Our general treatment approach to most types of noninfectious uveitis has been to employ different routes of corticosteroids to control the inflammation as rapidly as possible to avoid structural and functional damage. We also use steroid-sparing agents (eg, antimetabolites) and, increasingly, biologics (eg, anti–tumor necrosis factor [TNF] agents), even at the initial stage, in an effort to achieve quiescence of the inflammation without associated adverse events from corticosteroids. However, current treatment strategies may have certain limitations. Therefore, the development of agents that are effective against uveitis but that do not have local or systemic side effects is a priority. This article reviews the latest options being explored for the treatment of patients with uveitis.

LOCAL STEROID IMPLANTS

Dexamethasone
The sustained-release dexamethasone intravitreal implant 0.7 mg (Ozurdex, Allergan) is approved by the US Food and Drug Administration (FDA) for treatment of noninfectious uveitis involving the posterior segment. In a 26-week randomized study comparing the safety and efficacy of two doses (0.35 mg and 0.7 mg) of the dexamethasone intravitreal implant with sham procedure in 229 patients, a higher proportion of patients showed improvement in vitreous haze score at week 8 in the dexamethasone groups compared with sham (47% and 36% for the 0.7-mg and 0.35-mg groups, respectively, vs. 12% for the sham group).1

Fluocinolone Acetonide 0.59 mg
The MUST trial compared the fluocinolone acetonide 0.59 mg intraocular implant (Retisert, Bausch + Lomb), which has been approved for noninfectious uveitis, with systemic therapy for the management of intermediate, posterior, and panuveitis.2

In my experience, patients who have received the fluocinolone acetonide 0.59 mg intraocular implant have seen significant improvements in vision. Although this implant is effective, it also comes with some well-known complications such as increased incidences of intraocular pressure (IOP) elevation and cataract development.

Fluocinolone Acetonide 0.19 mg
The fluocinolone acetonide intravitreal implant 0.19 mg (Iluvien, Alimera Sciences), is approved by the FDA to reduce macular edema and improve visual acuity in patients with diabetic retinopathy. No clinical data are available on the use of this implant in patients with noninfectious uveitis; thus, further studies assessing its long-term safety and efficacy in this patient population are warranted.
Fluocinolone Acetonide 0.18 mg

pSivida, whose sustained-release technology is licensed to Alimera Sciences for the fluocinolone acetonide intravitreal implant 0.19 mg, is independently developing a 0.18-mg fluocinolone acetonide injectable micro-insert (Medidur) for the treatment of posterior uveitis. Topline results from a phase 3 study of the 0.18 mg fluocinolone acetonide micro-insert were recently released, showing that the rate of uveitis recurrence at the 6-month primary endpoint in patients who received the fluocinolone acetonide 0.18-mg injectable insert was significantly less than that in the sham group.3 The probability value in the trial was small (P < .001), indicating a high degree of statistical significance. These clinical trial results also showed that there was potential for visual acuity to improve and much less visual loss among those who received the injectable implant.

A NONSTEROIDAL INJECTABLE

Sirolimus (Rapamune, Pfizer) is an inhibitor of the mammalian target of rapamycin (mTOR), which is a central regulator of immune responses, providing a critical link between metabolic demands and cellular function. A proprietary, depot-forming formulation of sirolimus for subconjunctival or intravitreal injection (intravitreal sirolimus, Santen) has been evaluated in a study in patients with noninfectious intermediate, posterior, and panuveitis.4 The phase 1 SAVE study evaluated the safety and bioactivity of subconjunctival or intravitreal sirolimus for noninfectious intermediate, posterior, and panuveitis.5 At the 6-month primary endpoint and 12-month outcomes, local administration of sirolimus, either intravitreally or subconjunctivally, appeared to be safe and tolerable.5 No drug-related systemic adverse events or serious adverse events were noted. The encouraging results from the SAVE study led to the initiation of the phase 2 SAVE-2 study, which evaluated two doses of intravitreal sirolimus with the possibility for bilateral treatments in patients with bilateral disease.6

The phase 3 SAKURA studies are designed to evaluate the safety and efficacy of intravitreal injections of sirolimus ophthalmic solution in three active doses (44 μg, 440 μg, and 880 μg) in two similarly designed consecutive studies: SAKURA 1 and SAKURA 2. The SAKURA 1 trial enrolled 347 patients with active, noninfectious uveitis of the posterior segment with a baseline vitreous haze score of 1.5 or greater on the modified Standardized Uveitis Nomenclature (SUN) scale.7 The study achieved its primary endpoint as well as its key secondary endpoints. Intravitreal sirolimus has also demonstrated the ability to enable reduction of the dosage of prednisolone among patients who were on 7.5 mg or more of prednisone daily at time of randomization. Maximum efficacy was observed with the 440-μg dose. Enrollment has been completed in the SAKURA 2 trial with patients being followed per protocol.

INHIBITORS OF TNF-α

Several TNF-α inhibitors have been employed off-label in managing uveitis, including adalimumab (Humira, AbbVie) and infliximab (Remicade, Janssen).

Adalimumab

Adalimumab is a monoclonal antibody that inhibits TNF-α and can be administered subcutaneously. As of July 2016 it is the first and only FDA-approved noncorticosteroid therapy for patients with noninfectious intermediate and posterior uveitis and panuveitis.

The double-masked, randomized, placebo-controlled phase 3 VISUAL-I study investigated the efficacy and safety of adalimumab in 217 adult patients with active, noninfectious intermediate, posterior, or panuveitis despite corticosteroid therapy.8 It was found that, compared with those receiving placebo, patients receiving adalimumab were less likely to experience treatment failure (hazard ratio = 0.5; 95% CI, 0.36–0.70; P < .001). Another study (VISUAL-II) comparing the safety and efficacy of adalimumab with placebo in adults with inactive noninfectious intermediate uveitis, posterior uveitis, or panuveitis has also been completed.9 Overall, the results of both studies were positive. The VISUAL-II study achieved its primary endpoint, but some of the secondary endpoints did not meet statistical significance.

Infliximab

Infliximab is a monoclonal mouse/human chimeric immunoglobulin G antibody directed against TNF-α. It is approved by the FDA for the treatment of a variety of conditions but is used off label in the treatment of uveitis. Its use has been documented in the management of juvenile idiopathic arthritis-related uveitis, among other indications.10-15

OTHER SYSTEMIC BIOLOGICS IN THE PIPELINE

The interleukin-6 (IL-6) inhibitors tocilizumab (Actemra, Genentech) and sarilumab (formerly REGN88, Regeneron/Sanoﬁ) have been evaluated in patients with uveitis.
It is hoped that ... we can gain further understanding of the pathophysiology of uveitis and potentially enhance the therapeutic armamentarium for patients with uveitis and ocular inflammatory diseases.

Tocilizumab

The STOP-Uveitis study evaluated the safety and efficacy of tocilizumab infusions for treatment of noninfectious posterior, intermediate, or panuveitis. In this multicenter, randomized, open-label safety, efficacy, and bioactivity clinical study, 37 patients with noninfectious uveitis were randomly assigned to one of two treatment groups in a ratio of 1:1. Group 1 received intravenous (IV) infusions of 4 mg/kg tocilizumab, and group 2 received IV infusions of 8 mg/kg tocilizumab. Infusions were given every 4 weeks in both groups until the primary endpoint of month 6. Treatment was given on an as-needed basis from month 6 until month 12. Primary outcome measures were mean change in visual acuity, vitreous haze, and foveal thickness at month 6 in the two groups. In the study, repeated IV administrations of tocilizumab were well tolerated, and both doses of tocilizumab were effective in improving visual acuity and reducing vitreous haze and retinal edema.

Sarilumab

Sarilumab is a fully human monoclonal antibody directed against the alpha subunit of the IL-6 receptor complex in development for the treatment of rheumatoid arthritis and noninfectious uveitis. The 52-week randomized, multicenter, double-masked study SATURN evaluated the efficacy and safety of 200 mg sarilumab administered subcutaneously every 2 weeks in 57 patients with posterior noninfectious uveitis. The study met its primary endpoints of reduction from month 6 until month 12. Primary outcome measures were mean change in visual acuity, vitreous haze, and foveal thickness at month 6 in the two groups. In the study, repeated IV administrations of tocilizumab were well tolerated, and both doses of tocilizumab were effective in improving visual acuity and reducing vitreous haze and retinal edema.

CONCLUSION

It appears likely that no single therapeutic agent could effectively be used as monotherapy to control all different types of uveitis because of the protean pathophysiology of these conditions. However, such challenges have not deterred the ophthalmic research community from searching for new therapeutic options. It is hoped that, with such efforts, we can gain further understanding of the pathophysiology of uveitis and potentially enhance the therapeutic armamentarium for patients with uveitis and ocular inflammatory diseases.