Advances in the Treatment of Noninfectious Uveitis with Biologics: Anti-TNF and Beyond

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Chapter: Treatment Strategies in Non-Infectious Uveitis: General Concepts

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Treatment Strategies in Non-Infectious Uveitis: General Concepts

Abstract

The term uveitis refers to a group of inflammatory disorders affecting the uvea, the middle layer of the eye. Endogenous or associated with a systemic disease, noninfectious uveitis accounts for approximately 75% of total cases comprising of a heterogeneous group of inflammatory conditions. There is a wide spectrum of clinical forms of uveitis that are mainly classified according to criteria of anatomical location (anterior, intermediate, posterior or panuveitis), laterality and clinical course (acute, recurrent or chronic). Chronic uveitis is associated with a greater degree of structural damage and is responsible for a greater percentage of visual loss than acute forms. Acute Anterior Uveitis (AAU) is the most prevalent form and usually requires only topical treatment with steroids and mydriatics. However, it is a cause of disability when flares are frequent or when tends to chronicity. Sulphasalazine and methotrexate have demonstrated a reduction in the number of flares and better control of inflammatory activity in cases of chronicity. Other patterns of uveitis with involvement of intermediate and posterior segments have a worse prognosis. Locally injected or systemic corticosteroids and/or immunosuppressive drugs are usually required in sight-threatening immune-mediated uveitis with involvement of posterior segment to halt the course of the disease. Treatment consists in a phase of induction of remission using high-dose of systemic corticosteroids administered orally or by means of intravenous infusion. The second phase is the maintenance of the long-term control of inflammatory activity. At this stage, the dose of corticosteroids is gradually reduced until withdrawal, and if necessary immunosuppressant’s are added. Biological therapies, that are widely described in this book, are promising therapeutic options in refractory patients as a rescue therapy. However, there is clinical evidence of the use of these powerful drugs as first line therapy in selected cases (top-down approach).

Introduction

The incidence of uveitis in the general population is between 17 and 52 cases per 100,000 habitants per year with a prevalence of 0.1% [1]. People aged 20-50 years are most commonly affected. Uveitis are responsible for about 10% of legal blindness in developed nations and more than 35% of patients with uveitis present significant visual loss in at least one eye [2-4]. These data reveal the magnitude of the epidemiologic, diagnostic, and therapeutic problem posed - by the uveitis, as well as healthcare costs generated. So, both for diagnosis and, especially, for the proper treatment, close cooperation between ophthalmologists, rheumatologists and general practitioners are required in order to correctly classify the pattern of uveitis and associated comorbidities to establish the most appropriate therapeutic scheme.

General Principles and Treatment Strategies

Before starting the treatment, a number of considerations should be taken into account (Table 1).

<table>
<thead>
<tr>
<th>General aspects related to uveitis treatment</th>
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<tbody>
<tr>
<td>■ The majority of patients with uveitis can modify significantly the course of their illness if they receive proper early treatment [10].</td>
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<tr>
<td>■ It is recommended to work in Multi-disciplinary Units to facilitate handling of the drugs used and early detection of side effects.</td>
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<tr>
<td>■ Infectious causes and masquerade syndromes should always be excluded before considering an immune-mediated mechanism.</td>
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<tr>
<td>■ Macular edema is the main cause of vision loss in uveitis patients.</td>
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<tr>
<td>■ Always analyze what is the cause of poor vision in a specific case. Is it reversible? Are there other causes of poor vision, such as cataract, glaucoma or macular edema that could require specific treatment?</td>
</tr>
<tr>
<td>■ Zero tolerance to inflammation</td>
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<tr>
<td>■ Limited tolerance to the use of corticosteroids.</td>
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Table 1: General aspects related to uveitis treatment.

Infectious causes and masquerade syndromes should always be excluded before considering an immune-mediated mechanism, since therapeutic scheme is completely different. Some infectious causes, such as toxoplasmosis, herpes, syphilis and tuberculosis could produce uveitis and, frequently, clinical signs are indistinguishable from those produced by the immune-mediated uveitis. Some malignancies, especially CNS lymphoma, can also simulate a uveitis. Also traumatic, postoperative and drug-induced uveitis must be discarded [5-7].

Find out what factors, as well as inflammation, may be influencing the visual loss of the patient and their reversibility. There can be
comorbidities such as glaucoma, cataract, persistent vitreous opacities or macular ischemia that have their particular management. It also kept in mind that some lesions are irreversible (macular or optic atrophy, advanced glaucoma …) before starting an immunosuppressive treatment with iatrogenic potential risks in eyes without the possibility of visual recovery.

The most frequent cause of loss of visual acuity in patients with uveitis is macular edema (ME). When ME is chronic produces lesions in the retinal photoreceptors, which can potentially be irreversible [8,9]. For this reason, early and appropriate treatment is essential.

A fourth point that we must always consider is a general attitude of zero tolerance to inflammation. Sustained inflammation, even in low grade, can cause severe structural damage (Figure 1 A-D).

Figure 1: A-D. Structural damage in patients with chronic long-standing uveitis.

(A) Ultrasound biomicroscopy (UBM) in a patient with juvenile chronic arthritis (JIA) and chronic anterior uveitis. UBM shows a cyclitic membrane that causes a detachment of ciliary body and chronic hypotony.

Figure 1: B. Posterior pole of a patient with long-standing Behçet disease. There is optic atrophy with macular ischemia and diffuse occlusive vasculopathy.

Treatment is usually performed in two phases: induction of remission and maintenance. Due to its high and immediate efficacy, corticosteroids administered by different routes, are the drugs of choice in the induction of remission. However, in many cases, corticosteroids are not enough to sustained control of the inflammation in the long term. In other situations, the control of the inflammatory activity is not maintained when trying to reduce the dose of corticosteroids, or side effects of the treatment are not tolerable. In these cases, an immunosuppressive treatment for the maintenance of remission is necessary (Table 2). It is necessary to maintain immunosuppressant’s for long time, in order to achieve a stabilization of inflammatory parameters and avoid relapses and new flares. Multidisciplinary units (ophthalmologists with internists or rheumatologists) have been developed to achieve a close follow-up both at the level of efficacy and for early detection of side effects, allowing a better management and control of these therapies.

Figure 1: (C) Chronic refractory inflammatory glaucoma associated with uveitis. A tube shunt was required to control the intraocular pressure.
Figure 1: (D)Chronic uveitic macular edema with severe disruption of photoreceptor layer and coalescence of large cystic spaces.

General recommendations of steroid-sparing immunosuppressant’s in uveitis

<table>
<thead>
<tr>
<th><strong>Sight-threatening immune-mediated intraocular inflammation and</strong></th>
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<tr>
<td>■ Inflammation is not controlled with corticosteroids used in an appropriate schedule.</td>
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<tr>
<td>■ Unacceptable adverse effects or contraindications of corticosteroids</td>
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<tr>
<td>■ Chronic treatment with corticosteroids for more than 3 months in doses higher than 5 - 10 mg/day.</td>
</tr>
<tr>
<td>■ Specific entities with poor response to steroid immunotherapy (Behçet disease, Birdshot chorioretinopathy, serpiginouschorioidopathy...).</td>
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A different therapeutic algorithm should be used depending on the type of uveitis and anatomical location.

**Therapeutic Algorithm for Anterior Uveitis (AU)**

The AU is the most frequent form of uveitis, accounting for approximately 90% of uveitis in primary care and 50-60% in referral centers [11-13]. The most common form is AAU HLA B27+, associated or not with seronegative arthropathy: Ankylosing Spondylitis (AS), reactive arthritis, psoriatic arthritis and arthritis associated with Inflammatory Bowel Disease (IBD) [14]. Other etiologies associated are Fuchs disease, Juvenile Idiopathic Arthritis (JIA), sarcoidosis, Behçet's disease and Multiple Sclerosis (MS) or TINU syndrome.

Most cases respond well to topical treatment and have an excellent prognosis if treatment is early and adequate. Exceptions to this rule are chronic AU associated with JIA or Behçet's disease, which often requires systemic immunosuppressant associated with topical treatment [15].

Treatment of AU is a medical emergency because delayed treatment may result in complications, sometimes irreversible, including anterior and posterior synechiae, secondary glaucoma, cataract or CME, that make the disease difficult to treat, and sometimes, with a very poor final visual function.

**Control of Inflammation**

Treatment always starts with topical corticosteroids, usually eye drops during the daytime and ointment at bedtime. The steroid must have high anti-inflammatory activity and easy intraocular penetration. The most widely used topical steroids are dexamethasone, betamethasone and prednisolone. The frequency of instillation varies with the intensity of the inflammatory reaction, but in general, the initial treatment should be aggressive for controlling the process as soon as possible. The initial dose may be a drop every 1-3 hours, but there are cases where the inflammation is so severe that requires more frequent instillation (one drop every 15 to 30 minutes) or so slight that it can be controlled with more spaced doses. It is very important to use the right dose, since the use of a less aggressive regimen may lead to the erroneous conclusion that is a refractory uveitis [15].

When the inflammatory process begins to subside, the dosage must be gradually lowered. Steroid withdrawal should not be very fast (not less than 4-6 weeks of treatment) that may predispose a rebound of inflammation [16]. The most recurrent cases need a slower decrease in dose. Some patients require a minimum dose of topical corticosteroids for a long time to keep the eye without inflammation. During the active phase, the patient should be reviewed weekly or biweekly [15] to monitor changes of inflammation and possible side effects of treatment (ocular hypertension, cataract, increased susceptibility to infections...).

Sometimes is necessary the use of periocular corticosteroid infiltration. The most common situation is CME associated with AU, but also in cases of therapeutic noncompliance or very severe flares with slow response to intensive topical treatment.

Exceptionally, systemic corticosteroids may be indicated to control inflammation. We have already mentioned that AU associated with JIA or Behçet’s disease often requires systemic immunosuppression associated with topical treatment [15].

Treatment of AU also requires cycloplegic-mydriatic eye drops for control of pain caused by the ciliary muscle spasm and to prevent synechiae or break already present [16,17]. The most widely used cycloplegic-mydriatic drops, from highest to lowest potency and duration of action, are atropine, homatropine, cyclopentolate and tropicamide. Atropine is used in severe inflammation, with intense pain, because it is the one that best controls the pain. Tropicamide, however, is used in milder uveitis or when inflammation has decreased to not interfere daytime vision. The dose should be adjusted to the severity of inflammation and withdrawing completely by the end of steroid treatment. To break synechiae already present, we can associate phenylephrine eye drops in the office, but not as an outpatient basis due to the risks related to its use.

Although AU has usually good prognosis, there are cases with multiple flares annually, with great impact in quality of life due to...
pains, decreased vision and discomfort associated with pharmacological mydriasis. Furthermore, recurrent inflammation and treatment with topical steroids can produce structural damage to the eye such as cataract, synechiae or glaucoma. For these reasons, a treatment to reduce relapses should be very useful in this clinical setting [16,17].

- In AU B27-related, there is evidence that chronic administration of Sulphasalazine (SSZ) reduces the frequency and severity of recurrent episodes of uveitis [18-22]. Although medication is generally well tolerated, it is necessary to take into account the risk of adverse events like skin reactions, blood dyscrasias or Stevens-Johnson syndrome. Isolated episodes of uveitis not justify its use, it may be reasonable when there are three or more flares of AAU in the last year. The dose of SSZ is between 1.5 and 3 g/day divided into three doses.

- The incidence of AU in patients with AS treated with anti-TNF agents is less than in untreated patients, being lower in the group receiving infliximab or adalimumab than in the etanercept-treated group [23,24].

- Methotrexate may also prevent recurrences of AAU in cases with a high number of relapses [25].

### Therapeutic Algorithm in Endogenous Intermediate Uveitis (IU)

When inflammation affects the intermediate or posterior uvea, topical corticosteroids are not going to significantly change the course of the disease, so it will be necessary other forms of treatment to control uveitis.

The classic treatment of IU is based on the four-step algorithm proposed by Kaplan [26], in which visual acuity is fundamental when starting treatment. Currently, many authors prefer early and aggressive treatment to preserve better visual acuity [27].

Periocular injection of corticosteroids is the first-line of treatment in most patients with IU; especially in unilateral or very asymmetric cases. We used different techniques for periocular administration, including subtenon, orbital floor or retrobulbar injections [28]. A small amount (1ml) of a depot preparation of a corticosteroid is placed in the orbit, usually through the eyelid skin, either upper or lower or through the conjunctiva. The most popular choice is triamcinolone acetonide, but it is possible to use other corticosteroids such as betamethasone acetate and betamethasone sodium phosphate solution. Thus, using a fast-acting combined with a depot formulation, it is assumed that the onset of effect is earlier than with triamcinolone. The injections can be repeated every 4-6 weeks according to clinical response. After 3 injections without clinical response, it is considered that this treatment is not effective and must be changed to another form of treatment.

Periocular injections are generally well tolerated and have few adverse effects, but there may be potential complications of injections (ocular perforation, hemorrhage, fat herniation, ptosis or orbital fat atrophy), and especially intraocular hypertension and cataract. Steroid-induced ocular hypertension occurs in up to 27% of patients treated. Uveitis patients have more risk than those treated by other causes. The risk is greater in patients with a history of hypertensive response to topical corticosteroids. Another side effect is cataract progression in up to 31% of patients [29,30].

Periocular treatment with corticosteroids is also used in other forms of uveitis, especially if there is associated CME. In certain forms of posterior uveitis or panuveitis with unilateral or highly asymmetric relapses, it is possible to use periocular corticosteroids, usually associated with systemic treatment. Clinical response to treatment depends on the inflammatory phenomena. Positive responses have been published in 96% of treated vitritis, 82% of the CME and only 33% in the case of vasculitis [30].

If periocular administration is ineffective or insufficient, other forms of administration should be considered, such as intravitreal or systemic treatment. The intravitreal route is a very attractive form of administration because it provides a maximum concentration of corticosteroid at the posterior segment with minimal systemic absorption. Treatment of uveitis and/or uveitic CME may be performed with intravitreal triamcinolone acetonide [31,32]. The effectiveness of treatment is rapid but is limited in time, so it is necessary to repeat injections. In order to avoid this inconvenience, it has been developed slow-release devices that maintain effective levels of intravitreal steroids for extended periods of time, reducing the complications of multiple injections. Fluocinolone acetonide [33,34] has been used in the past, but currently the most widely used implant in clinical practice is the dexamethasone implant (Ozurdex®), with a better benefit/risk profile [35-37]. So, intravitreal administration of steroids is a very effective treatment in managing endogenous uveitis, which allows

![Therapeutic Algorithm in Endogenous Intermediate Uveitis (IU)](image-url)

**Figure 2:** Therapeutic algorithm in endogenous Anterior Uveitis (AU).
significant decrease in systemic medication necessary for control of these patients and, therefore, their side effects. We must always take into account the risks associated with the procedure (endophthalmitis, retinal detachment, hemovitreous, ocular hypertension and cataracts) [38].

Systemic treatment is generally used, as first choice, in most cases of bilateral IU and, as a second option, in IU unresponsive or intolerant to local treatment. Systemic treatment is described in the next section of this chapter in the therapeutic algorithm for posterior uveitis and panuveitis.

Cryotherapy has proved to be an effective treatment for IU. Ablation of the peripheral retina eliminates the source of inflammatory mediators and the stimulus for neovascularization [26,27]. Currently, it tends to be replaced by photocoagulation usually associated with vitrectomy [39]. Vitrectomy acts eliminating the hazy vitreous and, therefore, improves the patient’s vision and also reduces the burden of inflammatory mediators in the vitreous [40] improving the control of the inflammatory process and macular edema. Figure 3 shows our therapeutic algorithm for intermediate uveitis.

Therapeutic Algorithm in Posterior Uveitis and Panuveitis

In posterior uveitis, retina and/or choroid are the principal site of inflammation, having either multiple spots or single large lesions. In panuveitis or diffuse uveitis, inflammatory cells are spread roughly between the anterior chamber and vitreous cavity, and also there are inflammatory foci at the level of the retina, choroid or inflammation of the central retinal vessels.

Systemic corticosteroid treatment is usually used as first choice in the majority of the posterior uveitis, panuveitis and bilateral intermediate uveitis. Oral prednisone is the most commonly used steroid. The initial dose of oral prednisone is 1 mg/kg/day which is maintained until a satisfactory anti-inflammatory response is achieved, usually in 2-4 weeks. Thereafter, a gradual dose tapering process can begin. It can be performed following the recommendations of an expert panel (Table 3) [41]. Initially this can be quite rapid, but the lower the current dose, the slower the necessary reduction. During the process of dose reduction, the patient should be carefully monitored to ensure that inflammatory parameters are under control and there is a sustained suppression of the inflammation. If there is a relapse during dose reduction, a substantial increase of the dose is required to regain control (at least a doubling of current dose). Then, a gentler taper should be prescribed. A majority of cases of chronic uveitis may be controlled with dosage levels below 10 mg/day, but sometimes, higher doses are required. The maintenance of systemic steroid treatment, even at low dose, are associated with important side-effects, such as dyspepsia, osteoporosis and risk of low-trauma fractures, weight gain, steroid myopathy, avascular bone necrosis, skin changes (acne, subepidermal atrophy, capillary fragility), inter-current infections, growth suppression in children, adrenocortical suppression and ocular side effects (cataract, ocular hypertension) [42]. Due to its multiple adverse effects, the dose of corticosteroids as maintenance therapy in uveitis should be the lowest possible and its withdrawal should always be attempted.

<table>
<thead>
<tr>
<th>Corticosteroid dosage</th>
<th>Suggested guideline</th>
</tr>
</thead>
<tbody>
<tr>
<td>Initial dose</td>
<td>1 mg/kg/dia</td>
</tr>
<tr>
<td>Maintenance dose (adult)</td>
<td>&lt; 10 mg/dia</td>
</tr>
<tr>
<td>Tapering Schedule</td>
<td>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 to 2.5 mg/day every 1-4 weeks</td>
</tr>
<tr>
<td>Monitor</td>
<td>Blood pressure, weight, glucose levels every 3-6 months. Lipids (cholesterol and triglycerides) annually. Bone density within first 3 months and annually thereafter.</td>
</tr>
<tr>
<td>Supplemental treatment</td>
<td>Calcium 1500 mg daily and vitamin D 800 IU daily Omeprazol 20 mg/day if dose of prednisone 40 mg/day or more, history of peptic ulceration or also taking NSAID Estrogens and anti resorptive agents as needed.</td>
</tr>
</tbody>
</table>

Table 3: It shows the general indications of steroid-sparing immunosuppressants.

Inpatients with particularly severe acute uveitis, for instance, Behçet disease, sympathetic uveitis or severe Vogt-Koyanagi-Harada syndrome, intravenous methylprednisolone should be considered. Methylprednisolone is administered in pulses of three daysby slow intravenous infusion over 1-2 h from 500 to 1000 mg/ day. The effect of this mode of treatment can be very rapid and uveitis usually responds in 48-72 h, then oral steroids with or without immunosuppressant can maintain inflammatory control.
Other route of administration is perocular or especially intravitreal steroid injection. This treatment can be used in patients with unilateral or asymmetrical macular edema even in spite of long-term immunosuppression, unilateral flare-up of inflammation especially in Behçet’s disease, repeatedly where immunosuppressant is intolerable and as an adjunct to cataract, glaucoma or vitrectomy surgery in uveitis patients. It is possible to use direct intravitreal injection of triamcinolone acetonide (IVTA) at a dose of 2-4 mg in 0.05-0.1 mL. This treatment is effective enough to permit reduction in steroids or oral immunosuppressant’s in about 50% [43]. However, ocular side effects have limited their usage. At present, there are injectable sustained-release dexamethasone implant (Ozurdex®) that can be inserted by the pars plana and have a better benefit-risk profile compared with other implants such as fluocinoloneacetonide (Retisert®) [44].

In patients with severe uveitis in whom the dose of corticosteroids required to control the inflammation leads to unacceptable side effects or any other issues in Table 2, an immunosuppressant agent should be added. The aim is to maintain quiescence at a lower steroid dosage. This combination has been used with success in various forms of uveitis. There are few qualities randomized clinical trials on the topic, and most are retrospective reviews or case series without comparison. Recently, working groups of uveitis of the Spanish society of Rheumatology have carried out a work of evidence-based systematic review of the literature on treatment with immunosuppressant and biological agents in uveitis [45]. In chapter 3, there is a detailed description of the different immunosuppressant that can be used as a second-line therapy in the management of chronic severe uveitis. Regular assessment, usually each 6-8 weeks, of safety parameters is essential when monitoring immunosuppressive treatment.

There is a subgroup of patients with severe sight-threatening uveitis that are refractory or intolerant to conventional immunosuppressive treatments. In these cases, biological agents can be used. These are drugs specifically targeting pro-inflammatory cytokines involved in the immune response (TNF-α, IL-1, IL-2, etc). Biological compounds potentially offer a safer profile and faster response than traditional immunosuppressant agents [46]. Among the biologics drugs, tumor necrosis factor-α (TNF-α) blockers (especially infliximab and adalimumab) have demonstrated promising results for the treatment of ocular inflammatory conditions in case series or retrospective reviews [47]. At present, there is a lack of evidence-based recommendations regarding the use of these agents for managing uveitis. In addition, there is no approval for use in uveitis in technical sheet and, in clinical practice; these drugs are used as compassionate use. Throughout this book, available drugs, dosages, safety issues and experience of use in uveitis have been described in detail. Figure 4 shows our therapeutic algorithm for immune-mediated posterior uveitis or panuveitis.

In current uveitis practice, biologics are usually used as third-line agents as rescue therapy for refractory cases in a step-up approach. However, there is ongoing arguments between uveitis specialists as to whether biologics should be considered as first-line therapy in certain cases (for instance, panuveitis in Behçet disease with macular involvement) following a top-down approach [48] (Figure 5).
Another important issue regarding the use of anti-TNF-α is if this therapy could be discontinued in patients achieving sustained control of their uveitis. Some studies show that this option may be possible, although most patients were on other immunomodulatory treatment at this time [49,50].

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