Noninfectious Uveitis: New Treatment Possibilities with Intravitreal Immunoregulatory Therapy

BY QUAN DONG NGUYEN, MD, MSc

Uveitis can be a daunting disease both to diagnose and to treat. About one-third of individuals with uveitis experience significant visual impairment or legal blindess.[1] Diagnosis is usually made based on clinical manifestations and presentations, including ocular inflammation that may occur in the anterior chamber, the vitreous humor, the optic nerve, or the retina and choroid. This inflammatory response may be due to infections, masquerades such as tumors, or immune-mediated diseases.

Before initiating treatment, it is important to identify whether the etiology is infectious or noninfectious. For patients with noninfectious uveitis, the studies described in this article are giving hope that we may soon have additional new therapeutic approaches.

CURRENT TREATMENT PARADIGMS

Corticosteroids—administered orally, via intravitreal injection, or in extended release devices—are the only class of drugs currently approved by the US Food and Drug Administration (FDA) for the treatment of uveitis. However, many studies have shown that chronic use of corticosteroids, especially at a high dose, is associated with systemic and local adverse effects.[2] Patients needing no less than 7.5 mg of prednisone or an equivalent daily medication to control inflammation are indicated for a corticosteroid-sparing agent; between 28% and 59% of uveitis patients will require therapy beyond corticosteroids.[3]

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A number of published studies describe the proper utilization of corticosteroids in the management of uveitis; however, a study of physicians managing uveitis patients published in 2011 demonstrated that a majority of ophthalmologists and rheumatologists either do not comprehend or do not follow the established guidelines.[4]

There is a role for other immunomodulatory therapies (IMT) as alternatives to corticosteroids in the management of these patients. Although various classes of immunomodulators have been successfully used off label, there has been a dearth of randomized trials comparing potential agents with corticosteroids. The

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challenge has been that most insurance providers consider many IMT agents not indicated for uveitis because of a lack of FDA-approved indications and hence do not cover their use. I have personally heard from many clinician scientists who manage patients with uveitis who have witnessed patients losing their vision because they could not pay privately for IMT agents.

SIROLIMUS

Sirolimus (rapamycin; Rapamune, Pfizer) is an inhibitor of the mammalian target of rapamycin (mTOR), which is appreciated to be a central regulator of immune responses, providing a critical link between metabolic demands and cellular function.[5] Inhibition of mTOR interrupts T-cell proliferation and the release of interleukin 2 (IL-2) and other proinflammatory cytokines.[6] The potential of sirolimus as an immunoregulatory agent was established via its use with organ transplantation.[7] It has also been used systemically in patients with coronary artery disease and arterial intimal thickening.[8] Low doses of rapamycin were found to be effective against experimental autoimmune uveoretinitis in rats,[9] leading to the initiation of a clinical trial in individuals with refractory noninfectious uveitis.[10]

A proprietary, depot-forming formulation of sirolimus for subconjunctival or intravitreal injection has been developed (intravitreal sirolimus, Santen Pharmaceutical Co.). The local formulation has been employed in studies for geographic atrophy[11] as well as noninfectious uveitis of the posterior segment.[12] The phase 1 SAVE study was the first worldwide to evaluate the safety and efficacy of subconjunctival or intravitreal sirolimus for noninfectious intermediate, posterior, and pan-uveitis. At the 6-month primary endpoint in the SAVE study, local administration of sirolimus, either to the vitreous or subconjunctivally, appeared to be safe and tolerable. No drug-related systemic adverse events or serious adverse events were noted.

Sirolimus delivered as either an intravitreal or subconjunctival injection has demonstrated bioactivity as an immunoregulatory and corticosteroid-sparing agent, reducing vitreous haze and cells, improving visual acuity, and decreasing the need for systemic corticosteroids.[12,13] 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 possibilities for bilateral treatment in subjects with bilateral disease, and the phase 3 SAKURA studies (Study Assessing Double-masked Uveitis Treatment; NCT01358266) for noninfectious uveitis.

SAKURA

SAKURA was 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 and SAKURA 2. SAKURA completed enrollment of 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. The study achieved its primary endpoint as well as its two key secondary endpoints (see below), with maximum efficacy observed with the 440-µg dose. SAKURA 2 is ongoing and currently recruiting patients.

Both SAKURA studies investigated the use of sirolimus as monotherapy. With the exception of systemic corticosteroids, which were tapered beginning at study start, subjects were required to taper off all other treatments for noninfectious uveitis of the posterior segment prior to enrollment. The primary endpoint was achieving a vitreous haze score of 0 at month 5, and the key secondary endpoints included achieving a vitreous haze score of 0 or 0.5+ at month 5 and an improvement in vitreous haze score to 0 or by at least 2 units at month 5.

In addition to meeting the primary and key secondary endpoints with the 440 µg dose, SAKURA also achieved success in corticosteroid tapering (defined as the overall prednisone equivalent dose tapered to ≤ 5 mg/day at Month 5), positive visual acuity outcomes, and reduction in central retinal thickness.

CONCLUSION

It is exciting to see an immunoregulatory agent, especially one that can be administered locally, providing results on par with corticosteroids but with fewer side effects than steroids. Also beneficial is that intravitreal injections are a well-known and comfortable drug delivery method for retina specialists, many of whom manage patients with noninfectious uveitis. With therapies such as intravitreal sirolimus, the outlook is

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positive for patients with noninfectious uveitis of the posterior segment seeking an effective option to control their disease without experiencing the common side effects associated with corticosteroids. ■

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