# Treatment of chronic non-infectious uveitis and scleritis

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## Summary

Ocular inflammations such as uveitis and scleritis can lead to significant visual impairment if not treated properly. To limit potentially sight-threatening complications, good control of the inflammation in the acute phase is necessary. Corticosteroids have been the mainstay of ocular therapies for many years, but high doses of corticosteroids, which are required to maintain quiescence in severe uveitis, can be associated with many systemic and ocular complications. In order to limit steroid side-effects, classic immunosuppressant and immunobiologic agents have been widely used as steroid-sparing agents. In this review, we summarise the immunosuppressive drug therapy utilised in the treatment of ocular inflammatory diseases.

*Keywords: uveitis, scleritis, azathioprine, methotrexate, mycophenolate mofetil, immunosuppressive agents, anti-TNF agents, biological therapy*

## Introduction

Ocular inflammatory diseases, such as severe uveitis and scleritis, may require intense immunosuppressive therapy to control ocular inflammation and prevent irreversible visual impairment. Non-infectious uveitis consists of a wide group of ocular inflammatory diseases and ocular complications and accounts for 10–15% of preventable blindness in developed countries [1, 2]. Ocular inflammation may be restricted to the eye or can be associated with systemic disease. According to the Standardization of Uveitis Nomenclature (SUN) working group, uveitis can be classified, according to the primary anatomical location of the inflammation, as anterior, intermediate, posterior, or panuveitis when affecting all three areas [3]. Intermediate, posterior and panuveitic disease have a higher risk of vision loss compared to anterior uveitis. Recent epidemiological data give yearly incidences of uveitis of between 14 and 17 per 100,000. The prevalence is between 58 and 115 per 100,000 [4–6]. The large variation in prevalence is due to variation in diagnostic workup, heterogeneity of the disease, lack of uniform classification and referral or selection bias [7]. The median age of onset of uveitis is around 35 years [8]. About 35% of all uveitis patients have been reported to suffer significant visual impairment or legal blindness [1, 9]. Prompt therapy and rapid control of ocular inflammation are the key to maintaining good visual acuity.

Uveitis and scleritis can have a devastating effect on visual acuity. Before the era of corticosteroids, about 50% of juvenile idiopathic arthritis-associated uveitis cases had a poor visual outcome of legal blindness [10, 11]. Corticosteroids have been the mainstay of ocular therapies for many years, but high doses of corticosteroids are necessary to maintain quiescence in severe uveitis, particularly in severe ocular inflammatory diseases. However, their long-term use is associated with many systemic and ocular complications. Common systemic complications include cortico-induced diabetes, systemic hypertension, osteoporosis and mood disorders [12]. Ocular complications include cataracts and a rise of ocular pressure in steroid responder patients. The risk of ocular hypertension increases with the potency of the steroids and is directly related to the administered dose. In order to limit steroid side-effects, classic immunosuppressant agents have been widely used as steroid-sparing agents, particularly with steroid doses still over 10mg/day after six months of therapy [13–15].

Current disease-modifying antirheumatic drugs (DMARDs) include methotrexate, mycophenolate mofetil, cyclosporine A and azathioprine. However, in severe uveitis, systemic steroid therapy remains necessary to control ocular inflammation. The recent development of biological agents, particularly anti-TNFα agents, has opened up a new era in the treatment of uveitis. The aim of this paper is to review recent ophthalmological literature concerning new treatment modalities for non-infectious uveitis and scleritis, and to offer a practical guide for internists and general practitioners.

## Uveitis generalities

The standardization of uveitis nomenclature (SUN) project considerably improved the assessment of drug efficacy in uveitis, with classification based on the primary site of inflammation within the eye and standardised use of clinical grading as a tool for assessing the degree of inflammation [3]. Uveitis can be classified as anterior, intermediate or posterior uveitis, according to the primary site of inflammation [3]. In anterior uveitis, the anterior chamber is the

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main site of inflammation and it includes iritis, iridocyclitis and anterior cyclitis. In intermediate uveitis, the vitreous is the main site of inflammation and it includes posterior cyclitis, hyalitis and pars planitis. Finally, posterior uveitis affects the retina and/or choroid. If all three eye segments are involved, the term panuveitis is used.

Uveitis can also be classified, according to the type of presentation, as acute, recurrent or chronic [3].

In terms of etiology, the two major categories are infectious and non-infectious uveitis. The latter includes the following etiologies: sarcoidosis, Behçet's disease, ankylosing spondylitis, inflammatory bowel disease, Juvenile idiopathic arthritis, seronegative arthropathy, reactive arthritis, multiple sclerosis and Vogt-Koyanagi-Harada syndrome.

## Scleritis generalities

Scleritis is associated with a systemic inflammatory disease in over 50% of cases [16]. The disease is classified as anterior or posterior, diffuse or nodular, necrotising or non-necrotising and infectious or non-infectious [17]. In severe, non-infectious scleritis, therapy is mostly guided by the presence of an underlying systemic disease, mainly rheumatoid arthritis, relapsing polychondritis, granulomatosis with polyangiitis (GPA, formerly Wegener's granulomatosis) and systemic lupus erythematosus. According to Baeten et al, disease entities should be classified by pathogenesis rather than phenotypic disease classification [18], but anatomical localisation of inflammation will also guide the speed of introduction of therapies. Necrotising scleritis (also referred to as scleromalacia perforans) associated with granulomatosis with polyangiitis or rheumatoid arthritis requires the introduction of bDMARDs such as rituximab at an early stage to avoid ocular perforation [19].

## Treatments generalities

To limit potentially sight-threatening complications, good control of the inflammation in the acute phase is necessary. Two strategies can be used to control intraocular inflammation, the classical "step-up" approach and the "top-down" approach. In the step-up approach, therapies are progressively introduced in a stepladder fashion until sufficient control of the intraocular inflammation is reached [20]. First-line therapy consists of topical corticosteroids. In the absence of response or if topical corticosteroids induce ocular hypertension/glaucoma or cataracts, systemic corticosteroids are introduced at an initial dosage of 1 mg/kg/day, followed by immunosuppressive drugs 2–3 months later, in an attempt to minimise corticosteroid systemic side effects (steroid-sparing agents) [20].

Immunosuppressive therapy is introduced in the following cases: to control inflammation in the case of failure of or insufficient response to treatment with corticosteroids, particularly in the case of high-risk uveitis syndrome, and/or to prevent cortico-induced toxicity (steroid-sparing agents).

It should be noted that, despite an increasing number of randomised clinical trials studying the effectiveness of immunosuppressive therapies in uveitis, most of our knowledge in this area comes from retrospective studies. This is principally due to the large heterogeneity, and also the relative rarity, of uveitides.

Several promising new treatments for inflammatory ocular diseases are under investigation, such as JAK inhibitors [21], but here we shall mainly focus on the currently approved treatments for inflammatory eye diseases, namely glucocorticoids, anti-metabolites (azathioprine, methotrexate and mycophenolate mofetil), T cell/calcineurin inhibitors (cyclosporine A) and biologics.

## Glucocorticoids

Corticosteroids have inhibitory effects on a broad range of immune responses, via inhibitory effects on the gene transcription of several pro-inflammatory cytokines, effects on post-translational events, including the suppression of COX-2 synthesis, and also through the non-genomic activation of anti-inflammatory proteins [22]. In uveitis, corticosteroids can be used topically, periocularly, intraocularly or systemically. The limits and risks of local therapies compared to systemic therapies are the key factors determining the therapeutic decision. Local corticosteroids have an efficacy mainly on anterior uveitis, with poor efficacy on the posterior segment of the eye. Corticosteroids are associated with multiple ocular complications, such as ocular hypertension in steroid responder patients. *Amarly et al* demonstrated that about one third of patients had an increased ocular pressure after initiation of topical dexamethasone drops TID [23]. The severity of ocular hypertension is directly correlated with the potency of corticosteroids. The two topical steroids with the greatest potency, 0.1% dexamethasone and 1% prednisolone acetate, had the greatest effect on ocular pressure, with rises in IOP of $22.9 \pm 2.9$ and $10 \pm 1.7$ mmHg respectively [24]. A recent study was able to stratify the relative risk of ocular hypertension, which was directly correlated with the number of daily doses administered. With a mean administration of eight drops per day, the adjusted hazard ratio (HR) of increase in IOP was around eight in children, while one drop daily had almost no effect on ocular pressure, with an HR of 1 [25]. In the adult population, the same trend was observed but with lower limits, eight drops a day producing an HR of about 3 [26].

Periocular administration of corticosteroids is particularly interesting for the avoidance of systemic side effects. This consists of the subconjunctival injection of betamethasone, the sub-tenon injection of triamcinolone acetonide suspension and the intravitreal injection of a long-term dexamethasone delivery system, used for inflammatory cystoid macular edema in particular [27]. Periocular or intraocular steroid injections are, however, mainly used as adjuvant therapy to systemic therapies [28].

Systemic steroid therapy is reserved for bilateral, intermediate and posterior uveitis, panuveitis, or any form of sight-threatening uveitis. The classical dosage is 1–1.5 mg/kg/day of prednisone/prednisolone *p.o.* or 250–1,000 mg of methylprednisolone IV daily for three days, followed by oral therapy [29]. The rate of corticosteroid decrease should be adapted by ophthalmologists according to the uveitis activity and should not be more than 10% every 2-3 weeks to avoid a relapse of inflammation.

## Cyclosporine A

Cyclosporine A (CycA) is a lipophilic cyclic peptide, comprised of 11 amino acids and derived from fungi, which selectively inhibits calcineurin, thereby impairing the transcription of interleukin-2, TNFα and several other cytokines in T lymphocytes. Unlike other immunosuppressive agents such as azathioprine and the alkylating agents, CycA lacks clinically significant myelosuppressive activity [30]. Calcineurin inhibitors have been used for immunosuppression in solid organ transplantation for over three decades. Nephrotoxicity and arterial hypertension represent the major side effects of cyclosporine [31]. Classical dosage for ophthalmologic indications is 150–200 mg/day (2.5–5 mg/kg/day). Typical ocular indications for CycA are ocular Behçet's disease, birdshot chorioretinopathy, ocular sarcoidosis, pars planitis, VKH syndrome, tubulointerstitial nephritis and uveitis syndrome (TINU), sympathetic ophthalmia, idiopathic posterior uveitis, peripheral ulcerative keratitis and scleritis (particularly in GPA) [20]. However, in recent studies, biological therapies such as anti-TNFα agents were preferred for first-line therapy in sight-threatening uveitis, and cyclosporine was usually used as second- or third-line therapy [20, 32, 33].

Interestingly, CycA was shown to selectively attenuate Th17 cells, a T-helper memory-derived cell population that seems to play an important role in the mechanism of corticosteroid-resistance in inflammatory conditions. This finding opens up new possibilities for the development of drugs that could be used in cases of corticosteroid-resistant intraocular inflammation [34].

## Azathioprine

The prodrug azathioprine (AZA) is an immunosuppressive agent, metabolised in the liver to its active form 6-mercapto-purine, that inhibits maturation of B and T lymphocytes through its activity as an antagonist of purine metabolism, resulting in the inhibition of DNA, RNA, and consequently protein synthesis. AZA is widely used in the management of uveitis [35, 36].

AZA is generally used at an initial dose of 1mg/kg/day, and the dose is then progressively increased to 2–2.5mg/day in the absence of haematological and hepatic adverse events. AZA has been shown to successfully controlled ocular inflammatory disease in 62% of patients [37]. As AZA is moderately effective for controlling inflammation when used in monotherapy, it is typically used in combination with other immunosuppressive agents. AZA seems to be more effective in patients with intermediate uveitis (90% with sustained inactivity within one year) [37].

AZA is typically prescribed for juvenile idiopathic arthritis (JIA) iridocyclitis, Behçet's disease, GPA, sympathetic ophthalmia, VKH's syndrome, ocular sarcoidosis and pars planitis. Patients under AZA should be regularly monitored with a complete blood counts and hepatic tests. Both AZA and CicA are considered safe options for pregnant women that need to pursue treatment in sight-threatening ocular inflammatory disease.

## Methotrexate

Methotrexate (MTX) is a structural analogue of folic acid that can competitively inhibit the binding of dihydrofolic acid (FH2) to the enzyme dihydrofolate reductase (DHFR), thereby interfering with purine and pyrimidine metabolism and therefore inhibiting DNA and RNA synthesis, DNA repair and cell division. At lower doses MTX achieves anti-inflammatory effects.

MTX can be administered for ocular sarcoidosis, JIA-associated uveitis, reactive arthritis-, ankylosing spondylitis- and inflammatory bowel disease (IBD)-associated uveitis, scleritis, and sympathetic ophthalmia [20]. It can be used as a first-line corticosteroid-sparing drug or in combined therapy. MTX has been shown to successfully control ocular inflammation in 66-76.2% of patients in combination with low doses of corticosteroids (<10 mg/day) [38, 39]. In a prospective study of a large cohort of 3,512 JIA patients, Tappeiner et al. showed that the early use of MTX or MTX + TNFα inhibitors within the first year of active arthritis has a highly protective effect against development of uveitis [40].

In adults, MTX should be preferentially administered as weekly subcutaneous injections. Biodisponibility of oral MTX is erratic, digestive side-effects are common and there is a risk of accidental daily intake. Subcutaneous MTX is started at an initial dose of 7.5–15 mg/week and may be increased to 20–25 mg/week. Five mg of oral folic acid is administered the day after the weekly MTX injection to limit haematologic toxicity. The main side effects of MTX include myelosuppression (leucopenia and thrombocytopenia) due to folic acid antagonism, infections, liver toxicity and pneumonitis. MTX is contra-indicated in pregnancy.

## Mycophenolate mofetil

Mycophenolate mofetil (MMF) is a selective inhibitor of inosine monophosphate dehydrogenase that interrupts guanosine synthesis. It suppresses T and B lymphocyte proliferation, reduces antibody production and inhibits transmigration of leukocytes. This drug is used as an anti-rejection drug in transplant patients and has shown efficacy in the treatment of systemic autoimmune disease [41]. MMF has been widely tested for treating refractory uveitis and severe scleritis [42]. Complete control of inflammation was achieved in 53% of patients at six months and 73% within one year [43, 44]. MMF is teratogenic, and contraceptive measures are needed in women of child-bearing age.

## Anti-TNFα

TNFα is a pleiotropic, pro-inflammatory cytokine which plays an important role not only in host defence against intracellular pathogens, but also in the pathogenesis of numerous inflammatory diseases such as non-infectious uveitis (NIU). TNFα was shown to be up-regulated in the aqueous humour and serum of patients with uveitis and is thought to play a key role in the physiopathology of uveitic inflammation [45].

At the molecular level, TNFα is synthesised as a transmembrane protein that is then cleaved by a TNFα converting enzyme (TACE) to release soluble TNFα. TNFα exerts its function by acting on two distinct receptors: TNF receptor 1 (TNFR1) and TNFR2. The understanding of TNFα-induced signalling has been enriched in the last few decades,

revealing the formation of distinct signalling protein complexes that lead to different functional outcomes such as inflammation, apoptosis and necroptosis [46].

Interestingly, TNFR1 binds both soluble (sTNFα) and membrane bound TNFα (mTNFα), and principally mediates inflammation and cell death. In contrast, TNFR2 binds only mTNFα and plays a role in tissue homeostasis, regeneration and immune regulation. The current approved anti-TNFα treatments inhibit both pathways and therefore interfere with the homeostatic functions of TNFα. A new concept in the therapeutics of TNF-mediated diseases is to selectively inhibit the pathogenic effects of TNFα, preserving its homeostatic functions by targeting specifically sTNFα or TNFR1 [47].

Currently, five biologic agents targeting TNFα are approved for the treatment of rheumatoid arthritis, inflammatory bowel disease, psoriasis, psoriatic arthritis, ankylosing spondylitis and juvenile idiopathic arthritis (JIA). These are infliximab (Remicade®), adalimumab (Humira®), certolizumab pegol (Cimzia®), golimumab (Simponi®) and etanercept (Enbrel®) [46]. In addition to the approved indications, anti-TNFα is also used, off-label, in sarcoidosis, Behçet disease, non-infectious ocular inflammation, pyoderma gangrenosum and in patients with TNF receptor-associated periodic fever syndrome (TRAPS) and adult-onset Still's disease [48]. To date, adalimumab (Humira®) is the only immunobiologic agent that has been approved in Switzerland in the indication of non-infectious intermediate or posterior uveitis, or panuveitis, as a corticosteroid sparing agent in the absence of adequate response to corticosteroids with or without immunosuppressive agents.

Recent studies have shown the beneficial role of the anti-TNFα adalimumab in active and inactive, non-infectious intermediate and posterior uveitis and panuveitis (NIIPPU). The VISUAL I study, a multicentre, double-masked, randomised, placebo-controlled phase 3 trial, showed that patients with active NIIPPU who were treated with adalimumab presented a lower risk of uveitic flare or visual impairment than patients who received a placebo [49]. The parallel study, VISUAL II, a multicentre, double-masked, randomised, placebo-controlled phase 3 trial, showed that adalimumab significantly lowered the risk of uveitic flare or loss of visual acuity upon corticosteroid withdrawal in patients with inactive NIIPPU controlled by systemic corticosteroids [50]. VISUAL III is the open label extension of VISUAL I and II. This study was able to demonstrate a numerical improvement in steroid-free quiescence and steroid dose reduction [51]. Finally, among children and adolescents with active JIA-associated uveitis who were taking a stable dose of methotrexate, the SYCAMORE study showed control of inflammation in the adalimumab treated group compared with a placebo, as observed in the adult population [52].

Anti-TNFα represents an extraordinarily effective treatment for many auto-immune diseases, including NIIPPU, even though these compounds may, in rare cases, cause autoimmune conditions such as drug-induced lupus (DIL), demyelinating disease, autoimmune hepatitis, psoriasis and even uveitis [53]. The mechanisms underlying these auto-immune conditions is unclear, but could be partially due to the TNFα antagonists-induced production of autoantibodies such as antinuclear antibodies (ANA) and anti-double-stranded DNA antibodies (anti-dsDNA) [54, 55]. The risk of developing auto-antibodies is lower if TNFα antagonists are administered in combination with an immunosuppressive treatment, such as MTX. The exact molecular mechanisms responsible for autoantibody formation remain unknown. Multiple sclerosis-associated uveitis (MS-associated uveitis) may be present in 5-16% of intermediate uveitis cases [56]. A brain MRI should be performed in the presence of uveitis associated with neurologic systemic symptoms in order to rule out the presence of MS before the introduction of an anti-TNF agent. According to the SABER Study, a retrospective, population-based cohort study, optic neuritis is rare among patients who initiate anti-TNF therapy, and occurs with similar frequency among those with classic immunosuppressant exposure [57].

Finally, the use of monoclonal antibody therapies targeting TNFα can result in immunisation, with the apparition of anti-drug antibodies. The latter may give rise to low serum drug levels, loss of therapeutic response, and adverse events such as infusion reactions. The use of concomitant MTX may attenuate the frequency of anti-drug antibodies (ADA) [58]. The ARMADA trial showed an incidence of anti-adalimumab antibodies lower than 1% in rheumatoid arthritis patients who were taking concomitant MTX, compared to an incidence of 12% in patients treated with adalimumab as monotherapy [59, 60].

## Conclusion

In summary, non-infectious uveitides represent a heterogenous group of ocular inflammatory diseases affecting a broad range of age groups, with a high potential for blindness if not treated adequately. Increasing evidence supports the effectiveness and safety of using immunosuppressive drug therapy to treat ocular inflammatory diseases. The antimetabolites (AZA, MTX) and the biologics (anti-TNFα), in particular, appear to offer the best balance between effectiveness and safety, and represent an excellent alternative to corticosteroid therapy. Immunosuppressive drugs should be used in the case of corticosteroids failure or insufficient control of inflammation to prevent corticosteroid-induced side effects, and to treat high-risk uveitis syndromes.

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