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REVIEW

# Optimising drug therapy for non-infectious uveitis

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## Abstract

*Introduction* Uveitis encompasses a wide variety of sight-threatening diseases characterized by intraocular inflammation. It is often classified as infectious and non-infectious uveitis. Unlike infectious uveitis, a distinct infectious agent cannot be identified in non-infectious uveitis and disease origin is usually autoimmune, drug related, or idiopathic.

*The Issue at Hand* Non-infectious uveitis can often have a relapsing-remitting course, making it difficult to treat, and poses a significant challenge to ophthalmologists. The autoimmune nature of non-infectious uveitis warrants the use of anti-inflammatory and immunomodulatory agents for disease control. However, a subset of patients has persistent or recurrent ocular inflammation despite appropriate treatment, stressing the need for newer therapies aimed at more specific inflammatory targets such as tumour necrosis factor (TNF) alpha agents, anti-interleukin agents, and anti-interleukin receptor agents.

*Objectives* This article discusses the various medical options available for the treatment of non-infectious uveitis in the light of the most recent evidence.

*Conclusion* Successful management of non-infectious uveitis requires the clinician carefully balance advantages and disadvantages of each new and old therapy while considering individual circumstances. Counselling regarding the benefits and complications of each therapy can help patients make an informed choice.

**Keywords** Anti-TNF · Biologics · Corticosteroids · Uveitis

## Introduction

Uveitis is a term used to describe a group of heterogeneous diseases characterised by inflammation of the uveal tract and is broadly classified as infectious and non-infectious. Non-infectious uveitis is often related to systemic autoimmune conditions or is idiopathic. Clinical presentation is variable, and symptoms may include blurred vision, ocular pain, photophobia, and significant visual impairment [1]. Uveitis accounts for 15–20% of all cases of legal blindness in the USA [2], with uveitic macular oedema being a common cause of vision loss [2, 3].

The relapsing–remitting disease course makes management of non-infectious uveitis difficult. Traditionally, local or systemic corticosteroids have been the mainstay of treatment, but the associated side effects often limit their use [4].

With this in view, there have been new developments for treatment of non-infectious uveitis. The

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agents gaining recent recognition are sustained release corticosteroid implants and biologic agents, including agents targeting TNF alpha, a pro-inflammatory cytokine implicated in intraocular inflammation.

Non-infectious uveitis is a heterogeneous disease entity, with each specific aetiology leading to different presentations and complications. One would be remiss to generalise treatments from one disease entity to all non-infectious uveitis.

This article discusses the various medical options available for the treatment of different forms of non-infectious uveitis in the light of the most recent evidence with emphasis on the novel biologic agent adalimumab (ADA).

## Corticosteroids

### Systemic steroids

#### *Mechanism of action*

Corticosteroids suppress inflammation by inhibiting the expression of various pro-inflammatory factors. They also promote the expression of various anti-inflammatory factors.

*Summary*

Systemic corticosteroid treatment has been one of the reliable treatments for uveitis for many years. Cortisone, hydrocortisone, prednisone, and fludrocortisone are some of the steroids available for oral use. Prednisone is the most common oral steroid used for uveitis. It is initiated at 0.5–1 mg/kg daily, followed by slow tapering once inflammation control is achieved. Ideally, the dose should be less than 0.1 mg/kg daily within 3 months of initiation [5]. Table 1 summarises prednisone's ideal dosage and tapering schedule, as well some relevant points to consider. Certain baseline investigations must be undertaken before initiating therapy. Blood pressure, weight, fasting glucose (or HbA1C), lipids, and bone mineral density should be recorded prior to therapy. Details of a representative monitoring schedule are listed in Table 1. If chronic suppression requires an excess of 10 mg/day of prednisone/prednisone equivalent, a concurrent immunosuppressive agent should ideally be considered. This would necessitate further baseline testing, listed later in this article in other tables. A physician is obliged to counsel the patient extensively prior to therapy regarding possible side effects and the fact that sudden cessation can precipitate adrenal crisis.

**Table 1** Suggested guidelines on systemic prednisone use in non-infectious uveitis

| Parameter | Suggested guidelines |
| --- | --- |
| Initial dose | 1 mg/kg/day (when immediate effect is needed, intravenous methylprednisolone may be initiated at 1 gm/day for 3 days, initiating oral prednisone after this) |
| Maximum dose (adult) | 60–80 mg/day |
| Maintenance dose (adult) | 7.5 mg/day |
| Tapering schedule | Over 40 mg/day, decrease by 10 mg/day every 1–2 weeks |
| | 40–20 mg/day, decrease by 5 mg/day every 1–2 weeks |
| | 20–10 mg/day, decrease by 2.5 mg/day every 1–2 weeks |
| | 10–0 mg/day, decrease by 1–2.5 mg/day every 1–4 weeks |
| Monitoring schedule | Blood pressure, weight, glucose every 3 months |
| | Cholesterol and triglycerides annually |
| | Bone density within first 3 months and then annually |
| | If evidence of prior VZV infection, monitor for possible shingles |
| Supplements | Calcium 1500 mg, vitamin D 800 IU daily |
| | Estrogens and antiresorptive agents if required |

### Side effects

Despite their effectiveness, their side effects limit corticosteroid use. Long-term systemic therapy is associated with hypertension, osteoporosis, opportunistic infections, mania, and hyperglycaemia [4].

### Local steroids

### Periocular and intravitreal injections

### Mechanism of action

The mechanism of action of local steroids is identical to that of systemic; the only difference between the two is the mode of delivery to the eye.

*Summary* Triamcinolone acetonide injections (TAIs) have been approved by the FDA for intraocular use [6] and have shown to be effective in the treatment of posterior uveitis [7]. Bleriot et al. [8] assessed the safety and efficacy of subconjunctival TAIs retrospectively in 2014. The 12-month follow-up for 31 eyes showed that the mean logMAR visual acuity improved from $0.36 \pm 0.27$ at baseline to $0.24 \pm 0.21$ ($p = 0.0371$) at 12 months and there was no significant increase in IOP or rate of cataract development.

Sen et al. [9] evaluated the effectiveness and complications of periocular depot corticosteroid injections in a retrospective cohort of 1192 eyes of 914 patients with ocular inflammatory disorders and found 72.7% of eyes in remission. Improvement in visual acuity was noted in 50%.

Both intravitreal and orbital floor TAIs have been used in practice [10]. Roesel et al. [11] compared the two in a retrospective study of 97 uveitis patients with macular oedema resistant to other treatments. They reported no significant difference in visual acuity between the two groups at the 3-month follow-up point ($p = 0.23$), and macular oedema was significantly reduced in the intravitreal group compared to the orbital floor group ($p < 0.01$). Ocular hypertension (IOP > 21 mmHg) was noted in 21% of the intravitreal group and none of the orbital floor group ($p < 0.01$).

*Side effects* Intraocular hypertension, cataract development, and cataract progression are all possible side effects of these local injections. Clinicians should be wary of the serious adverse effect of endophthalmitis, which is a possibility with multiple intravitreal injections to the same eye. Retinal tears and detachments are also a possibility and should be considered as well.

### Sustained release steroid implants

### Mechanism of action

The implants are inserted directly into the posterior segment, and release corticosteroids over an extended period (months).

*Summary* Ozurdex (IDX), an intravitreal sustained release 0.7 mg dexamethasone implant, was FDA approved in 2010 for non-infectious uveitis involving the posterior segment. Zarranz-Ventura et al. published an 82-eye (63 patient) multicentre retrospective cohort study in 2014. The 63 patients received 142 IDX injections over 35 months. The mean logMAR visual acuity improved from $0.68 \pm 0.4$ (mean $\pm$ standard deviation) at baseline to $0.52 \pm 0.5$ at 12 months ($p < 0.01$). At the 12-month follow-up, 40.7% of 54 remaining eyes had undergone 2 injections and 11.2% had required $\geq$ 3 injections [12].

Retisert (AFI), a non-biodegradable 0.59 mg fluocinolone acetonide pellet, was FDA approved for use in non-infectious posterior uveitis in 2005 [13]. Sangwan et al. published the results of a 3-year, 239-patient, RCT evaluating AFI with non-infectious uveitis in 2015. They compared two implants: the standard 0.59 mg AFI and a newer 2.1 mg AFI. Overall, recurrence rates for eyes treated with any AFI decreased significantly from 42.3% prior to implantation, to 25.9% during the 3-year post-implantation period ($p = 0.0003$). Significantly more eyes receiving AFI gained $\geq$ 3 lines of BCVA compared to fellow eyes that did not receive AFI ($p \leq 0.005$). However, nearly all eyes receiving AFI (94.9%) required cataract surgery subsequent to treatment, and IOP elevations were noted in noted in 68.6% of study eyes. Comparing the two implants, there was no significant difference in IOP elevations [14].

A similar study comparing AFI and IDX in non-infectious uveitis was published by Arcinue et al. in 2013. It was a 27-eye comparative case series

evaluating recurrence rates of uveitis after implantation. They found no statistically significant difference between the two implants' recurrence rates ($p = 0.41$). However, eyes receiving IDX were 5 times more likely to require a second implant ($p = 0.02$). Eyes receiving AFI were likelier to require more glaucoma medications, surgery, or laser ($p = 0.02$), and were 4.7 times more at risk of cataract progression than IDX eyes ($p = 0.04$) [15].

Iluvien (IFI) is an injectable intravitreal fluocinolone acetonide. It releases lower amounts of the drug than AFI (0.2 ug or 0.5 ug/day vs. 0.59 ug/day) [16]. It was approved for use in diabetic macular oedema by the FDA in 2014. There are currently no published studies exploring IFI's utility in non-infectious uveitis. However, there is a pilot phase-I study underway to investigate this [17].

*Side effects* Notable side effects have been mentioned previously for local steroid injections. However, AFI appears to have the worst side-effect profile, with glaucoma and cataract progression being more prevalent in AFI compared to the other implants. A summary of steroidal treatment options is presented in Table 2.

## Antimetabolites

Methotrexate (MTX)

*Mechanism of action*

Methotrexate inhibits dihydrofolate reductase and causes a defect in purine and pyrimidine synthesis, thereby inhibiting DNA production. However, a second mechanism is the suppression of amino-imidazole-carboxamide-ribonucleotide transformylase, which causes a build-up on adenosine. Adenosine suppresses lymphocytes, macrophages, dendritic cells, and neutrophils; therefore, this suppresses inflammation.

*Summary* In 2001, Samson et al. published one of the largest case series studying MTX use in controlling ocular inflammation in 160 patients with non-infectious uveitis. Inflammation was successfully controlled in 76% of patients. Gangaputra et al. identified 384 patients from the Systemic

Immunosuppressive Therapy for Eye Diseases (SITE) cohort retrospectively and evaluated MTX treatment outcomes in non-infectious ocular inflammatory diseases. They reported that ocular inflammatory disease was suppressed in 66% of patients at 1 year. Treatment success was highest for anterior uveitis and scleritis [18].

*Side effects* Adverse effects of MTX therapy include fatigue, stomatitis, debilitating nausea and are usually transient. Hepatotoxicity, cytopenia, and interstitial pneumonitis are amongst the more serious effects [18–21].

### Mycophenolate Mofetil (MMF)

*Mechanism of action*

Mycophenolate Mofetil is an inhibitor of inosine monophosphate dehydrogenase, the rate-limiting enzyme responsible for the de-novo synthesis of guanosine. Lymphocytes are somewhat more dependent on this pathway than other cell types, and the drug has a higher affinity for the isoform present in activated lymphocytes. This results in a cytostatic effect on lymphocytes and a decrease in inflammation.

*Summary* The multicentre SITE retrospective cohort conducted in 2010 reported control of ocular inflammation with MMF in 55, 65, and 51% of the 236 patients with anterior, intermediate, and posterior/panuveitis, respectively, within 6 months that improved to a mean of 73% at 1 year [22].

*Side effects* GI-related symptoms are most commonly seen. Other less frequently reported included leucopenia and opportunistic infections.

### Azathioprine (AZT)

*Mechanism of action*

Azathioprine is a purine analog, a pro-drug of 6-mercaptopurine. It incorporates into replicating DNA and blocks the replication process. It also hinders the de-novo synthesis of purines, making it more specific to lymphocytes, as they lack the salvage pathway.

**Table 2** Summary of steroidal treatment options for non-infectious uveitis

| Name | Target | Efficacy | Dose | Mode of administration | Side effects (potential) |
|---|---|---|---|---|---|
| *Systemic* | | | | | |
| Systemic corticosteroids | Multiple | Variable; usually used as last line of treatment. Mostly high efficacy | See Table 1 for representative dosing schedule | PO | Hypertension; osteoporosis; opportunistic infections; mania; hyperglycaemia [4] |
| *Local injections* | | | | | |
| Triamcinolone acetonide (subconjunctival) | Multiple | Early studies are promising | 40 mg in 1 ml; schedule individualised according to patient response | S-Conj | Intraocular hypertension; cataract development; cataract progression; **intravitreal injections have the possible vision-threatening adverse effect of endophthalmitis (especially with repeated injections)** |
| Triamcinolone acetonide (orbital floor) | | Up to 76% response rate 1 month after injection, in uveitis of multiple aetiology [11] | 40 mg in 1 ml; schedule individualised according to patient response | O-Floor | |
| Triamcinolone acetonide (intravitreal) | | Up to 100% response rate 3 months after injection, in uveitis of multiple aetiology [11] | 4 mg in 0.1 ml; schedule individualised according to patient response | IVT | |
| *Sustained release steroid implants* | | | | | |
| Ozurdex | Multiple | Up to 88% probability of vitreous haze improvement at 12 months, in uveitis of multiple aetiology [12] | 0.7 mg per implant; schedule individualised according to patient response | IVI | Significant intraocular hypertension; almost certain cataract development; almost certain cataract progression; **intravitreal implants have the possible vision-threatening adverse effect of endophthalmitis (especially with repeated implantation)** |
| Retisert | | Up to 80% decrease in requirement of adjunctive therapy 3 years post-implantation, in uveitis of multiple aetiology [14] | 0.59 mg per implant; schedule individualised according to patient response | INS | |

*PO* per oral, *S-Conj* subconjunctival injection, *O-Floor* orbital floor injection, *IVT* intravitreal injection, *IVI* intravitreal implant, *INS* incision, insertion, and suturing; response rate refers to suppression of inflammatory activity unless noted otherwise

*Summary* Pasadhika et al.'s [24] retrospective review of the SITE cohort demonstrated that AZT controlled inflammation in 62% of the studied cohort of 145 patients. A RCT of 73 patients by Yazici et al. in 1990 showed inflammation free rates in more than 50% patients [25]. Incidence of side effects was reported to be higher in the AZT group (0.29/PY) by Galor et al. [21] compared to the other antimetabolites (0.14/patient years [PY] for MTX and 0.18/PY for MMP). Rate of discontinuation was similarly higher with AZT in a study conducted by Pasadhika et al. [24]; AZT was discontinued due to side effects at a rate of 0.16/PY, versus 0.13/PY for MTX.

*Side effects* Common reported side effects causing discontinuation in Pasadhika et al.'s study included gastrointestinal reactions, bone marrow suppression, elevated liver enzymes, infection, and allergic reactions.

*Cyclophosphamide (CYCP)*

*Mechanism of action*

Cyclophosphamide alkylates the guanine base in DNA, leading to cell death. It has a cytotoxic effect on both resting and dividing lymphocytes.

*Summary* The SITE retrospective cohort of 215 patients evaluating cyclophosphamide found ocular inflammation in uveitis to be controlled in 50% patients within 6 months that subsequently improved to 81% by 12 months. Steroid sparing effect similarly showed a time dependent improvement from 30.1% at 6 months to 61.2% at 12 months. Ocular remission rates with subsequent discontinuation of therapy were highest with CYCP at 63% compared to SITE cohorts [26].

*Side effects* Most common adverse effects include leucopenia and cystitis/haematuria. Opportunistic infections especially *Pneumocystis carinii* pneumonia have also been noted [26, 27]. Other serious effects include secondary malignancy, teratogenicity, and gonadal dysfunction. Treatment with CYCP is hence recommended in severe, vision-threatening causes of ocular disease [26].

*Cyclosporine A (CsA)*

*Mechanism of action*

Cyclosporine blocks the calcineurin pathway in T cells, blocking transcription of DNA. It also blocks the JNK and p38 signalling pathways in T cells, which results in it being a very potent T cell inhibitor.

*Summary* There are multiple studies establishing cyclosporine's efficacy in rapidly controlling ocular inflammation. The SITE CsA report published in 2010 by Kacmaz et al. reported that 33.2% of the 373 patients had complete control of disease by 6 months that went up to improve by 12 months at 51.9% [28]. Cyclosporine is contraindicated in neuro-Behcet's disease, as CsA has serious neurological side effects [29].

*Side effects* Side effects include metabolic abnormalities, nephrotoxicity, gingivitis, and hirsutism. Out of 373 patients in Kacmaz et al's study, 11% had to cease the drug within a year due to side effects [28]. The most common adverse effect appears to be neurotoxicity, which occurs in up to 40% of patients. The most serious complication is a reversible posterior leukoencephalopathy syndrome [30].

Tacrolimus

*Mechanism of action*

Like CsA, tacrolimus too is a calcineurin inhibitor. After it binds to FK506 binding protein, the complex formed inhibits calcineurin in a manner similar to CsA.

*Summary* Multiple, non-randomised clinical studies have shown tacrolimus' effectiveness in uveitis cases refractory to CsA, including Behcet's disease-associated uveitis [31, 32]. The favourable outcomes were maintained in a long-term follow-up study. A recent RCT by Murphy et al. comparing the two calcineurin inhibitors in 37 patients found them to be comparable with response rates of 67% for CsA versus 68% for tacrolimus [33].

*Side effects* Tacrolimus, however, has a significantly more favourable side-effect profile than CsA, particularly its effect on systemic blood pressure, serum cholesterol level, hyperglycaemia, and overall cardiovascular morbidity [33, 34].

## Biologics

Anti-TNF agents

Tumour necrosis factor plays a key role in the inflammatory process, and molecules targeting it are particularly useful in halting the process and therefore in various forms of non-infectious uveitis. To this effect, various monoclonal antibodies are employed in this class. A side effect of using them is the sensitisation of the body to their use and development of antibodies against these molecules. However, adalimumab, being a fully human antibody, has a lower risk of this happening and is therefore less immunogenic.

*Adalimumab (ADA)*

*Mechanism of action* Adalimumab is a fully human monoclonal antibody targeting TNF alpha.

*Summary* Adalimumab's role in the treatment of non-infectious uveitis was first recognised in 2008 by Diaz-Llopis et al. [35]. Several studies have

subsequently established the effectiveness of ADA in non-infectious uveitis associated with autoimmune systemic diseases. In 2009, Rudwaleit et al. published a 1250-patient phase-III prospective study on the use of ADA for anterior uveitis in ankylosing spondylitis and reported 51% of patients as having experienced a significant decrease in anterior uveitis flares ($p < 0.001$) [36]. In 2012, Diaz-Llopis et al. published a 131-patient prospective multicentre case series evaluating ADA therapy in refractory non-infectious uveitis of multiple aetiologies. They found a statistically significant improvement in the mean intraocular inflammation between baseline and the 6-month visit ($p < 0.001$). A statistically significant improvement in mean baseline logMAR Best Corrected Visual Acuity (BCVA) and the mean logMAR BCVA at the 6-month visit ($p < 0.001$) was also reported. In a study by Bawazeer et al., complete resolution of ocular inflammation was reported in 10 out 11 patients with Behcet's disease-associated uveitis within 4 weeks of initiation of ADA therapy [37]. Suher et al. assessed the use of ADA in a prospective, multicentre trial in 31 subjects with refractory non-infectious uveitis including those with Vogt–Koyanagi–Harada (VKH) disease, and birdshot retinochoroidopathy (BSCR). 68% of the participants achieved clinical response at 10 weeks of treatment initiation, and 39% had sustained effect after 50 weeks [38].

In 2014, Simonini et al. published a meta-analysis comparing ADA, infliximab (IFN), and etanercept (ETA), in paediatric autoimmune chronic uveitis. Data analysed from a total of 23 studies (229 patients) showed ADA to have superior efficacy resulting in improvement of inflammation in 87% of patients, compared to IFN (72%) and ETA (33%) [39].

The major trials evaluating ADA's efficacy and safety were the VISUAL I and VISUAL II trials. VISUAL I was a multicentre randomised controlled trial (RCT) assessing ADA's efficacy and safety in 217 patients with *active*, non-infectious uveitis while receiving systemic corticosteroid treatment. Results showed that patients receiving ADA were less likely to experience treatment failure ($p < 0.001$) and had a statistically significant improvement in logMAR BCVA compared to the placebo group (26.2, 95% CI 7.0–45.3; $p = 0.008$). The median time to treatment failure was 13 weeks for the placebo group and 24 weeks for the ADA group. Macular oedema risk

was reduced by 67% in the ADA group versus placebo ($p = 0.023$) [40, 41].

VISUAL II was a 229-patient multicentre RCT which assessed ADA in patients with *inactive*, non-infectious uveitis while on systemic corticosteroid therapy. The study showed that patients who received ADA were less likely to have treatment failure when compared to the placebo group ($p = 0.004$). Median time to treatment failure was 8.3 months for the placebo group and could not be estimated for the ADA group, as over 50% of the ADA-treated patients did not experience treatment failure [42].

Based on the findings of the VISUAL I and VISUAL II trials, ADA was approved by the FDA for use in non-infectious uveitis in 2016 and is currently the only non-steroid treatment approved for this purpose [43].

*Side effects*  In 2012, Burmester et al., in an analysis of 71 clinical trials, noted serious opportunistic infection as the most commonly encountered side effect of ADA. Malignancy risk, which was an initial concern, was not higher than the general population [44]. Notably, there were no serious opportunistic infections reported for psoriasis patients. While this study was published prior to ADA's approval for uveitis, the dosage and treatment regimen for psoriasis and uveitis is similar (80 mg loading dose, then 40 mg every other week starting one week after loading) [45]. It is therefore reasonable to assume that adverse effects reported for psoriasis would be comparable to those in non-infectious uveitis.

### Infliximab (INF)

*Mechanism of action*  Infliximab is a chimeric (human/mouse) monoclonal antibody targeting TNF alpha.

*Summary*  Infliximab's use in uveitis was first reported in 2001 [46]. In 2012, Markomichelakis et al. undertook a prospective, pilot study of 15 patients that assessed the safety and efficacy of intravitreal (IV) INF for sight-threatening uveitis due to Behcet disease. They found that patients suffered no ocular or extra-ocular side effects in the first month and there was a significant increase in logMAR BCVA (mean = 0.30; $p < 0.0001$). Anterior chamber cells and vitreous haze also decreased significantly (both

$p < 0.0001$). Central macular thickness decreased from a baseline mean of 434–309 μm at the end of follow-up ($p < 0.0001$) [47]. A second study undertaken by the same author comparing a single infliximab infusion (5 mg/kg, 19 eyes), methylprednisolone (1 g/day for 3 days, 8 eyes), and intravitreal triamcinolone acetonide injection (4 mg, 8 eyes), demonstrated that those receiving infliximab achieved significantly faster resolution of panuveitis attacks in Behcet's disease than those given corticosteroid therapy. They concluded that single infliximab infusions should thus always be considered, even if only as adjunct [48]. Similar results on its efficacy were demonstrated by Suhler et al. in 4 patients with Behcet's-related panuveitis, and it has also been shown to be more effective than conventional therapy [49, 50].

In 2016, Vallet et al. published a 160-patient multicentre retrospective chart review comparing the ADA and INF [51]. They found the two agents did not differ significantly in achieving complete response ($p = 0.39$), and side effects ($p = 0.089$). Overall response rate was 97% amongst the INF group and 95% in the ADA group.

Infliximab may also be effective for management of uveitis associated with Vogt–Koyanagi–Harada disease, sarcoidosis, HLA-B27 birdshot retinochoroidopathy, par planitis, multifocal choroiditis, and idiopathic uveitis [52].

*Side effects*  As with ADA, the most serious side effect appears to be opportunistic infection. Infusion reactions are one of the more common side effects [53].

### Etanercept (ETA)

*Mechanism of action*  Etanercept is a dimeric fusion protein consisting of the extracellular ligand-binding portion of the p75 TNF receptor that is covalently bonded to the Fc portion of human IgG1. It functions as a decoy receptor for TNF alpha.

*Summary*  Etanercept was investigated as a possible agent for non-infectious uveitis in 2001 by Reiff et al. in a prospective study that included 16 paediatric eyes [54]. A 20 patient RCT assessing the efficacy of ETA was published in 2003 by Foster et al. They found no significant difference in the efficacy of ETA as

compared to placebo in preventing relapses in patients being tapered from methotrexate ($p = 0.66$; Fisher exact test) [55]. Etanercept appeared to perform poorly against ADA and INF in the meta-analysis published by Simonini et al., with both ADA ($p < 0.001$) and INF ($p < 0.001$) exhibiting superior efficacy compared to ETA [39]. Although etanercept has been successfully shown to control Behcet's uveitis-related inflammation in different case reports, the resolution was not sustained once the drug was stopped. Based on existing data, etanercept is currently recommended as a second line agent for management of ocular inflammation after infliximab and adalimumab, which are believed to be more effective [21, 56, 57].

*Side effects*  Injection site reactions are the most common side effect. There are concerns about demyelinating diseases caused by etanercept, but the most serious side effect remains opportunistic infection [53].

### Golimumab (GOL)

*Mechanism of action*  Golimumab is a fully human monoclonal antibody targeting TNF alpha.

*Summary*  Currently, there are only a small number of studies published using GOL in non-infectious uveitis, with relatively small sample sizes [58–61]. A retrospective case series of 34 eyes by Miserocchi et al. found that there was a decrease in flare, before and after treatment and that stabilisation of visual acuity in most eyes ($n = 26$) and improvement in 7. The conclusion was that GOL was a viable candidate for the treatment of non-infectious uveitis in cases recalcitrant to treatment with other biologic agents [62].

Santos-Gomez et al. assessed the use of alternative biologics in 7 patients (golimumab = 4, tocilizumab = 2 and rituximab = 1) with refractory Behcet's unresponsive to ADA and infliximab. In all 7 patients, complete resolution of ocular inflammation was achieved and maintained up to 1 year of follow-up [63].

*Side effects*  Injection site reactions are the most common adverse effect, with mild infections being the second most common [64]. Clinicians should always

be on the lookout for the potential of serious opportunistic infections.

Immunomodulatory agents

*Abatacept (ABA)*

*Mechanism of action*

Abatacept is a humanised CTLA-4-immunoglobulin-Fc fusion protein that binds the CD80 and CD86 ligands, preventing CD28 stimulation on T lymphocytes.

*Summary* Tappeiner et al. published a multicentre retrospective analysis on the efficacy of ABA in 21 patients with severe JIA-associated uveitis. They observed that although 11 (52.4%) patients had uveitic inactivity during at least one follow-up visit, 8 had recurrences in subsequent visits. Ten patients did not respond to ABA during the entire course of the follow-up. There was no significant difference in uveitis activity before and after initiating ABA treatment and no significant change in visual acuity [65].

*Side effects* Opportunistic infections appear to be a significant concern, but the side effect to keep in mind for ABA is a notable blunting of the response to vaccination; patients failed to achieve seroprotective levels after influenza vaccination while on ABA [66].

*Rituximab (RIT)*

*Mechanism of action*

Rituximab is a chimeric (mouse/human) monoclonal antibody that targets CD20.

*Summary* Rituximab has shown promising results in uveitis of varying aetiologies [67, 68]. In 2015, Miserocchi et al. published a 15-eye retrospective study which assessed the response of treatment-refractory JIA-related uveitis to RIT. They found mean number of uveitis recurrences decreased from 0.7 to 0.2 episodes per year after treatment with RIT. At the end of follow-up, only 3 patients needed daily low dose prednisolone (2.5–7.5 mg) [69].

A pilot study involving 20 patients with severe manifestations of Behcet's uveitis reported significant improvement in the total adjusted disease activity index (TADAI) in the rituximab group compared to the cytotoxic group receiving cyclophosphamide and methotrexate [68].

*Side effects* Infusion reactions are the most commonly reported adverse effect. However, minor bacterial infections, serious viral infections, arrhythmias, and malignancies have all been reported in past [70].

*Interferon alpha-2a*

*Mechanism of action*

Interferon alpha-2a is a cytokine, and its mechanism of action is largely unclear. It has been suggested it may reduce HLA-1 on monocytes. However, the exact mechanism is not yet discovered.

*Summary* In 2016, Hasanreisoglu et al. published a 39-patient retrospective study, comparing 23 patients receiving azathioprine-cyclosporine and 16 patients receiving Interferon alpha-2a. They found a significant decrease in uveitis attacks/year after initiation of Interferon treatment ($2.4 \pm 1.8$ vs. $1.3 \pm 2.0$; $p = 0.041$), but this was not statistically significant ($p > 0.05$). They concluded that interferon alpha-2a is a viable alternative to conventional combination therapy for Behcet's uveitis [71]. A systematic review evaluating efficacy of IFN-alpha in Behcet's uveitis ($n = 182$ patients) observed 94% of the cohort achieved partial or complete resolution of inflammation. They suggested IFN-alpha as a reliable and effective modality for management of Behcet's uveitis with low relapse rates on treatment cessation [72]. The results of a RCT using Interferon alpha-2a in Birdshot Chorioretinopathy-related uveitis are yet awaited [73].

*Side effects* The main side effect appears to be a flu-like syndrome that responds well to oral acetaminophen. Hair loss, rash, and possible marrow suppression are also to be considered.

Anti-interleukin agents

### Secukinumab

*Mechanism of action*

Secukinumab is a human monoclonal anti-IL17A antibody.

*Summary* Secukinumab (SEC): Secukinumab is a human monoclonal anti-IL17A antibody. Subcutaneous Secukinumab has not shown promise in non-infectious uveitis, as published by Dick et al. in 2013. They published the results of three RCTs; the SHIELD, INSURE and ENDURE trial. The SHIELD trial results showed no statistically significant difference between treatment and placebo groups for Behcet's uveitis recurrence rates ($p = 0.445$), and the INSURE trial was terminated early due the lack of efficacy of SEC in the SHIELD trial. ENDURE too showed no significant difference between treatment and placebo groups [78]. Secukinumab is currently not employed for Behcet's management.

An RCT by Letko et al. published in 2015 hypothesised that a different mode of administration would yield better results. They compared different intravenous (IV) and SC doses of SEC in 37 patients with non-infectious uveitis requiring corticosteroid-sparing immunosuppressive therapy. The IV route in comparison, produced higher response rates (72.7 and 61.5% vs. 33.3%, respectively) and remission rates (27.3 and 38.5% vs. 16.7%, respectively). Their conclusion was that the SC route used by the previous studies was insufficient to deliver substantial therapeutic benefit and that high-dose IV SEC should be used in the future [79].

*Side effects* Paradoxically, Dick et al. report that their patients encountered exacerbation of systemic Behcet's, uveitis, and folliculitis. Nasopharyngitis, headache, and arthralgias seemed to be most common side effects [78].

### Gevokizumab (GEV)

*Mechanism of action* Gevokizumab is a monoclonal anti-IL1-beta antibody and currently does not have FDA approval for any indication.

*Summary* Gevokizumab is a monoclonal anti-IL1-beta antibody and currently does not have FDA approval for any indication. Evidence related to its safety and efficacy is scarce. A phase-III study conducted with gevokizumab for Behcet's disease uveitis concluded that compared to placebo, gevokizumab did not significantly reduce risk of uveitis exacerbations, the primary outcome being evaluated. However, it was suggested that gevokizumab could positively affect visual outcome and reduce disease severity (EYEGUARD) [80]. Tugal-Tutkun et al. published a 21-patient prospective RCT in 2016, assessing the efficacy of GEV in Behcet's disease-related uveitis. Response to *GEV* was defined as improved vitreous haze score by $\geq 2$ units, $\geq 15$-letter improvement in BCVA, and resolution of retinal inflammation. They reported that most patients responded within 1 week of initiation of treatment and that there was a mean improvement of BCVA from baseline of $22.40 \pm 15.37$ letters [81].

*Side effects* Evidence related to its safety and efficacy is scarce.

Anti-interleukin receptor agents

### Anakinra

*Mechanism of action* It is a recombinant version of the human IL-1 receptor antagonist protein.

*Summary* Although recognised to be effective in animal models of uveitis [74], to date there has been no RCT testing the use of this drug in patients with non-infectious uveitis and a clinical trial of Anakinra for the treatment of Behcet's disease is now recruiting participants. The evidence related to its use is mostly derived from isolated case reports or series reporting good results [75, 76]. The most recent case series was published by Cantarini et al. in 2015, in which Anakinra was used in 9 patients with drug-resistant Behcet's disease. Three patients had complete resolution of intraocular inflammation initially, but suffered a relapse after an average period of 24 weeks [77].

*Side effects* Anakinra's most common side effect is injection site reaction. If used in concert with anti-TNF agents, neutropenia and opportunistic infections

**Table 3** Summary of non-steroidal treatment options for non-infectious uveitis

| Name | Target | Efficacy | Dose | Mode of administration | Side effects (potential) |
|---|---|---|---|---|---|
| *Anti-TNF alpha agents* | | | | | |
| Adalimumab | TNF alpha | Up to 95% response rate in uveitis including Behcet's disease, JIA, spondyloarthropathy, and sarcoidosis [50] | 80 mg loading dose, then 40 mg at 1 week, then every 2 weeks | SQ | Injection site reactions; hypersensitivity reactions; increased susceptibility to infections; reactivation of latent infections (TB, histoplasmosis, fungal infections); malignancy; increased risk of thromboembolic events; congestive heart failure |
| Infliximab | | Up to 97% response rate in uveitis including Behcet's disease, JIA, spondyloarthropathy, and sarcoidosis [50] | 3–5 mg/kg at 0, 2, and 6 weeks, and then every 8 weeks | IV | |
| Etanercept | | Equivalent to placebo in uveitis including idiopathic, HLA-B27, systemic lupus erythematosus, and rheumatoid arthritis [38] | 50 mg weekly | SQ | |
| Golimumab | | Early studies are promising in refractory Behcet's unresponsive to Adalimumab and infliximab [62] | 50 mg monthly | SQ | |
| *Immunomodulatory agents* | | | | | |
| Abatacept | CTLA-4 | Not particularly promising in JIA-associated uveitis; other results awaited [64] | 500 or 1000 mg at 0, 2, and 4 weeks. Repeat every 4 weeks thereafter | IV | Increased infection susceptibility; malignancy; respiratory issues in chronic obstructive pulmonary disease patients, failure to achieve seroprotection following vaccination |
| Rituximab | CD20 | Early studies are promising in JIA and Behcet's [67, 68] | 500 or 1000 mg at 0, and 2 weeks. Repeat at 6–12 months if needed | IV | Increased infection susceptibility; infusion reactions; gastrointestinal upset |
| Interferon alpha-2a | Multiple; largely unclear | Up to 94% response rate in Behcet's uveitis [71] | 3 to 6 million U/day, tapered over 6 months | SQ | Injection site reactions; flu-like constitutional symptoms; marrow suppression |

**Table 3** continued

| Name | Target | Efficacy | Dose | Mode of administration | Side effects (potential) |
|---|---|---|---|---|---|
| *Anti-interleukin agents* | | | | | |
| Secukinumab | IL17A | Early studies suggested placebo equivalency, later studies suggest IV administration versus SQ having incr. efficacy [74] | Effective but experimental IV doses tested were 30 mg/kg every 4 weeks for 2 doses and 10 mg/kg every 2 weeks for 4 doses; SQ dose is 300 mg every 2 weeks for 4 doses | SQ/IV | Upper respiratory tract infections; neutropenia; candidiasis |
| Gevokizumab | IL1-beta | Failed phase-III trial in Behcet's uveitis [75] | 60 mg once monthly | SQ | Not enough data to reasonably associate side effects with causality |
| *Anti-interleukin receptor agents* | | | | | |
| Anakinra | IL-1R | Early studies on Behcet's disease are promising; further investigation is warranted [78, 79] | 100 mg/day (with concurrent 25 mg/day Prednisone for severe Behcet's cases) | SQ | Infections (particularly if used in concert with TNF inhibitors); injection site reactions |
| Tocilizumab | IL-6R | Early studies are promising; particularly useful in JIA [86] | 4–12 mg/kg every 2–4 weeks | IV | Infections; hypersensitivity reactions; intestinal perforation |
| Daclizumab | IL-2R | Discontinued by the manufacturer | NA | NA | NA |
| *Antimetabolites* | | | | | |
| Methotrexate | Dihydrofolate reductase | Up to 76% response rate in patients with chronic uveitis of multiple aetiology unresponsive to conventional treatment [18] | 7.5 to 25 mg/week every week and titrated to effect, max 50 mg/week (with concurrent 1 mg/day folic acid supplementation) | PO/IM/SQ | Fatigue; stomatitis; hair loss; nausea; neutropenia; foetal death; infections; hepatotoxicity; interstitial pneumonitis |
| Azathioprine | Purine metabolism | Up to 62% response rate at 1 year, in the SITE cohort with multiple ocular inflammatory disorders [23] | 1–4 mg/kg/day | PO | Gastrointestinal disturbance; nausea; hepatotoxicity; marrow suppression; allergic reaction; **more side effects than other antimetabolites** [20] |
| Mycophenolate Mofetil | Inosine monophosphate dehydrogenase | Up to 73% response rate at 1 year, in the SITE cohort with multiple ocular inflammatory disorders [22] | 500 mg BID/day, increased to 1000 mg BID/day after 2 weeks | PO | Gastrointestinal upset; leucopenia; opportunistic infection |

**Table 3** continued

| Name | Target | Efficacy | Dose | Mode of administration | Side effects (potential) |
|------|--------|----------|------|------------------------|--------------------------|
| Cyclophosphamide | Nucleic acid alkylator | Up to 81% response rate at 1 year, in the SITE cohort with multiple ocular inflammatory disorders [25] | 1–3 mg/kg/day | PO | Opportunistic infections esp. PCP pneumonia; marrow suppression; haemorrhagic cystitis; malignancy; hair loss; infertility |
| Tacrolimus | T cells | Up to 68% response rate within 3 months of treatment in posterior and intermediate uveitis of multiple aetiologies [32] | 0.15–0.30 mg/kg/day | PO | Nephrotoxicity; hypertension; drug-induced diabetes mellitus; electrolyte imbalances |
| Cyclosporine A | | Up to 51.9% response rate at 1 year, in the SITE cohort with multiple ocular inflammatory disorders [27] | 2–5 mg/kg/day BID tapered every 2–3 months by 10% to prevent recurrence of inflammation | PO | **Nephrotoxicity (avoid doses > 5 mg/kg/day to minimise risk)**; hypertension; hirsutism; gingival hyperplasia; **more side effects than tacrolimus** [30] |

*PO* per oral, *IM* intramuscular, *IV* intravenous, *SQ* subcutaneous; response rate refers to suppression of inflammatory activity unless noted otherwise

are side effects that may occur. There have been reports of elevated liver enzymes and lipids.

*Daclizumab (DAC)*

*Mechanism of action* Daclizumab is a humanised monoclonal antibody targeting IL-2 receptors.

*Summary* Daclizumab has been studied extensively in the last decade with respect to non-infectious uveitis [82–84]. Most of these studies did not report any substantial increase in visual acuity of patients. Yeh et al. conducted a prospective pilot study of high-dose intravenous daclizumab therapy in active uveitis of various etiologies including BSRC, VKH, and idiopathic uveitis. All 5 patients demonstrated a decrease in vitreous haze and intraocular inflammation at the end of final follow-up [85].

Buggage et al. conducted a 17-patient RCT in 2007 to investigate the safety and efficacy of DAC in controlling the ocular manifestations of Behcet's disease. Primary efficacy outcomes were the number of ocular attacks, and no significant differences were reported between placebo and treatment groups [84].

Despite promising results in managing uveitis, daclizumab was discontinued by the manufacturer in 2009 due to diminishing market demand with available alternative treatments [52].

*Side effects* Safety data outlining DAC use in uveitis are relatively limited in the literature. In 2011, Wroblewski et al. published a 39-patient retrospective chart review assessing the efficacy and safety of DAC over a mean of 40.3 months. They reported stabilisation of visual acuity and prevention of uveitic flares in most cases. Cutaneous reactions were a common adverse effect; 4 patients developed solid tumours during treatment [86].

*Tocilizumab*

*Mechanism of action* Tocilizumab is an anti-IL-6 receptor monoclonal antibody.

**Table 4** Suggested screening tests prior to initiation of therapy

| Drug | Recommended pre-treatment screening and assessment |
|---|---|
| **Steroids** | |
| *Systemic corticosteroids* | Ophthalmic and systemic history |
| | Slit-lamp exam |
| | IOP |
| | Dilated fundal exam |
| | Blood pressure |
| | Weight |
| | Glucose/HbA1c |
| | Cholesterol & triglycerides |
| | Bone density |
| | VZV quantitative titres |
| | Counselling |
| *Local injections* | Ophthalmic and systemic history |
| | Slit-lamp exam |
| | IOP |
| | Dilated fundal exam |
| | Monitoring of relevant rheumatic disorder |
| **Biologics and others** | |
| *Anti-TNF alpha agents* | Ophthalmic and systemic history |
| *Immunomodulatory agents* | Slit-lamp exam |
| *Anti-Interleukin agents* | IOP |
| *Anti-Interleukin receptor agents* | Dilated fundal exam |
| *Antimetabolites* | Complete blood count |
| | Liver function tests |
| | HIV, HBsAg, Anti-HBs, Anti-HBc, Anti-HCV |
| | Glucose/HbA1c |
| | Cholesterol & triglycerides |
| | TST/IGRA |
| | ESR, CRP |
| | Chest radiograph |
| | Electrocardiogram/echocardiogram |
| | Urine analysis |
| | Pregnancy test |
| | Antinuclear antibodies |

*Summary* Tocilizumab is an IL-6 receptor monoclonal antibody, currently approved for the treatment of RA, as well as polyarticular and systemic JIA. It has also demonstrated efficacy in successfully managing JIA-associated uveitis refractory to methotrexate, adalimumab and etanercept [87]. Resolution has also been reported for additional ocular inflammatory conditions as reported in literature [88, 89].

*Side effects* Side effects include injection site reactions, nasopharyngitis, increased liver transaminases, dose-dependent neutropenia, lipid elevations and mouth ulceration. Pancreatitis and Steven–Johnson Syndrome have also been reported as serious adverse effects. There is a rare side effect of intestinal perforation.

A summary of non-steroidal treatment options is presented in Table 3.

## Conclusion

At present the treatment of non-infectious uveitis poses a significant challenge to ophthalmologists due to its relapsing nature and varied disease aetiology. Local and systemic steroids have conventionally been used for disease control. However, corticosteroid-sparing agents are now becoming an integral component in the long-term management of non-infectious uveitis. Biologic agents such as adalimumab and infliximab have proven to be highly effective, and there is growing evidence to suggest that other anti-TNF alpha biologics, anti-interleukin, and anti-interleukin receptor agents may also be beneficial. Immunomodulatory agents as well as antimetabolites have a long history of being useful in uveitis related to systemic inflammatory disorders. Successful management of non-infectious uveitis often requires the clinician to carefully balance the advantages and disadvantages of each therapy while considering individual patient circumstances. A summary of the recommended screening tests that should be undertaken for each class of drug is presented in Table 4. Adequate counselling regarding the potential benefits and reported complications of each therapy can help the patient make an informed choice, which is imperative before initiating therapy (Table 3).

### Compliance with Ethical Standards

**Conflict of interest** The authors declare that they have no competing interests.

**Ethical approval** This article does not contain any studies with human participants or animals performed by any of the authors. Therefore, no informed consent was necessary.

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