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Efficacy and Safety of Intravenous Secukinumab in Noninfectious Uveitis Requiring Steroid-Sparing Immunosuppressive Therapy

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Purpose: Secukinumab, a fully human anti−interleukin-17A monoclonal antibody, exhibited promising activity in a proof-of-concept study when administered in intravenous (IV) doses to patients with active, chronic, noninfectious uveitis. This study compared the efficacy and safety of different IV and subcutaneous (SC) doses of secukinumab in patients with noninfectious uveitis.

Design: Multicenter, randomized, double-masked, dose-ranging, phase 2 clinical trial.

Participants: Thirty-seven patients with active noninfectious intermediate uveitis, posterior uveitis, or panuveitis who required corticosteroid-sparing immunosuppressive therapy.

Methods: Patients were randomized to secukinumab 300 mg SC every 2 weeks for 4 doses, secukinumab 10 mg/kg IV every 2 weeks for 4 doses, or secukinumab 30 mg/kg IV every 4 weeks for 2 doses. Intravenous or SC saline was administered to maintain masking. Efficacy was assessed on day 57 (2−4 weeks after last dose).

Main Outcome Measures: Percentage of patients with treatment response, defined as (1) at least a 2-grade reduction in vitreous haze score or trace or absent vitreous haze in the study eye without an increase in corticosteroid dose and without uveitis worsening or (2) reduction in corticosteroid dosages to prespecified levels without uveitis worsening. Percentage of patients with remission, defined as anterior chamber cell and vitreous haze scores of 0 or 0.5+ in both eyes without corticosteroid therapy or uveitis worsening.

Results: Secukinumab 30 mg/kg IV and 10 mg/kg IV, compared with the 300 mg SC dose, produced higher responder rates (72.7% and 61.5% vs. 33.3%, respectively) and remission rates (27.3% and 38.5% vs. 16.7%, respectively). Statistical and clinical superiority for the 30 mg/kg IV dose compared with the 300 mg SC dose was established in a Bayesian probability model. Other measures, including time to response onset, change in visual acuity, and change in vitreous haze score, showed numeric trends favoring IV dosing. Secukinumab, administered in IV or SC formulations, appeared safe and was well tolerated.

Conclusions: Intravenous secukinumab was effective and well tolerated in noninfectious uveitis requiring systemic corticosteroid-sparing immunosuppressive therapy. Greater activity with IV dosing suggests that patients may not receive sufficient drug with SC administration. High-dose IV secukinumab may be necessary to deliver secukinumab in therapeutic concentrations. *Ophthalmology 2015;■:1−10 © 2015 by the American Academy of Ophthalmology.*

*Supplemental material is available at www.aaojournal.org.

Noninfectious uveitis is an inflammatory disorder of the uveal tract that is a major cause of vision loss.[1−3] In the United States, uveitis occurs at an incidence of 24.9 to 52.4 cases per 100 000 person-years and a prevalence of 57.5 to 115.3 cases per 100 000 persons[4−6] and is responsible for 10% to 15% of bilateral blindness and 22% of unilateral blindness.[7] Corticosteroids are typically used as first-line therapy, but their long-term use to maintain disease control is associated with safety concerns, which prompted the development of steroid-sparing immunosuppressive therapies.[8,9] Steroid-sparing agents are associated with adverse effects of their own,[8,9] however, and the need remains for safer and more efficacious alternatives.

The immunopathology of uveitis is thought to be driven by autoreactive T cells targeting ocular tissues and acting in concert with cells of the innate immune system.[7,10] Interleukin (IL)-17A, which is produced by T-helper (Th) 17 and other immune cells, is one of the major proinflammatory cytokines in immunoinflammatory disorders.[11] Circulating Th17 cell levels are elevated during active uveitis and reduced following effective treatment.[12] Under normal conditions, circulating IL-17A levels are extremely low or

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undetectable, but in patients with active uveitis associated with systemic immune disorders such as Behçet's disease, increased serum and ocular IL-17A concentrations are seen.[13–15] Moreover, IL-17A is produced in experimental models of T-cell–mediated uveitis and blocking IL-17A reduces ocular inflammation in these models.[12,16–18] These clinical and experimental observations suggest that IL-17A may be an attractive therapeutic target in patients with noninfectious uveitis.

Secukinumab is a selective, high-affinity, fully human immunoglobulin G1κ monoclonal antibody that binds to and neutralizes human IL-17A. In a proof-of-concept study, intravenous (IV) secukinumab 10 mg/kg produced positive treatment responses in a majority of patients with active chronic noninfectious uveitis who required systemic immunosuppressive therapy.[19] However, secukinumab administered at subcutaneous (SC) doses of 150 or 300 mg every 2 or 4 weeks did not meet primary efficacy end points in 3 phase 3 trials involving patients with Behçet's uveitis, active noninfectious non–Behçet's uveitis, or quiescent noninfectious non–Behçet's uveitis.[20] These unexpected findings raised the possibility that sufficient levels of secukinumab may not have been achieved with SC dosing. Therefore, the current dose-ranging study was designed to compare the IV dose used in the positive proof-of-concept study, a higher IV dose, and the highest SC dose used in the phase 3 trials. The primary objectives were to compare dose levels for clinically significant reductions in uveitis severity, ability to induce sustained uveitis remission, and safety and tolerability in patients with noninfectious uveitis who required systemic steroid-sparing immunosuppressive therapy.

Methods

Study Design

This double-masked, dose-ranging study was conducted at 10 sites in the United States and 4 sites in Germany. Eligible patients were stratified by uveitis severity (vitreous haze <2+ vs. ≥2+) and then randomly assigned (1:1:1) to receive secukinumab 300 mg SC every 2 weeks (days 1, 15, 29, and 43), secukinumab 10 mg/kg IV every 2 weeks, or secukinumab 30 mg/kg IV every 4 weeks (days 1 and 29). Intravenous or SC saline was administered as needed to maintain masking of treatment groups. Intravenous doses were delivered over approximately 2 hours by infusion pump or a gravity infusion method. Investigators and other study personnel were masked to the treatment assignment. All patients were followed to day 85. Patients were assessed on day 57, and subsequent treatment was provided on the basis of their response. Patients in remission were treated only if disease flared (anterior chamber cell score or vitreous haze score ≥1+); all others had study medication discontinued. Patients who remained in remission at study completion had the option of enrolling in an open-label extension study with eligibility to receive additional secukinumab doses.

This study was performed in accordance with the principles of the Declaration of Helsinki and Good Clinical Practices and at US sites compliant with the Health Insurance Portability and Accountability Act. Institutional review board approval was obtained at all study sites, and written informed consent was obtained from all patients. All US patients signed a Health Insurance Portability and Accountability Act consent form. The study details were registered on ClinicalTrials.gov (NCT00685399). A list of study investigators is provided online (available at www.aaojournal.org).

Patients

Male and female subjects aged 18 to 75 years with active chronic noninfectious intermediate uveitis, posterior uveitis, or panuveitis (≥1+ vitreous haze in study eye) were eligible if they were in need of steroid-sparing immunosuppressive therapy. All patients of childbearing potential agreed to use 2 acceptable methods of contraception throughout the study; women were required to have a negative pregnancy test result at screening and before each dose of study treatment. Patients with concurrent medical conditions unrelated to uveitis that required immunosuppressive/immunomodulatory therapy or with conditions that could be exacerbated by such therapy were excluded. Also ineligible for enrollment were patients who had forms of uveitis that might resolve spontaneously or who had an uncertain underlying diagnosis that could reasonably include a disease for which immunosuppression would be contraindicated (e.g., ocular lymphoma, histoplasmosis, or toxoplasmosis) or for which immunosuppression was not proven to be beneficial (e.g., acute zonal occult outer retinopathy, progressive outer retinal necrosis, or acute retinal necrosis syndrome). Other exclusion criteria were recent active infection, history of chronic or recurrent infection, or history of infection that could spontaneously reemerge, body weight more than 120 kg, history of lymphoproliferative disease or malignancy, and history of drug or alcohol abuse within the preceding 6 months. Patients were also excluded if they had received therapy with IV or SC immunosuppressive monoclonal antibodies within 4 months (or 12 months for efalizumab or rituximab), periocular or intravitreal drugs within 3 months, fluocinolone acetonide intravitreal implant in the study eye within 3 years, nondiagnostic ocular surgery in the study eye within 4 months, laser photocoagulation in the study eye within 3 months, or a topical ocular steroid at a dose equivalent to prednisolone acetate 1% every hour while awake within 1 week of the first dose of study treatment. Use of stable doses of oral immunosuppressive agents was allowed until the baseline day.

Tapering of Concurrent Steroid Therapy

Concomitant immunosuppressive medications other than oral prednisone or topical ocular steroid therapy were not allowed during the study treatment period. Oral prednisone dosage was tapered at the discretion of the investigator using the following guidance. For patients receiving oral prednisone up to 1.5 mg/kg/day, the dose was tapered weekly to 85%, 67%, 50%, 33%, 17%, 8%, and 0% of the baseline dose during the first 7 weeks of the study treatment period. Exact doses were rounded to the nearest 5 mg. The prednisone dose was to be tapered more quickly if the patient's uveitis was rapidly subsiding and the investigator considered it safe to accelerate the tapering schedule or if the investigator thought more rapid tapering was required because of corticosteroid-related side effects. Patients receiving topical steroid therapy at a dose up to or equivalent to prednisolone acetate 1% had treatment tapered and discontinued over a 4-week period.

Efficacy Assessments

Identical examinations were performed on both eyes at screening (within 7 days before randomization); before dosing on days 1 (baseline), 15, 29, and 43; and on days 57 and 85 (study completion visit). One eye was selected at screening by