Expert Opinion on Investigational Drugs

ISSN: 1354-3784 (Print) 1744-7658 (Online) Journal homepage: informahealthcare.com/journals/ieid20

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To cite this article: Luca Cantarini, Gabriele Simonini, Bruno Frediani, Ilaria Pagnini, Mauro Galeazzi & Rolando Cimaz (2012) Treatment strategies for childhood noninfectious chronic uveitis: an update, Expert Opinion on Investigational Drugs, 21:1, 1-6, DOI: 10.1517/13543784.2012.636350

To link to this article: https://doi.org/10.1517/13543784.2012.636350

Published online: 11 Nov 2011.

Expert Opinion

Treatment strategies for childhood noninfectious chronic uveitis: an update

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Background: Uveitis is an inflammatory disorder involving inflammation of the uveal tract. It is classified as anterior, intermediate, posterior or panuveitis, depending on the part of eye affected by the inflammatory process. In children, noninfectious, chronic uveitis is a relatively uncommon but serious disease, with the potential for significant long-term complications and possible blindness. Although frequently associated with an underlying systemic disease, for example, juvenile idiopathic arthritis, a significant number of cases in children show no associated signs or symptoms and are labeled as idiopathic.
Results: We reviewed the available literature. Taking into account this evidence, an anti-inflammatory therapy based on an immunomodulatory approach seems a reasonable strategy for noninfectious chronic uveitis, in children as well as in adults. Due to a lack of controlled studies regarding uveitis in children, immunosuppressive strategy is supported only at evidence level III. Our aim is to review the currently available medical strategies for the treatment of childhood sight-threatening chronic uveitis.
Conclusion: Uveitis in children can be severe. Methotrexate is the drug of choice for recalcitrant cases, and biologic therapies can be useful in selected situations.

Keywords: biological modifier drugs, childhood noninfectious chronic uveitis, immunosuppressant therapy, juvenile idiopathic arthritis

Expert Opin. Investig. Drugs (2012) 21(1):1-6

Uveitis is an inflammatory disorder involving inflammation of the uveal tract. In children, it is a relatively uncommon but serious disease, with the potential for significant long-term complications and possible blindness. Uveitis is frequently associated with an underlying systemic disease [1]; however, a significant number of cases in children show no associated signs or symptoms and are labeled as idiopathic. The most common causes of uveitis in the pediatric age are idiopathic, related to autoimmune diseases, and infectious. Autoimmune diseases include juvenile idiopathic arthritis (JIA), systemic vasculitides, inflammatory bowel disease, hereditary autoinflammatory syndromes and tubulointerstitial nephritis and uveitis syndrome, while infectious etiologies include *Bartonella, Borrelia*, cytomegalovirus, Epstein–Barr virus, human immunodeficiency virus, herpes simplex virus, herpes zoster virus, syphilis, *Toxocara canis*, tuberculosis and West Nile virus. This review mostly focuses on uveitis related to autoimmune diseases, in particular JIA, which is the most common chronic rheumatic disease of childhood.

Strong evidence supports that genetic background plays a major role in the susceptibility of this group of diseases, together with environmental factors, leading to the release of proinflammatory cytokines [2]. An autoimmune pathogenesis can be hypothesized for the ocular damage during uveitis: an inflammatory process

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10.1517/13543784.2012.636350 © 2012 Informa UK, Ltd. ISSN 1354-3784

during an immune response activation takes place against ocular self-antigens, driven by cellular and/or humoral mechanisms, in subjects with specific background [3].

An anti-inflammatory therapy based on an immunomodulatory approach seems a reasonable strategy for noninfectious chronic uveitis in children as well as in adults; however, there are much less experience and cumulative data in treating children [4]. A lack of controlled studies regarding uveitis in children means that treatment with immunosuppressive drugs is supported only at evidence level III (expert opinion, clinical experience or descriptive study), while studies on certain TNF-α blocking agents achieve an evidence level II – III. However, the use of immunosuppressive therapy is a reasonable approach to control/reduce inflammation, achieve a corticosteroid-sparing effect and decrease the risk of sight-threatening ocular complications.

1. Corticosteroids

Corticosteroids can be used topically, in periocular injections, or systemically, orally and/or intravenously. Topical corticosteroids are very useful in the management of most cases of anterior uveitis and scleritis.

Systemic corticosteroid therapy is prescribed for systemic immunosuppression and severe ocular inflammation. Prednisone is the most commonly used drug, at the dose of 2 mg/kg for remission induction, with a quick taper once inflammation is controlled. Ideally, corticosteroids should be taken as a single dose in the morning because of the timing of the endogenous peak of corticosteroid production by adrenal glands. Systemic steroids remain the gold standard treatment in pediatric patients with anterior uveitis and visually significant cystoid macular edema, as well as in those with sight-threatening complications of posterior uveitis. Intravenous corticosteroids are sometimes needed in patients who need aggressive management of inflammation, such as those with resistant uveitis, optic nerve involvement, serpiginous choroiditis or panuveitis. The most commonly used drug is methylprednisolone, at 30 mg/kg (maximum dosage 1 g) intravenously over 3 h, for 3 consecutive days or every other day three times in a week. Additional intravenous pulse(s) can be useful to maintain remission.

However, systemic corticosteroids can cause a number of side effects, particularly in growing children. The most common side effects are cushingoid face, hypertension, peptic ulceration, hyperglycemia, osteoporosis and electrolyte imbalance. In general, the risk of growth retardation and the development of cataract are the main reasons for switching from systemic corticosteroids to other immunosuppressives much earlier in children than adults.

2. Immunosuppressants

2.1 Methotrexate

Methotrexate (MTX) is administered to children at the dosage of 10 – 15 mg/m^2 once a week, and therapeutic effect is usually seen after 6 – 10 weeks [4]. A retrospective pediatric series showed 84% percentage of remission in JIA-associated uveitis after treatment with MTX at mean dosage of 15.6 mg/m^2; remission was maintained up to a mean duration of 10.3 months [5]. In another study, quiescence of uveitis was obtained in 32/35 children with JIA after 27.6 months of follow-up, in 25 patients as the sole immunosuppressant and in 7 with additional systemic immunosuppressives [6].

2.2 Azathioprine

Azathioprine (AZA) is recommended as a baseline oral treatment for patients with uveitis at the dosage of 1 – 2 mg/kg/day (30 to 60 mg/m^2). Its beneficial effects in the treatment of 40 children with uveitis have been reported in a 5-year study: when steroid treatment was associated with AZA, a 61% improvement in visual activity was achieved [7]. However, limited data are available and its routine use in treating childhood uveitis is not recommended.

2.3 Mycophenolate mofetil

The largest cohort of childhood noninfectious ocular diseases on mycophenolate mofetil (MMF) is a retrospective series of 17 children with uveitis of different etiologies. During a 3-year average duration of follow-up, among 17 children with chronic noninfectious uveitis on MMF, 88% achieved a steroid-sparing effect, 24% remained relapse-free during treatment, 76% experienced increased or maintained visual acuity and a reduction in the relapse rate was observed [8,9]. A dose of 600 mg/m^2 twice daily is used. MMF seems to have a lower rate of success with JIA–uveitis [10]. Taking together the above data, some concerns about the real advantage of choosing MMF as a second immunosuppressive agent in MTX-refractory JIA–uveitis may arise.

2.4 Cyclosporine A

Cyclosporine A (CyA) is effective in refractory noninfectious uveitis and is one of the few agents with evidence from randomized clinical trials to support its effectiveness [11]. Its recommended dose in children is 2.5 – 5 mg/kg/day [12]; however, pediatric data are limited. A retrospective study on 14 children with uveitis showed that it was able to control intraocular inflammation in all patients: as monotherapy in 4 patients, in combination with prednisolone in 7 and with prednisolone plus AZA or MTX in 3 [13]. For JIA-associated uveitis, MTX rather than CyA is thought to be an effective agent for stable remission [14]. A recent multicenter retrospective study on 82 children with JIA-associated uveitis demonstrated a limited efficacy of CyA monotherapy; however, when it was added to other systemic immunosuppressives, quiescence was achieved in 48.6% of patients [15]. These data suggest that CyA cannot be considered a typical first-line agent in the treatment of JIA-associated uveitis and that it may only be considered as adjunct therapy.

3. Biological modifiers (biologics)

3.1 Infliximab

Infliximab is a chimeric mouse–human monoclonal antibody against TNF-α. It has been found to be effective as a short-term immunosuppressive agent in noninfectious uveitis in childhood and effective in the treatment of both anterior and posterior uveitis [16].

A retrospective review of 21 children showed that patients with active uveitis who had previously failed other treatment responded to infliximab significantly better than to etanercept with regard to improvement of visual acuity, presence of glaucoma and other complication rates [17].

In another study, infliximab, mostly in combination with methotrexate, determined the resolution or marked reduction of anterior chamber inflammation at 3, 6, 9 and 12 months in 16 children with chronic uveitis (due to JIA or idiopathic uveitis) [18].

Because of its reported success, infliximab is being studied with increasing frequency in JIA-associated uveitis and in Behçet disease. Nonetheless, its efficacy seems to wane over the time, as recently demonstrated by our group [19]. In addition, in most published case series, children were treated with the combination of infliximab and methotrexate, so any clinical improvement must be attributed to the combination rather than to infliximab alone [18,20,21]. To date no randomized, placebo-controlled trials have been performed to assess the efficacy of infliximab in pediatric uveitis.

3.2 Etanercept

Etanercept, usually administered subcutaneously at 0.4 mg/kg per injection twice weekly, has been proven to be effective for rheumatoid arthritis, ankylosing spondylitis, JIA and psoriatic arthritis, but does not appear to be a very effective treatment for uveitis [22].

A small, double-blinded, randomized placebo-controlled trial (12 patients with JIA-associated uveitis) at the National Institutes of Health showed no difference between etanercept and placebo and, at 6-month follow-up, none of the patients showed significant reduction in ocular inflammation [23].

Tynjälä *et al.* studied 24 patients with chronic uveitis associated with refractory JIA treated with etanercept and 21 treated with infliximab [24]. The ocular inflammatory activity (number of anterior chamber cells) improved more frequently ($p = 0.047$) in patients taking infliximab than in those taking etanercept, and the number of uveitis flares/year was higher ($p = 0.015$) in patients taking etanercept than those taking infliximab. In addition, four patients developed uveitis for the first time while taking etanercept.

The high rates of recurrence and development of uveitis while on etanercept therapy suggest that it may not be the most effective option [25] and that it might be less efficacious than infliximab or adalimumab.

3.3 Adalimumab

Adalimumab is a humanized antibody, administered subcutaneously every other week at the dosage of 24 mg/m^2. Vazquez Cobain described 14 children with uveitis (9 JIA-associated and 5 idiopathic) treated with adalimumab for an average of 18.1 months: reduced inflammation was reported in 21/26 eyes (80.8%), stable situation in 4 eyes (15.4%) and worsening in 1 (3.8%) [26]. No adverse effects were reported.

Biester *et al.* also found that adalimumab was effective in 10/16 patients with JIA-related uveitis and mildly effective in 3 others, while 3 children did not show any response [27]. In the same study, adalimumab was effective in 16/18 children with idiopathic uveitis, mildly effective in 1 child and ineffective in 1 child. Additional immunosuppressive treatment was used in seven of the effectively treated children. In 15 children, treatment allowed the discontinuation of systemic corticosteroids, and in the remaining 3 patients, a reduction to low doses was achieved.

Tynjälä *et al.* recently treated 20 children with JIA and chronic uveitis with adalimumab [28]. Of that, 17 patients had polyarticular JIA and 19 had previously received another anti-TNF agent. Of the 20 patients, 7 showed an improved inflammatory uveitis activity, 1 patient worsened and 12 patients showed no change. The mean number of flares/year decreased from 1.9 to 1.4 during adalimumab treatment.

Recently, in a comparative cohort study of 33 children with chronic uveitis, we reported that adalimumab is more efficacious than infliximab in a 3-year period of treatment, with regard to time of the first flare, once remission has been achieved [29].

3.4 Daclizumab

Daclizumab is a humanized immunoglobulin G monoclonal antibody produced by recombinant DNA technology that binds specifically to CD25, the alpha chain of the human IL-2 receptor expressed on activated T lymphocytes. Recently, intravenous infusion of high-doses daclizumab determined a decrease in inflammation in four of six children with JIA–uveitis [30]. However, it has been withdrawn from European market.

3.5 Abatacept

Abatacept is a soluble fusion protein consisting of the extracellular domain of human cytotoxic T lymphocyte antigen 4 (CTLA4) linked to the modified Fc domain of human IgG1. It has been recently described as useful and well tolerated in the short term in the treatment of JIA-related uveitis [31]. We recently participated in a multicenter case series in which the efficacy of abatacept in treating children with JIA–uveitis refractory to previous anti-TNF therapy was studied [32]. Seven patients who had failed previous immunosuppressive therapy and two or more anti-TNF-α treatments were included in the study. All patients received 10 mg/kg intravenous infusions of abatacept given initially and at week 2, and additional doses were given once every

Table 1. More commonly used drugs for pediatric uveitis, with dosage and adverse events.

	Dosage	Adverse events
Corticosteroids		
Topical	Prednisolone acetate 1% (2 – 4 drops every 4 h)	Increase in intraocular pressure, cataract formation and increased infection rates
Systemic	1 – 2 mg/kg/day	Cushingoid face, hypertension, gastrointestinal discomfort, peptic ulceration, hyperglycemia, psychosis, insomnia, osteoporosis, electrolyte imbalance, growth retardation, cataract
Immunosuppressants		
Azathioprine	1 – 2 mg/kg/day	Bone marrow suppression, hepatotoxicity
Mycophenolate mofetil	600 mg/m^2/day	Hair loss and fatigue, leukopenia, nausea/ gastrointestinal discomfort/diarrhea
Cyclosporine A	3 – 5 mg/kg/day	Nephrotoxicity, hypertension, hepatotoxicity, anemia, hypercholesterolemia, gum hyperplasia, hypertrichosis, nausea, vomiting, tremor
Chlorambucil	0.1 – 0.2 mg/kg/day	Alopecia, teratogenicity, azoospermia and ovarian deficiency, severe gastrointestinal toxicity, liver enzyme elevation, risk for opportunistic infections and hematologic toxicity, hemorrhagic cystitis
Biological modifiers		
Infliximab	6 mg/kg as intravenous infusion at week 0, 2, 6 and then depending on clinical scores, every 4 – 8 weeks	Infections, infusion-associated reactions, reactivation of granulomatous infection, development of antinuclear antibodies, pulmonary embolism, congestive heart failure, lupus-like reaction and vitreous hemorrhage
Etanercept	Twice weekly as a subcutaneous injection at a dosage of 0.4 mg/kg	Gibert's pityriasis rosea, systemic lupus erythematosus, pneumonia, pulmonary tuberculosis, opportunistic infections
Adalimumab	24 mg/m^2 subcutaneously, every 2 weeks	Low frequency of injection-site reactions
Daclizumab	1 mg/kg every 4 weeks	Cutaneous lesions (rash or hives), elevation of liver enzymes, edema of lower extremities, upper respiratory tract infection and neuralgia of upper extremities
Abatacept	10 mg/kg i.v. at 0, 15 days, then monthly	Mild viral infections mainly involving the upper respiratory tract. Gastrointestinal disorders (abdominal pain, nausea, diarrhea). Ovarian cysts, headache

4 weeks. All patients responded rapidly to abatacept administration, and six out of seven maintained a clinical remission after a mean of 9.2 months of treatment. These observations suggest that abatacept might represent an alternative therapeutic approach for treating uveitis children refractory to anti-TNF therapy.

3.6 Rituximab

Rituximab (RTX) is a chimeric monoclonal antibody directed against the B-cell marker CD20. A recent retrospective multicenter study has evaluated its efficacy in the treatment of 10 patients with JIA and severe uveitis with vision-threatening complications [33]. In all cases uveitis was active and refractory to topical and systemic corticosteroids, as well as to immunosuppressives and at least one TNF inhibitor. After one RTX cycle, uveitis inactivity was achieved in seven patients, for a prolonged period of time (mean 7.5 months, range 6 – 9 months), while three patients were nonresponders. In three of the responders, uveitis recurred, and RTX retreatment led to remission. This therapy seems, therefore, promising, but its potential side effects limit its use to cases that have already failed conventional therapies and at least another biologic.

Table 1 summarizes the characteristics of the main drugs used. In conclusion, to date there are no generally approved treatment guidelines for childhood chronic uveitis derived from prospective controlled clinical trials. The currently available literature suggests a step-by-step drug therapy for childhood chronic noninfectious uveitis. The first common step is topical application of corticosteroids. In case of failure to achieve remission and/or in the presence of complications and prognostic factors for visual loss, systemic corticosteroid therapy in addition to topical use is usually required. When no quiescence is obtained, and/or in the case of reactivation and/or additional uveitis complications, the use of immunosuppressants is advocated as a second step, and in this case, MTX represents the first-line agent. In this case, the dosage of associated systemic steroids can be reduced and stopped once quiescence is obtained. If no quiescence is obtained, or in the case of frequent flares, a biological modifier can be used. If a concomitant dose of systemic steroid is administered, it can be reduced based on the reduction of clinical signs of uveitis and stopped once quiescence is obtained. New molecules such as abatacept have been employed for the treatment of chronic childhood uveitis, but more clinical

trials are needed to require their efficacy. Currently, they can be considered as a rescue therapy when previous approaches have failed. Controlled studies that have led to the approval of drugs for JIA are needed for uveitis in order to determine the safest and most effective therapy for children who do not respond to conventional therapy with local and systemic steroids. As the medical treatment of uveitis in children is quite challenging, combination of several immunomodulating treatments has been advocated. Multicenter prospective controlled trials are still urgently required to determine the role for immunomodulating agents in childhood uveitis.

Declaration of interest

The authors state no conflict of interest and have received no payment in preparation of this manuscript.

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