CHAPTER 6

Therapy for Uveitis

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Highlights

- Therapy for uveitis consists of local (ocular) or systemic administration of anti-inflammatory and/or antimicrobial agents. Ocular medications may be delivered topically, by ocular injection, or via surgical implantation.
- The goal of uveitis treatment is to prevent vision loss from uncontrolled inflammation while minimizing the ocular and systemic adverse effects of therapy.
- Infectious causes of uveitis must be investigated and treated before corticosteroids, especially the periocular and intravitreal forms, are administered.

Introduction

Therapy for uveitis ranges from observation to complex medical and/or surgical intervention. In cases of suspected chronic or vision-threatening uveitis, uveitis specialists can help confirm the diagnosis and determine a therapeutic regimen. Factors influencing therapy decisions include the risk of morbidity from ocular inflammation as well as the potential adverse effects of the treatments. Management may require coordination with rheumatologists and other medical or surgical subspecialists; in general, early involvement of subspecialists can improve prognosis.

Medical Management of Uveitis

The goals of management of uveitis and other forms of ocular inflammation are to control disease activity and to reduce the risk of vision loss from structural complications of inflammation. It is critical to determine whether the uveitis is related to a systemic or ocular infection, as anti-inflammatory therapy may severely exacerbate an untreated infection. Once infection is properly addressed, residual inflammation may be cautiously treated with adjuvant anti-inflammatory therapy, as many types of infectious uveitis have a significant inflammatory component. Some diseases, such as multiple evanescent white dot syndrome or acute posterior multifocal placoid pigment epitheliopathy, are self-limited and usually resolve without treatment. Other diseases, such as Fuchs uveitis syndrome and mild pars planitis,

are chronic but do not require treatment. However, the majority of patients with chronic ocular inflammation will benefit from sustained suppression of inflammation.

Corticosteroids are the most effective agents to control ocular inflammation quickly. Drug route and dose are tailored to each patient depending on disease severity and the duration of and response to therapy. Additional factors to consider when choosing a corticosteroid are the presence of systemic disease and the patient's age, weight, immune status, and tolerance of adverse effects. It is common practice to use systemic immunomodulatory therapy (IMT) to decrease or stop corticosteroids. In the appropriate clinical scenario, cycloplegic agents, nonsteroidal anti-inflammatory drugs (NSAIDs), fibrinolytic agents, and carbonic anhydrase inhibitors may also be used as adjunctive therapy.

The remainder of this chapter offers a detailed discussion of corticosteroids and systemic IMT for the management of uveitis.

TREATMENT OF NONINFECTIOUS OCULAR INFLAMMATORY DISEASE

The basic principles of treatment of noninfectious ocular inflammatory disease are summarized as follows:

1. The absence of infection should be confirmed.
2. The inflammation is quieted with some form of corticosteroids. If inflammation worsens, an infectious etiology should be reconsidered.
3. Corticosteroids are slowly tapered off completely or down to a medically safe dose.*
4. If inflammation recurs upon corticosteroid taper, a longer-acting or stronger option is indicated:
    - For example, if topical corticosteroids are being used, a periocular, intravitreal, or systemic formulation can be considered.
    - When corticosteroids are maximized or cannot be continued, systemic corticosteroid-sparing immunomodulatory therapy (IMT) may be added.
5. Antimetabolites have historically been considered first-line treatment. In certain cases, a biologic agent (usually a tumor necrosis factor inhibitor) or, less likely, an alkylating agent, may be used first.
6. IMT takes time to achieve a therapeutic effect, and not every agent works in every situation. These factors should be considered in assessing efficacy. Adding or switching to another agent may be necessary. When effective and well tolerated, IMT is maintained for at least 1–3 years.
7. For certain ocular inflammatory diseases, especially those with systemic manifestations, IMT may be indicated as first-line treatment.

* A maximum of 7.5 mg/day oral prednisone, or a topical drug at a dose low enough to avoid ocular side effects.

Corticosteroids

Corticosteroids are often the first-line treatment for all forms of ocular inflammation as well as for complications such as macular edema. They may be administered locally (eg, as topical eyedrops or as periocular or intraocular injections) or systemically (eg, orally, intravenously, or less frequently, intramuscularly).

The corticosteroid dose, duration of therapy, and route of administration must be individualized. For maximum effect, corticosteroid therapy is usually started at a high dosage (ie, topical or systemic) and then tapered as the inflammation subsides, rather than initiated at a low dose that may have to be progressively increased to control inflammation. To minimize side effects, the maintenance dose should be the lowest amount necessary to control inflammation. If systemic corticosteroids are administered for more than 2 to 3 weeks, they must be tapered gradually (ie, over days to weeks) to prevent cortisol deficiency from hypothalamic–pituitary–adrenal axis suppression.

For uveitis that is not immediately vision threatening or chronic, corticosteroids are slowly tapered, and the disease is closely monitored. If inflammation recurs before a low corticosteroid dose is reached, then additional anti-inflammatory treatment is usually required to control ocular inflammation. Systemic corticosteroids are often used as a therapeutic bridge to long-term immunosuppressive therapy. When ophthalmic surgery is performed on an eye with uveitis, the corticosteroid may need to be increased or restarted to prevent postoperative uveitis exacerbation.

Any route of corticosteroid administration can cause adverse effects, so the risk–benefit ratio of treatment should be considered carefully and discussed with the patient before initiation. Local corticosteroids convey the highest risk of ocular adverse effects, notably posterior subcapsular cataract and ocular hypertension. Compared with adults, children are more likely to have ocular adverse effects, and they can be more severe. The systemic risks of corticosteroids are discussed later in this chapter. See also BCSC Section 1, *Update on General Medicine,* and Section 2, *Fundamentals and Principles of Ophthalmology*.

CLINICAL PEARL

The following are some important points to remember when local corticosteroid treatment for noninfectious uveitis is being considered:

- Anterior and mild intermediate uveitis may be initially treated with topical corticosteroids.
- Local corticosteroid injections achieve a greater depth of penetration than topical formulations and may be used for a more posterior effect or as an adjunct to systemic treatment.
- Serial short-acting corticosteroid injections should be avoided as the sole treatment for chronic uveitis.
- Ocular hypertension and cataract formation are common adverse effects of local corticosteroid treatment and may be more frequent and severe in children than in adults.

Topical corticosteroid administration

Topical corticosteroid drops are effective primarily for anterior uveitis, although they may have beneficial effects on vitritis or macular edema in some patients. These drops are given at intervals ranging from once daily to hourly. The drugs can also be prescribed in ointment form for nighttime use. Difluprednate (0.05%), a fluorinated corticosteroid, is highly potent and penetrates tissue more deeply than other topical preparations; 4 drops per day of difluprednate are considered the equivalent of 8 or more total drops per day of prednisolone acetate (1%). Clinical studies suggest that the adverse effect profile of difluprednate is similar to that of prednisolone; however, difluprednate is associated with more frequent and severe ocular hypertension, especially in children. Of the topical preparations, loteprednol and fluorometholone produce the lowest ocular hypertensive effect; however, these drugs are not as effective as prednisolone in controlling more severe uveitis. Of note, when branded versus generic suspensions of prednisolone acetate are being considered, differences in the physical properties of the formulations can affect bioavailability, although this discrepancy may be partially overcome by vigorous agitation of the drug before instillation. See Part V, Ocular Pharmacology, in BCSC Section 2, *Fundamentals and Principles of Ophthalmology,* for additional discussion.

Slabaugh MA, Herlihy E, Ongchin S, van Gelder RN. Efficacy and potential complications of difluprednate use for pediatric uveitis. *Am J Ophthalmol.* 2012;153(5):932–938.

Local corticosteroid administration

When a more posterior effect is needed to treat uveitis or when a patient is nonadherent with or only partially responsive to topical corticosteroids, corticosteroids may be delivered directly into the vitreous cavity or into the periocular space—as long as an infectious cause has been sufficiently investigated. In addition, intermediate-acting and short-acting local corticosteroid injections may be used intermittently to treat breakthrough inflammation in otherwise well-controlled or mild uveitis. In certain clinical settings, long-acting intravitreal corticosteroids may be alternatives to long-term IMT. However, a limitation of local therapies is the variable duration of effect, with relapse being the only sign of waning corticosteroid efficacy. Relapses before reinjection or reimplantation may cause cumulative damage, creating a "saw-tooth decline," a phenomenon in which patients initially improve after injection but then worsen below the point of their previous baseline. Each subsequent spike of improvement and valley of decline are progressively lower, like the teeth of an angled saw. This type of decline is disguised by the peaks of improvement and may go unnoticed by the treating physician without careful long-term analysis. In patients with chronic uveitis, scheduled replacement or reinjection of local corticosteroid before the effect wears off may improve long-term prognosis.

Periocular corticosteroid administration Periocular corticosteroids are traditionally given as depot injections into the sub-Tenon space or orbital floor. Triamcinolone acetonide (40 mg) and methylprednisolone acetate (40–80 mg) are the most commonly used periocular drugs. Short-acting nondepot corticosteroids, such as dexamethasone or betamethasone, may be injected subconjunctivally for a limited duration of effect. Periocular injections can be performed using either a transseptal or a sub-Tenon (Nozik technique) approach (Fig 6-1).

Figure 6-1 Posterior sub-Tenon injection of triamcinolone acetonide demonstrating correct position of the clinician's hands and the needle. A 25- or 27-gauge, ⅝-inch needle on a 3-mL syringe is advanced to the hub with a gentle side-to-side motion to detect any scleral engagement and directed caudad and nasally before injection of the corticosteroid. The ideal position of the tip of the needle is between the Tenon capsule and the sclera. *(Courtesy of Ramana S. Moorthy, MD.)*

For a sub-Tenon injection given in the superotemporal quadrant, the technique is as follows:

1. The upper lid is retracted and the patient instructed to look downward and nasally.
2. After proparacaine or tetracaine is applied with a cotton swab, a 25- or 27-gauge, ⅝-inch needle on a 3-mL syringe is placed bevel down against the globe and advanced through the conjunctiva and Tenon capsule using a gentle side-to-side movement, allowing the physician to determine whether the needle has entered the sclera. If the globe does not torque with the side-to-side movement of the needle, the physician can be reasonably sure that the needle has not penetrated the sclera.
3. Once the needle has been advanced to the hub, the corticosteroid is injected into the sub-Tenon space.

Complications of this superotemporal approach include upper eyelid ptosis, periorbital hemorrhage, and globe perforation. To avoid the risk of upper eyelid ptosis, an inferotemporal sub-Tenon injection, also using the Nozik technique, can be performed.

A transseptal, orbital floor approach (Fig 6-2) using a 27-gauge, ½-inch needle on a 3-mL syringe is another alternative for periocular injections, as follows:

1. The index finger is used to push the temporal lower eyelid posteriorly and to locate the equator of the globe.
2. The needle is inserted inferior to the globe through the skin of the lower eyelid and directed straight back through the orbital septum into the orbital fat.
3. The needle is advanced to the hub, and then aspirated; if there is no blood reflux, the corticosteroid is injected.

Complications of the inferior approach include periorbital and retrobulbar hemorrhage, lower eyelid retractor ptosis, orbital fat prolapse with periorbital festoon formation, orbital fat atrophy, and skin discoloration.

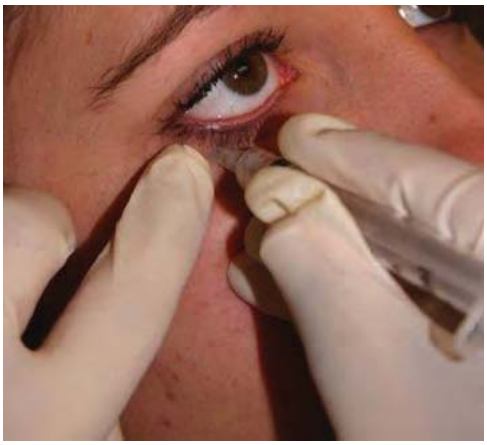

Figure 6-2 Inferior transseptal (orbital floor) injection of triamcinolone acetonide in the right eye. A 27-gauge, ½-inch needle on a 3-mL syringe is inserted through the skin of the lower eyelid and the inferior orbital septum. By using the index finger of the opposite hand, the physician can determine the location of the equator of the globe to prevent perforation and to place the depot corticosteroid as posteriorly as possible. *(Courtesy of Ramana S. Moorthy, MD.)*

Periocular injections are contraindicated in certain patients, including those with active infectious uveitis. They are also not recommended in patients with necrotizing scleritis because of cases of scleral thinning and perforation (see Chapter 7). Although systemic absorption of periocular corticosteroids is minimal, the drugs can still cause systemic adverse effects similar to those of oral corticosteroids. The physician should be aware that periocular corticosteroid injections have the potential to raise intraocular pressure (IOP) precipitously or for an extended period, particularly when longer-acting depot drugs are used. If this effect occurs, the periocular corticosteroid may be removed surgically if it is located anterior to the septum or in a subconjunctival space.

Suprachoroidal corticosteroid administration In 2021, the US Food and Drug Administration (FDA) approved a novel suprachoroidal drug delivery system to treat macular edema associated with noninfectious uveitis using a preservative-free triamcinolone suspension (CLS-TA). An integrated 30-g microinjector is used to administer 4 mg/0.1 mL of the drug. The microinjector is held perpendicular to the sclera, where it is inserted 4–5 mm posterior to the limbus. The short 900-μm or 1100-μm needle penetrates only to the level of the suprachoroidal space (SCS) between the sclera and the choroid. The drug is then slowly administered, allowing a fluid wave to propagate posteriorly and circumferentially and resulting in low levels of corticosteroid in the anterior segment and high levels in the posterior segment.

Phase 3 data from the PEACHTREE study with post hoc analysis and the MAGNOLIA extension study comparing SCS CLS-TA injection with sham injection (2 administrations 12 weeks apart) for the treatment of macular edema secondary to noninfectious uveitis revealed that 47% of patients receiving CLS-TA treatment achieved the primary endpoint of improvement of ≥15 ETDRS letters (vs 16% of patients receiving sham treatment). In addition, compared with sham treatment, SCS CLS-TA resulted in superior reduction in mean central subfield macular thickness, 152.6 μm vs 17.9 μm, CLS-TA vs sham, respectively. Approximately 50% of patients receiving SCS injection did not require additional treatment at 9 months. Percentages of patients with elevated IOP (11.5% vs 15.6%) and cataract formation (7.3% vs 6.3%) were comparable in the SCS CLS-TA and sham treatment groups, respectively.

Leder HA, Jabs DA, Galor A, Dunn JP, Thorne JE. Periocular triamcinolone acetonide injections for cystoid macular edema complicating noninfectious uveitis. *Am J Ophthalmol.* 2011;152(3):441–448.e2.

Yeh S, Khurana RN, Shah M, et al; PEACHTREE Study Investigators. Efficacy and safety of suprachoroidal CLS-TA for macular edema secondary to noninfectious uveitis: phase 3 randomized trial. *Ophthalmology*. 2020;127(7):948–955.

Intravitreal corticosteroid administration Intravitreal therapy achieves a higher, more predictable concentration of corticosteroids in the posterior segment than traditional periocular injection. In the United States, intravitreal corticosteroid administration for uveitis currently takes several forms:

- triamcinolone acetonide (4 mg/0.1 mL), preservative-free, via pars plana injection with a 30-gauge needle
- dexamethasone pellet (700 μg), biodegradable, via shelved pars plana injection with an integrated 22-gauge injector
- fluocinolone acetonide intravitreal insert (0.18 or 0.19 mg), via pars plana injection with integrated 25-gauge injector
- fluocinolone acetonide implant (0.59 mg), surgically implantable, via pars plana incision

In nonvitrectomized eyes, intravitreal injections of preservative-free triamcinolone acetonide (2–4 mg) through the pars plana have produced sustained visual acuity improvements for 3–6 months; the technique is the same as for standard intravitreal injection (see BCSC Section 12, *Retina and Vitreous*). For recalcitrant uveitic macular edema, published literature on intravitreal triamcinolone administration suggests a definite treatment benefit, although of limited duration. However, IOP may be transiently elevated in more than half of these patients, up to 25% may require topical medications to control IOP, and 1%–2% may require filtering surgery. Infectious endophthalmitis and rhegmatogenous retinal detachment may also occur, but these complications are rare when proper technique is used. Of note, this method of treatment does not cure chronic uveitic conditions and should be used judiciously because its effects are relatively short-lived.

A biodegradable injectable pellet containing 700 μg of dexamethasone has been approved in the United States and in Europe for the treatment of retinal vein occlusion and noninfectious uveitis affecting the posterior segment of the eye. With this therapy, an injector is used to create a shelved wound, and the pellet is injected through the pars plana into the vitreous cavity (Video 6-1). A prospective, randomized, controlled clinical trial demonstrated that at 8 weeks, 47% of eyes treated with the dexamethasone pellet had improved vitreous haze compared with 12% of eyes in the sham treatment group. Statistically significant improvements in visual acuity and macula thickness were also reported with the pellet, and fewer eyes required rescue medication. IOP elevation and cataracts were the most commonly reported treatment-related ocular adverse effects in this study. Several longer-term, multicenter, retrospective studies have reported relatively positive safety and efficacy results with repeated dexamethasone intravitreal pellets in patients with uveitis and refractory macular edema, with an average time to reinjection of 6 months. Relative contraindications to the dexamethasone pellet are aphakia, prior vitrectomy, and absence of lens capsule owing to the risk of implant migration into the anterior chamber.

VIDEO 6-1 Injection of dexamethasone pellet.
Courtesy of Thomas A. Albini, MD.

Sustained-release, injectable fluocinolone acetonide intravitreal inserts (0.18- or 0.19-mg inserts) are approved in the United States and Europe for the treatment of noninfectious posterior uveitis. The nonbioerodible insert is injected via a nonshelved wound through the pars plana into the vitreous cavity and releases approximately 0.2 mg/day over 36 months. A prospective, randomized, placebo-controlled clinical trial of a fluocinolone acetonide insert in noninfectious intermediate uveitis, posterior uveitis, or panuveitis demonstrated statistically significant lower uveitis recurrence rates in the insert group (87 patients) than in the placebo group (42 patients) at 6 months (27.6% vs 90.5%), 12 months (37.9% vs 97.6%), and 3 years (65.5% vs 97.6%), respectively. However, cataract surgery was required more frequently in the insert treatment group (73.8% vs 23.8%, respectively). At 3 years, IOP was similar for both study groups, and approximately half as many eyes in the fluocinolone acetonide intravitreal insert group underwent IOP-lowering surgery (5.7% vs 11.9%, respectively), possibly because of the adjunctive corticosteroid treatments administered in the sham treatment group.

In the United States, a surgically implantable, sustained-release 0.59-mg fluocinolone acetonide implant has been approved by the FDA for the treatment of chronic noninfectious uveitis affecting the posterior segment. The implant is inserted through a small pars plana incision and sutured to the sclera. The implant is effective in controlling inflammation for a median of 30 months, reducing recurrence rates and allowing discontinuation of systemic therapy and other corticosteroid injections. Visual acuity outcomes are equivalent to those associated with systemic immunosuppressive therapy for up to 4.5 years. The 7-year data strongly favor systemic treatment, presumably because of retinal damage from relapse of the uveitis before reimplantation. Postoperative complications (eg, endophthalmitis, wound leaks, hypotony, vitreous hemorrhage, and retinal detachments) have been reported with this therapy, and reimplantation or exchange may be performed. Adverse event rates are high in eyes treated with the implant, with nearly all phakic eyes developing cataract within 2 years after implantation, 75% experiencing IOP elevation requiring topical therapy, and nearly 40% requiring filtering surgery (Table 6-1).

The prospective, multicenter, randomized, controlled POINT trial compared the effectiveness of three of these local corticosteroid injections for uveitic macular edema: periocular triamcinolone acetonide, intravitreal triamcinolone acetonide, and intravitreal dexamethasone pellet. All three modalities decreased central subfoveolar thickness, but statistically significantly greater improvements were observed with the two intravitreal modalities versus periocular triamcinolone acetonide. In contrast, IOP ≥24 mm Hg or ≥10 mm Hg from baseline was more likely in the two intravitreal corticosteroid groups than in the periocular group (see Table 6-1).

Goldstein DA, Godfrey DG, Hall A, et al. Intraocular pressure in patients with uveitis treated with fluocinolone acetonide implants. *Arch Ophthalmol.* 2007;125(11):1478–1485.

Jaffe GJ, Pavesio CE; Study Investigators. Effect of a fluocinolone acetonide insert on recurrence rates in noninfectious intermediate, posterior, or panuveitis: three-year results. *Ophthalmology*. 2020;127(10):1395–1404.

Table 6-1 Selected List of Major Treatment Studies in Uveitis

Study/Year	Study Questions	Results
Local therapy		
Fluocinolone Acetonide Insert (FAi) Trial/2020 Effect of a Fluocinolone Acetonide Insert on Recurrence Rates in Noninfectious Intermediate, Posterior, or Panuveitis • Participants: 129 patients with noninfectious uveitis involving the posterior segment; 87 eyes randomly assigned to 0.2-µg/day FAi treatment, 42 eyes to sham treatment • Primary endpoint: uveitis recurrence rates at 6 months	Efficacy and safety of intravitreal injection of a slow-release (approximately 0.2 mg/day over 36 months) FAi or sham (plus reference standard) treatment	Significantly lower rates of uveitis recurrence were observed in the FAi group compared with the sham group at 6 months (27.6% vs 90.5%), 12 months (37.9% vs 97.6%), and 3 years (65.5% vs 97.6%), respectively. Cataract surgery was required significantly more frequently in the treatment group than in the sham group (73.8% vs 23.8%, respectively). IOP was similar for both study groups. Approximately half as many eyes in the FAi-treated group vs the sham-treated group underwent IOP-lowering surgery (5.7% vs 11.9%, respectively).
POINT/2019 Periocular Triamcinolone vs. Intravitreal Triamcinolone vs. Intravitreal Dexamethasone Implant for the Treatment of Uveitic Macular Edema • 192 patients (235 eyes) with uveitic macular edema (ME) • Endpoint: improvement in uveitic ME on OCT at 8 weeks	Comparative effectiveness of periocular triamcinolone (PTA), intravitreal triamcinolone (ITA), and intravitreal dexamethasone implant (IDI) for treatment of uveitic ME	At 8 weeks, eyes in all 3 treatment arms had improvements in ME on OCT. ITA and IDI groups had significantly greater reductions in ME (39% and 46%, respectively) than the PTA group (23%). Risk of having IOP ≥24 mm Hg or an increase of ≥10 mm Hg from baseline in IOP was higher in the ITA and IDI groups than in the PTA group. No significant difference was observed between the 2 intravitreal treatment groups.
Local vs systemic therapy		
MUST/2010 Multicenter Uveitis Steroid Treatment Trial • 255 patients (479 eyes) with noninfectious intermediate uveitis, posterior uveitis, or panuveitis • Endpoint: change in BCVA	Efficacy and safety of local therapy of a surgically placed 0.59-mg fluocinolone acetonide slow-release (36-month) intravitreal implant compared with systemic therapy (corticosteroid monotherapy or combination steroid-IMT therapy)	2- and 4.5-year analyses: There was no significant difference in BCVA or systemic outcomes between the two groups but more local adverse outcomes in the implant group. 7-year analysis: Systemic therapy was favored for BCVA outcome by 7.1 letters as a result of visual decline in the implant group, likely due to loss of efficacy of the implant.

(Continued)

Table 6-1 *(continued)*

Study/Year	Study Questions	Results
Systemic therapy		
SITE/2009, 2019 Systemic Immunosuppressive Therapy for Eye Diseases Cohort Study • 7957 patients expanded to 15,938 patients with noninfectious ocular inflammatory disease treated with systemic immunosuppression; analysis of 187,151 person-years • Endpoint: cancer mortality	To determine overall and cancer mortality rates in patients with uveitis receiving systemic immunosuppression for ocular inflammatory disease	Cancer mortality rates were not increased in patients treated with azathioprine, methotrexate (MTX), mycophenolate mofetil, cyclosporine, or systemic corticosteroids. Extension of follow-up study confirmed that TNF inhibitors were not associated with increased overall cancer or cancer mortality rates. Alkylating agents were associated with higher overall mortality, but not after confounding factors were excluded. Mortality was higher in patients receiving tacrolimus and etanercept, which might reflect selection factors (eg, transplantation). Further study is required.
SYCAMORE/2017 Adalimumab (ADA) plus Methotrexate (MTX) for juvenile idiopathic arthritis (JIA)–associated uveitis • 60 children and adolescents with active uveitis taking a stable MTX dosage randomly assigned (2:1) to ADA vs placebo • Endpoint: time to treatment failure	Efficacy and safety of adding ADA in active JIA-associated uveitis treated with MTX	The ADA group was less likely than the placebo group to have treatment failure (HR, 0.25; 95% CI, 0.12–0.49). Significantly greater proportions of patients in the ADA group were able to eliminate or reduce topical corticosteroids. Adverse events (AEs) and serious adverse events (SAEs) were more common in the ADA group than in the placebo group (10.07 vs 6.51 AEs and 0.29 vs 0.19 SAEs per patient-year, respectively).
VISUAL I, II, III/2016–2018 ADA for noninfectious intermediate uveitis, posterior uveitis, or panuveitis • I: 217 patients with active disease • II: 226 patients with controlled disease • III: 371 patients from I or II who completed the study or met treatment failure criteria • Endpoint: time to treatment failure	I: Efficacy and safety of ADA in controlling inflammation in active noninfectious uveitis II: Efficacy and safety of ADA in preventing flare-up in pharmacologically (prednisone and/or 1 immunomodulatory therapy) controlled noninfectious uveitis III: Long-term efficacy and safety of ADA in active or controlled noninfectious uveitis	I: The ADA group was less likely than the placebo group to have treatment failure (HR, 0.50; 95% CI, 0.36–0.70). AEs and SAEs were more common in the ADA group (1052 vs 972 AEs and 29 vs 14 SAEs, respectively, per 100-person-years). II: The ADA group was less likely than the placebo group to have treatment failure (HR, 0.57; 95% CI, 0.39–0.84). The incidences of AE and SAEs were similar between treatment groups.

Study/Year	Study Questions	Results
		III: Of 242 patients with active uveitis, 60% achieved quiescence at week 78, 66% of whom were corticosteroid free. Of 129 patients with inactive uveitis, 74% achieved quiescence at week 78, 93% of whom were corticosteroid free. AEs and SAEs were comparable to those in previous VISUAL trials.
FAST/2018 Effect of Corticosteroid-Sparing Treatment With Mycophenolate Mofetil vs Methotrexate on Inflammation in Patients With Uveitis • 194 patients with noninfectious uveitis • Endpoints: corticosteroid-sparing[a] disease control in both eyes and absence of treatment failure due to safety or intolerability at 6 months	Comparative efficacy and safety of systemic mycophenolate mofetil vs MTX for first-line treatment of noninfectious uveitis.	Treatment was successful in 66.7% of patients in the MTX group vs 57.1% in the mycophenolate mofetil group, a nonstatistically significant difference.

BCVA = best-corrected visual acuity; IMT = immunomodulatory therapy; IOP = intraocular pressure; OCT = optical coherence tomography; TNF = tumor necrosis factor.
[a] Less than or equal to 7.5 mg daily oral prednisone and ≤2 drops of prednisolone acetate 1%.

Khurana RN, Appa SN, McCannel CA, et al. Dexamethasone implant anterior chamber migration: risk factors, complications, and management strategies. *Ophthalmology.* 2014;121(1):67–71.

Lowder C, Belfort R Jr, Lightman S, et al; Ozurdex HURON Study Group. Dexamethasone intravitreal implant for noninfectious intermediate or posterior uveitis. *Arch Ophthalmol.* 2011;129(5):545–553.

Thorne JE, Sugar EA, Holbrook JT, et al; Multicenter Uveitis Steroid Treatment Trial Research Group. Periocular triamcinolone vs. intravitreal triamcinolone vs. intravitreal dexamethasone implant for the treatment of uveitic macular edema: the PeriOcular vs. INTravitreal corticosteroids for uveitic macular edema (POINT) Trial. *Ophthalmology.* 2019;126(2):283–295.

Tomkins-Netzer O, Taylor SRJ, Bar A, et al. Treatment with repeat dexamethasone implants results in long-term disease control in eyes with noninfectious uveitis. *Ophthalmology.* 2014;121(8):1649–1654.

Writing Committee for the Multicenter Uveitis Steroid Treatment (MUST) Trial and Follow-up Study Research Group; Kempen JH, Altaweel MM, Holbrook JT, et al. Association between long-lasting intravitreous fluocinolone acetonide implant vs systemic anti-inflammatory therapy and visual acuity at 7 years among patients with intermediate, posterior, or panuveitis. *JAMA.* 2017;317(19):1993–2005.

Zarranz-Ventura J, Carreño E, Johnston RL, et al. Multicenter study of intravitreal dexamethasone implant in noninfectious uveitis: indications, outcomes, and reinjection frequency. *Am J Ophthalmol.* 2014;158(6):1136–1145.e5.

CLINICAL PEARL

The following are some important points to remember when systemic corticosteroid treatment for noninfectious uveitis is being considered:

- Systemic corticosteroids are used for immediate control of severe uveitis when local corticosteroids are insufficient or contraindicated or when systemic inflammatory disease also requires treatment.
- Prescribers need to be aware of the myriad adverse effects of corticosteroids, and a team approach with specialists in rheumatology, internal medicine, or pediatrics may be used to improve patient safety.
- When systemic corticosteroids cannot be tapered to 7.5 mg/day or less, additional immunosuppression (systemic or regional) is required.
- Systemic IMT should be favored over long-term/high-dose corticosteroid use.

Systemic corticosteroid administration

Systemic corticosteroids are used for vision-threatening uveitis when local corticosteroids are insufficient or contraindicated or when systemic inflammatory disease also requires therapy. Of the many oral corticosteroid formulations available, prednisone is most commonly used. Of note, the readily available blister packages of methylprednisolone, which contain predetermined taper schedules, should not be used to treat uveitis because the

dose is too low and the duration is too short. Most patients require a starting prednisone dose of 1 mg/kg/day (up to 60 mg/day), which is gradually tapered every 1–2 weeks. Doses greater than 60 mg/day are avoided because of an increased risk of avascular bone necrosis. The goal is to control ocular inflammation *and* minimize adverse effects by tapering to the lowest possible prednisone dose (preferably with prednisone tapered off completely). When prednisone cannot be tapered to 7.5 mg/day or less within 3 months, systemic IMT is typically initiated. Prednisone doses of 7.5 mg/day or less are believed to be safe in the intermediate and long term, although some data suggest increased cardiovascular risks with large cumulative doses of prednisone (eg, 5 mg/day over 20 years).

For severe cases of noninfectious uveitis or scleritis, the most aggressive immediate treatment is intravenous, high-dose, pulse methylprednisolone (1 g/day infused over 1 hour) for 3 days, followed by a gradual taper of oral prednisone starting at 1 mg/kg/day. Although this mode of therapy may control ocular inflammation, it should only be administered by a physician experienced with the approach, as multiple adverse effects have been observed, some of which may be life-threatening.

The many adverse effects associated with short-term and long-term use of systemic corticosteroids must be discussed with patients, and their general health must be closely monitored, often with the assistance of an internist. Short-term risks include ocular hypertension, hyperglycemia, systemic hypertension, gastric reflux, insomnia, emotional lability, weight gain, and fluid retention. Intermediate-term risks include cataract, osteopenia, avascular necrosis of joints, and diabetes. If possible, corticosteroids should be avoided in patients at high risk for exacerbations of existing conditions (eg, diabetes, hypertension, congestive heart failure, peptic ulcer or gastroesophageal reflux disease, psychiatric conditions, or immune compromise). Alcohol intake can also increase risk of gastrointestinal ulcer in patients taking corticosteroids, whereas diet modification to reduce carbohydrates and simple sugars may help reduce the risk of hyperglycemia. Patients taking systemic corticosteroids and NSAIDs have an elevated risk of gastric ulcers; therefore, this combination is best avoided. Patients with risk factors for gastric ulcer should take a histamine-H2 receptor antagonist or proton-pump inhibitor.

Corticosteroid use can also lead to bone loss, osteoporosis, and bone fractures; thus, partnering with an internist or a patient's primary care physician for screening and treatment of corticosteroid-induced bone loss is common. Patients receiving long-term systemic corticosteroids are encouraged to supplement their diets with calcium and vitamin D to lower the risk of osteoporosis and typically undergo formal bone density screening via dual-energy x-ray absorptiometry scan. If indicated, medication may be prescribed for the prevention and treatment of corticosteroid-induced osteoporosis in at-risk men and women receiving prednisone. For patients taking corticosteroids at doses of 20 mg/day or greater for more than 4 weeks, clinicians may also consider trimethoprim-sulfamethoxazole every other day as prophylaxis against *Pneumocystis jirovecii* infection.

The systemic adverse effects and potency of commonly used corticosteroids are discussed further in BCSC Section 1, *Update on General Medicine*. See also BCSC Section 2, *Fundamentals and Principles of Ophthalmology*.

LoPiccolo J, Mehta SA, Lipson EJ. Corticosteroid use and *Pneumocystis* pneumonia prophylaxis: a teachable moment. *JAMA Intern Med*. 2018;178(8):1106–1107.

Systemic Immunomodulatory Therapy

Introduction

Patients with chronic, severe, or corticosteroid-dependent noninfectious uveitis may benefit greatly from the use of systemic IMT, sometimes referred to as *immunosuppressive* or *disease-modifying antirheumatic drugs (DMARDS)*. Depending on the class of the medications, these drugs can modify or regulate one or more immune functions via different mechanisms (see Chapter 1, Table 1-4).

Immunomodulatory medications may be loosely divided into nonbiologic IMT agents and biologic agents. Nonbiologic IMT agents are further divided into antimetabolites, T-cell inhibitors, and alkylating agents. Biologic agents are a newer and rapidly expanding group of genetically engineered proteins that target specific immune mechanisms. They include drugs that inhibit tumor necrosis factor (TNF)-α (ie, TNF inhibitors) and other pro-inflammatory immune mediators. In clinical practice, nonbiologic alkylating agents are reserved for the most severe or recalcitrant inflammation because of risks of malignancy and infertility. Currently, all systemic IMT is used off-label to treat uveitis, except for the TNF inhibitor adalimumab, which is FDA approved for noninfectious uveitis affecting the posterior segment.

Although many case series on use of nonbiologic IMT agents in uveitis have been published, most data come primarily from the Systemic Immunosuppressive Therapy for Eye Diseases (SITE) Cohort Study, a standardized retrospective study that evaluated the adverse effect profile and efficacy of azathioprine, methotrexate, mycophenolate mofetil, cyclosporine, or systemic corticosteroids in clinical practice (see Table 6-1 and further discussion later in this section). However, data on the comparative effectiveness of systemic immunomodulatory medications for treatment of uveitis are limited. See Table 6-2 for a list of relevant IMTs and suggested monitoring schedules.

Indications Systemic IMT should be considered for treatment of noninfectious ocular inflammation in the following settings:

- vision-threatening intraocular inflammation or necrotizing scleritis
- inadequate response to corticosteroid treatment
- cases in which systemic or local corticosteroids are contraindicated or intolerable because of systemic or ocular adverse effects (eg, glaucoma, cataract)
- cases in which systemic corticosteroids cannot be tapered below 7.5 mg/day

Certain ocular inflammatory diseases warrant the early use of IMT, including mucous membrane pemphigoid (also known as *ocular cicatricial pemphigoid*), serpiginous choroiditis, macula-threatening multifocal choroiditis with panuveitis, Behçet disease, sympathetic ophthalmia, Vogt-Koyanagi-Harada (VKH) syndrome, birdshot chorioretinopathy, and necrotizing scleritis associated with systemic vasculitis. Although these disorders may initially respond well to corticosteroids, the immediate use of IMT has improved long-term prognosis and lessened visual morbidity. Several expert-panel recommendations have established a consensus on how and when to select, initiate, modify, and withdraw nonbiologic IMT or biologic agents.

Table 6-2 Selected Immunomodulatory Medications Used in Noninfectious Uveitis

Class	Name	Adult Dosing	Potential Adverse Effects	Suggested Monitoring	Obstetric Complications
Antimetabolite	Methotrexate	Subcutaneous or oral: 15–25 mg/week	Fatigue, malaise, nausea, alopecia, transaminitis or cirrhosis, anemia, leukopenia, thrombocytopenia, mouth sores	CBC, CMP every 6–12 weeks	High risk (spontaneous abortion, fetal abnormalities)
	Mycophenolate mofetil	1–1.5 g bid	Diarrhea, transaminitis, anemia, leukopenia, thrombocytopenia	CBC, CMP every 6–12 weeks	High risk (fetal abnormalities)
	Azathioprine	2–2.5 mg/kg/day	Gastrointestinal upset, transaminitis, anemia, leukopenia, thrombocytopenia	CheckTPMT before initiation; CBC, CMP monthly × 3 months, then every 6–12 weeks	Minimal risk (preterm birth, IUGR)
T-cell inhibitor	Cyclosporine	2 mg/kg bid	Hypertension, nephrotoxicity, anemia, hypertrichosis, gingival hyperplasia, gastrointestinal upset, paresthesias	CBC, CMP every 6–12 weeks; blood pressure	Minimal risk (preterm birth and infants who are small for gestational age)
	Tacrolimus	1–3 mg bid	Tremor, hypertension, nephrotoxicity	CBC, CMP every 6–12 weeks; tacrolimus trough levels	Minimal risk (preterm birth and infants who are small for gestational age)
Alkylating agent	Chlorambucil	0.1–0.2 mg/kg/day	Infertility, malignancy, pancytopenia	CBC weekly	High risk (teratogenic)
	Cyclophosphamide	2 mg/kg/day	Bladder toxicity, infertility, malignancy, pancytopenia	CBC and urinalysis weekly to monthly	High risk (teratogenic)

(Continued)

Table 6-2 *(continued)*

Class	Name	Adult Dosing	Potential Adverse Effects	Suggested Monitoring	Obstetric Complications
TNF inhibitor	Adalimumab	Subcutaneous: 80 mg on day 1, 40 mg on day 8, then 40 mg every other week; may increase to weekly	Injection site reaction or infusion reactions, precipitation or unmasking of demyelinating CNS disease, congestive heart failure, opportunistic infection, possible increased lymphoma risk	Routine laboratory testing interval varies; ongoing monitoring for neurologic or cardiovascular symptoms; anti-drug antibody testing for loss of efficacy	Unknown risk; generally considered safe
	Infliximab	5–10 mg/kg intravenous induction at 0, 2, and 6 weeks followed by maintenance every 4–8 weeks May increase up to 20 mg/kg in children			Certolizumab has less third-trimester transplacental transfer than other TNF inhibitors
Anti-interleukin 6	Tocilizumab	4 mg/kg intravenously every 4 weeks or 162 mg subcutaneous every other week; uveitis dose has not been established	Injection site reaction or infusion reactions, opportunistic infection, gastric perforation, hepatotoxicity, cytopenias, lipid abnormalities	CBC, CMP every 4–8 weeks for 6 months Then every 3 months and lipid panel every 6 months	Unknown risk; generally considered safe
Glucocorticoids	Prednisone	0.5–1 mg/kg/day; individualized dosing, tapered to 7.5 mg/day or lower over 3 months	Acid reflux/gastritis, insomnia, hyperglycemia, hunger, emotional lability, weight gain Long-term use: osteopenia, hypertension, hypercholesterolemia, diabetes	Blood glucose monitoring while taking high dose; HgA_{1c} and lipid panel every 6 months while taking long-term low dose; bone density scan annually	Minimal risk (maternal diabetes, IUGR)

bid = twice a day; CBC = complete blood count; CMP = comprehensive metabolic panel; CNS = central nervous system; HgA_{1c} = glycosylated hemoglobin; IUGR = intrauterine growth restriction; TNF = tumor necrosis factor; TPMT = thiopurine S-methyltransferase.

CLINICAL PEARL

The following are some important points to remember regarding IMT for noninfectious ocular inflammation:

- Early use of IMT improves the prognosis for patients with a sight-threatening, chronic ocular inflammatory condition.
- IMT is generally well tolerated, but proper patient selection, patient education, and ongoing monitoring are mandatory.
- TNF inhibitors should be considered as first-line therapy for patients with Behçet uveitis and those with other severe ocular inflammatory disorders who have not had success with or are not candidates for conventional IMT.

Treatment IMT should be managed by a physician who is qualified to counsel, prescribe, and safely monitor such medications. Before initiation of IMT, the physician should assess patients for the following conditions:

- infection
- recent live vaccine administration
- hepatic, renal, and hematologic contraindications
- pregnancy or breastfeeding
- status of family planning and contraception
- disease activity that can be objectively and longitudinally monitored

Unlike biologic agents, which typically have a rapid onset, nonbiologic IMT takes weeks to months to develop therapeutic effectiveness. Until IMT takes effect, most patients require maintenance with a judicious amount of local and/or systemic corticosteroid. In addition, patients may need to trial more than one IMT agent to find a regimen that is effective and well tolerated; this therapeutic refinement may take 6–18 months. When ocular inflammation has been quiescent on IMT and the lowest possible dose of corticosteroids for at least 12 months (longer for pediatric patients), a slow drug taper may be considered. IMT discontinuation is tailored according to uveitis severity, the presence or absence of systemic features, and the plan for monitoring and rescue therapy.

The physician should thoroughly discuss the risks of adverse effects with the patient before initiating IMT. Although IMT is generally well tolerated, patients must be monitored regularly with laboratory testing because of the potential for serious complications. Depending on the IMT agent administered, monitoring may include complete blood count with differential and liver and renal function tests. Serious complications of nonbiologic IMT include renal and hepatic toxicity and bone marrow suppression. Alkylating agents may cause sterility and are associated with an increased risk of malignant diseases, such as leukemia or lymphoma. Certain biologic agents may cause an infusion or injection reaction; TNF inhibitors increase the risk of multiple sclerosis, congestive heart failure, and lymphoma. In addition, all IMT increases the risk of opportunistic and secondary infections.

Despite these risks, the SITE cohort study of 7957 US patients (66,802 patient-years) with noninfectious uveitis treated with IMT showed that patients who took azathioprine, methotrexate, mycophenolate mofetil, cyclosporine, or systemic corticosteroids had overall cancer mortality rates similar to those of patients who never used these IMT agents. The study was expanded to include 15,938 patients who were followed for 187,151 person-years and confirmed that most IMT agents, including TNF inhibitors, were not associated with increased overall or cancer-related mortality (see Table 6-1). Other data suggest that IMT may be associated with an increased risk of nonmelanoma skin cancer, warranting sunscreen counseling.

Other precautionary steps to avoid IMT-related adverse events include consideration of trimethoprim–sulfamethoxazole prophylaxis against *P jirovecii* infection in patients receiving alkylating agents or prolonged courses of high-dose corticosteroids and IMT. Ideally, all routine vaccines or boosters should be administered 2 weeks before the initiation of IMT (4 weeks for live vaccines). In addition to routine vaccines, pneumococcal vaccine should be given regardless of age. Additional suggested vaccinations include the inactivated zoster vaccine, an annual inactivated influenza vaccine, and the COVID-19 vaccine. Additional doses of COVID-19 immunization are typically indicated for immunosuppressed patients per evolving Centers for Disease Control and Prevention guidelines.

Finally, male and female patients require counseling regarding fertility, birth control, and family planning before initiation of IMT. Many IMT medications have absolute contraindications in pregnancy (ie, methotrexate, mycophenolate mofetil); these medications should be discontinued (in both men and women) at least 3 months before they try to conceive. See Table 6-2.

Dick AD, Rosenbaum JT, Al-Dhibi HA, et al; Fundamentals of Care for Uveitis International Consensus Group. Guidance on noncorticosteroid systemic immunomodulatory therapy in noninfectious uveitis: Fundamentals Of Care for UveitiS (FOCUS) initiative. *Ophthalmology.* 2018;125(5):757–773.

Jabs DA. Immunosuppression for the uveitides. *Ophthalmology.* 2018;125(2):193–202.

Kempen JH, Daniel E, Dunn JP, et al. Overall and cancer related mortality among patients with ocular inflammation treated with immunosuppressive drugs: retrospective cohort study. *BMJ*. 2009;339:b2480.

Kempen JH, Newcomb CW, Foster CS, et al. Risk of overall and cancer mortality after immunosuppression of patients with non-infectious ocular inflammatory diseases. *Invest Ophthalmol Vis Sci*. 2019;60(9):3854.

Leroy C, Rigot J-M, Leroy M, et al. Immunosuppressive drugs and fertility. *Orphanet J Rare Dis.* 2015;10:136.

Levy-Clarke G, Jabs DA, Read RW, Rosenbaum JT, Vitale A, Van Gelder RN. Expert panel recommendations for the use of anti-tumor necrosis factor biologic agents in patients with ocular inflammatory disorders. *Ophthalmology.* 2014;121(3):785–796e3.

Wakefield D, McCluskey P, Wildner G, et al. Inflammatory eye disease: pre-treatment assessment of patients prior to commencing immunosuppressive and biologic therapy: recommendations from an expert committee. *Autoimmun Rev.* 2017;16(3):213–222.

Yates WB, Vajdic CM, Na R, McCluskey PJ, Wakefield D. Malignancy risk in patients with inflammatory eye disease treated with systemic immunosuppressive therapy: a tertiary referral cohort study. *Ophthalmology.* 2015;122(2):265–273.

Nonbiologic immunomodulatory therapy

Antimetabolites The antimetabolites include azathioprine, methotrexate, and mycophenolate mofetil. Retrospective and prospective data support the use of antimetabolites for successful control of uveitis. In fact, antimetabolites are often the first IMTs used when corticosteroid sparing is necessary. Compared with the other antimetabolites, azathioprine has a slightly higher incidence of adverse effects, and mycophenolate mofetil has a significantly shorter time to therapeutic efficacy. A head-to-head prospective study of 216 patients with uveitis (FAST trial) randomly assigned to methotrexate or mycophenolate mofetil reported similar efficacy for the 2 medications (see Table 6-1). Antimetabolites require long-term use, as disease control may continue to improve for 6–12 months. Although antimetabolites are generally effective, ongoing low-dose systemic corticosteroid therapy is often necessary to achieve complete inflammatory control.

AZATHIOPRINE Azathioprine, a purine nucleoside analogue, interferes with DNA replication and RNA transcription. It is administered orally at a dose of up to 2–2.5 mg/kg/day in adults. On average, 25% of patients discontinue azathioprine therapy because of adverse effects, with nausea, vomiting, and upset stomach being the most common events. Bone marrow suppression is unusual at the doses used to treat uveitis; however, patients taking allopurinol and azathioprine concomitantly are at higher risk for bone marrow suppression. Azathioprine-related mild hepatic toxicity can usually be reversed by dose reduction. Complete blood count with differential and liver function tests must be closely monitored.

The variability of clinical response to azathioprine is probably related to genetic variability in the activity of thiopurine S-methyltransferase (TPMT), an enzyme responsible for the metabolism of 6-mercaptopurine. A genotypic test is available to classify a patient's TPMT activity level and to help clinicians individualize drug doses as appropriate:

- patients with low/no TPMT activity (0.3% of patients); azathioprine therapy not recommended
- patients with intermediate TPMT activity (11% of patients); azathioprine therapy at reduced dosage
- patients with normal/high TPMT activity (89% of patients); azathioprine therapy at higher doses than for intermediate TPMT activity

Azathioprine is beneficial in many types of noninfectious ocular inflammatory diseases, including Behçet disease, intermediate uveitis, VKH syndrome, sympathetic ophthalmia, and necrotizing scleritis. Overall, nearly 50% of patients treated with azathioprine achieve inflammatory control and can taper their prednisone dosage to 10 mg/day or less.

Pasadhika S, Kempen JH, Newcomb CW, et al. Azathioprine for ocular inflammatory diseases. *Am J Ophthalmol.* 2009;148(4):500–509.e2.

METHOTREXATE This agent is a folic acid analogue and inhibitor of dihydrofolate reductase; it inhibits DNA replication, but its anti-inflammatory effects result from extracellular release of adenosine. Unlike other antimetabolites, methotrexate is given as a *weekly* dose of 15–25 mg in adults. In children, the dosage is based on body surface area. Methotrexate can be given orally, subcutaneously, intramuscularly, or intravenously and is usually

well tolerated. The drug has increased bioavailability when given parenterally. Methotrexate may take up to 6 months to develop a full therapeutic effect in controlling ocular inflammation.

To reduce adverse effects of methotrexate, including hair loss and mouth sores, folate is given concurrently at a dose of 1–2 mg/day. Gastrointestinal distress and anorexia also occur in 10% of patients. Reversible hepatotoxicity has been reported in up to 15% of patients, and cirrhosis develops in fewer than 0.1% of patients receiving methotrexate long term. Methotrexate is teratogenic; data on the safety of male conception while receiving methotrexate therapy are mixed. Regular alcohol consumption is contraindicated with methotrexate. Complete blood count with differential and liver function tests should be monitored regularly.

Numerous studies have shown methotrexate to be effective for various types of ocular inflammation, including juvenile idiopathic arthritis (JIA)–associated anterior uveitis, sarcoidosis, panuveitis, and scleritis. It is often the first-line IMT choice for children. In uncontrolled clinical trials of methotrexate, corticosteroid sparing was successful in two-thirds of patients with chronic ocular inflammatory disorders. Intravitreal methotrexate is used to treat vitreoretinal lymphoma; its role in treating uveitis and uveitic macular edema is under investigation.

Gangaputra S, Newcomb CW, Liesegang TL, et al; Systemic Immunosuppressive Therapy for Eye Diseases Cohort Study. Methotrexate for ocular inflammatory diseases. *Ophthalmology.* 2009;116(11):2188–2198.e1.

Malik AR, Pavesio C. The use of low dose methotrexate in children with chronic anterior and intermediate uveitis. *Br J Ophthalmol.* 2005;89(7):806–808.

MYCOPHENOLATE MOFETIL This drug inhibits both inosine monophosphate dehydrogenase and DNA replication. It is given orally at a dosage of 1–1.5 g twice daily in adults. Median time to successful control of ocular inflammation (in combination with less than 10 mg/day of prednisone) is approximately 4 months. Fewer than 20% of patients receiving mycophenolate mofetil have adverse effects (reversible gastrointestinal distress and diarrhea are common), and these are usually managed by gradual dose up-titration or dose reduction. Few patients find the drug intolerable. Regular laboratory monitoring includes complete blood count with differential; in rare cases, CD4 T-lymphocyte deficiency may develop.

Two large, retrospective studies found mycophenolate mofetil was an effective corticosteroid-sparing agent in up to 85% of patients with chronic uveitis. It has similar efficacy in children (88%) and can be a safe alternative to methotrexate in pediatric uveitis. Mycophenolate mofetil is contraindicated in pregnancy and should be discontinued in men and women before conception.

Doycheva D, Deuter C, Stuebiger N, Biester S, Zierhut M. Mycophenolate mofetil in the treatment of uveitis in children. *Br J Ophthalmol.* 2007;91(2):180–184.

Rathinam SR, Gonzales JA, Thundikandy R, et al. Effect of corticosteroid-sparing treatment with mycophenolate mofetil vs methotrexate on inflammation in patients with uveitis: a randomized clinical trial. *JAMA.* 2019;322(10):936–945.

Siepmann K, Huber M, Stübiger N, Deuter C, Zierhut M. Mycophenolate mofetil is a highly effective and safe immunosuppressive agent for the treatment of uveitis: a retrospective analysis of 106 patients. *Graefes Arch Clin Exp Ophthalmol.* 2006;244(7):788–794.

Teoh SC, Hogan AC, Dick AD, Lee RWJ. Mycophenolate mofetil for the treatment of uveitis. *Am J Ophthalmol.* 2008;146(5):752–760.e1–3.
Thorne JE, Jabs DA, Qazi FA, Nguyen QD, Kempen JH, Dunn JP. Mycophenolate mofetil therapy for inflammatory eye disease. *Ophthalmology.* 2005;112(8):1472–1477.

T-cell inhibitors Cyclosporine, a macrolide product of the fungus *Beauveria nivea,* and tacrolimus, a product of *Streptomyces tsukubaensis,* are calcineurin inhibitors that eliminate T-cell receptor signal transduction and downregulate interleukin-2 gene transcription and receptor expression of $CD4^+$ T lymphocytes.

CYCLOSPORINE This drug is available in 2 oral preparations: microemulsion and standard. The microemulsion formulation has better bioavailability than the standard preparation. It is initiated at 2 mg/kg/day, and the standard formulation is initiated at 2.5 mg/kg/day in adults. Dosing is adjusted to 1–5 mg/kg/day based on trough levels, toxicity, and clinical response. The most common adverse effects with cyclosporine are systemic hypertension and nephrotoxicity. Additional adverse effects include paresthesia, gastrointestinal upset, fatigue, hypertrichosis, and gingival hyperplasia. Blood pressure, serum creatinine levels, and complete blood counts are assessed regularly. If serum creatinine levels rise by 30%, the dose is adjusted; sustained elevation usually results in discontinuation of the medication.

In a randomized, controlled clinical trial, cyclosporine was effective for the treatment of Behçet uveitis, controlling inflammation in 50% of patients. However, the dose used in this study was 10 mg/kg/day—substantially higher than current dosing (up to 5 mg/kg/day), which led to substantial nephrotoxicity. Even at standard dosages of cyclosporine, toxicity necessitating cessation of therapy is more common in patients older than 55 years. Overall, cyclosporine is modestly effective in controlling ocular inflammation (33.4% and 51.9% of patients achieved control by 6 and 12 months, respectively in the SITE Study). As with antimetabolites, ongoing low-dose systemic corticosteroid therapy is often necessary to achieve complete inflammatory control with cyclosporine.

Kaçmaz RO, Kempen JH, Newcomb C, et al. Cyclosporine for ocular inflammatory diseases. *Ophthalmology.* 2010;117(3):576–584.

TACROLIMUS This agent is given orally at 0.10–0.15 mg/kg/day in adults. Because tacrolimus is prescribed at a lower dose than cyclosporine and has increased potency, nephrotoxicity is less common with this drug than with cyclosporine. Nevertheless, serum creatinine level, complete blood count with differential, and serum potassium level are monitored regularly in patients taking tacrolimus, with the drug dose escalated until a therapeutic trough blood level has been reached.

A prospective trial comparing cyclosporine and tacrolimus suggested the agents had equal efficacy in controlling chronic posterior and intermediate uveitis, with tacrolimus demonstrating greater safety (ie, lower risk of hypertension and hyperlipidemia). Long-term tolerability and efficacy with tacrolimus are excellent as well, with patients having an 85% chance of reducing their prednisone dosage to less than 10 mg/day. A randomized trial of tacrolimus monotherapy versus tacrolimus plus prednisone for the treatment of uveitis showed no difference in uveitis activity between groups, confirming that corticosteroid discontinuation can be achieved in many cases.

Hogan AC, McAvoy CE, Dick AD, Lee RWJ. Long-term efficacy and tolerance of tacrolimus for the treatment of uveitis. *Ophthalmology.* 2007;114(5):1000–1006.

Lee RWJ, Greenwood R, Taylor H, et al. A randomized trial of tacrolimus versus tacrolimus and prednisone for the maintenance of disease remission in noninfectious uveitis. *Ophthalmology.* 2012;119(6):1223–1230.

Murphy CC, Greiner K, Plskova J, et al. Cyclosporine vs tacrolimus therapy for posterior and intermediate uveitis. *Arch Ophthalmol.* 2005;123(5):634–641.

Alkylating agents Alkylating agents, which include cyclophosphamide and chlorambucil, are generally used for uveitis only when other IMT agents fail to control the condition. Increasingly, alkylating agents are being bypassed in favor of biologic agents because of the latter's targeted efficacy and preferred safety profile.

The most serious adverse effect of alkylating agents is an increased risk of malignancy. Cyclophosphamide treatment may confer a more than 10-fold increased risk of bladder cancer that is dependent on cumulative dose, and a two- to fourfold elevated risk of other cancers. Chlorambucil treatment may increase risk of leukemia over baseline by more than 10-fold. Despite the risks, use of alkylating agents for a limited duration may be justified for patients with severe, vision- or life-threatening, recalcitrant disease such as necrotizing scleritis associated with systemic vasculitis (eg, granulomatosis with polyangiitis or relapsing polychondritis). The alkylating agents also have shown efficacy in severe intermediate uveitis, VKH syndrome, sympathetic ophthalmia, serpiginous choroiditis, and Behçet disease. These drugs should be used with great caution and only by clinicians experienced in their dosing and potential toxicities. Before beginning treatment, patients may consider sperm or egg banking owing to a high rate of sterility if the cumulative dose exceeds certain limits. Concomitant administration of gonadotropin-releasing hormone agonists may help preserve ovarian function and fertility.

CYCLOPHOSPHAMIDE Cyclophosphamide is an agent with active metabolites that can alkylate purines in DNA and RNA, impairing DNA replication and cell death. To control ocular inflammation, oral dosing (2 mg/kg/day in adults) may be more effective than intermittent intravenous pulses. Myelosuppression and hemorrhagic cystitis are the most common adverse effects of cyclophosphamide treatment. Complete blood counts and urinalysis results are monitored weekly to monthly. Microscopic hematuria is a warning for the patient to increase hydration, and gross hematuria is an indication to discontinue therapy. Other toxicities include teratogenicity, sterility, and reversible alopecia. Opportunistic infections such as *P jirovecii* pneumonia occur more often in patients receiving cyclophosphamide than in those being treated with other systemic IMT; trimethoprim–sulfamethoxazole prophylaxis is usually utilized in patients taking cyclophosphamide. In three-fourths of patients taking the drug, inflammation is controlled within 12 months, and two-thirds of patients achieve disease remission within 2 years. However, one-third of patients discontinue therapy within 1 year because of adverse effects.

Faurschou M, Sorensen IJ, Mellemkjaer L, et al. Malignancies in Wegener's granulomatosis: incidence and relation to cyclophosphamide therapy in a cohort of 293 patients. *J Rheumatol.* 2008;35(1):100–105.

Pujari SS, Kempen JH, Newcomb CW, et al. Cyclophosphamide for ocular inflammatory diseases. *Ophthalmology.* 2010;117(2):356–365.

CHLORAMBUCIL Chlorambucil is a very long-acting alkylating agent that also interferes with DNA replication. It is absorbed well when administered orally. The drug is traditionally given as a single daily dose of 0.1–0.2 mg/kg in adults. It may also be administered as a short-term, high-dose therapy for uveitis. Because chlorambucil is myelosuppressive, complete blood count values should be monitored closely while the patient takes the drug. Like cyclophosphamide, it is associated with increased risk of hematologic malignancy. It is also teratogenic and causes sterility. Uncontrolled case series suggest that chlorambucil is effective in 66%–75% of patients with recalcitrant sympathetic ophthalmia, Behçet disease, and other vision-threatening uveitic syndromes, providing long-term, drug-free remission of disease.

Patel SS, Dodds EM, Echandi LV, et al. Long-term, drug-free remission of sympathetic ophthalmia with high-dose, short-term chlorambucil therapy. *Ophthalmology.* 2014;121(2):596–602.

Biologic agents

Inflammation is driven by a complex series of cell–cell and cell–cytokine interactions. Inhibitors of various cytokines and inflammatory mechanisms are called *biologic agents* or *biologic response modifiers.* These drugs enable targeted immunomodulation, thereby theoretically reducing the short-term, systemic adverse effects associated with the previously discussed nonbiologic IMT. However, biologic agents are more expensive and may carry higher long-term risks of serious infections or secondary malignancies than antimetabolites and T-cell inhibitors.

Tumor necrosis factor inhibitors Tumor necrosis factor α is believed to play a major role in the pathogenesis of JIA, ankylosing spondylitis, and other forms of spondyloarthritis. For treatment of uveitis, the best-studied TNF inhibitors are adalimumab and infliximab; their high degree of efficacy and favorable side effect profile have improved the management of many types of uveitis. According to expert consensus, TNF inhibitors should be considered first-line treatment for Behçet disease. Data on the efficacy of the TNF inhibitors certolizumab and golimumab are more limited, and etanercept is not effective for ocular inflammatory diseases.

TNF inhibitors are usually prescribed by specialists (ie, rheumatologists, uveitis specialists) experienced with their use, adverse effects, and toxicities. They are relatively contraindicated in patients with congestive heart failure. Latent tuberculosis must be ruled out or treated with the oversight of a specialist in infectious diseases before drug initiation. TNF inhibitors have been associated with central nervous system demyelination (promoting or unmasking of multiple sclerosis), hepatitis B reactivation, and deep fungal and other serious atypical infections. Because TNF inhibitors themselves are sometimes immunogenic, patients can develop antibodies against the drug that lower its efficacy. Patients taking TNF inhibitors should also avoid live vaccines. Although there are individual case reports on the *intravitreal* administration of TNF inhibitors, this form of delivery has not been fully investigated and may be retinotoxic; further study is needed.

Sfikakis PP, Markomichelakis N, Alpsoy E, et al. Anti-TNF therapy in the management of Behçet's disease—review and basis for recommendations. *Rheumatology (Oxford).* 2007;46(5):736–741.

ADALIMUMAB Adalimumab, a fully human monoclonal immunoglobulin G1 antibody directed against TNF-α, is the first FDA-approved systemic medication for noninfectious uveitis. Self-administered via subcutaneous injection, the initial dosage is usually 80 mg, followed by a maintenance dose of 40 mg/0.8 mL every other week starting 1 week after the initial injection. Because adalimumab is a fully human antibody, risk of antidrug–antibody formation is lower than with infliximab, a mouse/human chimeric antibody. Injection site reactions may occur but are usually mild. When the drug is administered in conjunction with methotrexate, serum levels of adalimumab are higher, and rates of antidrug-antibody formation are reduced.

In an industry-sponsored, randomized, double-masked, controlled trial in adults with noninfectious uveitis (VISUAL I/II) that included an open-label extension arm (VISUAL III), adalimumab was associated with significant reductions in treatment failure compared with placebo for both active and controlled uveitis. Significantly higher rates of quiescence and corticosteroid-free quiescence were also achieved and maintained through 52 weeks, regardless of disease status at entry. However, adverse events and serious adverse events were reported more frequently among patients who took adalimumab than among those taking placebo (see Table 6-1).

Adalimumab has been as effective as infliximab in controlling inflammation, with success rates of up to 88% in pediatric patients with uveitis and at least 90% in adult patients with Behçet uveitis, posterior uveitis, and panuveitis. However, uveitis relapses requiring local corticosteroid injections may occur. Adalimumab has also reduced the rate of anterior uveitis flares and recurrences in HLA-B27–associated uveitis. In SYCAMORE, a randomized placebo-controlled trial involving pediatric patients with JIA-associated uveitis who were assigned to methotrexate alone versus methotrexate plus adalimumab, the addition of adalimumab delayed time to treatment failure and increased the likelihood of reducing topical corticosteroid use. Adverse events were seen in 5% of the adalimumab group, with 22% of these reports considered serious adverse events (see Table 6-1).

Ramanan AV, Dick AD, Jones AP, et al; SYCAMORE Study Group. Adalimumab plus methotrexate for uveitis in juvenile idiopathic arthritis. *N Engl J Med*. 2017;376(17):1637–1646.

Suhler EB, Adán A, Brézin AP, et al. Safety and efficacy of adalimumab in patients with noninfectious uveitis in an ongoing open-label study: VISUAL III. *Ophthalmology*. 2018;125(7):1075–1087.

INFLIXIMAB This agent is a mouse/human-chimeric immunoglobulin G1 kappa monoclonal antibody directed against TNF-α. It is administered through intravenous infusions of 5–10 mg/kg at weeks 0, 2, and 6 and then every 4–8 weeks thereafter for maintenance. Infliximab has been effective in controlling active inflammation and decreasing the likelihood of future attacks in more than 75% of patients, including those with Behçet uveitis, undifferentiated uveitis, sarcoidosis, VKH disease, and human leukocyte antigen (HLA)-B27–associated anterior uveitis. However, one study showed that despite treatment success, nearly one-half of patients could not complete 50 weeks of therapy because of adverse events, including drug-induced lupus, systemic vascular thrombosis, congestive heart failure, new malignancy, demyelinating disease, and vitreous hemorrhage. As many as 75% of patients receiving more than 3 infusions developed antinuclear antibodies.

To reduce the risk of infliximab-induced lupus syndrome and loss of efficacy due to the formation of anti-drug antibodies, low-dose methotrexate (5–7.5 mg/week) may be administered concurrently. Although increasing the dose and frequency of infliximab may achieve control in patients with the most severe ocular inflammatory diseases, antibody formation is more likely to occur.

Giganti M, Beer PM, Lemanski N, Hartman C, Schartman J, Falk N. Adverse events after intravitreal infliximab (Remicade). *Retina*. 2010;30(1):71–80.

Tugal-Tutkun I, Mudun A, Urgancioglu M, et al. Efficacy of infliximab in the treatment of uveitis that is resistant to treatment with the combination of azathioprine, cyclosporine, and corticosteroids in Behçet's disease: an open-label trial. *Arthritis Rheum*. 2005;52(8):2478–2484.

Other biologic agents *Tocilizumab,* an anti–interleukin-6 agent, may have efficacy in treating noninfectious uveitis in some patients. In the phase 1/2 STOP-Uveitis randomized clinical trial (n = 37), patients with noninfectious uveitis who received 4 or 8 mg/kg intravenous tocilizumab for 6 months showed improvements in visual acuity and a reduction in vitreous haze. In the APTITUDE study, a multicenter trial of subcutaneous tocilizumab in children with active JIA-associated uveitis recalcitrant to a TNF-inhibitor, 7 of 21 patients had decreased uveitis activity at 12 weeks and macular edema resolved in 3 of 4 patients. However, the primary outcome was not met, and a phase 3 trial was not justified. Nonetheless, several retrospective cohort studies have shown tocilizumab can effectively treat refractory uveitic macular edema.

Rituximab, a chimeric monoclonal antibody directed against $CD20^+$ cells (mainly B lymphocytes) is given as a set of intravenous infusions every 6 months. It may be useful in the treatment of Behçet retinal vasculitis, scleritis associated with granulomatosis with polyangiitis or rheumatoid arthritis, and mucous membrane pemphigoid. Case series have also reported success in treating refractory JIA-associated uveitis.

Interferon alfa-2a/2b, administered subcutaneously, has been beneficial in some patients with uveitis. Reports in the European literature indicate that interferon alfa-2a, which has antiviral, immunomodulatory, and antiangiogenic effects, is efficacious and well tolerated in patients with Behçet uveitis, controlling inflammation in almost 90%; it is somewhat less effective in non-Behçet uveitis, with inflammation control in 60% of patients. There are also reports of interferon alfa-2b successfully treating patients with uveitic macular edema.

Before initiation of interferon alfa-2a therapy, patients should discontinue any other immunomodulatory drugs, as a flulike syndrome has been observed, most frequently during the first weeks of therapy. However, symptoms may be reduced through prophylactic administration of acetaminophen. Despite the use of low interferon doses, leukopenia or thrombocytopenia may occur with the drug. Depression is another important adverse effect of interferon therapy.

Abatacept, a T-cell costimulation inhibitor given as a subcutaneous injection or an intravenous infusion, has been used with mixed results in patients with JIA-associated uveitis, including one small study suggesting that only 14% experienced sustained inflammation control. Another study showed a 49% success rate at 1 year.

Gueudry J, Wechsler B, Terrada C, et al. Long-term efficacy and safety of low-dose interferon alpha2a therapy in severe uveitis associated with Behçet disease. *Am J Ophthalmol*. 2008;146(6):837–844.e1.

Kötter I, Zierhut M, Eckstein AK, et al. Human recombinant interferon alfa-2a for the treatment of Behçet's disease with sight threatening posterior or panuveitis. *Br J Ophthalmol*. 2003;87(4):423–431.

Ramanan AV, Dick AD, Guly C, et al; APTITUDE Trial Management Group. Tocilizumab in patients with anti-TNF refractory juvenile idiopathic arthritis-associated uveitis (APTITUDE): a multicentre, single-arm, phase 2 trial. *Lancet Rheumatol*. 2020;2(3): e135–e141.

Sepah YJ, Sadiq MA, Chu DS, et al. Primary (month-6) outcomes of the STOP-Uveitis Study: evaluating the safety, tolerability, and efficacy of tocilizumab in patients with noninfectious uveitis. *Am J Ophthalmol*. 2017;183:71–80.

Other Therapeutic Agents

Topical mydriatic and cycloplegic drugs are beneficial for breaking or preventing the formation of posterior synechiae and for relieving photophobia secondary to ciliary spasm. Short-acting cycloplegics, such as tropicamide and cyclopentolate hydrochloride (1%) or phenylephrine (2.5%), allow the pupil to remain mobile and permit rapid recovery when discontinued.

Oral NSAIDs are used in the treatment of mild to moderate nonnecrotizing anterior scleritis (see Chapter 7). Potential complications of prolonged systemic NSAID use include cardiovascular, gastrointestinal, renal, and hepatic toxicity. (See also BCSC Section 1, *Update on General Medicine,* for more information.) Topical NSAIDs may be used in mild cases of diffuse episcleritis, as well as for macular edema. However, in rare instances, topical NSAIDs can cause severe corneal complications such as keratitis and corneal perforations. (See also BCSC Section 8, *External Disease and Cornea.*)

The use of oral *carbonic anhydrase inhibitors* as an adjunct in the treatment of uveitic macular edema is supported by a small but notable body of literature spanning several decades. These agents may be particularly useful in ameliorating diffuse leakage from the retinal pigment epithelium, rather than treating leakage from retinal vessels.

Intravenous immunoglobulin has been effective in some patients with uveitis that is otherwise refractory to IMT, as well as in patients with mucous membrane pemphigoid.

Intracameral *fibrinolytic agents* such as recombinant tissue plasminogen activator have been used to treat severe fibrinous reactions in the anterior segment after cataract surgery and in the setting of acute fibrinous HLA-B27–associated anterior uveitis.

Surgical Management of Uveitis

Drug delivery to the eye for treatment of uveitis may require a procedure involving ocular injection or surgical implantation, as discussed elsewhere in this chapter. For patients with uveitis, surgery in the operating room may be scheduled for diagnostic and/or therapeutic reasons. These additional therapeutic surgical procedures for uveitis and uveitic complications are discussed in Chapter 16.