


REVIEW

Update on the Treatment of Uveitis in Patients with Juvenile Idiopathic Arthritis: A Review

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Received: August 18, 2017 / Published online: November 16, 2017
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ABSTRACT

Chronic uveitis is a common extra-articular manifestation of juvenile idiopathic arthritis. The classic clinical picture is one of chronic anterior uveitis, which usually remains asymptomatic until ocular complications arise. The risk of uveitis is increased in girls with an early onset of oligoarthritis and positive antinuclear antibodies. Even though the inflammation in patients with juvenile idiopathic arthritis is initially limited in the anterior part of the eye, chronic active inflammation may eventually cause significant damage to the posterior pole. Complications may include band keratopathy, cataract, secondary glaucoma, posterior synechiae, cystoid macular edema, and hypotony. The cooperation of ophthalmologists with rheumatologists may help define the best

treatment plan. The ophthalmic therapeutic regimen includes topical corticosteroids and mydriatics, while in severe cases immunosuppressive and biological agents are introduced. Surgical management of complications might be needed.

Keywords: Anti-TNF; Biological agents; DMARDS; Juvenile idiopathic arthritis; JIA; Methotrexate; Topical steroids; Uveitis

INTRODUCTION

Juvenile idiopathic arthritis (JIA) constitutes the most common extraocular disease associated with childhood uveitis. Despite all contemporary advances in treating childhood arthritis, JIA-associated uveitis remains a frequent cause of ocular morbidity. First described by Ohm [1], JIA-associated uveitis can manifest in various forms, depending on the location and severity of the ocular inflammation, as well as on the type of arthritis. About 30% of antinuclear antibody (ANA) positive patients with JIA can have episodes of uveitis [2]. A combination of genetic and environmental factors may be involved in the etiopathogenesis of JIA-associated uveitis. The inflammatory response of the iris and the ciliary body typically involves lymphocytes, plasma cells and CD4-positive cells [3]. Risk factors for the onset of the disease

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include sex, age and ANA-positive arthritis [4]. Depending on the severity of the disease and the effectiveness of treatment, ophthalmic complications such as cataract, macular edema, ocular hypertension and secondary glaucoma may appear. The treatment aims to reduce the inflammation and prevent or ameliorate complications, having as an ultimate goal to maintain visual function. The treatment starts with the instillation of topical corticosteroids and, if this proves ineffective, systemic anti-inflammatory therapy is used. Biological agents and anti-TNF therapy that target cytokine receptors and lymphocyte antigens may also be administered [5]. The current review is based on previously conducted studies and does not involve any new studies of human or animal subjects performed by any of the authors.

CLINICAL ENTITIES OF JUVENILE IDIOPATHIC ARTHRITIS

JIA is a heterogeneous group of chronic childhood arthritides of unknown etiology, appearing before the 16th year of age and lasting for at least 6 weeks [6]. The types of JIA are as follows: oligoarthritis, rheumatoid factor (RF)-negative (RF-) polyarthritis, RF-positive (RF+) polyarthritis, psoriatic arthritis, enthesitis, and undifferentiated arthritis not classified in any of the above categories with duration exceeding 6 weeks [7].

CLINICAL TYPES OF UVEITIS IN PATIENTS WITH JUVENILE IDIOPATHIC ARTHRITIS

Uveitis is characterized by inflammation of the iris and ciliary body. In most cases, both eyes are affected, either simultaneously or sequentially within a period of some months [8, 9]. JIA-associated uveitis has many types, the most frequent being the asymptomatic chronic anterior uveitis. The grading system proposed by the Standardization of Uveitis Nomenclature (SUN) Working Group [10], which is based on the anatomical location and the initiation form of uveitis, can be used for the evaluation and

monitoring of the disease. According to this scheme, the disease can be distinguished in: acute anterior uveitis, intermittent anterior uveitis, chronic anterior uveitis and anterior uveitis with hyalitis. Chronic anterior uveitis is associated with oligoarthritis and commonly occurs in ANA-positive girls with negative RF factor, as opposed to acute anterior uveitis that is usually associated with enthesitis and is more common in boys over the age of 10 years [11, 12].

TREATMENT OF UVEITIS

Prompt treatment aims to set the disease under control and prevent or minimize the possibility of vision-threatening complications. In most cases, arthritis and uveitis manifest at the same time, so the systemic treatment also addresses the ocular manifestations. Although it is generally agreed that the prognosis is best when no cells can be found in the anterior chamber of any eye [13], our clinical experience suggests that some patients may have an excellent course over many months (or even years) despite the presence of few anterior chamber cells. The treatment includes topical corticosteroids and mydriatics, while in severe cases immunosuppressive and biological agents may need to be introduced. Surgical treatment of complications may have to be undertaken.

Corticosteroids

Topical corticosteroids such as prednisolone 1% and dexamethasone 0.1% are first-line treatment [13–15]. The frequency of application is related to the severity of uveitis. However, it is of great importance to monitor the intraocular pressure of the young patients regularly during treatment with corticosteroids. Non-steroidal anti-inflammatory drugs (NSAIDs) may also be added to topical corticosteroids.

In non-responding cases, systemic corticosteroids can be considered in doses of 0.15 mg/kg body weight per day for up to 4 weeks. Periocular injections with corticosteroids (methylprednisolone 20–30 mg/kg/day for 1–3 days) may be used in some severe cases [15]. The

newly administered intravitreal dexamethasone implant (Ozurdex®; Allergan, Irvine, CA, USA) is another option that may be associated with reduced risk of secondary glaucoma [16, 17]. In a retrospective study, 16 patients with JIA-related uveitis were administered intravitreal dexamethasone using the Ozurdex® sustained-release implant [18]. The patients of this study had chronic macular edema (6.2%), recalcitrant anterior segment inflammation (43.7%), or a combination of both (50%). Mean visual acuity improved from 25.2 ± 15.9 ETDRS letters at baseline to 39.6 ± 11 ETDRS letters within a month after the first injection ($P < 0.001$), mean anterior chamber (AC) cells measure improved from 2.03 from baseline to 0.79 in the first month and 0.75 at 3 months after the injection, whereas central retinal thickness (CRT) decreased from 437.6 ± 96.2 μm at baseline to 342.4 ± 79.3 μm at 1 month after the injection ($P < 0.01$) in the 9 of 16 eyes that had evidence of macular edema. Moreover, 1 month following the second dose, four out of five eyes exhibited reduction of macular edema with CRT of 250.4 ± 13.7 μm ($P < 0.01$). Of the 16 patients, 12 received a second dose, whereas five eyes received a third dose of the implant within 7.0 ± 4.6 months after the second dose. After the first dose, only one eye required topical antiglaucoma medication with maximum intraocular pressure of 25 mmHg [18]. Although these results appear promising, it should be noted that the Ozurdex® implant is not approved nor generally used for the treatment of anterior uveitis.

In chronic uveitis, low doses of topical prednisolone or dexamethasone (e.g., two or three times daily) are recommended. The dose can be decreased to once a day during the remission periods. Therapy could last for months or even years.

In severe cases of uveitis associated with macular edema or ocular hypotony, intraocular or periocular injections of steroids can be added to the treatment regimen. Since dexamethasone is short-acting, in cases where prolonged intraocular drug levels are deemed necessary, an intravitreal injection of triamcinolone (2–4 mg) or a peribulbar injection of triamcinolone (20–40 mg) can be used, especially in the

presence of cystoid macular edema. Short-acting mydriatics and cycloplegics (e.g., tropicamide, cyclopentolate) are administered in milder cases once to three times daily in order to avoid or eliminate anterior and posterior synechiae. Long-acting cycloplegic agents (e.g., atropine) are recommended only in severe cases.

Antimetabolites and Alkylating Agents

Some drugs used for arthritis are also effective for the treatment of uveitis (e.g., NSAIDs, corticosteroids, methotrexate, cyclosporine A, azathioprine), while others are not (e.g., hydroxychloroquine, gold) [19].

Methotrexate is the most widely used drug at a dose of 15 mg/m^2 per week, up to a maximum dose of 20–25 mg in subcutaneous injections [20]. Oral administration is also possible but may prove less effective due to variability in gastrointestinal absorption. Methotrexate was shown to be effective in pediatric patients and does not seem to increase the risk of future malignancies [21–26]. Approximately 60–82% of patients with JIA and uveitis showed improvement after being treated with methotrexate [21, 22, 26, 27]. Methotrexate treatment is often introduced relatively soon after the diagnosis and therapy is continued for at least 3 years. It has been suggested, however, that the remission period of the disease should be at least 2 years or more before discontinuing the treatment in order to reduce the likelihood of recurrence [27]. According to a retrospective study that assessed the usefulness of methotrexate in preventing the onset of uveitis, patients receiving this agent had a significantly lower frequency of uveitis (11.5%) compared to those who did not receive it (46.7%) [28]. Low doses of methotrexate (7.5–25 mg per week) are also effective in the management of chronic uveitis [29, 30]. The additional use of disease-modifying anti-rheumatic drugs (DMARDs) in patients with JIA further reduces the risk of uveitis. Specifically, the use of methotrexate up to the first year of the disease, as well as the combination of methotrexate with an anti-tumor necrosis factor (anti-TNF)

agent offer the greatest protective effect against uveitis. These data were obtained from a study conducted on 3512 patients with JIA who were followed for an average of 3.6 years [31]. In 180 patients, uveitis manifested within the first year of the onset of arthritis, whereas in 251 patients it was after the first year of the onset. Treatment with DMARDs decreased the risk of uveitis as follows: methotrexate: hazard ratio (HR) 0.63, $P = 0.022$; anti-TNF: HR 0.56, $P < 0.001$; and a combination of methotrexate with anti-TNF: HR 0.10, $P < 0.001$ [31].

This category also includes azathioprine and cyclosporine A, which are used when treatment with methotrexate fails. Cyclosporine A, a calcineurin inhibitor of T cells, has limited effect as a monotherapy against JIA-related uveitis [22] and has therefore been used as a combination treatment with methotrexate [32]; its usual dosage is 3–5 mg/kg/day [33]. Chlorambucil (0.1 mg/kg/day) and cyclophosphamide (1 mg/m² every 3–6 weeks) can occasionally be used in more severe cases. Concern has been expressed, however, about side effects observed with cyclophosphamide and chlorambucil, and more rarely with mycophenolate [34], so that these agents should be used with caution in children. Sulfalazine, though proven to reduce the number of ankylosing spondylitis occurrences in adults, does not exhibit the same effectiveness in children [34].

Another drug used for chronic anterior uveitis is leflunomide. A study that included 15 children with JIA-associated uveitis compared the efficacy of leflunomide versus methotrexate [35]. The average period of methotrexate treatment was 51 months while the average period of treatment with leflunomide was 12 months. A combination of anti-TNF- α and methotrexate was administered to four children, and a combination of anti-TNF- α and leflunomide to six children. The study indicated that children treated with methotrexate had 0.0247 flares/month in contrast to those treated with leflunomide who had 0.0607 flares/month ($P = 0.008$) [35].

Current treatment algorithms for JIA-associated uveitis suggest that if the condition deteriorates or AC cell grade 0 cannot be achieved after 3–4 months on methotrexate, a biologic

agent will have to be considered [36]. In practice, treatment with biological agents may not be necessary in closely-monitored cases with trace inflammation and no other sequelae.

Biologic Agents

The FDA-approved biologic agents for patients with JIA are the anti-TNF agents adalimumab, etanercept and infliximab, and the T cell inhibitor abatacept.

Adalimumab (Humira[®]) is used in children 4 years of age or older. It is a humanized monoclonal antibody and its common dosage is 20–40 mg administered subcutaneously every 7–14 days. In two separate clinical studies by Vazquez-Cobian et al. [37] and Biester et al. [38], adalimumab treatment was proven to be effective in 80.8% and 88% of the children with JIA-associated uveitis, respectively. The effectiveness of adalimumab was also reported in a 6-month study with 39 patients who were either nonresponding or intolerant to standard immunosuppressive therapy [39]. Patients aged 13–17 years were treated with 40 mg adalimumab every week for 6 months, and patients 4–12 years of age received a dose of 24 mg/m² of body surface area. This resulted in a significant alleviation of the anterior chamber inflammation during the first and final examination, as well as to the reduction of macular thickness from 304.54 (125.03) μm at baseline to 230.87 (31.12) μm ($P < 0.014$) at the final visit [39].

Infliximab (Inflectra[®]) is a chimeric mouse–human monoclonal antibody and is administered at a dosage of 5–20 mg/kg through intravenous infusion for 2 weeks as a loading dose and then once every 4 weeks [40].

Abatacept (Orencia[®]) is a chimeric fusion protein that joins the extracellular domain of CTLA-4 to the Fc fragment of human IgG1 and inhibits the activation of T-cells by blocking the interaction of CD28 to CD80 or CD86 cells [5]. After a mean follow-up period of 21 months on abatacept treatment, 90% of the patients demonstrated an improvement and achieved responses according to the American College of Rheumatology criteria “Pedi 30” for improvement in children [41]. Abatacept has been

reported to improve chronic JIA-associated uveitis, whether used as a first-line treatment or after one or more anti-TNF agents. In a clinical study conducted on 35 patients, abatacept was used as first-line biological agent in one group of patients and as second-line agent after one or more anti-TNF agents were used in a second group of patients. The mean number of uveitis flares was reduced from 4.1 to 1.2 in the first group and from 3.7 to 1.2 in the second group [42].

Eternacept (Enbrel®), another anti-TNF agent, is considered to be less effective in treating JIA-related uveitis despite its effectiveness against the rest of the JIA complications [43, 44].

Rituximab is a chimeric mouse-human monoclonal antibody that binds to the CD20 surface protein of B cells triggering their apoptosis [5]. In a recent study with patients who could not be controlled using one or more biological agents including anti-TNF and abatacept, rituximab was used. In particular, they underwent a rituximab treatment of 1000 mg per infusion on the 1st and the 15th days and then every 6 months. Uveitis control was ascertained in all patients except two who had to discontinue their treatment due to its ineffectiveness against arthritis [45].

Tocilizumab (Actemra®), a monoclonal humanized antibody which recognizes the IL-6 receptor, also has an important effect on treating uveitis and its complications [5]. Its effectiveness was demonstrated in a recent study in which uveitis and its complications, such as optic nerve edema, were set under control following tocilizumab treatment for an average of 5.7 months [46]. Another study with patients who had been previously administered corticosteroids, immunosuppressive and biologic agents including adalimumab ($n = 24$), etanercept ($n = 8$), infliximab ($n = 7$), abatacept ($n = 6$), rituximab ($n = 2$), anakinra ($n = 1$), and golimumab ($n = 1$), further supported the effectiveness of tocilizumab. Patients in most cases received 8 mg/kg tocilizumab every 4 weeks. Seventy-nine percent of the patients demonstrated improvement in the number of AC cells after 6 weeks of treatment, and 88% of the patients

after 1 year. Patients with cystoid macular edema also showed a significant improvement; the measurement of the central retinal thickness demonstrated a reduction of 401.7 ± 86.8 to $259.1 \pm 39.5 \mu\text{m}$ after 6 months of treatment with tocilizumab [47].

TREATMENT OF UVEITIS COMPLICATIONS

With regard to the surgical treatment of cataracts, there exists a long-lasting controversy regarding the placement of an intraocular lens in patients with JIA because of the high risk of secondary membrane formation and the development of ocular hypotony. Better prognosis after cataract removal and intraocular lens placement is ensured by rigorous control of uveitis for 3 months preoperatively and by appropriate immunotherapy. Specifically, the eyes to be operated should show no signs of inflammation 3 months prior to surgery. An aggressive anti-inflammatory treatment is vital both before and after surgery. Systemic treatment with corticosteroids (0.5–1 mg/kg/day) a few days prior to surgery, and up to 2–3 weeks postoperatively, is required [48, 49].

For treating secondary glaucoma, β -blockers and carbonic anhydrase inhibitors are used. However, the results are often poor and the implantation of a glaucoma drainage device may become necessary [50].

For cystoid macular edema, the choice of treatment is the administration of topical NSAIDs. If there is no response, then systematic corticosteroids are also added. The next step includes a local corticosteroid injection. In the case of band keratopathy, chelating agents or excimer laser are used with good results, although recurrences are frequent.

CONCLUSION

In paediatric patients, JIA is the underlying systemic condition most often associated with uveitis. Despite recent advances in the treatment of childhood arthritis and its

extra-articular manifestations, JIA-associated uveitis can occasionally cause significant ocular morbidity. The treatment stepladder of JIA-associated uveitis involves topical steroids and NSAIDs as first-line treatment. In cases with suboptimal response, peribulbar, subconjunctival, intravitreal or systemic steroids may need to be administered. Methotrexate, azathioprine and cyclosporine A can be useful in recalcitrant cases. However, if these drugs prove ineffective in controlling ocular inflammation, biologics such as an anti-TNF agent (adalimumab, etanercept or infliximab) or the T cell inhibitor abatacept needs to be administered. Close cooperation between ophthalmologists and rheumatologists is necessary in order to minimize the risk of significant handicap in these children.

ACKNOWLEDGEMENTS

No funding or sponsorship was received for the publication of this article. All named authors meet the International Committee of Medical Journal Editors (ICMJE) criteria for authorship for this manuscript, take responsibility for the integrity of the work as a whole, and have given final approval to the version to be published. No assistance with medical writing or editing was received for this paper.

Disclosures. Ioannis Asproudis, Alexandra Tantou and Nikolaos Kozeis have nothing to disclose. Andreas Katsanos has received honorariums from Allergan, Novartis and Vianex and had congress and travel expenses covered by Vianex and Laboratoires Thea. Anastasios GP Konstas has received honorariums from (and is a consultant for) Alcon, Allergan, Mundipharma, and Santen and had congress and travel expenses covered by MSD/Vianex.

Compliance with Ethics Guidelines. This article is based on previously conducted studies, and does not involve any new studies of human or animal subjects performed by any of the authors.

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