Uveitis for the non-ophthalmologist

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ABSTRACT

The uveitides are a heterogeneous group of diseases characterized by inflammation inside the eye. The uveitides are classified as infectious or non-infectious. The non-infectious uveitides, which are presumed to be immune mediated, can be further divided into those that are associated with a known systemic disease and those that are eye limited,—ie, not associated with a systemic disease. The ophthalmologist identifies the specific uveitic entity by medical history, clinical examination, and ocular imaging, as well as supplemental laboratory testing, if indicated. Treatment of the infectious uveitides is tailored to the particular infectious organism and may include regional and/or systemic medication. First line treatment for non-infectious uveitides is corticosteroids that can be administered topically, as regional injections or surgical implants, or systemically. Systemic immunosuppressive therapy is used in patients with severe disease who cannot tolerate corticosteroids, require chronic corticosteroids at >7.5 mg/day prednisone, or in whom the disease is known to respond better to immunosuppression. Management of many of these diseases is optimized by coordination between the ophthalmologist and rheumatologist or internist.

Introduction

The uveitides are a collection of more than 30 diseases characterized by inflammation inside the eye (table 1). They are distinct from and should not be confused with diseases of the ocular surface and sclera, which also may be affected by inflammation (eg, peripheral ulcerative keratitis, scleritis, etc), although these latter diseases may have an associated secondary intraocular inflammation (eg, keratouveitis or sclerouveitis). Although some of the uveitides are linked to a systemic infection or a rheumatologic disease, many, if not most, of the uveitides are eye limited, presumed to be immune mediated, and without any known systemic associations. The goal of the ophthalmologist is to identify the specific uveitic entity by medical history, clinical examination, ocular imaging, and supplemental laboratory testing, as indicated.

For patients with associated systemic disease or requiring systemic immunosuppression, management is optimized by collaboration between the ophthalmologist and rheumatologist and/or primary care physician. In this review, we provide an overview of the uveitides for the non-ophthalmologist clinician, including the clinical findings and diagnosis of the uveitides, and the treatment of the non-infectious uveitides, particularly through use of systemic therapy, including immunosuppressive drug therapy.

Epidemiology

Worldwide the uveitides are a major cause of visual impairment. They account for 10-15% of blindness in developed countries3,4 and collectively are the fifth or sixth leading cause of blindness worldwide.5 6 The prevalence of uveitis in the United States is estimated as 115-133 per 100 000.7-10 Unlike the other common causes of visual impairment, such as cataract, age related macular degeneration, and glaucoma, the uveitides affect all age groups, including children, have the potential to result in visual impairment over a longer portion of the patient’s lifetime, and have a much greater impact on years of potential vision lost.11 Early diagnosis and proper treatment can prevent blindness and long term disability.12 13

Clinical features

The uveitides have multiple distinct presentations. Uveitis can be classified across several dimensions,
Anatomically, uveitis is classified by the primary site of inflammation. Anterior uveitis affects the anterior chamber of the eye. Intermediate uveitis affects the intermediate anatomic location, including the vitreous, retina, or choroid, and Posterior uveitis affects the retina, choroid, or retinal blood vessels. A patient with inactive disease may still have decreased vision from complications of their disease. A patient with inactive disease may still have decreased vision from complications of their disease.

Table 1 | Anatomic classification of uveitis and associated diseases

<table>
<thead>
<tr>
<th>Anatomic class of uveitis</th>
<th>Primary site of inflammation</th>
<th>Systemic disease</th>
<th>Infection</th>
<th>No systemic disease</th>
</tr>
</thead>
<tbody>
<tr>
<td>Anterior uveitides</td>
<td>Anterior chamber</td>
<td>Spondyloarthritis/HLA B27 associated anterior uveitis, juvenile idiopathic arthritis associated chronic anterior uveitis, sarcoidosis, Behçet disease</td>
<td>Herpes simplex virus anterior uveitis, varicella zoster virus anterior uveitis, cytomegalovirus anterior uveitis, syphilis</td>
<td>Fuchs heterochromic iridocyclitis (Fuchs uveitis syndrome)</td>
</tr>
<tr>
<td>Intermediate uveitides</td>
<td>Vitreous</td>
<td>Multiple sclerosis associated intermediate uveitis, sarcoidosis, tubulointerstitial nephritis</td>
<td>Syphilis, Lyme disease</td>
<td>Pars planitis, undifferentiated intermediate uveitis (intermediate uveitis, non-pars planitis type)</td>
</tr>
<tr>
<td>Posterior uveitides</td>
<td>Retina and/or choroid</td>
<td>Sarcoïdosis</td>
<td>Toxoplasmic retinitis, syphilis, tuberculosis, cytomegalovirus retinitis, acute retinal necrosis (herpes simplex virus or varicella zoster virus retinitis), Bartonella, Lyme disease</td>
<td>Acute posterior multifocal placoid pigment epitheliotropic, birdshot choriotrepanopathy, multiple evanescent white dot syndrome, punctate inner choroiditis, relapsing placoid choroiditis, serpiginous choroiditis, multifocal choroiditis and panuveitis*</td>
</tr>
<tr>
<td>Panuveitides</td>
<td>Anterior chamber, vitreous, and retina or choroid (with no one site predominant)</td>
<td>Sarcoïdosis, Behçet disease, Vogt-Koyanagi-Harada disease (separated into early stage and late stage)</td>
<td>Syphilis, Lyme disease</td>
<td>Sympathetic ophthalmia</td>
</tr>
</tbody>
</table>

Anatomical classification of uveitis by primary site of inflammation, with examples of associated systemic diseases and infections for each type of uveitis.

*Classified as “posterior uveitis” because primary site of inflammation is the choroid, with minimal anterior/vitreous inflammation.

Adapted from the Standardization of Uveitis Nomenclature Working Group and Jabs and Businiger.

including disease course, laterality, primary anatomic location of inflammation, morphologic features, and the host, including the presence or absence of an associated systemic disease. In 2005, the Standardization of Uveitis Nomenclature (SUN) Working Group developed a classification scheme that structures the way clinicians and researchers describe uveitis and grade its severity (table 1). Anatomically, uveitis is classified by the primary site of inflammation.

Anterior uveitis, also termed iritis or iridocyclitis, is inflammation primarily in the anterior chamber of the eye. Intermediate uveitis describes inflammation primarily in the vitreous cavity. Posterior uveitis is inflammation in the retina, choroid, or retinal blood vessels. Of note, retinal edema and optic nerve edema may be structural complications of inflammation elsewhere in the eye and do not, in isolation, constitute “posterior uveitis.” Panuveitis describes inflammation involving anterior chamber, vitreous, and retina or choroid without a predominance of any one anatomic class. In general, eyes with posterior or panuveitis have a worse prognosis, given that inflammation may cause irreversible damage to structures critical to vision, including the macula and optic nerve.

Symptoms may vary greatly, even for patients with the same anatomic type of inflammation. For example, anterior chamber inflammation may cause a red, painful eye, spondyloarthritis/HLA B27 associated uveitis being a classic example. Other anterior uveitides may have no associated pain or conjunctival injection, such as juvenile idiopathic arthritis (JIA) associated chronic anterior uveitis. Similarly, the presence of symptoms does not necessarily indicate active disease. A patient with inactive disease may still have decreased vision from complications of their disease (eg, band keratopathy or choriotreinal scarring) and/or side effects of their treatment (eg, cataracts or glaucoma). In many cases, clinical examination, ocular imaging, or both are necessary to determine disease activity.

Examination

On ophthalmic examination with a slit lamp, it is possible to see and quantify or grade leukocytes in the anterior chamber and anterior vitreous. Other signs of anterior chamber inflammation include perlimbal injection, collections of inflammatory cells on the corneal endothelium (known as “keratic precipitates,” fig 1a), and iris nodules (fig 1b). Iris atrophy (fig 1c) is common in unilateral anterior chamber inflammation associated with the herpetic simplex (HSV) and varicella zoster (VZV) viruses.

On fundus examination, optic disc edema may be present (fig 2a) as a primary manifestation of optic nerve inflammation, or as a secondary structural complication of inflammation elsewhere in the eye. Macular edema, the most common cause of vision loss in uveitis, is caused by fluid leakage into the macula and is detected by either clinical examination or imaging (discussed below).

Inflammation of retinal blood vessels may appear as vascular sheathing (fig 2b) or as occlusive retinal vasculitis with associated retinal hemorrhages, cotton wool spots, and non-perfusion of the retina (fig 2c). Retinitis is almost always due to infection, such as with viruses—eg, cytomegalovirus (CMV) (fig 3a), HSV, or VZV (fig 3b), or parasites—eg, toxoplasmosis (fig 3c), although Behçet disease may also present this way.

Ocular nodules caused by granulomatous disease may be seen on the iris or in the choroid and may be the result of infections, such as tuberculosis, or non-infectious granulomatous disease, such as sarcoidosis (fig 4).

Disease course and severity

Disease course, anatomic class, and laterality (unilateral, bilateral, or unilateral alternating [one eye at a time, but either eye may be affected]) are important considerations in both diagnosis and treatment. Uveitides may be acute (characterized by sudden onset and duration <3 months) and
monophasic; acute and recurrent; or chronic. As with the diagnosis of the arthritides, course, laterality, and anatomic class are helpful in narrowing the differential diagnosis. For example, patients with an acute, unilateral alternating, anterior uveitis have an ~80% chance of carrying the HLA-B27 allele, and if HLA-B27 positive, a ~60-80% chance of having an associated spondyloarthritis.19-22

The ophthalmologist determines whether uveitis is active or inactive based on clinical examination, supplemented with ocular imaging. Fluorescein angiography can show retinal vascular leakage and/or non-perfusion (fig 5a); indocyanine green angiography can show choroidal lesions (fig 5b); and fundus autofluorescence often can distinguish between active choroidal lesions and inactive scars (figs 5c, 5d). Similarly, the presence of structural complications of uveitis, shown on examination and/or imaging, may help to determine disease activity and severity and to guide treatment decisions. In this regard, optical coherence tomography (OCT) has proven to be highly useful in managing uveitic macular edema (fig 5e).

**Diagnostic evaluation for associated systemic disease**

Uveitides are either infectious (ie, caused by organisms in the eye) or non-infectious. The non-infectious uveitides, which are presumed to be immune mediated, can then be divided into those with and without associated systemic disease; those without an associated systemic disease may either be diagnosable as a specific uveitic entity (eg, birdshot chorioretinitis) or be “undifferentiated.”

A selected laboratory evaluation should be conducted based on the clinical features of uveitis, the patient’s medical history, and a focused review of systems. The goals of a laboratory evaluation are to diagnose an infection (where antimicrobial or antiviral therapy is indicated) or to diagnose an associated systemic disease that can affect the patient’s systemic health.2 Identifying an infectious cause of uveitis is important, because treating infectious uveitides require antimicrobials or antivirals, while non-infectious uveitides require corticosteroids and immunosuppressive therapy. Identifying an associated systemic disease is important because it may prevent future morbidity and influence choice of therapy that would treat both systemic and ocular disease.

**Identifying infectious causes of uveitis**

Although the laboratory evaluation should be individualized, a syphilis test should be performed for all adolescents and adults with uveitis because syphilis is a treatable cause of uveitis that can present as any class of disease (fig 2a, 5d). Non-treponemal tests (eg, rapid plasma reagin) have an estimated 30% false negative rate, therefore a treponemal test should be first performed in all cases, utilizing the reverse screening algorithm from the Centers for Disease Control and Prevention.23 24
Lyme disease is an uncommon cause of uveitis. Serologic Lyme disease testing is appropriate in Lyme endemic regions for intermediate uveitis and for patients exposed to Lyme disease. However, in non-endemic regions positive test results are more likely to be false, and routine testing is not recommended.25 26

Tuberculosis is a more common cause of uveitis globally, but regional variation is great, and tubercular uveitis is very uncommon in the US, accounting for only 0.2-0.5% of uveitis cases.27 The positive predictive value of routine tuberculosis testing for patients with uveitis in the US is low (in the range 1 to ~10%).28 Routine tuberculosis testing is therefore not recommended for patients with uveitis, except those who have lived or travelled in endemic regions and those with clinical presentations highly suggestive of tubercular uveitis (figs 6a, 6b). Additionally, tuberculosis testing is recommended in patients with possible exposure to tuberculosis who are starting immunosuppression for non-infectious uveitis, and in all patients, regardless of risk factors, who are starting treatment with a tumor necrosis factor-α (TNF-α) inhibitor.

Testing for selected infections using polymerase chain reaction (PCR) technology has proven to be useful. Either the aqueous or vitreous can be sampled. Diseases in which such sampling often is performed include herpetic anterior uveitis, herpetic retinitis, and toxoplasmic retinitis.29-36 Because of the low yield in routine testing, PCR for these infections should be used selectively based on clinical findings, where there is a limited differential.37-39 Of note, the ability to perform PCR testing on ocular fluid requires a laboratory capable of handling small volumes (eg, 0.1 mL) and may not be available in all locations.

Identifying non-infectious systemic disease associated with uveitis
As with testing for infectious causes of uveitis, laboratory testing for systemic disease associated with non-infectious uveitis should be based on the specific uveitic features.

HLA-B27 associated disease
HLA-B27 associated spondyloarthritis is the most common systemic disease associated with adult anterior uveitis. It was reported in 18-32% of patients with anterior uveitis in Western countries, and in 6-13% of patients with anterior uveitis in Asia.40 When used in the appropriate clinical setting, HLA-B27 provides prognostic information; patients with spondyloarthritis/HLA-B27 associated anterior uveitis typically have recurrent acute, unilateral, or unilateral alternating episodes of anterior uveitis that often respond well to topical corticosteroid therapy.40,41

The average duration of an attack is around six weeks, and the average frequency of attacks is around one per year, although the interval between recurrences can be highly variable, even within the same patient.5 26 Because of the symptomatic nature

Fig 2 | Posterior segment findings in uveitis. (a) Optic disc swelling and hemorrhage in syphilitic uveitis (photograph courtesy of Matthew Star, MD). (b) Perivenular sheathing in sarcoidosis associated retinal vasculitis. (c) Fluorescein angiogram showing peripheral retinal non-perfusion in sarcoidosis associated retinal vasculitis
attacks, short duration, and limited frequency, chronic, suppressive therapy typically is not needed. However, ~40% of patients will have at least one attack that requires more than topical corticosteroids (eg, a short course of oral prednisone), and ~5-10% of patients will develop a crescendo pattern resulting in chronic uveitis that requires chronic therapy.

HLA-B27 testing is also helpful in identifying patients who may have undiagnosed spondyloarthritis. In a large multicenter prospective study of patients with anterior uveitis, those who were HLA-B27 positive were more frequently diagnosed with axial (69.8% vs 27.3%) and peripheral spondyloarthritis (21.9% vs 11.1%) than those who were HLA-B27 negative.\(^4^2\) Several studies also have suggested that among patients with HLA-B27 associated anterior uveitis who have a spondyloarthritis, in approximately half, the spondyloarthritis will have been undiagnosed or misdiagnosed before the uveitis consultation.\(^2^0\) These results indicate that 30-50% of patients with acute anterior uveitis may have undiagnosed spondyloarthritis.\(^4^3\) Early diagnosis may facilitate appropriate treatment of the spondyloarthritis and prevent future morbidity.\(^4^4\)

Patients with inflammatory bowel disease may have either of two distinct presentations of anterior uveitis; those who are HLA-B27 positive and have an axial spondyloarthritis typically have a recurrent acute anterior uveitis, whereas those who are HLA-B27 negative and have either no arthritis or the peripheral joint enteropathic arthritis may have a chronic unilateral or bilateral anterior uveitis.\(^4^5\) Although patients with psoriatic spondylitis may have an HLA-B27 associated recurrent acute anterior uveitis, some case series suggest that they are more likely to develop chronic anterior uveitis than are patients with ankylosing spondylitis or reactive arthritis.\(^4^5 \text{ } 4^6\)

With the exceptions of HLA-B27 testing, and HLA-A29 in patients with suspected birdshot chorioretinitis (an eye limited disease), the utility of HLA testing as part of a uveitis diagnostic evaluation is limited.\(^4^1\)

**Antinuclear antibody associated disease**

Antinuclear antibody (ANA) testing has poor utility when used routinely in patients with uveitis. Systemic lupus erythematosus (SLE) is uncommonly associated with uveitis.\(^2^7 \text{ } 4^7\) In a meta-analysis including 53,315 adult patients with uveitis, the prevalence of SLE was estimated to be 0.47%, and the positive predictive value of routine ANA testing in patients with uveitis was estimated to be 2.9%.\(^4^7\) An earlier analysis, using a prevalence of 0.1% for lupus in patients with uveitis, calculated an even lower positive predictive value of 0.6%.\(^2^7\) ANA testing in adult patients has value only for those in whom there is a high pretest probability of SLE, either in patients with clinical features suggestive of lupus or in patients with an occlusive retinal vasculopathy suggesting anti-phospholipid antibody syndrome in the context of SLE.

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**Fig 3** Infectious retinitis. (a) Cytomegalovirus retinitis in a patient with acquired immunodeficiency syndrome. (b) Acute retinal necrosis associated with varicella zoster virus. (c) Focal retinitis associated with toxoplasma gondii infection.
Juvenile idiopathic arthritis
Conversely, ANA testing is useful in children with chronic anterior uveitis, because JIA is the most common systemic disease associated with chronic anterior uveitis in childhood, and comprises 75% of all pediatric anterior uveitis cases.\(^\text{15-48} \) For children with JIA without uveitis, ANA testing is routinely performed as it identifies those at high risk for the development of an insidious onset, typically asymptomatic, and potentially blinding uveitis.

Chronic anterior uveitis occurs in 30% of children with JIA who are ANA positive, and the risk is similar for children with oligoarticular persistent, oligoarticular extended, and rheumatoid factor negative polyarthritis subsets.\(^\text{50} \) Because JIA associated uveitis is often asymptomatic until vision threatening complications occur, routine screening eye examinations are important, particularly for those at high risk, \(^\text{51-53} \) and screening algorithms have been developed based on the type of arthritis, ANA test results, age of the patient, and arthritis duration.

Early diagnosis and treatment, including immunosuppressive drug therapy as needed, markedly reduce the risk of vision loss in this patient population.\(^\text{54} \) Children with the enthesitis related arthritis subset of JIA, which is an HLA-B27 associated disease, develop a symptomatic recurrent acute anterior uveitis.

Sarcoidosis
Sarcoidosis associated uveitis accounts for 5-10% of cases in large case series and may present with an acute or chronic anterior uveitis, intermediate uveitis, focal posterior uveitis (fig 4), retinal vascular sheathing (figs 2b,c), or a panuveitis.\(^\text{55} \) Therefore, nearly all patients with uveitis should be screened for sarcoidosis with radiographic imaging of the chest.\(^\text{56-57} \)

Ophthalmic manifestations of sarcoidosis occur in 30-60% of patients with systemic sarcoidosis, with uveitis as the most common ocular manifestation.\(^\text{58} \) Definitive diagnosis is made by histologic confirmation on biopsy of an affected tissue. Conjunctival nodules, if present, may demonstrate granulomatous inflammation; frequently, however, there is no ocular pathology that is amenable to biopsy.

Previous studies have suggested that in patients with bilateral hilar adenopathy and uveitis, lung biopsy results nearly always confirm the diagnosis of sarcoidosis;\(^\text{59-60} \) however, in patients with asymptomatic bilateral hilar adenopathy with normal pulmonary function tests, a lung biopsy is often not performed, because a definitive diagnosis is unlikely to change management.

Debate surrounds the best approach to chest imaging—chest radiograph or chest computed tomography (CT). Chest CT is more sensitive than chest radiography, but most cases are detected by chest radiograph. Many uveitis experts use the chest radiograph as a screening tool and reserve the chest CT scan for cases in which the chest radiograph is equivocal or atypical, or in which the suspicion for sarcoidosis is high.\(^\text{59-60} \) The serum angiotensin converting enzyme levels and lysozyme tests have very poor positive predictive values (in the ~10-20% range) and have limited utility as screening tests for sarcoidosis.\(^\text{2} \)

“Eye limited” uveitis
One common misconception is that uveitis must be a manifestation of a specific underlying cause. In fact, many of the uveitides are presumed to be immune mediated and without a known association to any systemic disease.

Uveitis in patients with no associated infection or rheumatologic disease is classed as “eye limited.” Among these cases, some have clinical features that establish a specific diagnosis (eg, Fuchs heterochromic iridocyclitis or acute posterior multifocal placoid pigment epitheliopathy (fig 5c)). Identifying these morphologically distinct diseases provides information about management and prognosis.

If no identifiable infection, associated systemic disease, or specific ocular uveitic entity is present, we describe these cases as “undifferentiated” and add descriptors of course, laterality, and anatomic location (for example, “chronic, bilateral, panuveitis”).\(^\text{2} \)

In the past, these cases were often described as idiopathic, a practice that leads to the following illogical conclusion: cases of chronic anterior uveitis in a child without JIA are “idiopathic,” whereas those with juvenile idiopathic arthritis are not idiopathic, when in reality both are idiopathic (ie, of unknown cause). Hence, we recommend using the term undifferentiated instead of idiopathic.

Treatment of non-infectious uveitides
The treatment of non-infectious uveitis can be conceptualized as local therapy (including topical corticosteroids and regional injections or implants),
systemic therapy (including oral corticosteroids, immunosuppressive drug therapy, and biologics), or a combination of the two approaches. In general, the primary anatomic site of the inflammation determines the initial approach to therapy.

Patients with anterior uveitides typically are treated with topical corticosteroids, patients with posterior uveitides with systemic medications, and patients with panuveitis with topical corticosteroids and systemic medications. Some patients with intermediate uveitis can receive infrequent regional corticosteroid injections, but about one quarter will need systemic therapy. The predicted disease course determines the chronicity of therapy; patients
Specific uveitic diseases may be more or less likely to require systemic therapy. For example, in patients with JIA associated chronic anterior uveitis, the use of immunosuppression reduces the risk of vision loss by ~40%, as shown in retrospective cohort studies. Similarly, specific medications are also more effective for certain type of uveitis; patients with Behçet disease and an occlusive retinal vasculitis appear to respond well to antiTNF monoclonal antibody therapy. Studies have shown that the presence of even low levels of inflammation in patients with uveitis increase the risk of visual impairment and blindness by twofold to threefold; therefore the goal of therapy is complete suppression of inflammation, while minimizing systemic and ocular side effects.

Corticosteroid treatment

**Topical corticosteroids**

Corticosteroids in their various forms typically are first line treatment for non-infectious uveitis. Even in those diseases where immunosuppression is indicated, corticosteroids are part of the initial regimen. Anterior chamber inflammation is amenable to treatment with corticosteroid eye drops; however, they have poor penetration to the more posterior structures of the eye and are thus poorly suited to treat intermediate and posterior uveitis. Topical corticosteroid potency for treating anterior uveitis is dependent on the corticosteroid, the preparation (salt), and the concentration, all of which influence the penetrance into the anterior chamber.

Of the older topical corticosteroid preparations, prednisolone acetate 1% had the best potency for anterior uveitis and remains a standard therapy. Loteprednol is slightly less effective for uveitis, but is less likely to raise the intraocular pressure, and often is used when there is an intraocular pressure rise with topical corticosteroids. Difluprednate is twice as potent as prednisolone acetate 1%, allowing less frequent use and improved adherence to treatment but has been associated with marked and sometimes unpredictable elevations in intraocular pressure, particularly in children.

**Adverse effects**

As with corticosteroids in any form, the main risks associated with topical corticosteroid use are cataract and elevated intraocular pressure, which can lead to glaucoma. Cataract in children carries the additional risk of amblyopia, or permanent vision impairment from lack of stimuli to the visual pathways in the developing brain.

Untreated inflammation itself can cause cataract and glaucoma, as well as additional irreversible complications. In studies of JIA associated chronic anterior uveitis, active uveitis was a stronger risk factor for cataract than topical corticosteroid use, and in a long term study of a large uveitis cohort, active uveitis was a strong risk factor for subsequent
intraocular pressure elevation. The use of topical prednisolone acetate 1% three times a day has a minimal risk of cataract formation, and prednisone at a dose of ≤7.5 mg/day does not increase the risks of cataract formation and intraocular pressure elevation, according to a retrospective cohort study.

Thus, prioritizing treating inflammation using the necessary quantity of corticosteroids, minimizing long term corticosteroid use with immunosuppression, and managing any ocular complications of corticosteroid use is now the preferred treatment paradigm.

**Corticosteroid injections and implants**

Corticosteroids can be given into or around the eye with an injection. A periocular depot of triamcinolone acetonide (Kenalog®40), injected into the orbital floor or adjacent to the posterior globe, under the Tenon’s layer, is a safe and effective treatment for uveitis and uveitic macular edema. A single injection may be sufficient to control inflammation for three months or more, and one or two repeated injections, spaced >4 weeks apart, may have additional value.

Corticosteroids can be delivered to the vitreous cavity, in the form of injection or implant. Intravitreal triamcinolone acetonide (Triescence) is used to treat non-infectious intermediate, posterior, and panuveitis, as well as uveitic macular edema. Corticosteroid implants, available in both short acting and long acting forms, are injected into the vitreous cavity and provide sustained release of corticosteroid over time. The dexamethasone implant (Ozurdex) is a biodegradable implant that releases dexamethasone for up to six months, and the fluocinolone implant (fluocinolone acetonide 0.18 mg and 0.19 mg inserts (FAi) (Yutiq) was FDA approved for the treatment of non-infectious intermediate, posterior, and panuveitides. Patients in the MUST trial were followed for >7 years. Patients in the implant group underwent re-implantation of second and even third implants when the uveitis relapsed. Although both treatment approaches improved vision similarly, and successfully controlled inflammation for the first five years, eyes with implants had slightly better control of the inflammation; however, this effect disappeared after five years, and at seven years, eyes in the systemic treatment group had significantly better visual acuity than those in the implant group, with a near doubling of the risk of blindness in the implant group.

Injection of triamcinolone into the suprachoroidal space has emerged as an alternative technique that may offer more targeted delivery of corticosteroid to the macula and posterior segment, potentially reducing corticosteroid induced cataract and elevation of intraocular pressure. A randomized controlled trial of patients with uveitic macular edema showed a clinically significant improvement in vision in eyes treated with suprachoroidal triamcinolone compared with sham injection. The relative merits of this approach and its role in the management of patients with uveitis needs to be defined, preferably by comparative effectiveness trials.

Longer acting corticosteroid implants have also been available since the advent of the non-erodible fluocinolone acetonide 0.59 mg implant (Retisert), which was approved by the Food and Drug Administration (FDA) for the treatment of non-infectious intermediate, posterior, and panuveitides in 2005. The implant is sutured to the sclera, inside the vitreous cavity, and releases corticosteroid for up to three years with minimal systemic absorption. The implant may be replaced, if needed, to create space for additional implants. Consistent with the dose and duration of corticosteroid released by the fluocinolone acetonide implant, high rates of cataract and elevated intraocular pressure were recorded; nearly all eyes that had not had cataract surgery before placement of the implant developed a cataract and needed cataract surgery within three years of placement. Seventy eight per cent required intraocular pressure lowering medications, and 40% required glaucoma surgery to control eye pressure.

The Multicenter Uveitis Steroid Treatment (MUST) trial was a multicenter randomized clinical trial that compared systemic therapy with oral corticosteroids and immunosuppression to the fluocinolone acetonide implant for the treatment of non-infectious intermediate, posterior, and panuveitides. Patients in the MUST trial were followed for >7 years. Patients in the implant group underwent re-implantation of second and even third implants when the uveitis relapsed. Although both treatment approaches improved vision similarly, and successfully controlled inflammation for the first five years, eyes with implants had slightly better control of the inflammation; however, this effect disappeared after five years, and at seven years, eyes in the systemic treatment group had significantly better visual acuity than those in the implant group, with a near doubling of the risk of blindness in the implant group.

Ocular adverse effects were more common in the implant group. Specifically, the risk of glaucoma was around threefold higher in the implant group. Systemic therapy was well tolerated, with no significant differences between the MUST trial implant and systemic groups in terms of systemic adverse events, with the exception of a greater use of antibiotics in the systemic treatment group, which reflects good medical care in patients on immunosuppression. These results highlight the relative safety of systemic corticosteroids and immunosuppression when used correctly and suggest a potential role for the fluocinolone acetonide implant when systemic therapy cannot control the inflammation or be tolerated.

More recently, long acting, injectable fluocinolone acetonide 0.18 mg and 0.19 mg inserts (FAi) (Yutiq and Iluvien, respectively) have been developed. Yutiq was FDA approved for the treatment of non-infectious intermediate, posterior, and panuveitides in 2018; Iluvien had been approved for the same indication by...
the European Medicines Agency two years earlier. Similar to the dexamethasone implant described previously, the FAi inserts are injected into the vitreous cavity; however, unlike the dexamethasone implant, they are smaller, non-erodible, and release corticosteroid for around three years.

Results from a randomized controlled study of FAI compared with sham injection showed that the FAI controls inflammation, reduces the need for adjuvant therapy, and is reasonably safe to administer in a clinic setting (table 2). However, the FAI appears to be less effective than the fluocinolone acetonide implant; the FAI relapse rate at one year was 38%, whereas the fluocinolone acetonide implant rate was 4%. For both implants, cataract surgery was nearly universal, but the FAI may have a lower risk of elevated intraocular pressure. To date, there are no randomized trials comparing injectable FAI with surgically implanted fluocinolone acetonide implants.

Systemic corticosteroids

Systemic corticosteroids are used to treat severe inflammation and/or inflammation in the more posterior parts of the eye (eg, intermediate, posterior, and panuveitis). As with the treatment of rheumatologic diseases, our initial approach is to give prednisone 1 mg/kg/day, up to a maximum 60 mg/day. If an adequate response is achieved, we typically begin to taper the prednisone after 2-4 weeks. The goal of therapy is to achieve total suppression of inflammation at a prednisone dose of ≤7.5 mg/day, which has been shown to be relatively well tolerated over years with a low risk of systemic side effects.

For particularly severe, vision threatening disease, high dose intravenous corticosteroids are effective and safe for short term treatment of ocular inflammation. Although the MUST trial showed the superior efficacy of systemic therapy to relapse driven regional therapy, patients on systemic therapy with uveitic macular edema may benefit from a limited number of adjunctive regional corticosteroid injections. The MUST trial reported that, among patients with uveitic macular edema treated with systemic therapy, 62% needed at least one short acting regional corticosteroid injection, but that the median number over a two year period was 1.

Systemic corticosteroid sparing therapy

For patients requiring unacceptably high doses of corticosteroids to control their uveitis or for those in whom the disease is known to require immunosuppression for control, corticosteroid sparing therapy with immunosuppressive medication is indicated. Several medications—including antimitobalites, calcineurin inhibitors, alkyllating agents, and biologics—have been used successfully to treat non-infectious uveitides (table 3).
The Systemic Immunosuppressive Therapy for Eye Diseases (SITE) cohort study, a large retrospective study of 9250 patients with ocular inflammation, provides information on the long term outcomes of systemic therapy of eye diseases, including corticosteroids, alkylating agents, and non-alkylating agents.110-114 The study showed that treatment with non-alkylating agents was associated with control of inflammation in 52-73% of patients, depending on the drug. Successful corticosteroid sparing effect (prednisone <10 mg/day) was achieved in 36-58%; however, sustained, drug free remission was uncommon (<0.10 /person year) with non-alkylating agent therapy. In contrast, treatment with alkylating agents was associated with remission in 64-91% of patients, but current use of alkylating agents is limited by the risk of serious side effects and the availability of alternatives.114-117

Corticosteroid sparing medication

The antimetabolites methotrexate and mycophenolate mofetil are the two most widely used immunosuppressive medications for the treatment of uveitis.65 111 112 116 Our standard treatment approach is to start methotrexate at 15 mg/week and escalate to 25 mg/week in a single step, if 15 mg/week is insufficiently effective. This approach has been used as most patients who respond to methotrexate respond to 15 mg/week. Mycophenolate is initiated at 2 g/day and escalated to 3 g/day as needed.

A retrospective analysis of the SITE cohort suggested that mycophenolate and methotrexate are similarly effective for long term (9 months and beyond) use, but that mycophenolate achieves corticosteroid sparing success faster than methotrexate.90 However, methotrexate was given in a dose escalation as needed approach in this cohort.117 The First-Line Antimetabolites for Steroid-Sparing Treatment (FAST) trial randomized patients with intermediate, posterior, and panuveitides to an initial lower dose of either mycophenolate or methotrexate for two weeks and then, if tolerated, increased to the maximum dose (table 2).120 The study found that methotrexate was non-inferior to mycophenolate (ie, mycophenolate was less effective and more toxic)120, suggesting that, at maximum doses, both drugs are similarly effective.

Azathioprine, a less commonly used (in the US) antimetabolite for uveitis, appears to be similarly successful in achieving corticosteroid sparing success to mycophenolate in retrospective studies.110 However, azathioprine had a higher rate of treatment related side effects, compared with other anti-metabolites,121 and a greater proportion of patients (24% in one study) discontinued the medication because of them.110 Nevertheless, azathioprine is less expensive than mycophenolate, and is more widely used outside the US.

Although single agent antimetabolite therapy often is effective, ~20% to 25% of cases will need a second agent to control inflammation122; an antimetabolite and a calcineurin inhibitor are frequently paired together in this setting.65 Of the calcineurin inhibitors, ciclosporin and tacrolimus are most widely used in the treatment of uveitis. Both medications appear to be similarly effective, but tacrolimus is better tolerated.123 Ciclosporin in particular is less well tolerated with increasing age.113 124 The dose of ciclosporin is 2 mg/kg twice a day; tacrolimus is initiated at 1 mg twice a day, and the dose escalated every two to four weeks until a therapeutic blood level is attained (maximum dose 3 mg twice a day).65

Alkylating agents cyclophosphamide and chlorambucil are effective in the treatment of uveitis but used less frequently because of their potential toxicity.65 103 115 Unlike the non-alkylating agents, they are substantially more likely to induce drug-free remissions. In the SITE cohort, patients treated with cyclophosphamide had a 64% remission rate at two years. Two year remission rates were even higher (91%) in a study of patients being treated with cyclophosphamide for ocular mucous membrane pemphigoid, which is also an immune mediated ocular inflammatory disease.117 The relapse rate is considerably lower than that of non-alkylating agents.114 With the advent of newer alternatives for the management of uveitides, use of alkylating agent therapy has declined, and it is now used rarely.

Emerging treatments

Biologics

The advent of biologic medications has provided new therapeutic avenues for treating non-infectious uveitis. The tumor necrosis factor-α (TNF-α) α inhibitors—in particular, adalimumab and infliximab—are the most commonly used biologic agents in these patients.

Table 3 | Immunosuppressive medications for the uveitides

<table>
<thead>
<tr>
<th>Class</th>
<th>Generic name</th>
<th>Trade name</th>
<th>Suggested initial dose</th>
<th>Typical maximum dose</th>
</tr>
</thead>
<tbody>
<tr>
<td>Antimetabolite</td>
<td>Azathioprine, methotrexate, mycophenolate</td>
<td>Imuran, Rheumatrex, etc Celcipt</td>
<td>2 mg/kg/day</td>
<td>3 mg/kg/day</td>
</tr>
<tr>
<td></td>
<td></td>
<td></td>
<td>15 mg/week</td>
<td>25 mg/week</td>
</tr>
<tr>
<td></td>
<td></td>
<td></td>
<td>1 g BID</td>
<td>1.5 g BID</td>
</tr>
<tr>
<td>Calcineurin inhibitor</td>
<td>Ciclosporin, tacrolimus</td>
<td>Neoral, etc Prograf Prograf</td>
<td>2 mg/kg BID</td>
<td>2 mg/kg BID</td>
</tr>
<tr>
<td></td>
<td></td>
<td></td>
<td>1 mg BID</td>
<td>3 mg BID</td>
</tr>
<tr>
<td>Alkylating agent</td>
<td>Cyclophosphamide, chlorambucil</td>
<td>Cytoxan, Leukeran</td>
<td>2 mg/kg</td>
<td>250 mg/day</td>
</tr>
<tr>
<td></td>
<td></td>
<td></td>
<td>0.1 mg/kg/day</td>
<td></td>
</tr>
<tr>
<td>Biologic</td>
<td>Adalimumab, infliximab</td>
<td>Humira, Remicade, etc</td>
<td>40 mg/2 week*</td>
<td>40 mg/week</td>
</tr>
<tr>
<td></td>
<td></td>
<td></td>
<td>5 mg/kg/4 week*</td>
<td>10 mg/kg/4 week</td>
</tr>
</tbody>
</table>

BID=twice per day.
*After loading dose.
Adapted from Jabs11.
Adalimumab is FDA approved for the treatment of non-infectious uveitides. The results of two randomized placebo controlled trials, VISUAL I and VISUAL II, showed the safety and efficacy of adalimumab in patients with active and suppressed non-infectious intermediate, posterior, and pan-uveitides, respectively (table 2). In both studies, treatment with adalimumab was associated with reduced inflammation and lower risk of uveitis relapse and vision loss through 52 weeks. The open label extension study, VISUAL-III, showed similar results through 78 weeks, and suggested a high rate of corticosteroid sparing success.125

Adalimumab was effective in a randomized placebo controlled study of patients with JIA associated chronic anterior uveitis on a stable dose of methotrexate (table 2). Adalimumab has been reported to reduce attacks of recurrent uveitis in patients being treated with adalimumab for spondylitis.128 The efficacy of adalimumab versus conventional immunosuppressive therapy currently is unknown. For adult uveitis patients, adalimumab is typically given as a loading dose of 80 mg, followed one week later by a maintenance dose of 40 mg, which is then repeated every two weeks.129 For patients on the standard dose of adalimumab who have improved but have persistent inflammation, an increase to weekly dosing has been tried by some investigators with some apparent success, but has not been proven successful in a clinical trial.130 131

Compared with adalimumab, infliximab appeared to have similar efficacy in a retrospective study of uveitis patients.122 Infliximab is well tolerated and effective, with uncontrolled case series suggesting corticosteroid sparing success in −80%.129 133 Although infliximab is approved with a wide dose range (3-10 mg/kg every four to eight weeks), retrospective data suggest that doses ≥5 mg/kg every four weeks are needed to control uveitis.134

Anti-TNF therapy appears to be particularly effective for Behçet disease uveitis, and as a second line agent in JIA associated chronic anterior uveitis. Recommendations from an expert panel of uveitis specialists suggested anti-TNF monoclonal antibody therapy (eg, infliximab or adalimumab) as first line therapy for Behçet disease uveitis and as second line therapy for JIA associated uveitis.129

Some experts recommend concurrent use of a conventional immunosuppressive agent, such as methotrexate or mycophenolate, with infliximab to reduce the risk of anti-infliximab antibodies. This practice has been shown to reduce the formation of antibodies, prolong efficacy of treatment, and prevent infusion reactions in patients receiving infliximab for Crohn’s disease.116

Other TNF-α inhibitors have been used with varying success in the treatment of uveitis in retrospective case series. Data suggest that etanercept has substantially lower efficacy in treating uveitis than adalimumab or infliximab, and its use for uveitis generally is not recommended.129 137-141 Golimumab appears to reduce risk of uveitis in patients with ankylosing spondylitis but has not been widely studied.142

As of 2020, the data on other biologics for uveitis are fewer; however, preliminary case series of tocilizumab, an interleukin (IL)-6 receptor antagonist, have suggested that it may be effective in treating uveitis, including uveitic macular edema.143-145 Abatacept, a co-stimulation inhibitor, has not shown particular promise in early studies for JIA associated uveitis. One small study showed a sustained treatment response in less than 15% of patients with JIA associated uveitis,146 and a slightly larger study reported 49% success over a year.147

The combined results of three clinical trials for secukinumab, an IL-17A antagonist, did not show benefit in treating uveitis, despite secukinumab being very effective for psoriasis, psoriatic arthritis, and ankylosing spondylitis.148

Long term safety of systemic therapy

Seven year data from the MUST trial show that, with appropriate management, systemic therapy with corticosteroids and immunosuppressive medication is well tolerated.91 97 98 149 The question of long term safety was also addressed by the SITE study, which found no increased risk of mortality or cancer related mortality with corticosteroids, antimetabolites, or calcineurin inhibitors in this patient population. Although alkylation agent therapy carried no increased risk of mortality, there was a borderline significant suggestion of an increased risk of cancer related mortality.150 152

An Australian study published in 2015 reported an increased risk of non-melanotic skin cancer among patients with ocular inflammation treated with immunosuppression; however, the study included both alkylation and non-alkylating agents together.153 Moreover, given the relatively higher incidence of non-melanotic skin cancer in Australia, this study’s results may not be representative of skin cancer risk in the general population. Nevertheless, it would seem prudent to recommend the use of sunscreen and routine skin examinations in patients with uveitis on immunosuppressive drug therapy.

The long term risks associated with biologic agents in patients with uveitis are less clear, owing to the more limited amount of data available. The data from the SITE cohort were too few and the models too unstable to conclusively evaluate the risks or mortality and cancer related mortality in patients with eye disease treated with anti-TNF therapy.150

Large registries of patients with rheumatoid arthritis suggest only an increased risk of non-melanoma skin cancer.154 155 The risk of infection is increased, including with tuberculosis, with anti-TNF therapy156; hence, screening for tuberculosis, as well as hepatitis, before beginning anti-TNF therapy is recommended. Additionally, because anti-TNF therapy worsens multiple sclerosis, patients with intermediate uveitis, which is associated with a higher risk of multiple sclerosis, should be screened...
with magnetic resonance imaging of the brain before initiating therapy with an anti-TNF agent.61 129 157

Treatment duration
The decision to discontinue therapy may be based on several different factors, including disease course and severity, risks associated with recurrence, and the patient’s tolerance for the current therapy. When a patient with uveitis also has associated systemic disease, their ophthalmologist and rheumatologist or internist should be involved in the decision about if and when to discontinue therapy.

As previously discussed, achieving a sustained, drug-free remission in patients with uveitis treated with non-alkylating agents is uncommon. Data from a cohort of patients with JIA associated chronic anterior uveitis indicate that median time to a sustained, drug-free remission was about 10 years in patients with mild disease, and that less than 25% of patients with severe disease achieved remission even after 20 years.52 However, another study of patients with JIA associated chronic anterior uveitis showed that the risk of relapse is lower in patients treated with methotrexate for more than three years and in those who had inactive disease for more than two years.158 This paradigm has been adopted for the use of immunosuppression in the uveitides and, for a patient who is tolerating therapy well, it is our practice to treat with non-alkylating immunosuppressive therapy for at least two years after corticosteroids have been discontinued before considering tapering immunosuppression. Given concerns for toxicity and malignancy risk associated with alkylating agents, if used at all, the target duration is one year after achieving disease quiescence and discontinuing prednisone, with a goal of limiting total duration of therapy to fewer than 18-24 months.103 159

Guidelines
Three sets of published guidelines are available, written by expert panels of uveitis specialists, for the use of systemic medications in patients with non-infectious uveitis.103 109 129 The first set of guidelines was published before widespread use of biologics in the treatment of uveitis103; the second set focused specifically on the use of biologics.129 The most recent set of guidelines answered 10 specific questions, including those about the timing of treatment escalation and discontinuation.109 All of the guidelines advocate for early and aggressive use of corticosteroid sparing therapy in patients with severe, non-infectious uveitis. Additionally, as discussed above, they recommend the use of anti-TNF therapy early in the course of Behçet associated uveitis and as second line therapy for chronic JIA associated uveitis.

Conclusion
The uveitides are a collection of more than 30 distinct diseases, and the goal of the uveitis evaluation is the identification of the specific disease. Some uveitides are associated with infection or systemic disease; others are presumed to be immune mediated and limited to the eyes. The diagnosis of uveitis involves the intersection of clinical findings (both ocular and systemic) and focused laboratory testing. Treatment of the non-infectious uveitides involves both corticosteroids and, when indicated, immunosuppressive drug therapy. For patients with uveitis and associated systemic disease, collaboration of the ophthalmologist and rheumatologist facilitates treatment of both ocular and systemic disease and may prevent vision loss and other morbidity.

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QUESTIONS FOR FUTURE RESEARCH
- What is the role of molecular techniques such as metagenomic deep sequencing in pathogen discovery in patients with undifferentiated uveitis?
- What is the comparative effectiveness of adalimumab versus conventional immunosuppressive agents as corticosteroid sparing treatments for non-infectious uveitides?
- What is the comparative effectiveness of long acting injectable (eg, Yutiq) versus implanted (Retisert) corticosteroid for the treatment of non-infectious uveitis?
- What is the comparative efficacy of intravitreal versus suprachoroidal corticosteroid, and what are the relative risks of cataract and glaucoma?
STATE OF THE ART REVIEW


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