE) has organized three national conferences and has developed an interdisciplinary consensus procedure for follow-up and treatment of uveitis associated with JIA (publication pending). The objective of the treatment is no cells in the anterior chamber. The treatment should be initiated as soon as possible, and should be planned and monitored by the

ophthalmologist and the pediatric rheumatologist. Good communication between these professionals is therefore essential. The treatment algorithm is organized in a stepwise regimen:

1) topical corticosteroids;
2) methotrexate when there is no improvement on topical treatment; and
3) adalimumab.

If there is no improvement on adalimumab or if three or more flares of uveitis occur (with ocular complications), analysis of antidrug antibodies and drug levels is recommended. Depending on the results, there are three possible courses of action:

1) If drug levels are correct, a change in the therapeutic target is suggested (either abatacept or tocilizumab);
2) If drug levels are low because of the presence of antidrug antibodies, treatment should be changed to another anti-TNF agent or to other biologicals; and
3) If drug levels are low but no antibodies are present, adalimumab dose should be increased or interval of administration decreased.

For those patients who are still refractory to treatment, rescue therapy is individualized, using other biologicals in combination with different DMARDs.

Conclusions

Because of its aggressiveness and frequent complications, uveitis associated with JIA remains a challenging disease to treat. Current treatment recommendations are based mainly on retrospective case series lacking standardized disease assessments and outcome measures. For years, corticosteroids have been used for uveitis treatment; however, these have a high rate of side effects. Steroid-sparing therapeutic options include several immunomodulatory drugs, with methotrexate being the most common first-line systemic medication used for treating JIA-associated uveitis. Anti-TNF agents have been revealed to be effective for treating refractory uveitis, and their increasingly frequent use has definitely changed the outcome of this disease. The availability to test immunogenicity and drug levels may help in the medical decision-making process. However, there are still some patients who do not respond to treatment. Other biological therapies have been suggested as alternatives, but more studies are warranted to establish firm recommendations. Collaboration between pediatric rheumatologists and ophthalmologists is essential for advancing this field.

Compliance with Ethics Guidelines

Conflict of Interest Rosa Bou declares that she has received speakers' bureau fees from Novartis and Abbvie, and travel and expense payments from Abbvie and Pfizer. Estíbaliz Iglesias declares that she has no conflict of interest. Jordi Antón declares that his institution has received a PI grant from Pfizer and that he has received speakers' bureau fees from Pfizer, Roche, and GEBRO, and speakers' bureau fees and travel and expense payments from Abbvie.

Human and Animal Rights and Informed Consent This article does not contain any studies with human or animal subjects performed by any of the authors

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