Evidence-Based Treatment for Uveitis

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ABSTRACT: Uveitis is an inflammatory disorder of the uveal tract of the eye that can affect both adults and children. Non-infectious uveitis can be an expression of a systemic autoimmune condition, or it can be idiopathic. It is a serious disease, associated with possible severe complications leading to visual impairment and blindness. For this reason, a prompt diagnosis and assessment of an appropriate treatment, with the collaboration of specialists such as ophthalmologists and rheumatologists, are extremely important. Many treatment options may be associated to side effects; therefore, clinicians should follow a stepladder approach starting with the least aggressive treatments to induce remission of inflammation. In this review, we reported the current evidence-based treatments for non-infectious uveitis in pediatric and adult patients with particular attention to the biologic response modifier treatment options. Important multicenter studies have demonstrated the efficacy of adalimumab, both in adults (VISUAL I, VISUAL II, VISUAL III) and in children (SYCAMORE, ADJUVITE), while for other agents data are still scarce.

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Uveitis is an inflammatory disorder of the uveal tract, which is the middle layer of the eye, highly vascularized and pigmented. The uvea is composed of the iris, ciliary body, and choroid. The inflammation may involve only one anatomical part of the uvea and referred to as anterior, intermediate, or posterior uveitis, depending on the primary site of inflammation. The term panuveitis is used when inflammation occurs in all of the anatomical compartments of the eye. Uveitis can also be classified according to its presentation and evolution over time: acute forms have sudden onset and usually are symptomatic, whereas chronic forms tend to be asymptomatic for a long time and are characterized by relapse after discontinuation of therapy [1]. Uveitis can be primary or secondary to other conditions. While infectious uveitis is more common in developing countries, accounting for 30–50% of all cases, in Western countries an autoimmune etiology is present in the vast majority of cases. Non-infectious uveitis is most frequently associated with HLA–B27-positive seronegative spondyloarthropathies, sarcoidosis, Vogt-Koyanagi-Harada disease, sympathetic ophthalmia, and Behçet disease. The prevalence of non-infectious uveitis in adults is estimated to be 121/100,000 (98/100,000 anterior, 1/100,000 intermediate, 10/100,000 posterior, and 12/100,000 panuveitis) [4]. In children it is more rare than in adults, with an incidence estimated at 5–10 per 100,000/year and a prevalence estimated at 30 per 100,000. Usually it is associated with a systemic disease, especially juvenile idiopathic arthritis (JIA), but it can also be idiopathic [2]. Uveitis still represents a challenge for clinicians as, if not promptly diagnosed and treated, chronic eye inflammation can lead to cataract, glaucoma, keratopathy, macular edema, and permanent vision loss [3]. It is estimated to be responsible for 10–20% of preventable cases of blindness in Western countries. Prognosis in children compared to adults may be worse, as childhood uveitis is associated with tendency for being chronic and a higher risk of complications, with severe visual impairment in up to one-third of children. Moreover, a whole reduction in health-related quality of life for patients with uveitis has been noted, not necessarily correlated to the presence of severe inflammation or complications [4].

TREATMENT FOR UVEITIS

Treatment for uveitis is based on the degree of inflammation and the presence of risk factors and complications. It should be started as soon as diagnosis is made, and may follow a stepladder approach, which starts by using the least aggressive treatments to more aggressive treatments and continues to induce remission of inflammation.

Corticosteroids

First-line treatment for non-infectious uveitis is represented by corticosteroid monotherapy. Corticosteroids can be administered topically (preferably prednisolone 1% or dexamethasone 0.1%), especially in anterior uveitis as they are able to penetrate well only into the anterior segment of the eye [5]. Usually, other than corticosteroid topical therapy, mydriatic and cycloplegic agents are used to prevent the formation of posterior synechiae and for relieving photophobia and pain secondary to ciliary spasm. Systemic steroids are used when there is a severe ocular inflammation. Oral prednisone is the most commonly used drug, at an initial dose of 1–2 mg/kg, to be tapered based on clinical response. When the inflammation is severe, with involvement of all of the uveal layers and eventually the optic nerve, intravenous corticosteroids are needed to achieve ocular remission. Usually, methylprednisolone is the drug of choice, at 30 mg/kg (maximum dosage 1 gram) intravenously for three consecutive days or every

other day three times a week, followed by oral corticosteroids [6]. It is now well-known that long-term corticosteroid use for uveitis is associated with many side effects, including both ocular and systemic consequences, so it is very important to taper and discontinue the treatment as soon as possible. Ocular morbidity may be induced by topical and systemic corticosteroid administration and include cataract, glaucoma, and visual impairment [7]. Particular attention should be addressed to the pediatric population, as corticosteroids may also induce growth and pubertal development delay. In case of no response or worsening of the inflammation despite high dose corticosteroid therapy, other treatment options should be considered.

Other immunosuppressive agents

Immunosuppressive agents represent the therapeutic option when quiescence is not obtained with corticosteroids, or in case of reactivation or new complications onset, and are used as corticosteroid-sparing drugs to reduce inflammation and control the disease [8].

Methotrexate: In pediatric populations, in case of refractory uveitis, the treatment of choice is represented by methotrexate [6]. It is administered subcutaneously or orally once a week at a dosage of 10–15 mg/m² (maximum 25 mg/m²). In a review summarizing the best available evidence about methotrexate use in childhood refractory uveitis, a mean overall improvement of ocular inflammation in about 3/4 of subjects was estimated (95% confidence interval [95%CI] 0.66–0.81) [9]. In adult populations, there are limited data on methotrexate when compared to other immunosuppressive agents in non-infectious uveitis. In a multicenter randomized trial comprised of 80 patients aged 16 years or older, which compared methotrexate and mycophenolate mofetil, greater treatment success, although not significant, was recorded with methotrexate: 69% vs. 47% patients had controlled inflammation at 6 months. Methotrexate is usually well tolerated. Patients should be evaluated every 3 to 4 months with blood cell count and liver function tests. The most common side effect is represented by gastrointestinal discomfort and especially nausea, usually ameliorating with folic acid administration 24 hours after methotrexate assumption [10].

Uveitis is a sight-threatening disease that can lead to visual impairment and blindness. Prompt diagnosis and treatment are very important in addition to the collaboration of specialists such as ophthalmologists and rheumatologists

Mycophenolate mofetil and azathioprine: Azathioprine and mycophenolate mofetil are antimetabolites, both inhibitors of purine synthesis, which result in blocking the maturation of B- and T-lymphocytes. Azathioprine is able to control ocular inflammation in adults, as shown in a large inception-cohort study where 59% of patients maintained inflammatory remission after a year of follow-up, with a corticosteroid-sparing success in most cases [11] is administered orally at an initial dose of 1 mg/kg/day (maximum 100 mg/day), but dosage can be increased to 3 mg/kg/day (maximum 200–250 mg/day).

Mycophenolate mofetil is also administered orally, at the dose of 600 mg/m² twice daily. As demonstrated by the above mentioned trial, mycophenolate mofetil can control ocular inflammation in non-infectious uveitis, but seems to have less efficacy compared to methotrexate [12].

Both medications may increase the risk for bone marrow suppression, but the most common side effect is represented by gastrointestinal problems. Malignancies are extremely rare and have been reported only in long-term treatment [8]. Limited data are present for the use of these medications in childhood uveitis. In 2007, Schatz and colleagues [13] reported a 5-year follow-up of 40 children with chronic non-infectious uveitis treated with azathioprine and mycophenolate mofetil. They noted that when azathioprine and mycophenolate mofetil were associated to corticosteroids, 61% and 94% improvement respectively, was achieved [13]. Nevertheless, mycophenolate mofetil seems to have a lower success in juvenile idiopathic arthritis-related uveitis. In a 6-year-retrospective case series, mycophenolate mofetil achieved control of inflammation only in 36% of patients with JIA-related uveitis [14].

TNF-α INHIBITORS

The next medications in the stepladder approach to non-infectious uveitis are represented by biologic response modifiers. These medications are chosen, by adding or switching, when other immunosuppressive agents are not effective in obtaining quiescence, in case of too frequent flares (more than 3 flares/year) or if they are not well tolerated. The most widely used for treating uveitis are represented by the tumor necrosis factor alpha inhibitors (anti-TNF-α). TNF-α is an important cytokine involved in the ocular inflammation and tissue damage. Anti-TNF-α are also recommended for children [15].

Adalimumab: Adalimumab is a fully human anti-TNF-α monoclonal antibody, approved for the treatment of several immune-mediated inflammatory diseases, including non-infectious intermediate, posterior, and panuveitis [22]. Adalimumab efficacy and safety in non-infectious intermediate, posterior, and panuveitis was demonstrated. In a phase 3. a multicenter, randomized, placebo-controlled trial involving adult patients with active non-infectious uveitis, the efficacy of adalimumab as glucocorticoid sparing agent for the control of uveitis was evaluated (VISUAL I). Patients were randomly assigned in 1:1 ratio to receive adalimumab or matched placebo. All patients received oral prednisone for at least 2 weeks, tapered down in 15 weeks. The median time to treatment failure was 24 weeks in the adalimumab group, with consistent lower risk than the placebo

group where it was 13 weeks. Adverse events were reported more frequently among patients who received adalimumab compared to those who received placebo (971.7 per 100 person-years in the placebo group and 1052.4 per 100 person-years in the adalimumab group). They were especially injection-site and allergic reactions. Two cancers (carcinoid tumor of the gastrointestinal tract and glioblastoma multiforme), one event of active tuberculosis, one of latent tuberculosis, a lupus like reaction, and one case of demyelinating disorder were reported in the adalimumab group. Severe infections occurred in the two groups with a similar rate. The study demonstrated that adalimumab had a good control in multiple aspects of uveitic inflammation without glucocorticoid support, including posterior segment inflammation, a lower risk of uveitic flare and visual impairment, and a longer time to a flare than placebo [16]. In a subsequent multicenter double-masked, randomized, placebo-controlled phase 3 trial (VISUAL II), the efficacy of adalimumab was assessed in inactive non-infectious intermediate, posterior or panuveitis controlled by corticosteroids.

Adult patients from 21 countries with inactive corticosteroid-dependent uveitis were randomly assigned to receive adalimumab or placebo. Nguyen et al. [17] found that adalimumab was superior to placebo, since the percentage of patients reporting treatment failure was lower in the adalimumab group (39% vs. 55%), with longer time to failure. With regard to adverse and severe adverse events, in the adalimumab group one squamous-cell carcinoma and three events of latent tuberculosis occurred, while in the placebo group one event of latent tuberculosis. The study demonstrated the efficacy of adalimumab in preventing recurrence of ocular inflammation upon corticosteroid withdrawal, and, at the same time, in reducing side-effects of long-term corticosteroid therapy.

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Data were collected from the two previous cited studies and analyzed in another study called VISUAL III, with 78 weeks of follow-up. VISUAL III is an open-label multicenter extension study evaluating the safety and efficacy of adalimumab in patients with non-infectious uveitis who successfully completed the VISUAL I or VISUAL II trials without treatment failure (inactive uveitis in VISUAL III) or who experienced treatment failure in the parent trials (active uveitis in VISUAL III). All patients received open-label subcutaneous adalimumab 40 mg every other week for the duration of the study. Patients were allowed to initiate, continue, escalate, or taper concomitant topical or oral corticosteroid therapy, and/or other immunosuppressive therapy. Of the patients who entered VISUAL III defined as having active uveitis, 60% achieved quiescence by week 12 and remained stable at week 78. 66% of these patients were corticosteroid free at the end of the follow-up period, and only 7% were receiving > 7.5 mg/day corticosteroids. The majority of patients who entered the study as having inactive uveitis, met criteria for quiescence both at baseline and at week 78, remaining stable on no or low dose of systemic corticosteroids. These results confirmed that adalimumab is very effective in reducing risk of recurrence or worsening of ocular inflammation in patients with active and inactive intermediate, posterior or panuveitis, with a concomitant substantial decrease in systemic corticosteroid use [18].

The efficacy and safety of adalimumab was also demonstrated in children with JIA-related uveitis in two recent multicenter, double blind, randomized, placebo-controlled trials (SYCAMORE [19] and ADJUVITE [20]). Juvenile idiopathic arthritis is the most common rheumatic disease in children and approximately 15% of these patients develop uveitis within 7 years after the onset of arthritis. In the SYCAMORE trial, patients aged 2 to 18 years with active JIA-associated uveitis were randomly assigned to receive placebo or adalimumab, and then followed for 2 years. All patients were under stable methotrexate treatment, with constant method of administration for at least 12 weeks. Treatment failure occurred in 27% of patients receiving adalimumab and methotrexate, and in 60% of patients receiving methotrexate alone (relative risk 0.40; 95%CI 0.22–0.73; $P = 0.002$). Time to treatment failure was also longer in the adalimumab group. Moreover, in the adalimumab group a greater reduction in corticosteroid topical use and discontinuation, compared to the placebo group, was shown. However, more adverse events in the adalimumab group occurred (10.07 vs. 6.51 events per patient-year), including minor infections, nausea and vomiting, diarrhea, headache, and pyrexia. The follow-up period during the course of the trial was too short to detect more severe events as cancer and demyelinating diseases. These data confirmed that adalimumab can reduce inflammation and prevent uveitis worsening in children with JIA-associated uveitis. An overall good safety profile was expected [19].

In the ADJUVITE trial, adalimumab was also found to be superior to placebo in improving ocular inflammation in patients with JIA-associated chronic uveitis and inadequate response to corticosteroids and methotrexate.

Patients randomized for adalimumab and methotrexate experienced a reduction of ocular inflammation in 56% of cases after 2 months, compared to 20% in the methotrexate group ($P = 0.038$) defined as a 30% improvement of anterior chamber inflammation measured by laser flare photometry. The early improvement on ocular examination was maintained and even ameliorated after 12 months in most cases [20].

OTHER TNF-α INHIBITORS

- *Infliximab* is a chimeric mouse-human monoclonal antibody against TNF-α. Infliximab is effective in treating anterior and posterior uveitis, in both children and adults [21,22].

- *Posterior uveitis* is associated with Behçet's disease. Often it is refractory to other treatments and also can respond to infliximab [23]. However, infliximab seems to lose its efficacy over time [24,25]. It is administered intravenously at the dose of 5 to 10 mg/kg, initially every 2 weeks and then extended to every 4 weeks if inflammation is well controlled. Among its side effects, of note is the risk of reactivation of latent tuberculosis infection.
- *Etanercept* is used with success for juvenile idiopathic arthritis, rheumatoid arthritis and psoriatic arthritis, but is not suggested as a treatment option for uveitis. A systematic review about the effectiveness of anti-TNF-α treatments in childhood uveitis, showed a major improvement of ocular inflammation with adalimumab and infliximab compared to etanercept, with a proportion of responding subjects that was respectively 87% (95%CI 75–98%), 72% (95%CI 64–79%), and 33% (95%CI 19–47%) [26]. There are also suggestions that etanercept may favor the development of endogenous uveitis [27].
- *Golimumab* is indicated for adult with rheumatoid arthritis. There are at the moment only few reports regarding its use in patients with uveitis refractory to other treatments, especially other anti-TNFα [28].
- *Certolizumab* is administered subcutaneously 400 mg every 4 weeks. There are only a few reports regarding its use or efficacy in treating ocular inflammatory disease [29].

The use of biologics has greatly improved the outcome of non-infectious uveitis both in pediatric patients and adults. Randomized controlled trials have confirmed the efficacy of adalimumab, while for other agents data are still scarce

OTHER TREATMENTS

Besides anti-TNF-α, other biologic modifier treatments have been tried both in adult and in children with uveitis refractory to the previously mentioned and more commonly used immunosuppressive agents [30].

- *Abatacept* is a fusion protein consisting of the extracellular domain of human cytotoxic T-lymphocyte antigen-4 (CTLA-4) linked to the Fc domain of human IgG. It binds to CD80/CD86 on antigen-presenting cells thus increasing the threshold for T-cell activation. It is approved for the treatment of rheumatoid arthritis and JIA, while its use for uveitis is still off-label. It is administered intravenously at the dose of 10 mg/kg (maximum 1000 mg) at week 0, 2, 4 and then every 4 weeks. Despite limited data about its efficacy, abatacept seems to be a valid alternative treatment, especially in patients with JIA-related uveitis resistant to anti-TNF-α agents, with a recorded reduction of ocular inflammation and number of flares, and at the same time a corticosteroid-sparing effect. No new ocular complications onset, nor worsening of the existing ones, have been reported [31,32]. Moreover, a comparable efficacy of abatacept when used as a first-line biological agent or as a second-line treatment after one or more anti-TNF-α agents was shown in patients with severe JIA-related uveitis [33].
- *Rituximab* is a monoclonal antibody directed against CD20. Currently, it is approved for the treatment of lymphoma and chronic lymphocytic leukemia, but has also shown its efficacy in autoimmune diseases, including rheumatoid arthritis and systemic lupus erythematosus. Furthermore, it has been used for the treatment of severe forms of uveitis, not responding or tolerating other immunosuppressive treatments [34]. In a retrospective multicenter study including 10 patients with active uveitis refractory to topical and systemic corticosteroids, immunosuppressives, and at least one of the TNF-α inhibitors, rituximab was able to induce remission in 7 patients [35]. In a randomized single-blind study, 20 patients with Behçet disease and severe ocular involvement were randomly assigned to receive either rituximab or a cytotoxic combination therapy (cyclophosphamide, azathioprine, and prednisolone). At 6 months, treatment with rituximab was able to control and improve ocular inflammation compared to the combined cytotoxic treatment [36].
- *Tocilizumab* is a recombinant human monoclonal antibody directed against IL-6 receptor, and inhibits the downstream signaling of the pro-inflammatory cytokine IL-6. It is approved for the treatment of rheumatoid arthritis, polyarticular juvenile idiopathic arthritis and systemic juvenile idiopathic arthritis. It may also represent an emerging treatment for severe uveitis, especially if complicated by cystoid macular edema. In a recent multicenter study of 25 patients with JIA-related uveitis refractory to conventional immunosuppressive drugs and anti-TNF-α agents, a rapid and maintained improvement of ocular inflammation was recorded, and at the same time a significant reduction of oral corticosteroid dosage. After a median follow-up of 12 months a complete remission of uveitis was seen in 88% of patients, including the ones with cystoid macular edema. A rapid and sustained response to tocilizumab therapy, was similarly achieved in 7 adult patients with refractory uveitis-related macular edema [37].
- *Anti-IL-1 (anakinra, canakinumab)* is an important cytokine implicated in autoinflammatory diseases. Anti-IL-1 treatments have been tried rarely on severe forms resistant to standard therapies. Results have been published as small case series with variable success. In a retrospective observational study, 19 patients with Behçet disease-related uveitis were treated with anti-IL-1. Of these, 13 received anakinra and 6 received canakinumab. At 6 months, 23% of patients on anakinra and 17% on canakinumab had discontinued treatment for loss of efficacy. No adverse events were detected

[38]. Two pediatric patients with JIA-related uveitis refractory to previous treatments, showed a good response to canakinumab with stable remission after 12 months [39]. Anti-IL-1 has also been used with success in monogenic autoinflammatory disorders-associated uveitis, such as Blau syndrome [40].

CONCLUSIONS

The use of biologics has greatly improved the outcome of non-infectious uveitis. Randomized-controlled trials have confirmed the efficacy of adalimumab, while for other agents mainly case series have been published. While evidence-based data are scanty, new trials are planned or ongoing, and in the future other drugs are likely to be approved.

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