



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

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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,

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 \pm 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 \geq 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 \geq 25 mmHg requiring \geq 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 (\leq 30 or \leq 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

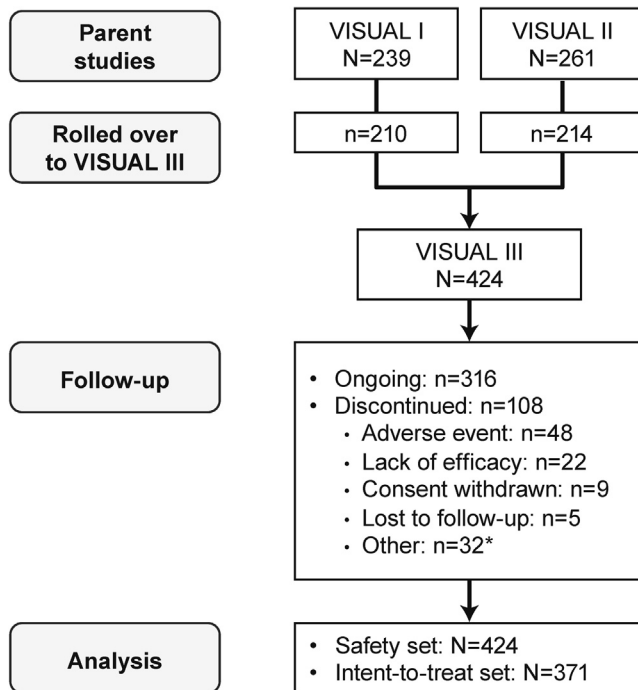


Figure 1. Patient disposition in the VISUAL III study. Patients with multiple reasons for discontinuation were included in the count for each reason. *Other reasons for discontinuation included patient relocation, noncompliance, planned pregnancy, and investigative site stopped participating in the registry.

in the parent study and general compliance issues at the study site in the parent studies. An additional 5 patients with macular hole or rhegmatogenous retinal detachment were excluded from analysis of central subfield thickness (CST).

Treatment

All patients received open-label subcutaneous adalimumab 40 mg every other week for the duration of the study regardless of treatment assignment in the parent studies. Patients were allowed, at the investigator's clinical discretion throughout the study, to initiate, continue, escalate, or taper concomitant oral or topical corticosteroid therapy (all corticosteroids were systemic unless noted otherwise) and/or any one of the immunosuppressive therapies permitted in the parent study to control intraocular inflammation (methotrexate ≤ 25 mg/week; cyclosporine ≤ 4 mg/kg/day; mycophenolate mofetil ≤ 2 g/day; azathioprine ≤ 175 mg/day). Additionally, patients were allowed 2 periocular corticosteroid injections per eye per year; intraocular or intravitreal injections were not allowed.

Outcome Measures

The main outcome measure was quiescence, defined as no active inflammatory chorioretinal and/or inflammatory retinal vascular lesions (inflammatory lesions), anterior chamber cell grade $\leq 0.5+$, and vitreous haze grade $\leq 0.5+$ in both eyes, similar to the quiescence criteria used in the VISUAL I and II trials.^{17,19} Efficacy variables included no active inflammatory lesions, anterior chamber cell grade $\leq 0.5+$, vitreous haze grade $\leq 0.5+$, central retinal thickness, BCVA, and the dose of uveitis-related corticosteroids and

immunomodulators. There was no designated study eye; outcomes were evaluated in both eyes at every study visit from weeks 0 through 78.

The absence or presence of new inflammatory chorioretinal and/or inflammatory retinal vascular lesions (compared with the findings of the final visit of the parent study) was determined using dilated indirect ophthalmoscopy and was based on the investigators' clinical judgment. Vitreous haze was evaluated using dilated indirect ophthalmoscopy and comparison with standard photographs, as described in the National Eye Institute Criteria adapted by the Standardization of Uveitis Nomenclature Working Group (score range, 0 [no vitreous haze] to 4+ [optic nerve head is obscured]).^{21,22} Anterior chamber cells (within a 1×1 -mm slit beam) were counted using slit-lamp examination and graded according to Standardization of Uveitis Nomenclature Working Group criteria (score range, 0 [<1 cell in field] to 4+ [>50 cells in field]).²¹ Anterior chamber cell evaluation was performed before mydriatic eye drops were instilled to dilate the pupil. CST (center 1-mm subfield) was determined by optical coherence tomography (OCT) with 1 of 3 instruments: Stratus OCT (Carl Zeiss Meditec, Inc, Jena, Germany), Cirrus HD-OCT (Carl Zeiss Meditec, Inc), or Spectralis (Heidelberg Engineering, Heidelberg, Germany). Each system's software identifies the internal limiting membrane as the inner retina. For the outer retinal boundary, the Stratus OCT uses the ellipsoid zone, the Spectralis uses the Bruch membrane, and Cirrus HD-OCT uses the inner third of the retinal pigment epithelium.^{23,24} BCVA was determined for each eye separately using appropriate corrective lenses based on patients' current refraction using a standard ETDRS chart at a distance of 4 or 1 m. BCVA was recorded as the number of letters read and was transformed into logMAR units for analysis. Dose of uveitis-related corticosteroids was recorded throughout the study, as were the doses of other permitted immunosuppressives.

Safety was monitored through adverse event (AE) collection, physical examination, vital signs, and laboratory testing. AEs were coded using the Medical Dictionary for Regulatory Activities (version 19.0). Active or latent tuberculosis was determined by the investigator.

Statistical Analysis

Efficacy variables were analyzed using data from the ITT data set. Outcomes were analyzed by uveitis status at baseline (active or inactive uveitis as defined above) and overall. Binary data were analyzed descriptively as observed and using the nonresponder imputation (NRI) method, and exact 95% Clopper-Pearson confidence intervals (CIs) were calculated. Corticosteroid dose and corticosteroid-free quiescence were summarized descriptively as observed. BCVA and CST were analyzed descriptively as observed and using last observation carried forward (LOCF) as the imputation method; data from left and right eyes were analyzed separately. CST was analyzed separately for left and right eyes by OCT machine software. The 95% CI for means and logMAR were calculated.

Analysis of AEs was conducted using the safety data set, including all patients who received at least 1 dose of adalimumab. AEs were reported as the total number of events and number of events per 100 patient-years (PY).

Results

Patients

In the ITT set, 49% of patients (182/371) entered from the VISUAL I trial and 51% of patients (189/371) entered from the VISUAL II trial. Most patients were female (58%, 214/371) and

Table 1. Patient Demographics and Characteristics (Intent-to-Treat Data Set)

| Variable | Active Uveitis* (N = 242) | Inactive Uveitis* (N = 129) | Total (N = 371) |
|---|---------------------------|-----------------------------|-----------------|
| Age, y | | | |
| Mean ± SD | 42.6±14.5 | 42.4±13.0 | 42.5±14.0 |
| Range | 19–80 | 19–81 | 19–81 |
| Sex, n (%) | | | |
| Female | 135 (56) | 79 (61) | 214 (58) |
| Male | 107 (44) | 50 (39) | 157 (42) |
| Race, n (%) | | | |
| White | 172 (71) | 105 (81) | 277 (75) |
| Asian | 37 (15) | 8 (6) | 45 (12) |
| Black or African American | 17 (7) | 7 (5) | 24 (7) |
| American Indian or Alaska native | 2 (0.8) | 0 | 2 (0.5) |
| Multiracial | 3 (1) | 0 | 3 (0.8) |
| Other | 11 (5) | 9 (7) | 20 (5) |
| Type of uveitis, n (%) | | | |
| Panuveitis | 133 (55) | 57 (44) | 190 (51) |
| Posterior | 52 (22) | 52 (40) | 104 (28) |
| Intermediate | 55 (23) | 19 (15) | 74 (20) |
| Intermediate/posterior | 2 (0.8) | 1 (0.8) | 3 (0.8) |
| Diagnosis, n (%) | | | |
| Idiopathic | 91 (38) | 31 (24) | 122 (33) |
| Vogt-Koyanagi-Harada | 48 (20) | 24 (19) | 72 (19) |
| Sarcoid | 34 (14) | 18 (14) | 52 (14) |
| Birdshot choroidopathy | 24 (10) | 27 (21) | 51 (14) |
| Behçet | 11 (5) | 16 (12) | 27 (7) |
| Multifocal choroiditis and panuveitis | 11 (5) | 3 (2) | 14 (4) |
| Other | 23 (10) | 10 (8) | 33 (9) |
| Duration of uveitis, mo | | | |
| Mean ± SD | 63.1±74.2 | 62.0±52.2 | 62.7±67.3 |
| Range | 2.8–558.4 | 4.5–260.3 | 2.8–558.4 |
| Immunomodulator use at baseline, n (%) | | | |
| Azathioprine | 67 (28) | 54 (42) | 121 (33) |
| Cyclosporine | 8 (3) | 9 (7) | 17 (5) |
| Cyclosporine | 12 (5) | 13 (10) | 25 (7) |
| Methotrexate | 24 (10) | 17 (13) | 41 (11) |
| Mycophenolate mofetil or equivalent | 23 (10) | 15 (12) | 38 (10) |
| Uveitis-related corticosteroid use at baseline, n (%) | | | |
| Oral | 142 (59) | 9 (7) | 151 (41) |
| Topical | 117 (48) | 7 (5) | 124 (33) |
| Other | 59 (24) | 3 (2) | 62 (17) |
| Other | 7 (3) | 0 | 7 (2) |

SD = standard deviation.

*Uveitis status at VISUAL III entry. Patients with active uveitis at VISUAL III entry experienced treatment failure in VISUAL I or VISUAL II trials. Patients with inactive uveitis at VISUAL III entry completed the VISUAL I and VISUAL II trials without experiencing treatment failure.

white (75%; 277/371) (Table 1). The mean ± standard deviation (SD) patient age was 42.5±14.0 years, and the mean duration of diagnosed uveitis was 62.7±67.3 months. At study entry, 65% of patients (242/371) had active uveitis (i.e., experienced TF in VISUAL I or II) and the remaining 35% (129/371) had inactive uveitis (i.e., completed the parent trials without experiencing TF). A total of 121 of 371 (33%) patients were receiving immunomodulators and 151 of 371 (41%) were receiving corticosteroids (systemic and nonsystemic) at VISUAL III baseline; 30 patients (8%) started immunomodulators and 65 patients (18%) started corticosteroids during the study. Throughout VISUAL III, 33 of 371 (9%) patients received concomitant local corticosteroid injections.

As of the interim cutoff, 316 patients (75%) were ongoing, and 108 of the 424 patients (25%) in the safety set discontinued the study before week 78 (Fig 1). Reasons for premature discontinuation before week 78 were AEs (11%, 48/424), lack of efficacy (5%, 22/424), withdrawal of consent (2%, 9/424), loss to follow-up (1%; 5/424), or other reasons (8%, 32/424).

Quiescence

At week 0 of VISUAL III, 93% of patients defined as having active uveitis (i.e., patients who experienced TF in the parent trials) were not in quiescence (224/242, NRI). By week 12, 60% (144/242, NRI) of patients achieved quiescence, which remained stable at week 78 (60%; 145/242, NRI; Fig 2A). Of patients who achieved quiescence, 66% were corticosteroid free (95/143, as observed) at week 78, and 23% were receiving corticosteroid doses of ≤7.5 mg/day (33/143, as observed; Fig 2B).

Of the patients who entered VISUAL III defined as having inactive uveitis (i.e., patients who completed the parent trials without experiencing TF), 85% met criteria for quiescence at week 0 (109/129, NRI; Fig 2A). By week 78, the percentage of patients in quiescence remained stable at 74% (96/129, NRI). Of patients in quiescence, 96% (105/109, as observed) were not receiving uveitis-related corticosteroids at week 0, and 93% (89/96, as observed) were not receiving any corticosteroids at week 78 (Fig

2B). Only 2 patients with inactive uveitis at study entry were receiving >7.5 mg/day corticosteroids at week 78 to maintain quiescence.

The trends observed in patients who entered VISUAL III with active or inactive uveitis were also reflected in the overall patient population (Fig S1A and B, available at www.aaojournal.org).

Quiescence data were also analyzed in patients who were stratified by placebo or adalimumab treatment during the parent VISUAL I and VISUAL II trials. At week 0, 27% of patients who received placebo (49/185; NRI) and 42% of patients who received adalimumab (78/186; NRI) during the VISUAL I and II trials were in quiescence. At week 78, 67% of patients who received placebo (124/185; NRI) and 63% of patients who received adalimumab (117/186; NRI) during the VISUAL I and II trials achieved quiescence (Fig S2A, available at www.aaojournal.org). Of patients in quiescence, 80% (99/123; as observed) who received placebo and 73% (85/116; as observed) who received adalimumab during VISUAL I and II trials were corticosteroid free at week 78 (Fig S2B, available at www.aaojournal.org).

Other Efficacy Variables

Chorioretinal Lesions. In patients with active uveitis at study entry, there was an improvement in percentage of patients with no active chorioretinal lesions, from 64% at week 0 (154/242, NRI) to 83% at week 12 (200/242, NRI), followed by a decline to 69% at week 78 (166/242, NRI) (Fig 3A).

Anterior Chamber Activity. The percentage of patients with anterior chamber cell grade $\leq 0.5+$ in both eyes increased from 50% at week 0 (120/242, NRI) to 81% at week 12 (197/242, NRI), followed by a decline to 66% at week 78 (159/242, NRI) (Fig 3B).

Vitreous Activity. The percentage of patients with vitreous haze grade $\leq 0.5+$ increased from 41% at week 0 (98/242, NRI) to 65% at week 78 (157/242, NRI) (Fig 3C).

In patients with inactive uveitis at study entry in VISUAL III, the percentage of patients with no active inflammatory lesions, anterior chamber cell grade $\leq 0.5+$, and vitreous haze grade $\leq 0.5+$ remained stable from week 0 to week 78 (Fig 3).

Efficacy variables in the overall population are described in Figure S3 (available at www.aaojournal.org).

After a small initial decrease, CST was generally stable throughout follow-up, regardless of the OCT machine type used (LOCF; Fig 4A–C). Patients who entered the study with active uveitis had greater central retinal thickness than those with inactive uveitis observed with the Stratus OCT and Spectralis. CST decreased through week 78 in patients with active uveitis and was generally stable in patients with inactive uveitis. In all left eyes at week 0, mean CST observed with the Stratus OCT, Spectralis, and Cirrus HD-OCT was 246.8 μm ($n = 105$), 321.2 μm ($n = 183$), and 302.4 μm ($n = 70$), respectively, compared with 227.2 μm ($n = 72$), 295.7 μm ($n = 136$), and 256.8 μm ($n = 56$) at week 78 (as observed). In all right eyes at week 0, mean CST observed with the Stratus OCT, Spectralis, and Cirrus HD-OCT was 269.1 μm ($n = 105$), 311.9 μm ($n = 181$), and 312.4 μm ($n = 71$), respectively, compared with 242.6 μm ($n = 71$), 280.5 μm ($n = 135$), and 287.9 μm ($n = 56$) at week 78 (as observed).

For patients with active uveitis, mean change in CST at week 78 from week 8 for the Stratus OCT, Spectralis, and Cirrus HD-OCT was $-14.2 \mu\text{m}$ (95% CI, -30.5 to 2.1), $-7.1 \mu\text{m}$ (95% CI, -17.7 to 3.5), and $-27.0 \mu\text{m}$ (95% CI, -48.0 to -6.0), respectively, for the left eyes and $-6.4 \mu\text{m}$ (95% CI, -30.6 to 17.7), $-18.3 \mu\text{m}$ (95% CI, -30.7 to -5.8), and $1.5 \mu\text{m}$ (95% CI, -24.0 to 26.9), respectively, for the right eyes (as observed). For patients with inactive uveitis, mean change in CST at week 78 from baseline for the Stratus OCT, Spectralis, and Cirrus HD-OCT was $-17.5 \mu\text{m}$ (95% CI, -30.8 to -4.1), $0 \mu\text{m}$ (95% CI, -12.4 to 12.4),

and $-6.3 \mu\text{m}$ (95% CI, -16.8 to 4.1), respectively, for the left eyes and $-35.9 \mu\text{m}$ (95% CI, -75.5 to -3.8), $-11.5 \mu\text{m}$ (95% CI, -21.5 to -1.5), and $-3.1 \mu\text{m}$ (95% CI, -10.4 to 4.2), respectively, for the right eyes (as observed).

The percentage of eyes with BCVA < 0.05 logMAR increased from week 0 (35%) to week 78 (49%) in patients with active uveitis at study entry but remained stable in eyes with inactive uveitis (63% and 64% at weeks 0 and 78, respectively; as observed; Fig 5A). Mean BCVA improved over time in patients with active uveitis at study entry (left eyes: week 0, 0.27 logMAR [$n = 242$], 95% CI, 0.23–0.31; week 78, 0.14 logMAR [$n = 175$], 95% CI, 0.10–0.18; right eyes: week 0, 0.27 logMAR [$n = 242$], 95% CI, 0.22–0.31; week 78, 0.14 logMAR [$n = 175$], 95% CI, 0.10–0.19; as observed), whereas mean BCVA remained stable over time in patients with inactive uveitis (left eyes: week 0, 0.06 logMAR [$n = 129$], 95% CI, 0.02–0.10; week 78, 0.04 logMAR [$n = 104$], 95% CI, 0–0.09; right eyes: week 0, 0.05 logMAR [$n = 129$], 95% CI, 0.01–0.08; week 78, 0.06 logMAR [$n = 104$], 95% CI, -0.01 to 0.13 ; as observed; Fig 5B). Overall, mean BCVA improved in the left eyes from 0.20 logMAR at week 0 ($n = 371$; 95% CI, 0.16–0.23) to 0.10 logMAR at week 78 ($n = 279$; 95% CI, 0.07–0.13) and in the right eyes from 0.19 logMAR at week 0 ($n = 371$; 95% CI, 0.16–0.22) to 0.11 logMAR at week 78 ($n = 279$; 95% CI, 0.07–0.15; Fig 5B).

Among patients with active uveitis at study entry, the observed mean \pm SD corticosteroid dose was 13.6 \pm 19.1 mg/day at week 0 ($n = 237$), 6.1 \pm 9.3 mg/day at week 12 ($n = 224$), and 2.6 \pm 5.2 mg/day at week 78 ($n = 173$; Fig 6), representing an overall mean dose reduction of -11.3 mg/day. The observed mean corticosteroid dose for patients who entered the study with inactive uveitis was low at baseline, with little change throughout the follow-up period (week 0, 1.5 \pm 7.2 mg/day [$n = 128$]; week 12, 0.9 \pm 4.1 mg/day [$n = 119$]; week 78, 1.2 \pm 5.0 mg/day [$n = 104$]; Fig 6). In the overall population, the observed mean \pm SD daily corticosteroid dose was 9.3 \pm 16.9 mg at study entry ($n = 365$). The observed mean \pm SD daily corticosteroid dose decreased by 75% to 2.1 \pm 5.1 mg at week 78 ($n = 277$; Fig 6). The change from baseline was -7.1 (95% CI, -9.2 to -5.1).

Of patients who received immunomodulators at baseline, 78% with active uveitis at study entry (36/46; 95% CI, 63.6–89.1; as observed) and 89% with inactive uveitis at study entry (32/36; 95% CI, 73.9–96.9; as observed) still received immunomodulators at week 78. However, at week 78 there was a 26% mean decrease in the dose of immunomodulators compared with week 8 of VISUAL III for patients with active uveitis at study entry ($n = 47$; 95% CI, -39.6 to -11.5) and a 15% mean decrease in dose compared with week 0 of VISUAL III for patients with inactive uveitis at study entry ($n = 37$; 95% CI, -26.1 to -4.7). Additionally, at week 78, 47% of patients with active uveitis at study entry achieved a $\geq 50\%$ reduction in immunosuppression load (corticosteroids and/or immunomodulators) compared with week 8 (52/110; 95% CI, 37.7–57.0; as observed), whereas 13% of patients with inactive uveitis at study entry achieved a $\geq 50\%$ reduction in immunosuppression load (corticosteroids and/or immunomodulators) compared with week 0 (5/39; 95% CI, 4.3–27.4; as observed).

Safety

For all patients enrolled in VISUAL III ($N = 424$), mean \pm SD exposure to adalimumab was 117 \pm 70 weeks, representing 953.7 PY of exposure. The overall exposure-adjusted rate of any AE was 424 events/100 PY. As summarized in Table 2, there were 82 AEs leading to study discontinuation (8.6 events/100 PY; Table S2, available at www.aaojournal.org), 157 serious AEs (16.5 events/100 PY), of which 36 (3.8 events/100 PY; Table S3, available at

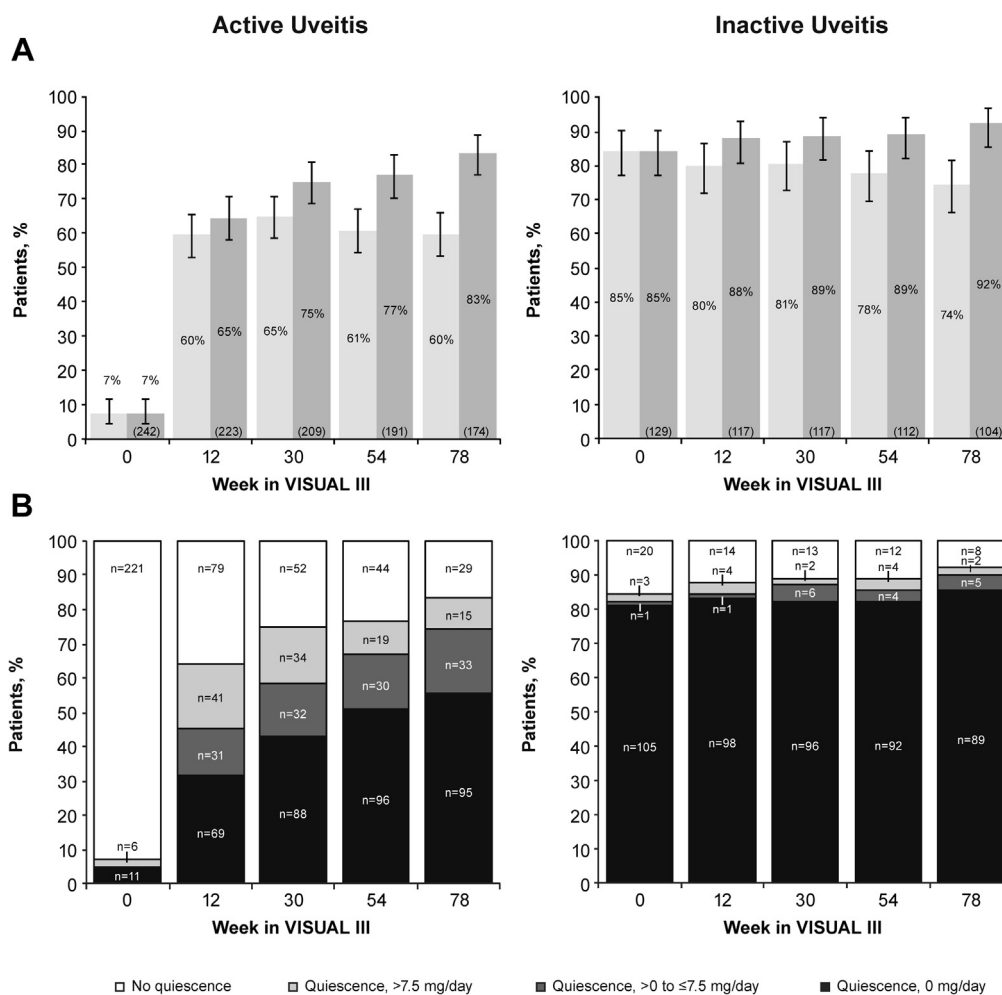


Figure 2. Percentage of patients achieving quiescence according to disease activity at baseline (A) and according to concomitant dose of steroids (B). Data are presented as percentage \pm exact 95% Clopper-Pearson confidence interval (A). *Light bars* indicate nonresponder imputation analysis (active, $n = 242$; inactive, $n = 129$); *dark bars* indicate observed-case data with the number of patients observed indicated within the base of the bar. Quiescence was defined as no active inflammatory lesions, anterior chamber cell grade $\leq 0.5+$, and vitreous haze grade $\leq 0.5+$ in both eyes. Doses of uveitis-related systemic corticosteroids were converted into prednisone equivalents.

www.aajournal.org) were judged by the investigators as at least possibly related to adalimumab, and 30 nonserious allergic reactions (3.2/100 PY). There was a low incidence of active tuberculosis (0.1 event/100 PY), opportunistic infections (0.5 events/100 PY), serious infections (4.0 events/100 PY), and malignancies (1.3 events/100 PY). Fifteen patients (1.6 events/100 PY) described asymptomatic latent tuberculosis based on the positive findings of annual tuberculosis testing. The event of active tuberculosis was considered not related to adalimumab by the investigator and probably related to adalimumab by the sponsor. Study drug was discontinued in this patient with active tuberculosis, and antituberculosis therapy was provided. Five patients (0.5 events/100 PY) experienced demyelinating disorders, including multiple sclerosis ($n = 1$), demyelination ($n = 2$; 1 case with magnetic resonance imaging [MRI] was suggestive of multiple sclerosis), and optic neuritis ($n = 2$; neither MRI showed central nervous system findings of demyelination). All 5 patients with demyelinating disorders were discontinued from the study. Two of these patients had intermediate uveitis, 2 had posterior uveitis, and 1 had panuveitis. The 1 patient with multiple sclerosis had intermediate

uveitis and was reported to have an abnormal baseline MRI. Four deaths (0.4 events/100 PY) were reported (1 event each of metastatic pancreatic carcinoma, brain abscess, B-cell lymphoma [without ocular involvement], and accidental death). All fatal events except brain abscess (possibly related) were considered by the investigator as not related or probably not related to study drug.

Discussion

Effective corticosteroid-sparing therapies are needed to maintain disease control in eyes with noninfectious intermediate, posterior, and panuveitis and, thereby, to reduce the risk of visual complications and corticosteroid-related side effects.

A substantial proportion of patients who entered VISUAL III with active uveitis (i.e., experienced TF in the parent studies) were in quiescence at week 78 compared with baseline (60% vs. 7%, respectively; NRI). By week 78, two thirds of these patients were in corticosteroid-free

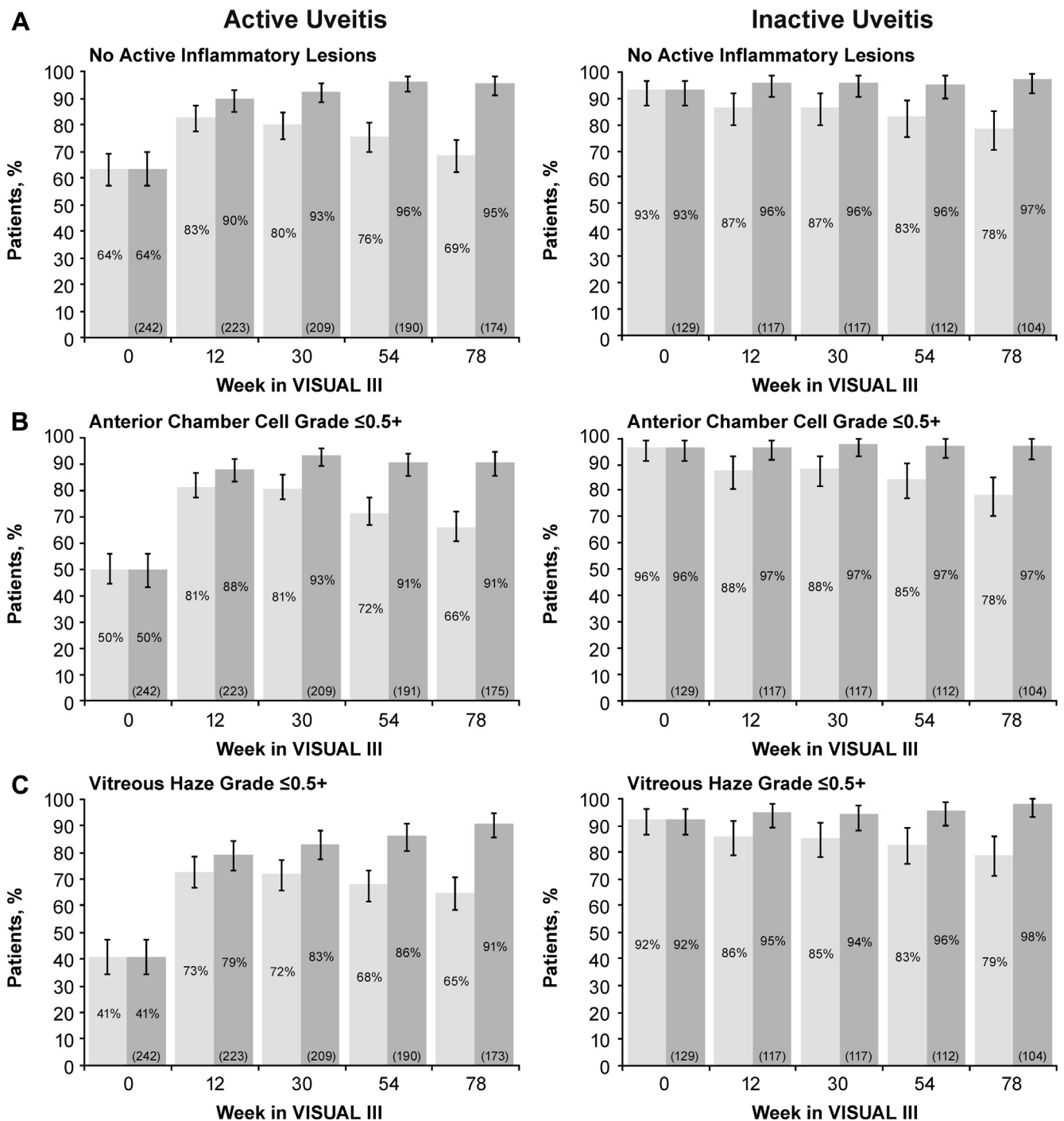


Figure 3. Percentage of patients with active or inactive uveitis at study entry who had no active inflammatory lesions (A), anterior chamber cell grade $\leq 0.5+$ (B), and vitreous haze grade $\leq 0.5+$ (C) in both eyes (intent-to-treat data set). Data are presented as percentage \pm exact 95% Clopper-Pearson confidence interval. *Light bars* indicate nonresponder imputation analysis (active uveitis, $n = 242$; inactive uveitis, $n = 129$); *dark bars* indicate observed-case data with the number of patients observed indicated within the base of the bar.

quiescence, and only 7% of patients in quiescence were receiving >7.5 mg/day corticosteroids. The majority of patients with inactive uveitis (i.e., did not experience TF in the parent studies) were quiescent at baseline (85%) and the rate of quiescence remained stable (78%) at week 78, on no

or low-dose systemic corticosteroids. It is important to emphasize that not all patients responded to adalimumab (40% of patients with active uveitis and 26% of patients with inactive uveitis were not in quiescence at week 78), although these results suggest that adalimumab therapy

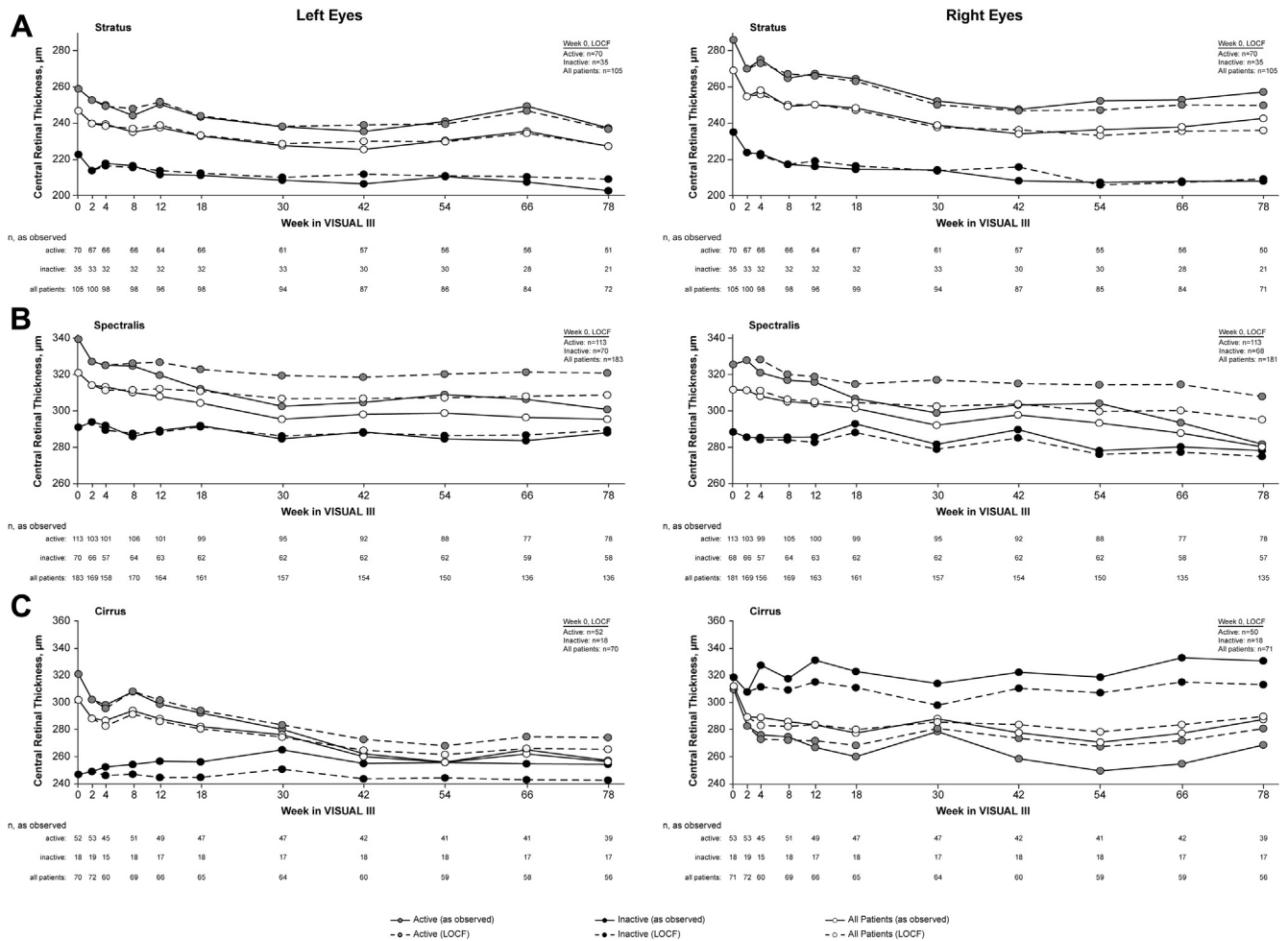


Figure 4. Mean central subfield thickness over time in left and right eyes as assessed by optical coherence tomography machine type (intent-to-treat data set): **A**, Stratus OCT; **B**, Spectralis; **C**, Cirrus HD-OCT. *Dashed line* indicates last-observation-carried-forward (LOCF) imputation analysis (patient numbers at week 0 are shown); *continuous line* indicates observed-case data (patient numbers are indicated below the x-axis). OCT = optical coherence tomography.

allows a substantial percentage of patients to achieve corticosteroid-sparing quiescence. These trends were also observed in the overall patient population.

Additionally, at least two thirds of patients with active or inactive uveitis who received adalimumab did not have active inflammatory lesions, had anterior chamber cell and vitreous haze grades $\leq 0.5+$ in both eyes, and had stable visual acuity during weeks 12 to 78 of follow-up. These results are consistent with both the VISUAL I and II trials, in which eyes treated with adalimumab had a significantly reduced risk of recurrence or worsening of BCVA in patients with uveitis.^{17,19}

Until recently, immunosuppressive medications were used routinely as steroid-sparing agents¹⁰ and were termed “conventional” despite being used off label for uveitis. The results of this study confirm and extend the findings of early open-label trials in which treatment with adalimumab enabled substantial tapering of immunosuppressive drugs while achieving disease control in eyes with corticosteroid-resistant uveitis.^{25,26}

In groups with and without previous exposure to adalimumab during the VISUAL I and II trials, the percentage of patients in quiescence at baseline was numerically greater in

patients who had received adalimumab vs. placebo (42% vs. 27%, respectively). The percentage of patients in quiescence increased from baseline to week 78 in both groups (adalimumab, 42% to 63%; placebo, 27% to 67%; NRI). Of those in quiescence at week 78, a slightly higher percentage of patients who had received placebo vs. those who had received adalimumab in the parent trials were steroid free (80% vs. 73%, respectively).

In the current open-label study, adalimumab controlled multiple signs of uveitic inflammation (i.e., inflammatory lesions, vitreous haze, anterior chamber cells, and central retinal thickening) for up to 78 weeks of follow-up in eyes with active or inactive uveitis at study entry while also permitting a substantial decrease in systemic corticosteroid use in patients who enrolled with active uveitis. At week 78, the as-observed analysis demonstrated that the majority of patients had anterior chamber cell grade $\leq 0.5+$ or vitreous haze grade $\leq 0.5+$ and no inflammatory lesions relative to baseline. These outcomes were likely reflected in the initial improvement and subsequent long-term stable visual acuity observed in VISUAL III. Additionally, CST decreased over time in patients with active uveitis. Because there are

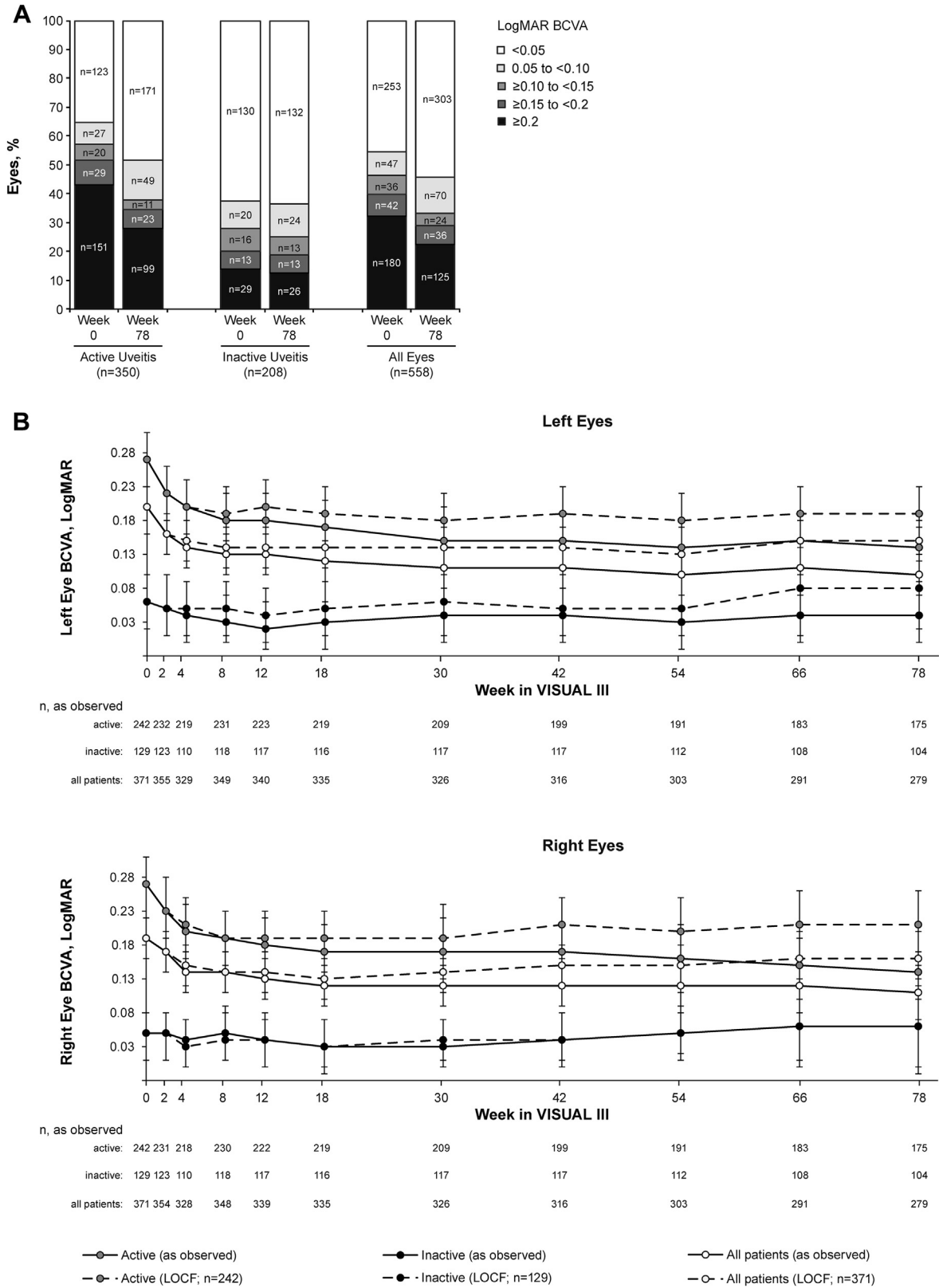


Figure 5. Percentage of eyes with categories of mean logMAR best-corrected visual acuity (BCVA), reported as observed for patients with values at weeks 0 and 78 (A), and BCVA over time, presented as mean \pm 95% confidence interval in left and right eyes (B; intent-to-treat set). Dashed line indicates last-observation-carried-forward (LOCF) imputation analysis (patient numbers at week 0 are shown); continuous line indicates observed-case data (patient numbers are indicated below the x-axis).

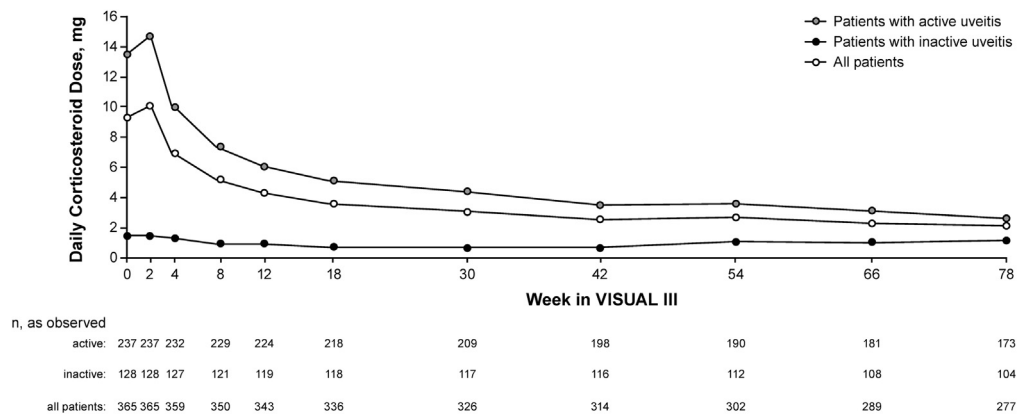


Figure 6. Mean daily dose of uveitis-related corticosteroids. Data represent the observed case analysis. Patient numbers are indicated below the x-axis.

differences in how the 3 OCT systems determine CST, we reported the data separately for each OCT system to control for differences in software algorithms.

Previous studies have demonstrated that treatment with adalimumab significantly prolongs time to TF (e.g., flare)

Table 2. Adverse Events (Safety Data Set)

| | Events (Events/100 PY) N = 424; PY = 953.7 |
|--|---|
| Any AE | 4043 (423.9) |
| AEs leading to death | 4 (0.4) |
| Accidental death | 1 (0.1) |
| B-cell lymphoma | 1 (0.1) |
| Brain abscess | 1 (0.1) |
| Metastatic pancreatic carcinoma | 1 (0.1) |
| AEs leading to discontinuation | 82 (8.6) |
| Serious AEs | 157 (16.5) |
| Infections | 787 (82.5) |
| Serious infections | 38 (4.0) |
| Opportunistic infections (excluding oral candidiasis and tuberculosis) | 5 (0.5) |
| Tuberculosis | 16 (1.7) |
| Active | 1 (0.1) |
| Latent | 15 (1.6) |
| Allergic reactions | 30 (3.2) |
| Malignancies | 12 (1.3) |
| Non-melanoma skin cancer | 6 (0.6) |
| Lymphoma | 1 (0.1) |
| Other* | 5 (0.5) |
| Sarcoidosis [†] | 4 (0.4) |
| Vasculitis [‡] | 8 (0.8) |
| Liver events including liver failure | 10 (1.1) |
| Demyelinating disorders | 5 (0.5) |

AE = adverse event; PY = patient-years.

*Adenocarcinoma of colon, colorectal cancer, lobular breast carcinoma in situ, pancreatic carcinoma, and rectal adenocarcinoma.

[†]Four events of sarcoidosis were reported by 4 patients, all of whom had sarcoid uveitis at baseline.

[‡]Eight events of vasculitis were reported by 5 patients; 2 patients reported 5 events of Behçet syndrome (1 patient had 1 serious AE leading to premature discontinuation, and 1 patient reported 4 episodes of Behçet syndrome); 3 patients described retinal vasculitis.

after corticosteroid discontinuation.^{17,19} However, in clinical practice, patients may receive systemic or topical corticosteroid support as needed for uveitis control; as such, corticosteroids were permitted as needed in the current trial. Patients who enrolled with active uveitis were receiving a mean corticosteroid dose of nearly 14 mg/day despite recommendations that prolonged use of doses >10 mg/day be avoided because of well-characterized systemic side effects, risk of cataract, and increased intraocular pressure.^{10,18,27} Adalimumab treatment decreased the mean dose of systemic corticosteroids in these patients by more than 80%, to <3 mg/day, which is below the commonly accepted clinical threshold of 5 mg of daily prednisone-equivalent dose.^{9,10,21} Furthermore, by week 78, only 5% of patients in the overall study population had discontinued the trial because of a lack of efficacy.

Treatment with adalimumab was well tolerated in this study. There was a low incidence of AEs of special interest, and no new safety signals were detected beyond those previously reported with biologic therapies targeting TNF- α .^{28,29} and those reported in the VISUAL I and II trials.^{8,17} The incidence of demyelinating disorders reported in the VISUAL III study (0.5/100 PY) was higher than that observed in clinical trials for other adalimumab indications ($\leq 0.1/100$ PY). However, the observed rate is comparable to the background rate reported in patients with uveitis who were not exposed to adalimumab (Guo D, et al, manuscript in progress).³⁰ Furthermore, there is a known association between anterior and intermediate uveitis and demyelinating disorders^{31–33}; for example, an estimated 7% to 10% of patients with intermediate uveitis also have multiple sclerosis.^{34,35} There were no significant changes from baseline for laboratory tests or vital signs (data not shown).

This study had limitations; because the VISUAL III study was meant to reflect real-life clinical practice, the use of concomitant immunosuppressants and corticosteroids was allowed. We hypothesized that adalimumab accounted for the favorable inflammation control observed during the VISUAL III trial, which occurred in the context of corticosteroid tapering, as described previously. However, in the absence of a control group and in the context of use of other immunosuppressive agents, drug efficacy cannot be

determined in comparison with eyes that were not treated with adalimumab. In addition, there was loss of patient data over time owing to premature discontinuation. Thus, our results using the conservative NRI method may underestimate the efficacy of adalimumab observed in a real-world setting. The true efficacy of adalimumab in patients with uveitis may lie somewhere between the as-observed analysis and the analysis imputing nonresponse for patients who discontinued. Additionally, in patients who entered the study with inactive uveitis, 15% were not in quiescence at baseline (i.e., did not meet the criteria of no active inflammatory lesions, anterior chamber cell grade $\leq 0.5+$, and vitreous haze grade $\leq 0.5+$ in both eyes); future analyses will need to address this patient subgroup. Additional studies are needed to further clarify the long-term efficacy of adalimumab, including analyses that stratify patients by response to adalimumab and permit other therapies for the nonresponder subgroups. Other caveats include inherent variations among the 3 OCT systems and possible bias in the LOCF analysis of OCT data; the last available CST values were assumed to remain constant in missing patients.

This study had several strengths. The patient population was large, considering that noninfectious uveitis is an uncommon disease, estimated to affect fewer than 0.4% of people worldwide.^{5,6} Notably, all patients had the opportunity to complete 78 weeks of follow-up by the interim cutoff date, October 31, 2016. Further, by allowing the use of concomitant treatments as needed (corticosteroids and systemic immunomodulators), this study reflected a clinically relevant, real-world approach to uveitis management.

In conclusion, in patients with noninfectious intermediate, posterior, or panuveitis who received adalimumab (40 mg every other week), disease was controlled with minimal corticosteroid support. About two thirds of patients who entered VISUAL III with active uveitis achieved quiescence by week 78 with a substantially reduced uveitis-related corticosteroid dose; additionally, mean BCVA was improved over time in patients with active uveitis. About three quarters of patients who entered VISUAL III with inactive uveitis had maintained quiescence at week 78, with 93% of these patients achieving corticosteroid-free quiescence; most patients had stable BCVA throughout follow-up. Most patients had no active inflammatory lesions and had anterior chamber cell and vitreous haze grades $\leq 0.5+$ through 78 weeks of open-label adalimumab treatment, regardless of active or inactive disease at VISUAL III entry. The safety profile was consistent with the known safety profile of adalimumab and the underlying disease. These data suggest that adalimumab can be used for intermediate, posterior, and panuveitis as an important therapeutic option allowing patients to achieve and maintain long-term disease control with or without adjunctive corticosteroids or immunomodulators. Longer-term follow-up in VISUAL III is ongoing.

References

- Rothova A, Buitenhuis HJ, Meenken C, et al. Uveitis and systemic disease. *Br J Ophthalmol*. 1992;76:137–141.
- Barisani-Asenbauer T, Maca SM, Mejdoubi L, et al. Uveitis - a rare disease often associated with systemic diseases and infections - a systematic review of 2619 patients. *Orphanet J Rare Dis*. 2012;7:57.
- Engelhard SB, Patel V, Reddy AK. Intermediate uveitis, posterior uveitis, and panuveitis in the Mid-Atlantic USA. *Clin Ophthalmol*. 2015;9:1549–1555.
- Thorne JE, Suhler E, Skup M, et al. Prevalence of noninfectious uveitis in the United States: a claims-based analysis. *JAMA Ophthalmol*. 2016;134:1237–1245.
- Gritz DC, Wong IG. Incidence and prevalence of uveitis in Northern California; the Northern California Epidemiology of Uveitis Study. *Ophthalmology*. 2004;111:491–500.
- Wakefield D, Chang JH. Epidemiology of uveitis. *Int Ophthalmol Clin*. 2005;45:1–13.
- Dick AD, Tundia N, Sorg R, et al. Risk of ocular complications in patients with noninfectious intermediate uveitis, posterior uveitis, or panuveitis. *Ophthalmology*. 2016;123:655–662.
- Nguyen QD, Callanan D, Dugel P, et al. Treating chronic noninfectious posterior segment uveitis: the impact of cumulative damage: proceedings of an expert panel roundtable discussion. *Retina*. 2006;26:1–16.
- Hale S, Lightman S. Anti-TNF therapies in the management of acute and chronic uveitis. *Cytokine*. 2006;33:231–237.
- Jabs DA, Rosenbaum JT, Foster CS, et al. Guidelines for the use of immunosuppressive drugs in patients with ocular inflammatory disorders: recommendations of an expert panel. *Am J Ophthalmol*. 2000;130:492–513.
- Niederer RL, Sharief L, Bar A, et al. Predictors of long-term visual outcome in intermediate uveitis. *Ophthalmology*. 2017;124:393–398.
- Taylor SR. Biologic therapy in uveitis. *Eur Ophthalmic Rev*. 2016;10:17–18.
- Ooi KG, Galatowicz G, Calder VL, Lightman SL. Cytokines and chemokines in uveitis: is there a correlation with clinical phenotype? *Clin Med Res*. 2006;4:294–309.
- Dick AD, Forrester JV, Liversidge J, Cope AP. The role of tumour necrosis factor (TNF-alpha) in experimental autoimmune uveoretinitis (EAU). *Prog Retin Eye Res*. 2004;23:617–637.
- Tracey D, Klareskog L, Sasso EH, et al. Tumor necrosis factor antagonist mechanisms of action: a comprehensive review. *Pharmacol Ther*. 2008;117:244–279.
- Humira® (adalimumab). Full Prescribing Information. North Chicago, IL: AbbVie Inc; 2016.
- Jaffe GJ, Dick AD, Brezin AP, et al. Adalimumab in patients with active noninfectious uveitis. *N Engl J Med*. 2016;375:932–943.
- Foster CS, Kothari S, Anesi SD, et al. The Ocular Immunology and Uveitis Foundation preferred practice patterns of uveitis management. *Surv Ophthalmol*. 2016;61:1–17.
- Nguyen QD, Merrill PT, Jaffe GJ, et al. Adalimumab for prevention of uveitic flare in patients with inactive noninfectious uveitis controlled by corticosteroids (VISUAL II): a multicentre, double-masked, randomised, placebo-controlled phase 3 trial. *Lancet*. 2016;388:1183–1192.
- Landewe R, van der Horst-Bruinsma I, Tari S, et al. THU0583 quiescence in active and inactive non-infectious, intermediate, posterior, or panuveitis in patients treated with adalimumab: Visual I and Visual II trials. *Ann Rheum Dis*. 2016;75:403.
- Jabs DA, Nussenblatt RB, Rosenbaum JT, Standardization of Uveitis Nomenclature Working Group. Standardization of uveitis nomenclature for reporting clinical data. Results of the First International Workshop. *Am J Ophthalmol*. 2005;140:509–516.

22. Nussenblatt RB, Palestine AG, Chan CC, Roberge F. Standardization of vitreal inflammatory activity in intermediate and posterior uveitis. *Ophthalmology*. 1985;92:467–471.
23. Warner CV, Syc SB, Stankiewicz AM, et al. The impact of utilizing different optical coherence tomography devices for clinical purposes and in multiple sclerosis trials. *PLoS One*. 2011;6:e22947.
24. Diabetic Retinopathy Clinical Research Network Writing Committee, Bressler SB, Edwards AR, et al. Reproducibility of spectral-domain optical coherence tomography retinal thickness measurements and conversion to equivalent time-domain metrics in diabetic macular edema. *JAMA Ophthalmol*. 2014;132:1113–1122.
25. Diaz-Llopis M, Salom D, Garcia-de-Vicuna C, et al. Treatment of refractory uveitis with adalimumab: a prospective multicenter study of 131 patients. *Ophthalmology*. 2012;119:1575–1581.
26. Suhler EB, Lowder CY, Goldstein DA, et al. Adalimumab therapy for refractory uveitis: results of a multicentre, open-label, prospective trial. *Br J Ophthalmol*. 2013;97:481–486.
27. Becker MD, Smith JR, Max R, Fiehn C. Management of sight-threatening uveitis: new therapeutic options. *Drugs*. 2005;65:497–519.
28. Desai RJ, Thaler KJ, Mahlknecht P, et al. Comparative risk of harm associated with the use of targeted immunomodulators: a systematic review. *Arthritis Care Res (Hoboken)*. 2016;68:1078–1088.
29. Lis K, Kuzawinska O, Balkowiec-Iskra E. Tumor necrosis factor inhibitors - state of knowledge. *Arch Med Sci*. 2014;10:1175–1185.
30. Guo D, Liu J, Gao R, et al. Prevalence and incidence of optic neuritis in patients with different types of uveitis. *Ophthalmic Epidemiol*. 2018;25(1):39–44.
31. Le Scuff J, Seve P, Renoux C, et al. Uveitis associated with multiple sclerosis. *Mult Scler*. 2008;14:415–417.
32. Messenger W, Hildebrandt L, Mackensen F, et al. Characterisation of uveitis in association with multiple sclerosis. *Br J Ophthalmol*. 2015;99:205–209.
33. Zein G, Berta A, Foster CS. Multiple sclerosis-associated uveitis. *Ocul Immunol Inflamm*. 2004;12:137–142.
34. Boskovich SA, Lowder CY, Meisler DM, Gutman FA. Systemic diseases associated with intermediate uveitis. *Cleve Clin J Med*. 1993;60:460–465.
35. Jakob E, Reuland MS, Mackensen F, et al. Uveitis subtypes in a German interdisciplinary uveitis center—analysis of 1916 patients. *J Rheumatol*. 2009;36:127–136.

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Abbreviations and Acronyms:

AE = adverse event; **BCVA** = best-corrected visual acuity; **CI** = confidence interval; **CST** = central subfield thickness; **ETDRS** = Early Treatment Diabetic Retinopathy Study; **ITT** = intent to treat; **LOCF** = last observation carried forward; **MRI** = magnetic resonance imaging; **NRI** = nonresponder imputation; **OCT** = optical coherence tomography; **PY** = patient-years; **TF** = treatment failure; **TNF- α** = tumor necrosis factor- α .

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