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AMERICAN ACADEMY OF OPHTHALMOLOGY®

Long-Term Safety and Efficacy of Adalimumab in Patients with Noninfectious Intermediate Uveitis, Posterior Uveitis, or Panuveitis

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Purpose: To evaluate long-term efficacy and safety of extended treatment with adalimumab in patients with noninfectious intermediate, posterior, or panuveitis.

Design: Open-label, multicenter, phase 3 extension study (VISUAL III).

Participants: Adults who had completed a randomized, placebo-controlled phase 3 parent trial (VISUAL I or II) without treatment failure (inactive uveitis) or who discontinued the study after meeting treatment failure criteria (active uveitis).

Methods: Patients received subcutaneous adalimumab 40 mg every other week. Data were collected for $\leq$ 362 weeks. Adverse events (AEs) were recorded until 70 days after the last dose.

Main Outcome Measures: Long-term safety and quiescence; other efficacy variables included inflammatory lesions, anterior chamber cell and vitreous haze grade, macular edema, visual acuity, and dose of uveitis-related systemic corticosteroids.

Results: At study entry, 67% of patients (283/424) showed active uveitis and 33% (141/424) showed inactive uveitis; 60 patients subsequently met exclusion criteria, and 364 were included in the intention-to-treat analysis. Efficacy variables were analyzed through week 150, when approximately 50% of patients (214/424) remained in the study. Patients showing quiescence increased from 34% (122/364) at week 0 to 85% (153/180) at week 150. Corticosteroid-free quiescence was achieved by 54% (66/123) and 89% (51/57) of patients with active or inactive uveitis at study entry. Mean daily dose of systemic corticosteroids was reduced from 9.4 $\pm$ 17.1 mg/day at week 0 (n = 359) to 1.5 $\pm$ 3.9 mg/day at week 150 (n = 181). The percentage of patients who achieved other efficacy variables increased over time for those with active uveitis at study entry and was maintained for those with inactive uveitis. The most frequently reported treatment-emergent AEs of special interest were infections (n = 275; 79 events/100 patient-years [PY]); AEs and serious AEs occurred at a rate of 396 events/100 PY and 15 events/100 PY, respectively.

Conclusions: Long-term treatment with adalimumab led to quiescence and reduced corticosteroid use for patients who entered VISUAL III with active uveitis and led to maintenance of quiescence for those with inactive uveitis. AEs were comparable with those reported in the parent trials and consistent with the known safety profile of adalimumab. *Ophthalmology 2020;■:1–11 © 2020 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/).*

Supplemental material available at www.aaojournal.org.

Noninfectious uveitis is one of the most common causes of vision loss or blindness in many population-based studies.[1] Recurrent inflammation in patients with uveitis leads to potentially sight-threatening ocular complications; however, long-term corticosteroid use for treatment of inflammation can also cause potentially serious systemic and ocular toxicity.[2–5] Biologic therapies, such as tumor necrosis factor-α antagonists that target immune-mediated

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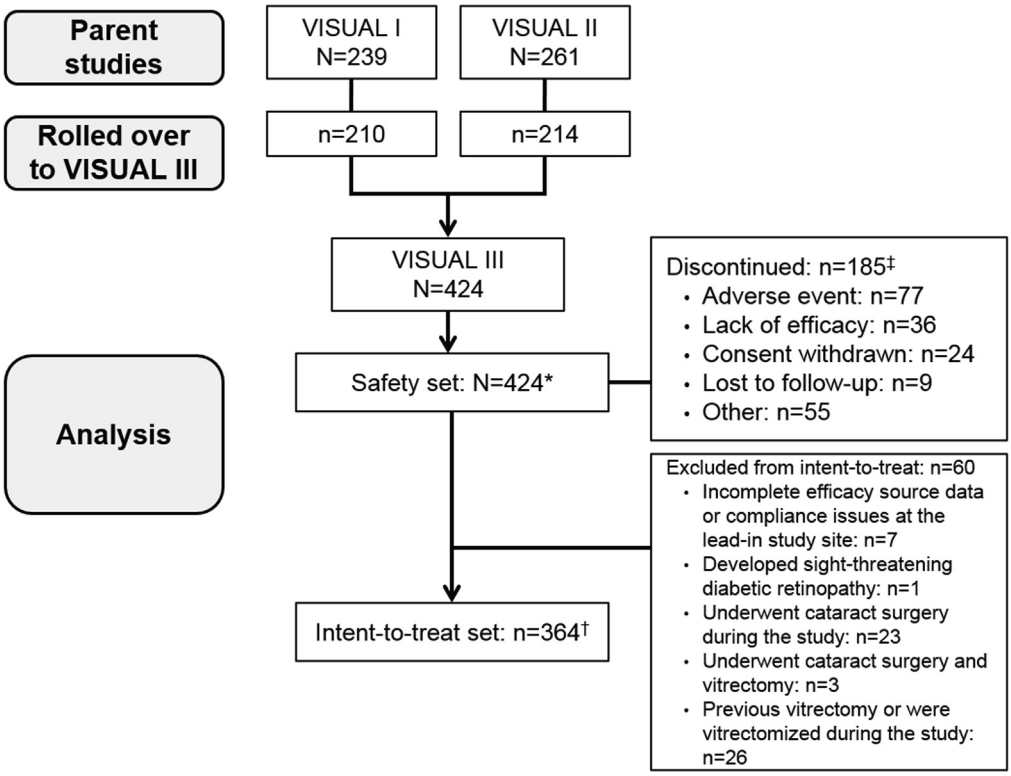

Figure 1. Flowchart showing study design. Patients who discontinued study drug prematurely were counted under each reason given for discontinuation; therefore, the sum of the counts given for the reasons may be greater than the overall number of discontinuations. Reasons for discontinuation from the study recorded as "other" included any reason for discontinuation, excluding adverse event, lack of efficacy, withdrawal of consent, and loss to follow-up. *Safety outcomes through last drug date plus 70 days of follow-up were assessed in the safety set. †Efficacy outcomes were assessed in the intention-to-treat set. ‡Discontinuations were cumulative through the last study visit.

pathways, may provide effective steroid-sparing treatment of uveitis.[6,7]

Adalimumab (Humira; AbbVie, Inc) is a human monoclonal antibody to tumor necrosis factor-α that is approved to treat noninfectious uveitis.[8] The VISUAL I and II studies were phase 3 randomized clinical trials of adalimumab efficacy and safety to treat active or inactive uveitis, respectively.[9,10] In these studies, treatment with adalimumab was associated with lower risk of uveitis recurrence or visual acuity loss compared with placebo during and after corticosteroid taper.[9,10] Adverse events (AEs) reported in the VISUAL studies were consistent with the safety profile established across the approved indications of adalimumab, with the exception of events associated with the underlying condition of noninfectious uveitis, such as demyelination and sarcoidosis.

The VISUAL III study was an open-label extension study of the VISUAL I and II studies that evaluated long-term efficacy and safety of extended treatment with adalimumab in patients with noninfectious intermediate uveitis, posterior uveitis, or panuveitis. Interim results from the VISUAL III study reported efficacy and safety through 78 weeks of adalimumab treatment.[11] This article reports final efficacy results through 150 weeks and safety results up to 362 weeks of treatment under conditions similar to real-world clinical practice.

Methods

Study Design

This open-label, multicenter, phase 3 extension study (VISUAL III; clinicaltrials.gov identifier, NCT01148225; and clinicaltrialsregister.eu identifier, 2009-016196-29) was conducted at 85 study sites in 21 countries in Europe, North and South America, Australia, and Japan. Study visits occurred at weeks 0, 2, 4, 8, 12, and 18 and every 12 weeks thereafter until the final visit. The study was conducted in accordance with the International Council for Harmonisation of Technical Requirements for Pharmaceuticals for Human Use guidelines and complied with the ethical principles of the Declaration of Helsinki. Protocol approval was obtained from appropriate review boards before study initiation (Table S1, available at www.aaojournal.org), and all patients gave informed consent before study enrollment.

Patients

Full inclusion and exclusion criteria were published previously.[11] Briefly, eligible adults with noninfectious intermediate uveitis, posterior uveitis, or panuveitis could enroll in the VISUAL III study if they had successfully completed the VISUAL I or II studies without treatment failure (inactive uveitis) or discontinued the parent study having met treatment failure criteria (active uveitis). Patients with active uveitis status determined at the final visit of the parent study could have been in quiescence at VISUAL III study

Table 1. Patient Demographics and Baseline Disease Characteristics (Intention-to-Treat Set)

	Active Uveitis (n = 240)	Inactive Uveitis (n = 124)	Total (N = 364)
Age, yrs			
Mean ± SD	42.3 ± 14.3	42.3 ± 13.1	42.3 ± 13.9
Range	19.0–80.0	19.0–81.0	19.0–81.0
Gender, no. (%)			
Female	134 (56)	76 (61)	210 (58)
Male	106 (44)	48 (39)	154 (42)
Race, no. (%)			
White	170 (71)	100 (81)	270 (74)
Asian	37 (15)	8 (6.5)	45 (12)
Black	17 (7.1)	7 (5.6)	24 (6.6)
American Indian or Alaska Native	2 (0.8)	0	2 (0.5)
Multiracial	3 (1.3)	0	3 (0.8)
Other	11 (4.6)	9 (7.3)	20 (5.5)
Type of uveitis, no. (%)			
Panuveitis	133 (55)	54 (44)	187 (51)
Posterior	50 (21)	51 (41)	101 (28)
Intermediate	55 (23)	18 (15)	73 (20)
Intermediate/posterior	2 (0.8)	1 (0.8)	3 (0.8)
Diagnosis, no. (%)			
Idiopathic disease	90 (38)	29 (23)	119 (33)
Vogt-Koyanagi-Harada disease	48 (20)	23 (19)	71 (20)
Sarcoidosis	34 (14)	17 (14)	51 (14)
Birdshot chorioretinopathy	23 (10)	26 (21)	49 (13)
Behçet disease	11 (4.6)	16 (13)	27 (7.4)
Multifocal choroiditis and panuveitis	11 (4.6)	3 (2.4)	14 (3.8)
Other	23 (10)	10 (8.1)	33 (9.1)
Duration of uveitis, mos			
Mean ± SD	62.4 ± 73.3	62.0 ± 52.6	62.3 ± 66.9
Range	2.8–558.4	4.5–260.3	2.8–558.4
Immunomodulator use at baseline, no. (%)	66 (28)	50 (40)	116 (32)
Azathioprine	8 (3.3)	8 (6.5)	16 (4.4)
Cyclosporine	11 (4.6)	12 (9.7)	23 (6.3)
Methotrexate	23 (9.6)	17 (14)	40 (11)
Mycophenolate mofetil (or equivalent)	23 (9.6)	13 (10)	36 (9.9)
Uveitis-related corticosteroid use at baseline, no. (%)	141 (59)	9 (7.3)	150 (41)
Oral	116 (48)	7 (5.6)	123 (34)
Topical	59 (25)	3 (2.4)	62 (17)
Other	7 (2.9)	0	7 (1.9)

SD = standard deviation.

entry because the week 0 visit in the VISUAL III study could have occurred up to 28 days later, during which time the patient's disease status may have changed.

Treatment

All patients received subcutaneous adalimumab 40 mg every other week. Patients with active disease at study entry could receive concomitant corticosteroid therapy, immunosuppressive therapy, or both as permitted in the parent study, and all patients were permitted to continue, taper, or discontinue concomitant corticosteroid therapy, immunosuppressive therapy, or both at investigator discretion. Patients were allowed 2 or fewer periocular corticosteroid injections per eye per year.

Outcome Measures

The main outcome measure was quiescence, defined as no new active inflammatory chorioretinal vascular lesions, inflammatory retinal vascular lesions, or both and anterior chamber cell grade and vitreous haze grade of 0.5+ or less in both eyes relative to baseline. Efficacy variables were measured as described previously[11] and included inflammatory chorioretinal vascular lesions, inflammatory retinal vascular lesions, or both; anterior chamber cell grade of 0.5+ or less; vitreous haze grade of 0.5+ or less; evidence of macular edema assessed by changes in central retinal thickness; proportion of patients without worsening of best-corrected visual acuity by 15 letters or more on the Early Treatment Diabetic Retinopathy Study chart; and dose of uveitis-related systemic corticosteroids and immunomodulators.

Safety Evaluations

All enrolled patients who received 1 dose or more of adalimumab were included in the safety analysis. Safety was monitored through collection of AEs that were coded using Medical Dictionary for Regulatory Activities version 19.0. Treatment-emergent AEs (TEAEs) were defined as events with an onset or worsening date on or after first study drug administration and until 70 days after last study drug administration. Adverse events were rated by severity and relationship to study drug. The AE described by the

Medical Dictionary for Regulatory Activities preferred term of *uveitis* corresponded to worsening of a patient's underlying uveitis.

Statistical Analyses

Efficacy data were analyzed through week 150; the sample size of available data after week 150 was too small for meaningful analysis. Efficacy analyses were performed with the intention-to-treat data set and stratified by patients who entered the study with active versus inactive uveitis. Changes were calculated relative to week 0 or week 8 for patients who entered the study with inactive or active uveitis, respectively. Efficacy was analyzed descriptively as observed to reflect real-world practice conditions. Adverse events were reported as number of events and as events per 100 patient-years (PY). A separate analysis was performed for AEs of special interest. Uveitis-related events were also analyzed separately and adjudicated by the sponsor (AbbVie) based on a list of preferred terms to be either related or not related to uveitis.

Results

Patients

A total of 424 patients were enrolled and received 1 dose or more of study drug; the intention-to-treat set included 364 patients (Fig 1). At study entry, 67% of patients (283/424) showed active uveitis, and 33% (141/424) showed inactive uveitis. Demographics are reported in Table 1. During the study, 37 patients (10%; active uveitis, 31/240; inactive uveitis, 6/124) started immunomodulators and 74 (20%; active uveitis, 56/240; inactive uveitis, 18/124) started systemic corticosteroids. Six patients received periocular corticosteroid injections.

Outcomes

Quiescence. Consistent with results from the interim analysis,[11] quiescence was maintained beyond week 78 in both active and inactive groups; 80% of patients in the active group (98/123) and 96% in the inactive group (55/57) showed quiescence at week 150 (Fig 2). At week 150, 54% (66/123) of patients with active uveitis at study entry and 89% (51/57) of patients with inactive uveitis achieved corticosteroid-free quiescence (including both systemic and non-systemic corticosteroids). For patients with active uveitis at study entry who were in quiescence at week 150 and receiving systemic corticosteroids, most were receiving 7.5 mg/day or less (Fig 3A); only 3 of the 55 patients who showed quiescence in the inactive group were receiving systemic corticosteroids (Fig 3B). Of patients receiving corticosteroids (systemic/non-systemic) to control active uveitis at study entry (n = 141), 68 remained in the study at week 150; 44% of those (30/68) showed corticosteroid-free quiescence at week 150. Of the 9 patients with inactive uveitis receiving corticosteroids at study entry, the 2 patients remaining in the study at week 150 showed corticosteroid-free quiescence. Of patients with active uveitis at study entry, 68% (157/232) experienced 1 or more episodes of uveitis recurrence between week 8 and the final visit, and 9% (21/232) discontinued from the study because of recurrence. Of patients with inactive uveitis at study entry, 39% (48/124) experienced 1 or more episode of uveitis recurrence between week 0 and final visit, and 0.8% (1/124) discontinued because of recurrence.

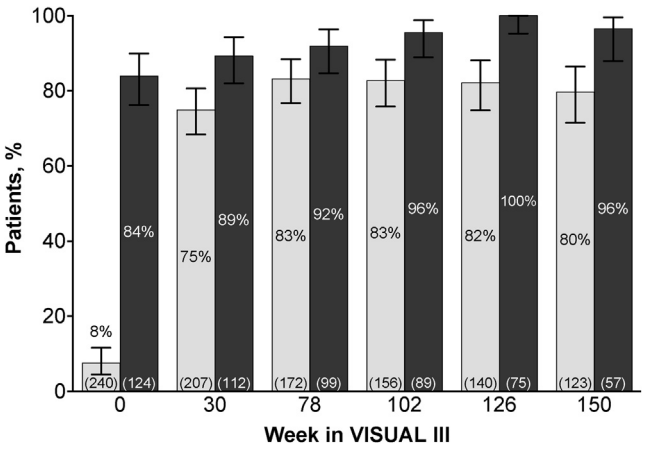

Figure 2. Bar graph showing the percentage of patients achieving quiescence stratified by disease activity at baseline. Data are presented as percentage ± exact 95% Clopper-Pearson confidence interval. The number of observed patients is indicated within the base of the bar. Gray bars = active uveitis; black bars = inactive uveitis.

Other Efficacy Variables. Overall, the trends observed for quiescence (i.e., improvement in patients with active uveitis at study entry and maintenance in those with inactive uveitis) were similar for other efficacy variables, including the proportion of patients with no active inflammatory lesions (Fig 4A), anterior chamber cell grade 0.5+ or less (Fig 4B), vitreous haze grade 0.5+ or less (Fig 4C), central retinal thickness (Fig S1, available at www.aaojournal.org), and visual acuity. Mean binocular best-corrected visual acuity at baseline versus week 150 was 0.27 logarithm of the minimum angle of resolution (logMAR) versus 0.14 logMAR, respectively, in patients with active uveitis at study entry and 0.05 logMAR versus 0.02 logMAR, respectively, in patients with inactive uveitis at study entry (Fig S2, available at www.aaojournal.org).

Corticosteroid and Immunomodulator Use. The mean daily dose of systemic corticosteroids was reduced from 9.4 ± 17.1 mg/day at week 0 (n = 359) to 1.5 ± 3.9 mg/day at week 150 (n = 181) for all patients (Fig 5). Of patients who received immunomodulators at baseline, 64% (23/36) and 85% (17/20) of patients with active and inactive uveitis at study entry, respectively, still received immunomodulators at week 150. However, at week 150, mean changes from baseline of −36% and −29% were observed in the dose of immunomodulators in patients with active and inactive uveitis at study entry, respectively.

Safety

Adverse Events. For all patients enrolled in the VISUAL III study (n = 424), the mean total number of doses of adalimumab received was 69.2 (minimum−maximum, 1−180 doses), and the mean exposure to adalimumab was 140.4 weeks (minimum−maximum, 2−362 weeks), corresponding to a total exposure of 1141.9 PY. Overall, 398 patients (94%; 396 events/100 PY) experienced 1 or more TEAEs

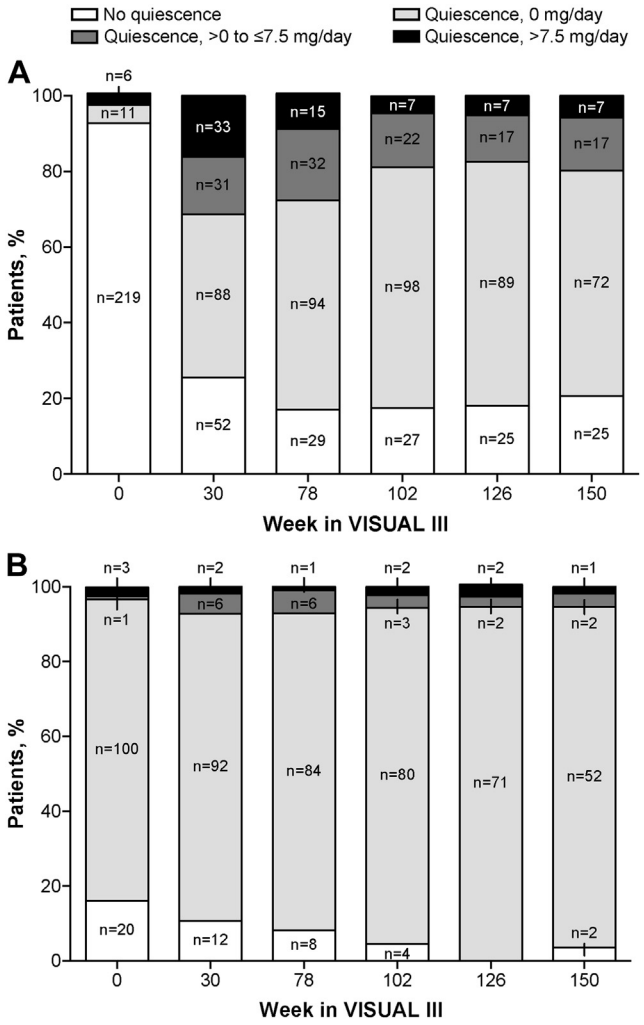

Figure 3. Bar graphs showing the percentage of patients achieving quiescence according to concomitant dose of systemic corticosteroids for patients who entered the study with (**A**) active uveitis and (**B**) inactive uveitis. Data are presented as observed. Doses of uveitis-related systemic corticosteroids were converted into prednisone equivalents; 4 patients in the active uveitis group received systemic corticosteroids that could not be transferred into prednisone equivalents and were excluded from analysis.

(Tables 2 and 3). Of these patients, 226 (53%; 80 events/100 PY) experienced 1 or more TEAEs that were considered by the investigator to be possibly or probably related to the study drug (Table 3). Most TEAEs (78%) were mild or moderate in severity. Four patients reported a severe TEAE of blindness (the Medical Dictionary for Regulatory Activities preferred term for loss of visual acuity): 1 patient with corneal edema in the right eye experienced a 30-letter vision loss and received a cornea transplant; 1 patient with pupillary membrane fibrosis experienced vision loss of 30 letters or more; 1 patient experienced uveitis recurrence with 12- and 21-letter vision loss from best in the right and left eyes, respectively, and received 80 mg prednisone; and 1 patient experienced angle-closure glaucoma with vision loss of 48 letters from

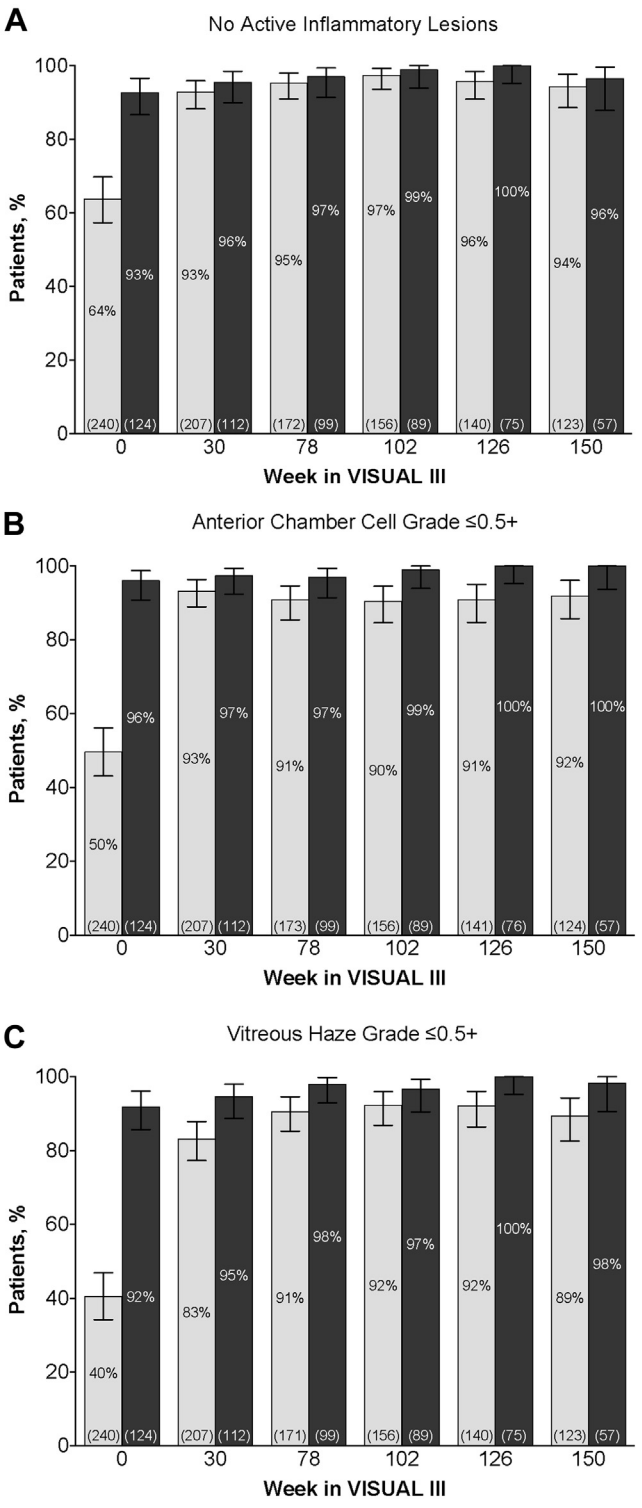

Figure 4. Bar graphs showing the percentage of patients with (**A**) no active inflammatory lesions, (**B**) anterior chamber cell grade of 0.5+ or less, and (**C**) vitreous haze grade of 0.5+ or less in both eyes, stratified by disease activity at baseline. Data are presented as percentage ± exact 95% Clopper-Pearson confidence interval. The number of observed patients is indicated within the base of the bar. Gray bars = active uveitis; black bars = inactive uveitis.

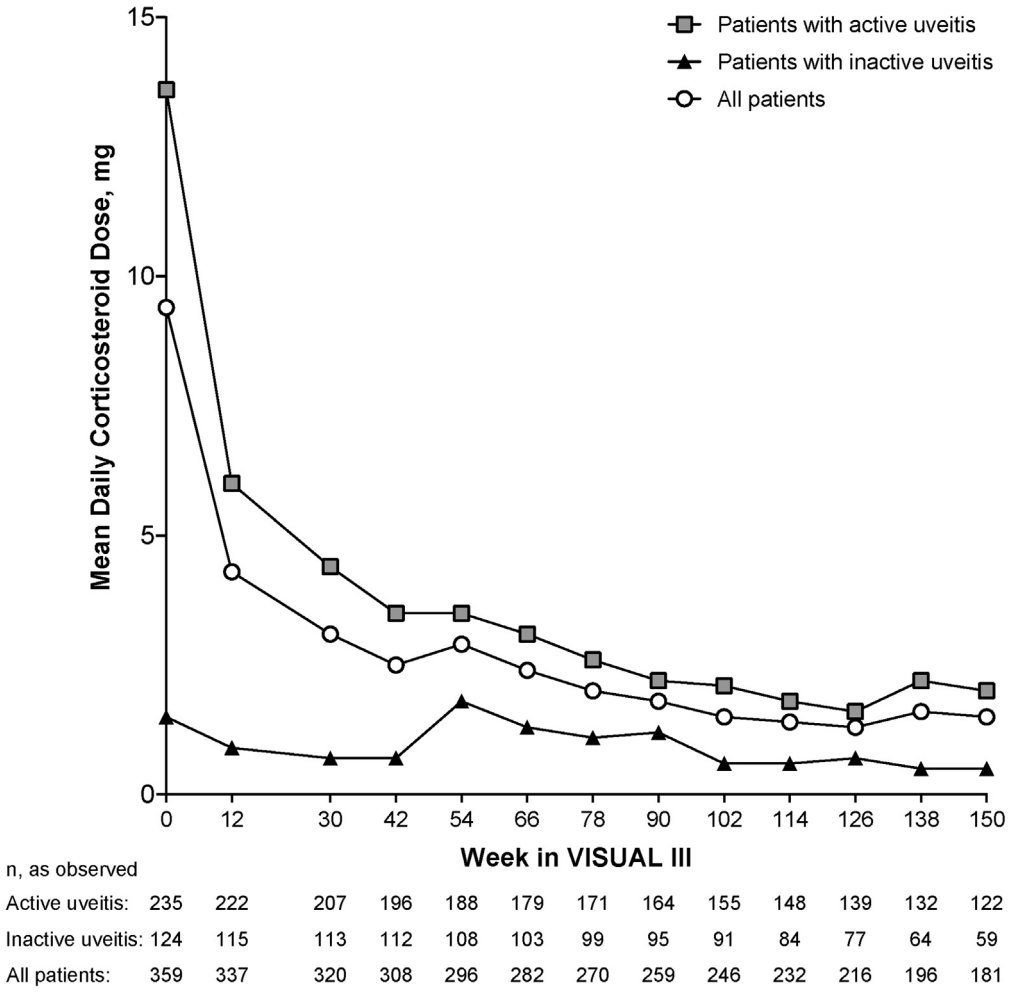

Figure 5. Line graph showing the mean daily dose of uveitis-related systemic corticosteroids.

Table 2. Summary of Adverse Events

Category	Adalimumab	
	No. (%), n = 424	*Events (Events/100 Patient-Years), 1142 Patient-Years*
TEAE	398 (94)	4516 (396)
TEAE at least possibly adalimumab related*	226 (53)	916 (80)
Severe TEAE†	85 (20)	158 (14)
SAE‡	101 (24)	176 (15)
SAE at least possibly adalimumab related*	29 (6.8)	39 (3.4)
TEAE leading to discontinuation of adalimumab§	77 (18)	91 (8.0)
TEAE leading to death	4 (0.9)	4 (0.4)
Uveitis-related TEAE by investigator	241 (57)	719 (63)
Uveitis-related TEAE by adjudication	218 (51)	520 (46)
Deaths‖	4 (0.9)	4 (0.4)

AE = adverse event; SAE = serious adverse event; TEAE = treatment-emergent adverse event.
*As assessed by investigator.
†Severe TEAEs reported in more than 2 patients included hypertension (n = 5 [1.2%]); blindness, reduced visual acuity, and urinary tract infection (n = 4 each [0.9%]); and uveitis, vitreous hemorrhage, and arthralgia (n = 3 each [0.7%]).
‡Serious adverse event reported in 3 patients or more included cataract in 7 patients (1.7% [0.96 event/100 patient-years]); uveitis and urinary tract infection in 5 patients each (1.2% [0.44 event/100 patient-years]); and retinal detachment, vitreous hemorrhage, cholelithiasis, pneumonia, and obesity in 3 patients each (0.7% [0.26 event/100 patient-years]).
§Treatment-emergent adverse events leading to discontinuation of adalimumab occurring in more than 5 patients included positive *Mycobacterium tuberculosis* complex test results (n = 10 [2.4%]), positive tuberculin test results (n = 7 [1.7%]), and cystoid macular edema (n = 6 [1.4%]).
‖Non–treatment-emergent deaths.

Table 3. Most Frequently Reported Treatment-Emergent Adverse Events in Patients Receiving Adalimumab

Medical Dictionary for Regulatory Activities Preferred Term	Adalimumab	
	Treatment-Emergent Adverse Events Occurring in ≥ 5.0% of Patients (n = 424), No. (%)	*Treatment-Emergent Adverse Events at Least Possibly Related to Study Drug (n = 424), No. (%)*
Patients with TEAE	398 (94)	226 (53)
Uveitis	128 (30)	16 (3.8)
Nasopharyngitis	105 (25)	37 (8.7)
Arthralgia	74 (17)	22 (5.2)
Headache	63 (15)	10 (2.4)
Urinary tract infection	52 (12)	24 (5.7)
Upper respiratory tract infection	43 (10)	13 (3.1)
Cystoid macular edema	43 (10)	3 (0.7)
Cough	42 (9.9)	6 (1.4)
Bronchitis	38 (9.0)	15 (3.5)
Cataract	37 (8.7)	1 (0.2)
Fatigue	36 (8.5)	16 (3.8)
Influenza	36 (8.5)	9 (2.1)
Sinusitis	35 (8.3)	35 (8.3)
Nausea	32 (7.5)	8 (1.9)
Oropharyngeal pain	32 (7.5)	6 (1.4)
Visual acuity reduced	32 (7.5)	2 (0.5)
Dry eye	30 (7.1)	N/A
Diarrhea	28 (6.6)	N/A
Hypertension	28 (6.6)	2 (0.5)
Back pain	26 (6.1)	3 (0.7)
Eye pain	25 (5.9)	N/A
Intraocular pressure increased	24 (5.7)	N/A
Macular edema	24 (5.7)	2 (0.5)
Pain in extremity	24 (5.7)	N/A
Pyrexia	24 (5.7)	6 (1.4)
Rash	24 (5.7)	7 (1.7)
Iridocyclitis	22 (5.2)	2 (0.5)
Aspartate aminotransferase increased	21 (5.0)	10 (2.4)
Conjunctivitis allergic	21 (5.0)	N/A
Vitreous floaters	21 (5.0)	1 (0.2)

N/A = not available; TEAE = treatment-emergent adverse event.

baseline in the right eye and underwent laser peripheral iridotomy. All severe TEAEs of blindness were determined by the investigator to be not related to adalimumab and related to uveitis or long-term complications of uveitis.

A total of 101 patients (24%; 15 events/100 PY; Table 2) experienced 1 or more serious AEs (SAEs); 29 patients (7%; 3.4 events/100 PY) experienced 1 or more SAEs that were considered by the investigator to be possibly or probably related to study drug. After adjudication by the sponsor, 51% of patients were reported to have 1 or more uveitis-related TEAEs, including uveitis (30%) and cystoid macular edema (10%).

Adverse Events of Special Interest for Treatment with Adalimumab. The most frequently reported TEAEs of special interest were infections, reported in 275 patients (65%; 79 events/100 PY; Table 4). One patient with cytomegalovirus chorioretinitis and 1 patient with *Aspergillus* infection discontinued study drug.

Injection site reactions were reported in 52 patients (12%; 11 events/100 PY); all were considered by the investigator to be mild or moderate in severity. Allergic reactions were reported in 28 patients (7%; 3.0 events/100 PY), nonserious, and mild to moderate in severity. Two patients discontinued study drug because of allergic reactions (1 event of urticaria; 1 event of drug eruption).

Seven patients had 1 or more positive tuberculosis test results at baseline. During the study, 20 patients (5%; 1.8 events/100 PY) reported treatment-emergent tuberculosis-related events, including 1 active case and 19 latent cases; of these, 6 were patients with 1 or more positive tuberculosis test results at baseline. Of the 19 patients who discontinued the study drug because of tuberculosis-related events, 4 events were considered serious.

Thirteen patients (3%; 1.3 events/100 PY) reported treatment-emergent malignancies (Table 4). One patient demonstrated B-cell lymphoma (0.2%; 0.09 event/100 PY) that resulted in death, determined by the investigator to probably not be related to adalimumab. Six patients experienced 8 events of nonmelanoma skin cancer (1.4%; 0.7 event/100 PY); of these, 4 events were considered by the investigator to possibly be related to the study drug and 3 events were SAEs. Six patients demonstrated other malignancies (metastatic pancreatic carcinoma, rectal adenocarcinoma, lymphoproliferative disorder, colon adenocarcinoma, lobular breast carcinoma in situ, and colorectal cancer), all of which were considered not related or

Table 4. Overview of Treatment-Emergent Adverse Events of Special Interest (≥ 2 Patients) and Infections

Adverse Event of Special Interest Category	Adalimumab	
	No. (%), n = 424	*Events (Events/100 Person-Years), Person-Years = 1141.9*
Infection	275 (65)	899 (79)
Serious infection*	33 (7.8)	40 (3.5)
Tuberculosis	20 (4.7)	20 (1.8)
Latent tuberculosis	19 (4.5)	19 (1.7)
Active tuberculosis	1 (0.2)	1 (0.09)
Injection site reaction	52 (12)	125 (11)
Allergic reaction, including angioedema, anaphylaxis	28 (6.6)	34 (3.0)
Hematologic disorders including pancytopenia	15 (3.5)	17 (1.5)
Malignancy	13 (3.1)	15 (1.3)
Nonmelanoma skin cancer	6 (1.4)	8 (0.70)
Lymphoma†	1 (0.2)	1 (0.09)
Other malignancy‡	6 (1.4)	6 (0.53)
Liver failure and other liver events	9 (2.1)	10 (0.88)
Vasculitis	6 (1.4)	8 (0.70)
Noncutaneous vasculitis	6 (1.4)	8 (0.70)
Demyelinating disorder	6 (1.4)	6 (0.53)
Diverticulitis	4 (0.9)	5 (0.44)
Opportunistic infection§	4 (0.9)	5 (0.44)
Worsening and new onset of psoriasis	5 (1.2)	5 (0.44)
Parasitic infection/infestation	4 (0.9)	4 (0.35)
Sarcoidosis	4 (0.9)	4 (0.35)
Cerebrovascular accident	2 (0.5)	2 (0.18)
Congestive heart failure	2 (0.5)	2 (0.18)
Lupus-like reaction and systemic lupus erythematosus	2 (0.5)	2 (0.18)
Myocardial infarction	2 (0.5)	2 (0.18)
Infections reported in ≥ 10.0% of patients, MedDRA preferred terms (n = 424), no. (%)		
Patients with a treatment-emergent infection	275 (65)	
Nasopharyngitis	105 (25)	
Urinary tract infection	52 (12)	
Upper respiratory tract infection	43 (10)	

AE = adverse event; MedDRA = Medical Dictionary for Regulatory Activities; TEAE = treatment-emergent adverse event.
*Serious infections in > 1 patient included urinary tract infection in 5 patients (1%); pneumonia in 3 patients (0.7%); and diverticulitis, sinusitis, and pyelonephritis in 2 patients each (0.5%).
†The observed case of lymphoma was B-cell lymphoma.
‡Excluding lymphoma, hepatosplenic T-cell lymphoma, leukemia, nonmelanoma skin cancer, and melanoma.
§Excluding oral candidiasis and tuberculosis.

probably not related to the study drug; of these patients, 5 discontinued study drug.

Six patients (1.4%; 0.5 event/100 PY) each reported treatment-emergent demyelinating events, including demyelination (n = 2), multiple sclerosis (n = 2), and optic neuritis (n = 2); 5 of these patients discontinued adalimumab (Table 5). Four patients (0.9%; 0.4 event/100 PY), all with a medical history of sarcoidosis, reported treatment-emergent sarcoidosis. One of the 2 uveitis-related sarcoidosis events was an SAE occurring in a patient with posterior uveitis. All other sarcoidosis events occurred in patients with panuveitis and were considered nonserious. Each event was judged not to be related to the study drug. Two patients (0.5%; 0.2 event/100 PY) reported lupus-like syndrome. Both events were moderate in severity and considered by the investigator to probably be related to study drug. One event led to discontinuation.

Four deaths (0.4 event/100 PY) were reported, caused by B-cell lymphoma, metastatic pancreatic carcinoma, trauma, and brain abscess. Of these, only the brain abscess was considered by the investigator to be possibly related to study drug.

Discussion

In this study, patients with noninfectious intermediate uveitis, posterior uveitis, or panuveitis who participated in the VISUAL I and II trials were observed for up to 7 years (median, 2.8 years) while receiving open-label adalimumab. Efficacy outcomes were consistent with interim results,[11] suggesting that long-term adalimumab therapy increased the likelihood of achieving and maintaining disease control and provided corticosteroid-sparing effects through week 150. Key long-term safety data showed that most AEs were mild or moderate in severity. The types and incidence rates of AEs were similar to those reported for adalimumab in the parent trials[9,10] and in studies of adalimumab for other approved indications.[8]

Table 5. Summary of 6 Treatment-Emergent Demyelinating Events

Medical Dictionary for Regulatory Activities-Reported Term	Type of Uveitis	Severity	Serious	Relation to Adalimumab	Magnetic Resonance Imaging Finding/Confirmation	Discontinuation of Adalimumab
Demyelination	Panuveitis	Moderate	Y	Possibly related	MRI showed an alternate cause of periventricular demyelinating brain lesions	Y
Demyelination	Intermediate	Mild	N	Possibly related	MRI confirmed demyelinating event	Y
Multiple sclerosis	Intermediate	Mild	Y	Possibly related	Alternate cause of nervous system inflammation reported	Y
Multiple sclerosis	Intermediate	Moderate	Y	Probably related	Initial MRI did not show cerebral demyelinating lesions; follow-up, confirmed diagnosis of multiple sclerosis approximately 5 mos after end of the study	N
Optic neuritis*	Posterior	Severe	N	Not related	No demyelination detected with MRI	Y
Optic neuritis	Posterior	Severe	N	Possibly related	MRI showed multiple white-matter lesions that may have been vascular or related to demyelination; subsequent neurology consultation confirmed diagnosis of optic neuritis and found no evidence of clinical demyelinating disease	Y

MRI = magnetic resonance imaging; N = no; Y = yes.
*Patient had a history of Behçet-associated disease at study entry; it was determined that the optic neuritis event may have had an underlying pathogenesis other than demyelinating disease.

Adverse events of special interest included serious infections in 8% of patients (3.5 events/100 PY), similar to the rate reported in patients with inactive uveitis controlled with corticosteroids (VISUAL II[10]; 3.2 events/100 PY) and lower than the rate reported in patients with active uveitis (VISUAL I[9]; 8.0 events/100 PY). Furthermore, the rate of serious infections in the VISUAL III study was within the range reported for other indications of adalimumab (1.4−6.7 events/100 PY; n = 23 458).[12] Rates of active and latent tuberculosis reported here (1.8 events/100 PY) were similar to rates reported in patients with active uveitis in the VISUAL I study (1.6 events/100 PY)[9]; in contrast, no cases of active tuberculosis were reported in patients with inactive uveitis in the VISUAL II study,[10] but a rate of 3.2 events/100 PY was observed for latent tuberculosis. In the current study, the rate of active tuberculosis (0.1 event/100 PY) was within the range reported for other indications of adalimumab (0−0.3 event/100 PY),[12] and the rate of latent cases (1.7 events/100 PY) aligned with the rate reported in the VISUAL I study (1.6 events/100 PY).[9]

Other AEs of special interest included malignancy (1.3 events/100 PY), which was lower or comparable with the rate reported in the parent trials.[9,10] Malignancy rates in the VISUAL III study were also similar to the rates reported for other indications of adalimumab[12] (malignancies excluding lymphoma and nonmelanoma skin cancer, 0.0−0.9/100 PY; lymphoma, 0.0−0.2/100 PY; and nonmelanoma skin cancer [serious events only], 0.0−0.3/100 PY).

Uveitis, particularly intermediate uveitis, is associated with demyelinating disorders such as multiple sclerosis.[13−17] Over the last few decades, the prevalence of demyelinating diseases has been increasing in many regions of the world.[18] In this study, demyelinating disorders were observed in 6 patients (3 with intermediate uveitis); the observed rate of demyelinating disorders was comparable with that reported for patients with uveitis not receiving adalimumab (data on file; AbbVie, Inc, North Chicago, IL). Caution is recommended in the prescribing information for use of adalimumab in patients with pre-existing or recent onset of central or peripheral nervous system demyelinating disorders.[8]

Although this study evaluated a relatively large number of patients, a key limitation was the decreasing number of patients with available data after week 78 because of sites closing on regulatory or reimbursement approval. Other limitations included the lack of a comparator group and the permitted use of other immunosuppressive agents and local corticosteroid therapy, as discussed previously.[11]

In summary, long-term, real-world use of adalimumab led to disease control in patients with active uveitis and to maintenance in patients with inactive disease. The long-term safety profile of adalimumab in adults with noninfectious intermediate uveitis, posterior uveitis, and panuveitis in the VISUAL III study was consistent with the safety profile established in the parent studies (VISUAL I and II studies)[9,10] and in studies of adalimumab for other indications;[12] no new safety signals were identified.

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Abbreviations and Acronyms:
AE = adverse event; **CNS** = central nervous system; **logMAR** = logarithm of the minimum angle of resolution; **MedDRA** = Medical Dictionary for Regulatory Activities; **MRI** = magnetic resonance imaging; **PY** = patient-years; **SAE** = serious adverse event; **TEAE** = treatment-emergent adverse event.

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