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Safety and Efficacy of Adalimumab in Patients with Noninfectious Uveitis in an Ongoing Open-Label Study: VISUAL III

Eric B. Suhler, MD, MPH,[1] Alfredo Adán MD, PhD,[2] Antoine P. Brézin, MD, PhD,[3] Eric Fortin, MD,[4] Hiroshi Goto, MD,[5] Glenn J. Jaffe, MD,[6] Toshikatsu Kaburaki, MD,[7] Michal Kramer, MD,[8] Lyndell L. Lim, MBBS, FRANZCO,[9] Cristina Muccioli, MD, MBA,[10] Quan Dong Nguyen, MD, MSc,[11] Joachim Van Calster, MD,[12] Luca Cimino, MD,[13] Martina Kron, PhD,[14] Alexandra P. Song, MD, MPH,[15] Jianzhong Liu, MD,[15] Sophia Pathai, MBBS, PhD,[16] Anne Camez, MD,[14] Ariel Schlaen, MD,[17] Mirjam E.J. van Velthoven, MD, PhD,[18] Albert T. Vitale, MD,[19] Manfred Zierhut, MD, PhD,[20] Samir Tari, MD, MBA,[15] Andrew D. Dick, MBBS, MD[21]

Purpose: To evaluate safety and efficacy of adalimumab in patients with noninfectious intermediate, posterior, or panuveitis.

Design: Phase 3, open-label, multicenter clinical trial extension (VISUAL III).

Participants: Adults meeting treatment failure (TF) criteria or who completed VISUAL I or II (phase 3, randomized, double-masked, placebo-controlled) without TF.

Methods: Patients received adalimumab 40 mg every other week. Interim follow-up data were described from VISUAL III weeks 0 through 78.

Main Outcome Measures: Disease quiescence, steroid-free quiescence, active inflammatory chorioretinal/retinal vascular lesions, anterior chamber cell grade, vitreous haze grade, best-corrected visual acuity (BCVA), and corticosteroid dose. Binary data were reported using nonresponder imputation (NRI), continuous data using last observation carried forward and as-observed analysis, and corticosteroid dose using observed-case analysis. Adverse events (AEs) were reported from first adalimumab dose in VISUAL III through interim cutoff.

Results: Of 424 patients enrolled, 371 were included in intent-to-treat analysis. At study entry, 242 of 371 (65%) patients had active uveitis; 60% (145/242, NRI) achieved quiescence at week 78, and 66% (95/143, as-observed) of those were corticosteroid free. At study entry, 129 of 371 (35%) patients had inactive uveitis; 74% (96/129, NRI) achieved quiescence at week 78, and 93% (89/96, as-observed) of those were corticosteroid free. Inflammatory lesions, anterior chamber grade, and vitreous haze grade showed initial improvement followed by decline in patients with active uveitis and remained stable in patients with inactive uveitis. BCVA improved in patients with active uveitis from weeks 0 to 78 (0.27 to 0.14 logMAR; left and right eyes; as-observed) and remained stable in patients with inactive uveitis. Mean corticosteroid dose decreased from 13.6 mg/day (week 0) to 2.6 mg/day (week 78) in patients with active uveitis and remained stable in those with inactive uveitis (1.5−1.2 mg/day). AEs (424 events/100 patient-years) and serious AEs (16.5 events/100 patient-years) were comparable with previous VISUAL trials.

Conclusions: Patients with active uveitis at study entry who received adalimumab therapy were likely to achieve quiescence, improve visual acuity, and reduce their daily uveitis-related systemic corticosteroid use. Most patients with inactive uveitis at study entry sustained quiescence without a systemic corticosteroid dose increase. No new safety signals were identified. *Ophthalmology 2018;■:1−13 © 2018 by the American Academy of Ophthalmology. This is an open access article under the CC BY-NC-ND license (http://creativecommons.org/licenses/by-nc-nd/4.0/).*

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Noninfectious intermediate, posterior, and panuveitis are uncommon, immune-mediated, inflammatory ocular diseases frequently associated with comorbid systemic inflammatory conditions.[1] Estimates suggest that these uveitides account for 19% to 40% of cases of noninfectious uveitis,[2−4] with a worldwide prevalence of 38/100 000 people.[5,6] In the United States, the overall prevalence of noninfectious uveitis among adults is estimated to be 121/100 000 (98/100 000 anterior, 1/100 000 intermediate, 10/100 000 posterior, and 12/100 000 panuveitis).[4] Compared with individuals without these conditions, patients with noninfectious intermediate,

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posterior, or panuveitis are estimated to have a 10-fold increased risk of blindness or low vision,[3,7] and cumulative damage caused by recurring uveitis flares can increase this risk.[8] Although corticosteroids are the mainstay of uveitis treatment, they are associated with common and potentially serious side effects accompanying long-term and high-dose use.[9–11] Additional therapies would ideally target specific mediators of the immune response underlying uveitic inflammation to achieve disease quiescence and allow reduced corticosteroid burden and related complications, while providing greater efficacy than conventional steroid-sparing immunosuppressive agents.[12]

Tumor necrosis factor−α (TNF-α) is a cytokine that contributes to inflammation in immune-mediated diseases, including noninfectious uveitis.[9,13,14] The human monoclonal antibody to TNF-α, HUMIRA (adalimumab; AbbVie Inc, North Chicago, IL), blocks the interaction between TNF-α and its cell surface receptors to inhibit inflammatory TNF-α signaling.[15] Adalimumab is approved for the treatment of several immune-mediated inflammatory diseases, including noninfectious intermediate, posterior, and panuveitis.[12,16] The efficacy of adalimumab in managing uveitis was demonstrated in 2 randomized, double-masked, placebo-controlled trials of patients with active uveitis despite treatment with high-dose (10–60 mg/day prednisone equivalent) systemic corticosteroids (VISUAL I)[17] or uveitis dependent on higher than recommended[10,18] doses of systemic corticosteroids for disease control (10–35 mg/day prednisone equivalent; VISUAL II).[19] In the parent studies, treatment failure (TF) was assessed and defined by a rigorous composite end point based on 4 components (new inflammatory chorioretinal and/or inflammatory retinal vascular lesions, anterior chamber cell grade, vitreous haze grade, and best-corrected visual acuity [BCVA]).[17,19] In these studies, adalimumab effectively reduced the risk of TF compared with placebo in patients with active or inactive uveitis.[17,19] Furthermore, significantly higher rates of quiescence (defined as no active inflammatory lesions, anterior chamber cell grade $\leq$ 0.5+, and vitreous haze grade $\leq$ 0.5+) and corticosteroid-free quiescence were achieved and maintained through 52 weeks in the VISUAL I/II studies in patients receiving adalimumab compared with placebo, regardless of disease status at study entry.[20]

The objective of the open-label extension study, VISUAL III, was to evaluate the safety and efficacy of extended adalimumab treatment in patients with noninfectious intermediate, posterior, or panuveitis who successfully completed the VISUAL I or VISUAL II trials without TF (defined as patients with inactive uveitis in VISUAL III) or experienced TF in the parent trials (defined as patients with active uveitis in VISUAL III). This report describes the interim analysis of VISUAL III through 78 weeks of follow-up.

Methods

Study Design

This was an open-label, multicenter, unmasked, uncontrolled, phase 3 extension study (VISUAL III; registered at www.clinicaltrials.gov, trial ID NCT01148225 and www.clinicaltrialsregister.eu, EudraCT number 2009-016196-29) conducted at sites in Argentina, Australia, Austria, Belgium, Brazil, Canada, the Czech Republic, Denmark, France, Germany, Greece, Israel, Italy, Japan, Mexico, Poland, Portugal, Spain, Switzerland, the United Kingdom, and the United States. Study visits occurred at week 0 (baseline); at weeks 2, 4, 8, 12, and 18; and every 12 weeks thereafter. The window for all scheduled visits was ±7 days. The trial extension is ongoing; this report describes follow-up efficacy and safety data through week 78, as of the interim cutoff of October 31, 2016. All patients had the opportunity to reach week 78 before the cutoff date. This interim analysis was conducted to provide real-world data after approval of adalimumab to treat uveitis. Efficacy data were collected from the first adalimumab dose in VISUAL III through 78 weeks of follow-up. Safety data were collected from the first adalimumab dose in VISUAL III and until up to 70 days after the last dose of adalimumab or up to the interim cutoff date of October 31, 2016, whichever occurred first.

The study complied with the ethical principles of the Declaration of Helsinki and the International Conference on Harmonisation Guidelines for Good Clinical Practice; sites in the United States conformed to the requirements of the Health Insurance Portability and Accountability Act. All patients signed a statement of informed consent before enrollment, and all procedures were reviewed and approved by appropriate institutional review boards or ethics committees before study initiation.

Patients

Eligible patients were aged ≥18 years and diagnosed with noninfectious intermediate, posterior, or panuveitis. Patients had either discontinued from a phase 3 parent study (VISUAL I, trial ID NCT01138657; or VISUAL II, trial ID NCT01124838) for having met predefined TF criteria or successfully completed the parent study without TF. Randomization from the parent studies was not disclosed before entry in VISUAL III. Enrolled patients were required to complete the VISUAL III baseline visit within 28 days of the final visit of the parent study. Patients who discontinued from a parent study for any reason other than TF were not eligible for participation in VISUAL III.

Key ocular exclusion criteria were corneal or lens opacity that precluded visualization of the fundus or that would likely require cataract surgery during trial participation; intraocular pressure ≥25 mmHg requiring ≥2 glaucoma medications, or having evidence of glaucomatous optic nerve injury; BCVA worse than 20/200 (Snellen; equivalent to logMAR >1.0 using an Early Treatment Diabetic Retinopathy Study [ETDRS] chart) in either eye; proliferative or severe nonproliferative diabetic retinopathy; neovascular age-related macular degeneration; or abnormality of the vitreoretinal interface with the potential for macular structural damage independent of the inflammatory process. Nonocular exclusions included a history of or neurologic symptoms suggestive of central nervous system demyelinating disease; evidence of dysplasia or history of malignancy (including lymphoma and leukemia); and treatment with intravenous or oral antibiotics (≤30 or ≤14 days before the baseline visit, respectively). Complete inclusion and exclusion criteria are listed in Table S1 (available at www.aaojournal.org).

Of 424 patients enrolled and included in the safety data set, 371 were included in the intent-to-treat (ITT) data set (Fig 1). Patients (n = 53) were excluded from the ITT set if they developed proliferative or severe nonproliferative diabetic retinopathy or clinically significant macular edema caused by diabetic retinopathy, underwent cataract surgery during the study, or had previous vitrectomy or underwent vitrectomy during the study (i.e., surgeries that could be a reason for a patient's improvement in vision other than the study drug). Additional reasons for exclusion from the ITT set were incomplete efficacy source data