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Pediatric uveitis: new and future treatments

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Abstract

Purpose of review—Pediatric uveitis is relatively uncommon, accounting for only 5–10% of all patients with uveitis. However, owing to high prevalence of complications and devastating outcomes, its lifetime burden can be significant.

Recent findings—Immunomodulatory therapy has been associated with better outcomes in noninfectious pediatric uveitis. However, effective treatments are limited by medication-related complications, including multiorgan toxicities and systemic side effects.

Summary—We review the current therapies available to treat pediatric uveitis, discuss novel and future therapies, and provide clinical recommendations utilizing these new agents. The consideration for treatment regimens in noninfectious pediatric uveitis is multifactorial. Understanding past, present, and future technology will aid in treatment of a complex and refractory disease.

Keywords

biologic agents; immunosuppressive therapy; juvenile idiopathic arthritis; pediatric uveitis; uveitis

INTRODUCTION

Pediatric uveitis is relatively uncommon, accounting for only 5–10% of all patients with uveitis. Owing to the extremely high prevalence of complications and disease burden over a lifetime, it presents a specific challenge. Historically, effective treatments were limited by complications of their own, including multiorgan toxicities and systemic side-effects. Better treatment options may dramatically improve visual prognosis, which worsens with delayed diagnosis and disease duration. Among pediatric uveitis cases, 25–33% results in severe vision loss [1]. Most patients are White females with median diagnosis at 8.6–9.4 years of age. The most common etiologic diagnosis is juvenile idiopathic arthritis (JIA) followed by pars planitis. Most individuals have an insidious onset and persistent duration, with anterior

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Conflicts of interest

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uveitis as the most common anatomical location. Structural complications such as cystoid macular edema (CME) and hypotony are common and 10–30% can be classified as legally blind at presentation [2,3]. Evidence suggests that early and more aggressive therapy improves ocular outcomes [4,5]. Immunomodulatory therapy has been associated with reduced risk of complication, and control of inflammation within 3 years has been associated with better visual outcomes. Several studies have indicated that strict control of inflammation and the use of immunosuppressive drugs significantly reduce the risk of vision loss [6,7].

There are relatively few medications with specific Food and Drug Administration (FDA) indications for pediatric uveitis. Methotrexate (MTX; Rheumatrex; Dava Pharmaceuticals, Fort Lee, New Jersey, USA, Trexall; Teva Pharmaceuticals, Philadelphia, USA) has been approved for use in children with JIA. Adalimumab (Humira; Abbott Laboratories, Abbott Park, Illinois, USA) is approved for JIA in patients over age 4. Safety and efficacy of many newer therapies are not well established in children. Oral and topical corticosteroids are approved for use in children, however the safety of fluocinolone acetonide intravitreal implant (Retisert; Bausch and Lomb, New York, USA) has not been established in patients less than 12 years [8]. The dexamethasone (Ozurdex; Allerga, Irvine, California, USA) implant also lacks safety information for children [9]. The current approach includes corticosteroids to treat acute inflammation with rapid instatement of corticosteroid-sparing agents (antimetabolites, T-cell inhibitors, alkylating agents, biologics). This review provides an understanding of current and future treatment strategies, and discusses newer generation biologics and corticosteroid implant options in children (Table 1) [10].

CAUSE

Noninfectious anterior uveitis is most prevalent among North American populations. Most pediatric uveitis cases are idiopathic. JIA is the most common systemic association of pediatric uveitis. JIA patients typically have chronic, bilateral, nongranulomatous, anterior uveitis with insidious onset. In North America, there is an estimated incidence of 4.9–6.9 per 100 000 person-years and prevalence of 13–30 per 100 000 population [7]. Oligoarticular onset JIA is the type most likely associated with uveitis. JIA patients have a high risk of developing band keratopathy, cataract, and posterior synechiae [1]. Risk factors for vision loss include presence of uveitis before arthritis, complications at initial examination, short duration between arthritis onset and uveitis, young age, multiple episodes, and male sex [11].

Treatment varies with severity and response to therapy, and should be tailored to cause and anatomic location. Infectious agents such as *Toxoplasma*, *Toxocara*, *Bartonella*, or those causing Lyme disease syphilis, or tuberculosis, and viruses can be common causes of pediatric uveitis [12], especially in developing countries, and should be ruled out. In developed countries, infectious uveitis constitutes 11–13% of all pediatric uveitides [13]. A growing body of evidence supports infection as the causative or triggering event in presumed idiopathic uveitis [14]. PCR analysis of aqueous and vitreous specimens can be helpful in such cases [15]. In noninfectious uveitis, the ultimate goal is to start immunosuppressives early and taper off therapy after a sufficient period of quiescence. The ‘sufficient’ period is

currently controversial, but there is consensus that at least 2–3 years of complete quiescence is needed before discontinuing immunomodulatory therapy.

CURRENT TREATMENTS

Current standard medical therapy for pediatric uveitis combines an older generation of medications that have been in use for decades, such as corticosteroids, with both old and new generation immunomodulatory agents. Corticosteroids are the mainstay therapy for noninfectious uveitis, but prolonged use can have significant side effects. Topical corticosteroids are effective for early control of uveitis, but a long-term corticosteroid-sparing immunomodulatory therapy plan should be discussed at the time of diagnosis, particularly for patients with ocular complications or who are at risk for new complications [16]. The most commonly used topical corticosteroid is prednisolone acetate 1%, however rimexolone 1% may be less likely to cause glaucoma [17]. Difluprednate Ophthalmic Emulsion 0.05%, a new and more potent topical corticosteroid, allows less frequent dosing but is more likely to cause corticosteroid-induced ocular hypertension. In a cohort of 14 pediatric uveitis cases (26 eyes), 50% of eyes developed a significant intraocular pressure increase [18].

Since the 1970s, peribulbar and intravitreal corticosteroids, most commonly triamcinolone acetonide, have been used to treat uveitis [19,20]. This modality is more effective in treating intermediate and posterior uveitis and has less systemic effects, but greater risk of cataract and glaucoma. Prolonged use of topical corticosteroids and repeated periocular injections further increases the risk of glaucoma and cataract in children [16]. Chronic topical corticosteroid use more frequently than three times a day is associated with increased risk of cataracts as well [21]. If uveitis requires extended or frequent corticosteroid drops, it is favorable to initiate systemic immunomodulatory therapy.

Long-term systemic corticosteroids are associated with adrenal suppression, causing growth retardation due to premature epiphyseal closure [22]. Other side-effects include weight gain, infection, osteoporosis, and hyperglycemia. Most pediatric uveitis patients requiring frequent corticosteroid drops will ultimately need immunosuppressive treatment. Systemic corticosteroids can be used as a short-term bridge to immunosuppressive therapy in patients not controlled with topical therapy.

The efficacy of NSAIDs has not been studied in depth for their specific role in treating uveitis. They are not considered a significant part of treatment regimen for pediatric uveitis.

IMMUNOMODULATORY AGENTS

Growing evidence supports earlier and more aggressive immunomodulatory therapy in pediatric uveitis. Studies indicate that systemic treatment with both conventional immunosuppressives and newer biological agents results in better outcomes.

Antimetabolites

MTX is commonly used as a first-line immunomodulatory agent in pediatric uveitis because of its long track record of both safety and efficacy. MTX is a folic acid analogue that inhibits dihydrofolate reductase and de-novo synthesis of purines. Folic acid supplementation prevents side effects [20,23]. Early aggressive treatment of JIA with MTX has significantly improved outcomes in pediatric uveitis, with about 60–80% of children showing a favorable response [24]. Long-term MTX use has been associated with a lower risk of relapse after its discontinuation [16].

Second-line immunosuppressives include azathioprine (AZA; Imuran; GlaxoSmithKline, Research Triangle Park, North Carolina, USA), mycophenolate mofetil (MMF; Cellcept; Genentech, South San Francisco, California, USA), and cyclosporine. AZA is a purine synthesis inhibitor interfering with DNA replication and RNA transcription. There are few studies regarding utility of AZA in pediatric uveitis. In JIA-associated active uveitis, AZA monotherapy was successful in controlling inflammation in 76% of cases, and in 56% when used in combination therapy. Its corticosteroid-sparing effect was moderate-to-poor in most cases, limiting its use in pediatric uveitis treatment [25].

MMF inhibits inosine monophosphate dehydrogenase, a pathway of guanosine nucleoside synthesis, used by B and T cells [20]. MMF is generally used for non-JIA uveitis, either as a first-line corticosteroid-sparing agent or as a second-line agent in MTX failures [26].

T-cell inhibitors

Cyclosporine A (CsA; Sandimmune; Novartis, East Hanover, New Jersey, USA, Gengraf; Abbott Laboratories, Neoral; Novartis), a calcineurin inhibitor, inhibits T-cell activation by blocking transcription of genes for cytokines such as interleukin-2 (IL-2). A powerful corticosteroid-sparing agent has been shown to be both effective and relatively well tolerated in low doses in treating refractory posterior uveitis in adults and children [27]. Cyclosporine is particularly effective in Behcet's disease-associated uveitis. There are few data regarding the efficacy of CsA therapy in childhood uveitis. A recent study of 82 children with JIA uveitis showed that CsA was minimally efficacious as monotherapy, but had a 50% success rate when used in combination with MTX [28].

Nephropathy is of concern in adult patients, but less so in children, possibly because of greater pediatric CsA clearance [29]. A retrospective case series in children with uveitis showed the efficacy of CsA in combination therapy but, more importantly, showed minimal adverse effects when used in low doses (<5.0 mg/kg per day). To minimize dose-dependent CsA-induced nephropathy we, and many others, maintain a CsA dose of 5 mg/kg per day or less [29].

Tacrolimus (FK506; Prograf Astellas Pharma, Northbrook, Illinois, USA) is a newer calcineurin inhibitor with a similar mechanism to CsA. It is not as widely used as CsA for treatment of ocular inflammatory disease despite a possibly better side-effect profile.

Alkylating agents

Chlorambucil (Leukeran; GlaxoSmithKline) and cyclophosphamide (Cytoxan; Bristol-Myers Squibb, Princeton, New Jersey, USA) cross-link DNA strands and decrease DNA synthesis, preventing cell division. Alkylating agents are typically avoided in children because of serious potential long-term side effects, except in cases of life-threatening systemic autoimmune diseases such as lupus, Behcet's disease, or other serious vasculitides [16]. The serious long-term side effects include leukopenia, gonadal atrophy, and malignancy [20].

NEWER TREATMENTS

Biologic drugs refer to drugs made from human or animal proteins derived from genes. Many are designed to inhibit specific components of the immune system that play key roles in inducing inflammation. Biologics have made an enormous impact in the treatment of pediatric uveitis in the last decade (Fig. 1) [30[■]].

TUMOR NECROSIS FACTOR INHIBITORS

Tumor necrosis factor (TNF) is a cytokine that plays a role in inducing inflammation in autoimmune processes, and has been found at increased levels in aqueous humor and serum of patients with uveitis. Anti-TNF- α agents have successfully been used to treat various forms of uveitis both in adults and children in the past decade [31]. Often these medications are selected when patients fail to respond to conventional immunosuppressive therapy and are at a high risk for visual loss. Anti-TNF drugs used in uveitis patients include infliximab (Remicade; Janssen-Horsham Biotech Inc., Malvern, Pennsylvania, USA), adalimumab, golimumab (Simponi; Janssen Biotech Inc.), and certolizumab (CIMZIA; UCB Inc., Atlanta, Georgia, USA). A fifth anti-TNF drug, etanercept (Enbrel Immunex Corporation, Thousand Oaks, California, USA), is no longer used in uveitis patients because of concerns of exacerbation or new-onset ocular inflammation when used to treat rheumatologic disorders [16]. It is important to rule out tuberculosis prior to treatment with TNF inhibitors.

Infliximab and adalimumab

Infliximab was the first commercially available drug targeting TNF- α for treatment of adult rheumatoid arthritis (RA); however, it is not FDA-approved for the treatment of JIA [32[■], 33]. Infliximab is 70–75% humanized chimeric mouse-human antibody. It is approved for use in various inflammatory diseases in adults, but the only pediatric indication is Crohn's disease in children over age 6. The recommended dose is three initial infliximab infusions at 0, 2, and 6 weeks in a dosage of 5 mg/kg; followed by maintenance therapy at a dose of 5 mg/kg every 8 weeks [33] (Fig. 2).

Adalimumab is a fully human monoclonal antibody against TNF-alpha and the third TNF-blocker approved in the USA [33–36]. It is FDA-approved for the treatment of RA, psoriatic arthritis, ankylosing spondylitis, plaque psoriasis, inflammatory bowel disease in adults, and polyarticular JIA in patients over age 4 and over 15 kg [34]. It is used either as monotherapy or in combination with MTX [32[■]]. The recommended dose is 20 mg every other week for

children weighing 15–30 kg; 40 mg every other week for children weighing more than 30 kg [34].

Neither infliximab nor adalimumab is approved specifically for the treatment of uveitis, but studies indicate that both can be effective. A recent prospective study reported improvement in 88.2% of pediatric patients with uveitis treated with infliximab or adalimumab, wherein half achieved remission. After 1-year follow-up of 108 patients with JIA-associated uveitis, the remission rate for adalimumab was 67.4 versus 42.8% with infliximab in a prospective registry [37[■]]. Adalimumab has been valuable for chronic recurrent anterior uveitis [32[■]]. Another recent prospective study of 38 pediatric uveitic eyes showed adalimumab to be good adjuvant therapy. Improvement was seen in about 76% of cases, stabilization in 16%, and relapse in 8% [38[■]]. A large prospective study of 131 adult patients with refractory uveitis showed similar results with 85% of patients able to reduce at least 50% of their baseline immunosuppressives [39[■]]. Data are equivocal regarding whether adalimumab or infliximab therapy is superior in uveitis treatment. Some studies suggest a slightly better remission rate with adalimumab [23]; others suggest that there is no difference between the two [40]. Adalimumab has the convenience of subcutaneous administration, more stable serum concentrations, and better safety profile. Infliximab has a faster onset for immediate ocular inflammatory control; however, tolerability is limited due to infusion reactions and higher risk of infection [16]. Infusion reactions are probably related to the development of human antichimeric antibodies and can be minimized with concomitant use of MTX [32[■]].

Other tumor necrosis factor inhibitors

Certolizumab pegol (CIMZIA) and golimumab are the two newest TNF antagonists. Certolizumab pegol is a PEGylated Fab fragment of a humanized anti-TNF antibody, without an Fc-region, potentially decreasing the risk for infectious diseases [32[■]]. Certolizumab is FDA-approved for the treatment of RA and Crohn's disease in adults at a dose of 400 mg given subcutaneously every 2 weeks for three loading doses. For maintenance, 400 mg monthly or 200 mg every 2 weeks is used. Golimumab is approved for treatment of RA, psoriatic arthritis, and ankylosing spondylitis in adults [32[■],41] at a dose of 30 mg/m² every 4 weeks, with maximum dose of 50 mg subcutaneously once monthly. There is a clinical trial in progress looking at higher dosages (100 mg per dose) of golimumab in adults with RA [Clinicaltrials.gov, NCT00299546]. Current use of certolizumab and golimumab in children is off-label, but studies suggest efficacy in select refractory cases with JIA or Behcet's disease [41–43]. A multicenter randomized-withdrawal trial to evaluate the efficacy and safety of golimumab in pediatric patients with active polyarticular JIA and poor response to MTX is expected to be completed in 2016 [Clinicaltrials.gov, NCT01230827].

OTHER BIOLOGIC THERAPIES

Alternate biologic agents, such as anakinra (Kineret; Amgen, Thousand Oaks, California, USA), canakinumab (Ilaris; Novartis), daclizumab (Zenapax, Hoffman La Roche, USA), abatacept (Orencia; Bristol-Myers Squibb), rituximab (Rituxan; Genentech), and tocilizumab (Actemra; Genentech), are used in patients refractory to anti-TNF agents. There

are limited data on the efficacy and safety of these agents, particularly in children. Risk of opportunistic infections and malignancies and other serious potential side effects should be carefully considered before use. Concomitant use of multiple biologics can dramatically increase risk and is generally contraindicated.

Daclizumab

Daclizumab is a humanized monoclonal antibody against IL-2R α receptor (CD25) and inhibits IL-2-mediated pro-inflammatory responses [44]. Daclizumab has been safely and effectively used in intermediate and posterior uveitis in adults and children as well as active JIA-associated anterior uveitis [45]. Its side-effect profile has been mild, but it was pulled from the market because of diminishing demand.

Interleukin-1 inhibitors

Anakinra is a recombinant IL-1 receptor antagonist (IL-1Ra) that blocks the biologic activity of IL-1 by competitively inhibiting IL-1 binding to the receptor. It is approved for the treatment of RA in adults. It has also been used in IL-1-mediated autoinflammatory diseases [46]. Despite evidence from animal models of uveitis, there is no clear evidence of its benefit in human uveitis. Canakinumab is a human anti-IL-1 β monoclonal antibody, which neutralizes the activity of IL-1 β . IL-1 β plays a dominant role in the pathophysiology of several autoinflammatory conditions, including JIA [47]. The recommended dose is 150 mg for children weighing more than 40 kg, and 2 mg/kg for those weighing 15–40 kg, administered every 8 weeks as a single dose via subcutaneous injection [48]. A recent study in patients with Blau syndrome showed clinical improvement with canakinumab [49] (Fig. 3 [50]). Both, canakinumab and anakinra, are being extensively studied in clinical trials for several inflammatory and chronic conditions.

Interleukin-6 inhibitors

Tocilizumab is a humanized monoclonal IL-6 receptor antagonist. IL-6 is a pleiotropic pro-inflammatory cytokine involved in the inflammatory immune response. Several case reports highlight interest in tocilizumab for the treatment of uveitis refractory to anti-TNF, including idiopathic uveitis, Birdshot chorioretinopathy [51], and Behcet's disease [52]. More recently, tocilizumab was successfully used in adult patients with JIA uveitis refractory to immunosuppressants and anti-TNF [53[■]]. There are a few ongoing clinical trials studying the safety, tolerability, and bioactivity of tocilizumab in patients with noninfectious uveitis, JIA-associated uveitis or Behcet's disease. Additionally, sirukumab by Janssen Research and Development, Spring House, Pennsylvania, USA [54] and sarilumab by Regeneron, Tarrytown, New York, USA and Sanofi, Bridgewater, New Jersey, USA are under investigation [www.clinicaltrials.gov (<http://www.clinicaltrials.gov/ct2/results?term=sarilumab>)].

Rituximab

Rituximab is a murine-human antibody against CD20, a B lymphocyte antigen, inducing apoptosis and temporarily depleting B cells for 6–9 months. Rituximab is FDA-approved for the treatment of lymphoma and leukemia, RA, granulomatosis with polyangiitis (formerly

Wegener's granulomatosis), and microscopic polyangiitis. Rituximab can be helpful in peripheral ulcerative keratitis, scleritis, and refractory JIA uveitis that fail to respond to anti-TNF agents [55]. Rituximab is administered by intravenous infusion. The most frequent side-effects are infusion reactions, which can be suppressed with concomitant intravenous corticosteroids. Neutropenia, reactivation of hepatitis B virus, heart failure, and progressive multifocal leukoencephalopathy have also been reported [56]. Safety and efficacy of rituximab in children is unknown.

Abatacept

Abatacept, a soluble CTLA4-IgFCg fusion protein, binds to CD80/CD86 on antigen-presenting cells, thereby preventing T-cell activation [32[■]]. It has been FDA-approved for JIA and RA. Although there are limited data to show the efficacy of this drug in pediatric and adult uveitis, numerous case reports indicated improvement of anti-TNF refractory uveitis within 2 weeks to 6 months [57–59]. Abatacept has a mild side-effect profile, but infection and malignancy can occur [60].

Local treatments

Injectable or surgically implantable corticosteroid devices provide a novel approach for the treatment of refractory uveitis. Implants provide long-term, slow release of intraocular corticosteroids [60].

The first FDA-approved implantable device for noninfectious posterior uveitis was fluocinolone acetonide (Retisert), containing 0.59 mg of fluocinolone acetonide, which is released over 30 months [8]. A recent retrospective study conducted on six eyes of children with intractable posterior uveitis showed controlled inflammation in all and significant visual acuity improvement in half. However, concerns for development of cataract and secondary glaucoma remain [30[■]]. Another recent development, Ozurdex, is a biodegradable dexamethasone implant, and has been reported to have an improved side-effect profile, at least in adults [61]. There are very limited data showing the efficacy and safety in children. One recent retrospective case series in 14 eyes of 11 children with posterior segment uveitis showed control of inflammation and improvement in CME and visual acuity in all but one eye within a month, but 31% had a relapse within 6 months with a median time to relapse at 4 months [62[■]]. A retrospective series showed Retisert and Ozurdex to be comparable in efficacy; however, cataract progression and need for glaucoma treatment and surgery were higher with the Retisert implant [63[■]].

FUTURE DIRECTIONS

As our understanding of the mechanisms involved in ocular inflammatory diseases expands, new therapies will emerge. Currently, there are over 40 clinical trials for the treatment of uveitis registered at clinical trials database (clinicaltrials.gov) that span five continents. Therapeutic agents used range from intravitreal or suprachoroidal injections of novel agents and orally administered tolerance inducing peptides to novel small molecules and biologic agents. A small minority of these trials focuses on childhood uveitis. There are several potential therapeutic agents that are currently under investigation in other rheumatologic or

retinal disorders. For example, biologics that target IL-17, IL12/23, IL15, IL-22, and B-cell activating factor (BAFF) can also prove useful in pediatric uveitis in the future. Small molecules, different intravitreal drug delivery techniques for sustained or combined drug delivery, small interfering RNA (siRNA), microRNA technology, and gene transfer techniques hold promise for the treatment of uveitis. More clinical trials are needed to establish appropriate therapy and identify ways to predict and individualize therapy for the most at-risk children with uveitis.

CONCLUSION

Pediatric uveitis is an uncommon but serious disease. New treatment options have been rapidly emerging over the last decade and promise to continue this trend into the future as new technology and our understanding of the disease-immune system interface evolves. In this article, we have summarized the past, present, and predictable future of pediatric uveitis treatments. The mainstays of therapy include corticosteroids, antimetabolites, and T-cell inhibitors. In the last decade, biologic therapies have revolutionized our armory for treating pediatric uveitis, and novel corticosteroid delivery devices have enhanced our ability to provide longer-lasting local disease control. Further research is needed to ensure that development of novel treatments can continue to grow and maintains the highest level of safety and efficacy.

REFERENCES AND RECOMMENDED READING

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Additional references related to this topic can also be found in the Current World Literature section in this issue (p. 517).

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KEY POINTS

- Pediatric uveitis is an uncommon but potentially blinding condition with a higher rate of complications and vision loss than adults.
- Treatment should be a sufficiently aggressive anti-inflammatory therapy to quiet inflammation quickly and then maintenance of quiescence for a period of 2–3 years, after which tapered discontinuation of immunosuppression can be considered.
- Methotrexate remains the first-line immunomodulatory agent in pediatric uveitis.
- Biologic therapy, particularly the anti-TNF agents, is the newer generation of gold standard therapy and is commonly used in methotrexate failures.
- Many novel therapies for pediatric uveitis are under investigation; promising future interventions include biologics targeting of IL-1, IL-2, IL-6, as well as CD 20 and CD 80/86.

FIGURE 1.

Treatment algorithm for noninfectious pediatric uveitis. Corticosteroid (CS) implants (i.e., Ozurdex and Retisert) are not regularly used in children because of risks of cataract and glaucoma and their implications in children [30[■]]. * Alkylating agents are not commonly used due to serious long-term adverse effects, especially in children. Source: Original.

FIGURE 2.

A 16-year-old White girl with idiopathic noninfectious intermediate uveitis. She failed treatment with mycophenolate mofetil (a) but responded favorably when infliximab treatment was added (b) at 5 mg/kg dose. Note the improvement in retinal vascular leakage within 3 months of therapy. Source: Original.

FIGURE 3.

A 7-year-old girl with Blau syndrome (NOD2 mutation) associated granulomatous panuveitis complicated with (a) posterior synechiae in both eyes secondary to anterior uveitis as well as iris nodules (blue arrow) in the left eye. (b) She had a small peripapillary granuloma (yellow arrows) in the right eye. She also had a history of (c) skin lesions and (d) arthritis, which are features of Blau syndrome [50]. Source: Original except the two pictures of hands and back (obtained permission from Elsevier by Copyright Clearance Center) [50].

Table 1

Mechanisms and side-effects of selected treatments for pediatric uveitis

Category	Drug (trade name)	Mechanism of action	Side-effects
Glucocorticoid	Deltasone (Prednisone)	Multiple mechanisms	Cataracts, weight gain, stunted growth (children), acne, osteoporosis
Antimetabolites	Methotrexate (Trexall)	Inhibits dihydrofolate reductase	Bone marrow suppression, stomatitis, hair loss, hepatotoxicity
	Azathioprine (Imuran)	A purine nucleoside analogue that interferes with DNA and RNA synthesis	Bone marrow suppression, gastrointestinal symptoms
	Mycophenolate mofetil (Cellcept)	Inhibits inosine monophosphate dehydrogenase	Diarrhea, nausea, neutropenia, infection
T-cell inhibitors	Cyclosporine (Neoral, Sandimmune, Gengraf)	Calcineurin inhibitor	Nephrotoxicity, tremor, hirsutism, gum hyperplasia, hypertension
	^a Voclosporin		Hypertension, decreased renal function, pyrexia, arthralgia [10]
	Tacrolimus (Prograf)		Nephrotoxicity, hypertension, neurotoxicity, hepatitis, diabetes
	^a Sirolimus (Rapamune)	Inhibits mTOR pathway	Nephrotoxicity, hypersensitivity reaction, peripheral edema, hypertriglyceridemia, hypertension, hypercholesterolemia, thrombocytopenia
Alkylating agents	Chlorambucil (Leukeran)	DNA crosslinking	Bone marrow suppression, malignancy, sterility, infection
	Cyclophosphamide (Cytosan)		Bone marrow suppression, hemorrhagic cystitis, malignancy, sterility, alopecia, infection
Biologics	Infliximab (Remicade)	TNF inhibitor	Infection, tuberculosis, lymphoma, autoantibodies, demyelinating disease, worsening heart failure; local skin reaction at injection site (golimumab, adalimumab)
	^a Adalimumab (Humira)		
	Golimumab (Simponi)		
	Certolizumab pegol (CIMZIA)		
	Etanercept (Enbrel)		
	Anakinra (Kineret)	Anti-IL1R	Injection site reaction, infection
	Canakinumab (Ilaris)	Anti-IL1 β Ab	Injection site reaction, infection
	Daclizumab (Zenapax)	Anti-IL2R Ab	Infection, lymphoproliferative disorder, severe hypersensitivity reactions; Note: No longer commercially available

Category	Drug (trade name)	Mechanism of action	Side-effects
	^a Tocilizumab (Actemra)	Anti-IL6R Ab	Infection, hypercholesterolemia, infusion-related reaction
	Rituximab (Rituxan)	CD20R Ab	Infection, infusion-related reaction, neutropenia
	Abatacept (Orencia)	T-cell costimulation inhibitor	Infection, malignancy
Intravitreal corticosteroid implants	Dexamethasone (Ozurdex)	Multiple mechanisms	Significant IOP increase, cataract formation (less than fluocinolone acetate)
	Fluocinolone acetonide (Retisert)	Multiple mechanisms	Significant IOP increase and cataract formation

Ab, antibody; mTOR, mammalian target of rapamycin; R, receptor.

^aPotential compounds for the treatment of uveitis (clinicaltrials.gov).