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An Update on Treatment of Pediatric Chronic Non-infectious Uveitis

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Opinion statement

There are no standardized treatment protocols for pediatric non-infectious uveitis. Topical corticosteroids are the typical first-line agent, although systemic corticosteroids are used in intermediate, posterior, and panuveitic uveitis. Corticosteroids are not considered to be long-term therapy due to potential ocular and systemic side effects. In children with severe and/or refractory uveitis, timely management with higher dose disease-modifying anti-rheumatic drugs (DMARDs) and biologic agents is important. Increased doses earlier in the disease course may lead to improved disease control and better visual outcomes. In general, methotrexate is the usual first-line steroid-sparing agent and given as a subcutaneous weekly injection at >0.5 mg/kg/dose or 10–15 mg/m^2 due to better bioavailability. Other DMARDs, for instance mycophenolate, azathioprine, and cyclosporine, are less common treatments for pediatric uveitis. Anti-tumor necrosis factor-alpha agents, primarily infliximab and adalimumab, are used as second-line agents in children refractory to methotrexate or as first-line treatment in those with severe complicated disease at presentation. Infliximab may be given at a minimum of 7.5 mg/kg/dose every 4 weeks after loading doses, and up to 20 mg/kg/dose. Adalimumab may be given up to 20 or 40 mg weekly. In children who fail anti-tumor necrosis factor-alpha agents, develop anti-tumor necrosis factor-alpha antibodies, experience adverse effects, or have difficulty with tolerance, there is less data available regarding subsequent treatment. Promising results have been noted with tocilizumab infusions every 2–4 weeks, abatacept monthly infusions, and rituximab.

Introduction

Uveitis is a broad term for inflammation involving the eye. It is classified according to the location of the inflammatory process, either anterior, intermediate, posterior, or panuveitis [1, 2]. Uveitis can be secondary to an infectious etiology, such as tuberculosis, *Toxocara canis*, toxoplasmosis, herpes virus, lyme, and syphilis [3]. Ocular inflammation can also be associated with an underlying systemic condition, including juvenile idiopathic arthritis (JIA), sarcoidosis, tubulointerstitial nephritis and uveitis (TINU), inflammatory bowel disease, Vogt-Koyanagi-Harada (VKH), and Behcet's disease [4]. Frequently, however, uveitis is not associated with an underlying condition and is termed "idiopathic" [4].

In pediatric rheumatology, JIA is the most commonly associated disease, and uveitis is typically anterior and bilateral. Pediatric uveitis accounts for 5–10% of patients with uveitis [5]. Thorne et al. reported a prevalence of pediatric uveitis of 31 per 100,000 patients. Of 291 pediatric cases in this study, nearly 95% were non-infectious uveitis, and JIA was associated with 26.2% of these cases [6•].

Prolonged intraocular inflammation can lead to significant visual impairment and blindness. Uveitis is estimated to cause 30,000 new cases of legal blindness each year [6•]. The problem is compounded in pediatric patients where there is often a delay in presentation and diagnosis. Furthermore, children commonly experience a chronic course with frequent remission and relapse that can lead to significant ocular morbidity [7]. Ocular complications such as cataract, glaucoma, posterior synechiae, and band keratopathy occur in up to 50% of children, vision loss (visual acuity 20/50 or worse) occurs in up to 50% of children, and legal blindness (visual acuity 20/200 or worse) occurs in up to 25% [8–11]. Early diagnosis and treatment can mitigate these complications and potentially reduce the burden of visual impairment and blindness.

Evidence suggests an environmental trigger in a genetically susceptible individual leads to a release of pro-inflammatory cytokines, including tumor necrosis factor-alpha (TNF-alpha) and interleukins (IL) [12–15]. With this understanding, an immunomodulatory therapy approach is a useful strategy for the management of non-infectious uveitis. However, there is a lack of randomized controlled studies in the treatment of pediatric uveitis. Most evidence is based on expert opinion or clinical experience and management remains non-standardized [16••]. As a result, multi-disciplinary panels have proposed treatment algorithms in an effort to standardize care [17–19]. Despite the lack of level one and two evidence, immunomodulatory therapy remains the most effective approach to control ocular inflammation, reduce exposure to systemic corticosteroids, and decrease the incidence of vision loss and blindness.

The focus of this review is to report the current treatment options for pediatric non-infectious uveitis. We will focus on medications described in pediatric uveitis patients enrolled in the Childhood Arthritis and Rheumatology Research Alliance (CARRAnet) Registry, a large registry of North American pediatric rheumatology patients to examine practice patterns of pediatric rheumatologists [16••]. Furthermore, we suggest a stepwise approach to the use of immunomodulatory therapy, in particular JIA, which is the most common rheumatologic condition in childhood (Fig. 1).
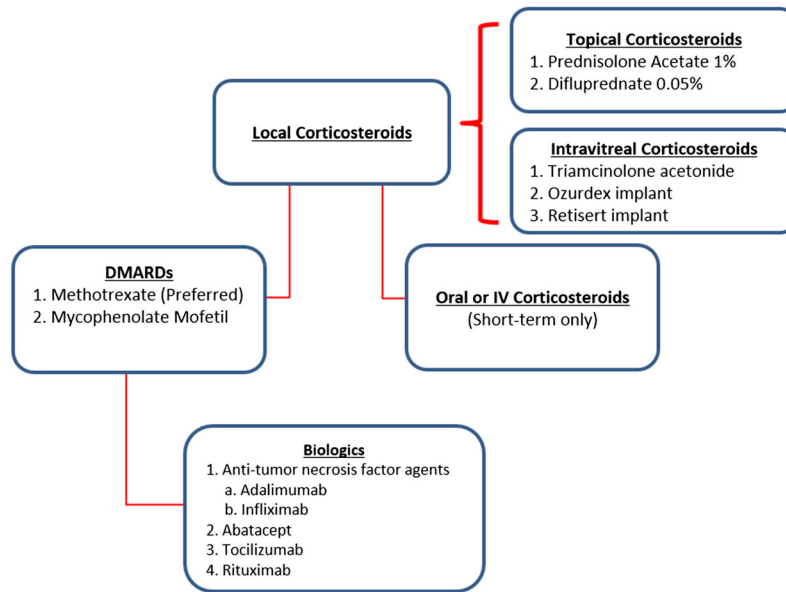
Treatment

Pharmacologic treatment

The goal for treatment of pediatric non-infectious uveitis is threefold: (1) resolve intraocular inflammation, (2) achieve remission and prevent recurrences, and (3) preserve vision and prevent ocular complications [8]. Corticosteroids (CS) are the first-line treatment for non-infectious uveitis and are effective for acute inflammation [2]. The mechanism of action involves modulating gene expression of pro-inflammatory cytokines. CS can achieve this effect either through local or systemic administration and the mode of administration typically depends on location of uveitis [15]. Local treatments include topical drops or periocular and intraocular injections or implants.

Treatment of Pediatric Non-Infectious Uveitis

Local Corticosteroids

Topical Corticosteroids
1. Prednisolone Acetate 1%
2. Difluprednate 0.05%

Intravitreal Corticosteroids
1. Triamcinolone acetonide
2. Ozurdex implant
3. Retisert implant

DMARDs
1. Methotrexate (Preferred)
2. Mycophenolate Mofetil

Oral or IV Corticosteroids
(Short-term only)

Biologics
1. Anti-tumor necrosis factor agents
   a. Adalimumab
   b. Infliximab
2. Abatacept
3. Tocilizumab
4. Rituximab

Fig. 1. Stepwise approach to the treatment of pediatric non-infectious uveitis. Topical corticosteroids are the typical first-line agent in anterior uveitis. Systemic corticosteroids may be used for rapid control of inflammation in intermediate, posterior, or panuveitic uveitis. In children with severe and/or refractory uveitis, DMARDs are the next step in management with methotrexate being the preferred agent. Anti-TNF agents are used as second-line agents in children refractory to methotrexate or as a first-line treatment in children with severe and complicated disease at presentation. In patients who fail anti-TNF agents, there is no agreement on subsequent therapy. Alternative biologics include abatacept, tocilizumab, and rituximab. Many patients require a combination of medications or require short-term systemic corticosteroids for intermittent flares.

Local corticosteroids

Topical corticosteroids are first-line treatment in anterior segment inflammation and were used in 90% of patients with idiopathic uveitis enrolled in the CARRAnet Registry [16••]. The most commonly used topical CS is prednisolone acetate 1%, which is administered at a frequency corresponding to the severity of inflammation. Topical difluprednate 0.05% (Durezol) is a more potent medication with superior intraocular penetration and requires less frequent dosing [20]. However, long-term use of topical CS, in particular Durezol, is associated with corticosteroid-induced ocular hypertension and cataracts [21, 22]. Evidence has shown that the need for >2 drops a day leads to increased ocular complications.

Periocular or intraocular injections of triamcinolone acetonide (TA) have been effective at treating intermediate, posterior, and panuveitis by providing a high concentration of drug at the site of inflammation [20]. While systemic side effects are minimized, local TA injections in the pediatric population often require general anesthesia, which poses its own risk to the patient. Moreover, the relatively short duration of action necessitates frequent repeat injections [23]. Longer duration intraocular therapy includes Dexamethasone implant (Ozurdex) and 0.59-mg Fluocinolone acetonide implant (Retisert) [23–28]. Ozurdex implantation lasts 6 months whereas Retisert implantation lasts for

nearly 3 years, which reduces the overall risk associated with anesthesia compared to repeat TA injections [24, 26]. An emerging option is a 0.19-mg Fluocinolone acetonide injectable (Illuvien) that was FDA approved for the management of diabetic retinopathy. Reddy et al. reported good outcomes on the off-label use of Illuvien in the management of uveitis and macular edema [29]. While more studies are needed, especially in the pediatric population, the Illuvien implant is a promising medication that lasts for nearly 3 years and is significantly less expensive than Retisert. Suprachoroidal TA administration is a novel route that is currently under investigation as another local treatment option for non-infectious uveitis [30]. As with all forms of local therapy, in particular periocular and intraocular CS, there is a high risk for cataract formation, elevated intraocular pressure, and worsening of pre-existing glaucoma [30–33].

Systemic corticosteroids

Systemic steroids are excellent for acute control of inflammation that is refractory to local therapy, especially in children with intermediate, posterior, or panuveitis. Approximately 94% of children with idiopathic uveitis in the CARRA registry were treated with systemic steroids during the disease course [16••]. Oral prednisone can be prescribed at a starting dose of 1–2 mg/kg body weight and tapered according to the inflammatory response. Intravenous (IV) corticosteroids are occasionally used in cases of severe ocular inflammation, including Behcet's disease, serpiginous choroiditis, or uveitis with optic nerve involvement [2]. However, long-term use of systemic steroids has potential adverse effects in the pediatric patient that include growth retardation, hyperglycemia, weight gain, hypertension, osteoporosis, peptic ulcers, cataracts, and glaucoma [23, 24].

Topical and systemic corticosteroids are not considered long-term treatment of chronic uveitis and there should not be a delay in initiating DMARDs or biologics.

Immunosuppressive therapy

Due to steroid toxicity, it is prudent to initiate steroid-sparing disease-modifying anti-rheumatic drugs (DMARDs) and biologics early in the disease course to control ocular inflammation and prevent complications and vision loss [15]. Options for long-term immunosuppression include first-line conventional immunotherapy with methotrexate (MTX), and less commonly, mycophenolate mofetil (MMF), and cyclosporine A (CsA).

Methotrexate

Methotrexate was used to treat 76% of patients with idiopathic juvenile uveitis enrolled in the CARRA Registry making it the most frequently used steroid-sparing agent [16••]. There are several reports of its use in pediatric patients with uveitis [34–38]. MTX is a folic acid analog that inhibits DNA replication and RNA transcription in B and T lymphocytes [2]. The recommended starting dose is 10–15 mg/m^2 once a week orally or subcutaneously. Dosing can be increased to 30 mg/m^2 if administered by the subcutaneous route. There is a

lack of evidence for preferred administration route. However, parenteral administration achieved higher efficacy and bioavailability in adult patients with rheumatoid arthritis and pediatric patients with JIA [39–43]. Foeldvari et al. reported good outcomes in JIA-associated uveitis (JIA-U) wherein 84% (21/25) of patients achieved remission after a mean treatment dose of 15.6 mg/m^2 (range 10–25 mg/m^2) for an average of 4.25 months (range 1–12) [37]. A recent meta-analysis suggests MTX is effective in controlling inflammation in pediatric non-infectious uveitis wherein the proportion of responding subjects in nine eligible studies was 0.73 (95% confidence interval 0.66–0.1) [44•]. Common side effects associated with MTX in children include gastrointestinal (GI) toxicity (oral ulcers, nausea, vomiting) and hepatorenal toxicity. Patients must have routine lab work to evaluate blood count and liver function (AST/ALT). In addition, folic acid should be supplemented on a daily basis to prevent GI-related toxicity.

Methotrexate is considered first-line therapy in most patients with chronic non-infectious uveitis and can be an effective treatment for ocular inflammation.

Mycophenolate mofetil

MMF inhibits inosine monophosphate dehydrogenase, which is an enzyme critical to the de novo pathway of purine synthesis [45]. Unlike other cell types, lymphocytes lack alternative pathways for purine synthesis and are therefore selectively suppressed by MMF [2]. The optimal dose for uveitis is unknown, but most pediatric rheumatologists initiate therapy at dosages used in pediatric renal transplant recipients—600 mg/m^2 twice daily or 2–3 g/day in divided doses. To date, there are only two reports of MMF therapy in pediatric uveitis [46, 47]. Chang et al. reported on 52 children with autoimmune uveitis treated with MMF monotherapy wherein 73% achieved uveitis control after 2 months. Approximately 60% (16/25) of patients with JIA-U achieved quiescence for at least 2 years of therapy. Furthermore, visual acuity was stable or improved in 94% [47]. MMF may be useful in the management of pediatric non-infectious uveitis, although less in JIA-U since it may not be as effective for arthritis compared to other agents. Side effects include hair loss, fatigue, gastrointestinal discomfort, and leukopenia [2, 15].

Cyclosporine A

CsA belongs to the class of calcineurin inhibitors (CNIs) whose mechanism is to block the activity of calcineurin, an enzyme that facilitates gene expression of IL-2 and other cytokines [48]. Down-regulation of these molecules impairs T cell proliferation resulting in immunosuppression. There are only a few studies reporting outcomes with CsA in pediatric non-infectious uveitis [49–52]. Tappeiner et al. reported on 82 patients with JIA-U, the largest retrospective series to date. CsA monotherapy had minimal efficacy in this study, with only 6/25 (24%) achieving inactivity. Efficacy increased to 48.6% (35/72) when combined with other immunosuppressive medications, suggesting the optimal role for CsA in treating pediatric non-infectious uveitis is as adjunct therapy [52]. Pediatric dosing of CsA is recommended between 2.5 and 5 mg/kg/day in divided doses to avoid systemic side effects [53]. Nephrotoxicity, hypertension, hepatotoxicity, anemia, nausea, vomiting, hirsutism, and hypercholesterolemia

are potential side effects [15]. Routine testing should include renal and liver function and blood pressure monitoring [2].

CsA is infrequently used to treat pediatric non-infectious uveitis, and other agents are preferred.

Biologics

Biologics represent a newer class of medications used to treat ocular inflammation. These agents target molecules in the immune system that play a key role in the ocular inflammatory process [54]. For example, TNF-alpha, interleukins (IL), and interferons are pro-inflammatory cytokines produced by immune cells and are consistently elevated in serum and aqueous fluid of patients with uveitis [55, 56]. Experimental autoimmune uveitis studies in animals also confirm the role of TNF-alpha in mediating intraocular inflammation [57–59]. Therefore, targeting these molecules with biologic therapy appears to be an attractive approach for long-term control of uveitis refractory to corticosteroids or conventional immunotherapy. Therapeutic options within the class of biologics include anti-TNF-alpha agents, anti-IL agents, and anti-B and T lymphocyte agents [19]. Screening for hepatitis and tuberculosis before initiation is important. Anti-TNF-alpha agents, specifically infliximab (IFX) and adalimumab (ADA), have been most commonly used with excellent success [60].

Anti-tumor necrosis factor agents

Infliximab

Infliximab is a chimeric (75% humanized, 25% mouse) monoclonal antibody that binds to and inhibits circulating and membrane bound TNF-alpha [61]. It is FDA approved for several autoimmune conditions, including rheumatoid arthritis, ankylosing spondylitis, psoriatic arthritis, plaque psoriasis, and inflammatory bowel disease [54]. Numerous prospective and retrospective studies support IFX's use for non-infectious uveitis, but dosage and interval vary [62, 63, 64•, 65–67]. Kahn et al. reported on 17 patients with refractory uveitis (10 JIA-U, 2 VKH, 2 sarcoidosis, 3 idiopathic) treated with 10–20 mg/kg of IFX every 4–8 weeks [64•]. Intraocular inflammation was undetectable after the first or second infusion in 76% (13/17). High-dose IFX was effective and well tolerated in all patients in this series. Ardoin et al. reported on a cohort of 16 children with uveitis (5 JIA-U, 11 idiopathic) treated with 8.2 mg/kg median dose (range 2.0 to 12.9) of IFX at median frequency of 5.6 weeks (range 4 to 10). At 1 year, 64% had no active inflammation and increased to 79% if criteria were modified to include zero inflammation or a 2-step decrease in AC inflammation. Furthermore, all patients were on topical CS at baseline, whereas by 12 months, approximately 69% (11/16) of patients discontinued use [67]. Sukumaran et al. compared varied doses of IFX: low dose (<10 mg/kg), moderate dose (≥10–15 mg/kg), and high dose (≥15–20 mg/kg) every 4 weeks in 34 children with refractory non-infectious uveitis [68]. After 1 year, there was significant improvement in anterior chamber cells, flare, and VA in all groups. However, escalated doses may be necessary to achieve disease control since >35%

required an increase in dose to ≥10 mg/kg, and 94% were on high dose at end of study.

IFX is administered intravenously with a loading dose of 3–5 mg/kg at weeks 0, 2, and 6 followed by maintenance dosing at 5 –10 mg/kg every 4–8 weeks. Additionally, methotrexate is recommended as an adjunct to prevent the formation of anti-TNF antibodies. In refractory uveitis, an increased dose of 20 mg/kg has been used successfully [64•, 68, 69]. Potential side effects include increased susceptibility to infections, reactivation of tuberculosis or histoplasmosis, malignancy, and development of lupus-like syndrome [2, 54]. Mild and moderate infusion reactions occurred in 17% of patients in one study [70].

IFX can be an effective treatment for uveitis but is often needed at high doses. There has been variability in the dosing and interval of IFX administration which may have led to the differences in patient outcomes.

Adalimumab

Adalimumab (ADA) is a fully humanized monoclonal antibody that also binds to and inhibits TNF-alpha and is the only US Food and Drug Administration (FDA)-approved non-corticosteroid medication for the treatment of non-infectious uveitis [71]. Jaffe et al. recently published results from a multi-national phase 3 randomized controlled trial assessing the efficacy and safety of ADA for adults with non-infectious intermediate, posterior, or panuveitic uveitis [72••]. All 217 patients had active, vision threatening, non-infectious uveitis and were randomly assigned to ADA 80-mg dose at baseline followed by 40-mg doses every 2 weeks (110 patients) or placebo (107 patients). They described a significantly lower risk of treatment failure compared to placebo wherein treatment failure occurred at 24 weeks in the ADA group and 13 weeks in the placebo group (HR, 0.50; 99% confidence interval, 0.36 to 0.70; $P < 0.001$).

Nguyen et al. reported on 229 patients with inactive uveitis on 10–35 mg/day of oral prednisone to maintain uveitis inactivity [73••]. They were randomly assigned to ADA (115 patients) or placebo (114 patients). Prednisone was tapered to 0 mg by week 19. Treatment failure was increased in the placebo group (61 (55%)) compared to the ADA group (45 (39%)), and there was significant improvement in time to treatment failure in patients receiving ADA.

Several prospective and retrospective studies support ADA treatment for pediatric uveitis [74–79, 80•, 81–84]. Diaz-Llopis et al. reported a prospective multi-center study of 131 patients (39 with JIA-U) treated with ADA for 6 months [75]. Children received 40 mg of ADA subcutaneously (SC) every other week (children between ages 4 and 12 received 24 mg/m^2 body surface area up to maximum dose of 40 mg SC every other week). There was a statistically significant decrease in anterior chamber and vitreous inflammation and overall gain in visual acuity [75].

There are reports on the development of antibodies against ADA (AAA) in other diseases, leading to decreased drug efficacy and adverse effects. Recently, Cordero-Coma described 25 patients (2 JIA-U) with active refractory uveitis who were followed prospectively for 6 months [85]. At least three trough serum ADA and AAA were measured prior to ADA administration. Only 11 (44%) had a complete clinical response, seven (28%) had a partial response, and seven (25%) no response. There were increased ADA levels in responders and an association between worse uveitis outcome in patients with permanent AAA (4

(14%)). Development of AAA was not associated with use of other immuno-suppressive agents which is interesting since methotrexate is often used in conjunction with IFX for JIA. The relevance of measurement of ADA trough levels and AAA remains unclear.

ADA is administered subcutaneously at a dose of 10 - 40 mg every 2 weeks. In children with severe uveitis, dose and interval of administration can be increased to 40 mg weekly to increase efficacy. Side effects are similar to IFX, including increased susceptibility to infections and reactivation of TB or histoplasmosis [2].

Reports on the successful use of ADA in pediatric uveitis and ease of administration at home versus infusions make it an excellent option for many families.

Golimumab

There have been limited reports on Golimumab, a fully humanized anti-TNF monoclonal antibody that is administered subcutaneously every 4 weeks. Miserocchi et al. examined 13 patients with JIA-U and 4 with HLA-B27 spondyloarthropathy who had an inadequate response to other TNF-alpha blockers or other biologics such as rituximab and abatacept [86]. Patients received golimumab 50 mg every 4 weeks as subcutaneous injections. They were all ≥18 years of age and had anterior uveitis or panuveitis. Response was evident in 14 patients, wherein two of the non-responders had JIA-U. At the last visit, 12 of 17 had inactive disease. This is a promising anti-TNF therapy for uveitis patients.

Emerging therapies

Abatacept

Abatacept (ABA) is a soluble fusion protein composed of human cytotoxic T lymphocyte antigen 4 (CTLA-4) and modified FC domain of human IgG. It binds to CD80/CD86 on antigen-presenting cells and prevents activation of T cells [87]. Abatacept is FDA approved for JIA and RA, but off-label use in pediatric and adult uveitis has been reported [87–89, 90•, 91]. In 2008, we first reported on a 16-year-old female with psoriatic arthritis with long-standing uveitis that was refractory to conventional IMT and biologics, including trials of rituximab, IFX, etanercept, and daclizumab. Abatacept infusions were started at 10 mg/kg. Ocular inflammation rapidly improved and remained well con-trolled 18 months after initiation of therapy [87]. A recent case series described three children with idiopathic uveitis that was successfully controlled with Abatacept [89]. However, Tappeiner et al. reported on the visual outcomes in 21 patients with JIA-U [90•]. All patients had severe and chronic uveitis with mean duration of 7.5 years and were treated with 10 mg/kg, max 750 mg every 4 weeks. Patients had previously failed tCS, systemic CS, methotrexate, and several biologics (IFX, etanercept, ritixuimab, golimumab). Uveitis inactivity was achieved in 11 patients after starting ABA (median time of 6 months) but recurred in eight of these patients. Abatacept failed to suppress inflammation in 10/21 (48%) of patients. In addition, new onset complications occurred in

three, and best corrected visual acuity (BCVA) did not significantly improve. Hence, ABA did not appear to be effective in this cohort compared to earlier studies. Birolo et al. compared ABA as a first-line or second-line biologic agent in 31 patients with severe JIA-U after 12 months of follow-up [92•]. Fourteen received ABA as first-line biologic therapy (at least 6 months of MTX) and 17 as a second-line biologic agent. Clinical remission was achieved in 54.8% of the total patients (17/31), but there was no significant difference in improvement in those who received ABA as first line (57%) versus second line (52.9) [92•]. Dosing is 10 mg/kg at 0 and 15 days followed by monthly administration [2]. Side effects include infections, gastrointestinal disorders, and low risk for malignancy [2, 20].

There are reports on the use of Abatacept in children with uveitis, but attainment of remission varied.

Tocilizumab

Interleukin-6 (IL-6) is a cytokine produced by T cells, B cells, and monocytes. Signaling through IL-6 appears to play a critical role in the immune system, including T cell activation, immunoglobulin secretion, and angiogenesis [93, 94]. The importance of IL-6 in mediating ocular inflammation has also been demonstrated in animal models of experimental uveitis that show that treatment with anti-IL6 receptor antibody reduces uveitic inflammation [95]. Furthermore, elevated IL-6 concentrations were noted in vitreous fluid of patients with VKH, Behcet's, sarcoidosis, and idiopathic uveitis compared to controlled non-uveitic patients [95]. Therefore, targeting IL-6 appears to be an attractive approach.

Tocilizumab (TCZ) is an IL-6 receptor antibody approved for RA and JIA and is an emerging treatment for uveitis and cystoid macular edema [93, 94, 96••, 97, 98, 99••]. It is a humanized recombinant antibody that binds the IL-6 receptor, leading to inhibition of the downstream signaling of IL-6 and pro-inflammatory effects. Tappeiner et al. reported on 17 patients treated with TCZ for chronic refractory JIA-U, including systemic corticosteroids, DMARDs, and 1 TNF-alpha inhibitor [97]. Patients were treated with intravenous TCZ 8 mg/kg body weight at 4 week intervals and were followed for a mean of 8.5 months. Inactive uveitis was observed in 10/17 patients after at least one follow-up, but there was a recurrence in three. In seven patients who did not respond to TCZ, four had improved ocular activity, two had no change, and one worsened. Additionally, four patients experienced new ocular complications during treatment, and there was no significant change in BCVA at the end of follow-up. There were no adverse events requiring discontinuation of TCZ in this study. In 2016, Silpa-archa et al. reported their experience with Tocilizumab in 17 patients with recalcitrant ocular inflammatory disease (10 uveitis, 6 scleritis, 1 orbital pseudotumor) [94]. In the uveitis cohort, five patients (age range 14–50 years) had inflammation associated with JIA. After 9 months of treatment, 71% of uveitis and 50% of scleritis patients achieved the primary outcome: absence of inflammation and achievement of steroid sparing. However, serious side effects requiring cessation of therapy were reported in 24% of patients, including neutropenia, severe angioedema, dizziness, and abdominal pain. Recently, Calvo-Rio et al. reported on the use of TCZ in 25 patients with JIA-U refractory to conventional IMT and at least one biologic agent including anti-

TNF-alpha drugs, abatacept, rituximab, and anakinra [99••]. Dosing was 8 mg/kg IV every 2, 4, or 8 weeks or 2.9 mg/kg/subcutaneously every week. At 6 months of follow-up in 23 patients, BCVA improved and anterior chamber cells decreased in 79%. This was consistent at 1 year in 15/17 patients (88%). Clinical trials evaluating the efficacy of TCZ in non-infectious intermediate, posterior, or panuveitis (STOP-Uveitis) and JIA-U are on-going (www.clinicaltrials.gov) [93].

TCZ is a promising treatment for pediatric uveitis, but additional studies are needed to determine optimal dosing and intervals.

Rituximab

Rituximab is a chimeric antibody directed against the B cell marker CD20 thereby inducing B cell apoptosis [100••]. Rituximab initially gained FDA approval in 1997 for the treatment of lymphoma and leukemia [101]. Since then, the medication has been approved for RA, microscopic polyangiitis, and granulomatosis with polyangiitis [54]. Rituximab's use in ocular conditions has been limited, but several reports have shown efficacy for the management of scleritis, peripheral ulcerative keratitis, VKH, and more recently, in JIA-U [102–105]. Miserocchi et al. reported on a cohort of eight patients (15 eyes) with severe JIA-U treated with rituximab who were previously resistant to IMT and TNF-alpha inhibitors [106]. The mean follow-up time on rituximab was 44.75 months with a mean number of 8.75 infusions. Uveitis was inactive in all patients at last follow-up, and improvement was noted 4 months after the first infusion. Mean systemic CS dose before initiating rituximab was 18 mg/day and decreased to 1.8 mg/day at final follow-up, with discontinuation in six patients. Similarly, conventional IMT was discontinued in 5/8 patients and reduced from MTX + CSA to only MTX in one patient. The two remaining patients continued with baseline MTX throughout rituximab treatment. These are promising results for refractory uveitis associated with JIA, but further prospective trials need to be conducted to assess the efficacy of rituximab in pediatric uveitis.

Rituximab is given intravenously and dosed at 1000 mg on days 1 and 14 and repeated after 6 months if needed. Effect on B cells lasts 6 to 9 months making this an attractive biologic compared to anti-TNF-alpha agents that require more frequent dosing [107]. Side effects include infusion reactions, which can be mitigated with corticosteroids, as well as neutropenia, heart failure, and rarely progressive multifocal leukoencephalopathy.

Future directions

Several challenges exist in the timely and optimal treatment of children with uveitis. There is a lack of randomized controlled trials, and adalimumab is the only FDA-approved drug for non-infectious intermediate, posterior, and panuveitic uveitis in adults. Thus, treatment is usually guided by collective expertise, case reports/case series, retrospective studies, and panel guidelines [17–19].

Advances have emerged in the study of biomarkers for early detection of disease, indicators of active disease, and targeted therapy. Potential biomarkers associated with pediatric chronic anterior uveitis and JIA-associated uveitis were detected in the iris, serum, and aqueous humor, but most studies have been

conducted in adults with varied involvement and associated diseases. Alterations in the inflammatory cells, autoantibodies, cytokines, chemokines, and soluble adhesion molecules have been reported, most recently erythrocyte sedimentation rate (ESR), plasma cells, interleukin-29/interferon-λ1, S100A8/A9, and S100A12 [108–118]. The analysis of tear fluid for biomarkers in chronic anterior non-infectious uveitis is a potential non-invasive collection method [119–121]. With further developments in research and science, the potential exists to utilize markers to inform clinicians of optimal therapy choice as we gain more insight into promising drug targets.

Conclusions

Chronic pediatric non-infectious uveitis can lead to severe ocular complications and permanent vision loss. Timely and optimal management improves visual outcomes. There are no standardized treatments and few randomized controlled trials for pediatric uveitis. We report on conventional DMARDs and anti-tumor necrosis factor agents but also discuss newer biologics for children with refractory uveitis. Additional studies are needed to determine optimal treatment and dose in this population.

Compliance with Ethical Standards

Conflict of Interest

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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•• Of major importance

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