ORIGINAL ARTICLE

Adalimumab in Patients with Active Noninfectious Uveitis

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ABSTRACT

BACKGROUND

Patients with noninfectious uveitis are at risk for long-term complications of uncontrolled inflammation, as well as for the adverse effects of long-term glucocorticoid therapy. We conducted a trial to assess the efficacy and safety of adalimumab as a glucocorticoid-sparing agent for the treatment of noninfectious uveitis.

METHODS

This multinational phase 3 trial involved adults who had active noninfectious intermediate uveitis, posterior uveitis, or panuveitis despite having received prednisone treatment for 2 or more weeks. Investigators and patients were unaware of the study-group assignments. Patients were randomly assigned in a 1:1 ratio to receive adalimumab (a loading dose of 80 mg followed by a dose of 40 mg every 2 weeks) or matched placebo. All patients received a mandatory prednisone burst followed by tapering of prednisone over the course of 15 weeks. The primary efficacy end point was the time to treatment failure occurring at or after week 6. Treatment failure was a multicomponent outcome that was based on assessment of new inflammatory lesions, best corrected visual acuity, anterior chamber cell grade, and vitreous haze grade. Nine ranked secondary efficacy end points were assessed, and adverse events were reported.

RESULTS

The median time to treatment failure was 24 weeks in the adalimumab group and 13 weeks in the placebo group. Among the 217 patients in the intention-to-treat population, those receiving adalimumab were less likely than those in the placebo group to have treatment failure (hazard ratio, 0.50; 95% confidence interval, 0.36 to 0.70; P<0.001). Outcomes with regard to three secondary end points (change in anterior chamber cell grade, change in vitreous haze grade, and change in best corrected visual acuity) were significantly better in the adalimumab group than in the placebo group. Adverse events and serious adverse events were reported more frequently among patients who received adalimumab (1052.4 vs. 971.7 adverse events and 28.8 vs. 13.6 serious adverse events per 100 person-years).

CONCLUSIONS

In our trial, adalimumab was found to be associated with a lower risk of uveitic flare or visual impairment and with more adverse events and serious adverse events than was placebo. (Funded by AbbVie; VISUAL I ClinicalTrials.gov number, NCT01138657.)

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Noninfectious uveitis is a group of vision-threatening diseases that are characterized by intraocular inflammation; it can occur as a syndrome isolated to the eye or in association with a systemic condition. Uveitis has an estimated incidence of 17 to 52 cases per 100,000 person-years[1] and is estimated to cause 10 to 15% of cases of blindness in Western countries.[2,3] Glucocorticoids remain the mainstay of therapy despite their well-known ocular and systemic adverse effects.[4-6] Thus, there is a large unmet medical need for and a great interest in identifying more effective, glucocorticoid-sparing therapies, ideally targeting specific mediators of the immune response.[4,5,7,8]

The proinflammatory cytokine tumor necrosis factor α (TNF-α) is thought to play a key role in uveitic inflammation,[9,10] and aqueous humor and serum levels of TNF-α are up-regulated in patients with uveitis.[11] Adalimumab, a fully human anti–TNF-α monoclonal antibody, is indicated for several inflammatory conditions that may be associated with intraocular inflammation.[12] Uncontrolled case series, retrospective chart reviews, and small open-label studies have suggested that adalimumab is effective in treating patients with chronic or refractory uveitis and in reducing glucocorticoid use.[13-19]

To evaluate the efficacy and safety of an anti–TNF-α drug in patients with active, noninfectious uveitis, we conducted a multicenter, randomized, placebo-controlled trial in which patients and investigators were unaware of the study-group assignments. The objective was to assess the efficacy of adalimumab as a glucocorticoid-sparing agent for the control of uveitis.

Methods

Trial Design and Oversight

We performed this phase 3 trial in 18 countries from August 2010 through August 2014. The trial protocol was approved by an independent ethics committee or institutional review board at each study site, and the trial was performed in compliance with the provisions of the Declaration of Helsinki, International Conference on Harmonisation Good Clinical Practice guidelines, and applicable local regulations. Patients provided written informed consent at enrollment. The trial was designed jointly by the investigators and the sponsor (AbbVie). The investigators collected the data, and the sponsor conducted the data analyses. All the authors had full access to the data; there was an agreement between the investigators and the sponsor not to disclose any trial information that was not publicly available. The first draft of the manuscript was written by a medical writer (paid with funds from the sponsor), with input from all the authors. All the authors reviewed and provided feedback on all subsequent manuscript drafts and made the decision to submit the manuscript for publication; the sponsor also reviewed and approved the manuscript. All the authors vouch for the completeness and accuracy of the data and analyses and affirm that the trial was conducted and reported with fidelity to the protocol, available with the full text of this article at NEJM.org. A small substudy involving 16 Japanese patients was conducted separately, as planned, because of the potential for regional heterogeneity; the results of the substudy are not reported here.

Trial Participants

Patients who were 18 years of age or older and had a diagnosis of active noninfectious intermediate uveitis, posterior uveitis, or panuveitis were eligible to participate in the trial. The key inclusion criteria were active disease characterized by at least one active inflammatory chorioretinal or retinal vascular lesion, anterior chamber cell grade of 2+ or higher (according to Standardization of Uveitis Nomenclature Working Group criteria; scores range from 0 to 4+, with higher scores indicating more cells visible in the anterior chamber and greater severity of uveitis),[20] or vitreous haze grade of 2+ or higher (according to National Eye Institute [NEI] criteria adapted by the Standardization of Uveitis Nomenclature Working Group; scores range from 0 to 4+, with higher scores indicating greater severity of uveitis)[20,21] despite the use of prednisone (10 to 60 mg per day) or an equivalent glucocorticoid for 2 or more weeks before screening. The full inclusion and exclusion criteria are provided in Table S1 in the Supplementary Appendix, available at NEJM.org. For all patients, both eyes were eligible for analysis.

Randomization and Treatment

At the baseline visit, patients were randomly assigned in a 1:1 ratio to the adalimumab group or the placebo group, with stratification according to baseline immunosuppressant treatment; randomization was performed with the use of a

random assignment sequence that was computer-generated in the AbbVie statistics department. An interactive voice-response or Web-response system was used to assign each patient a number and group.

Adalimumab and matched placebo were supplied in prefilled syringes and were administered subcutaneously. Patients in the adalimumab group received an 80-mg dose at baseline followed by 40-mg doses every 2 weeks starting at week 1 and continuing for the duration of the trial. All patients received a standardized, 60-mg-per-day prednisone burst at trial entry (week 0), after which a mandatory tapering schedule was followed (Table S2 in the Supplementary Appendix). All patients had discontinued prednisone treatment by week 15.

STUDY VISITS AND END POINTS

Clinic visits were scheduled to occur at screening; at baseline; at weeks 1, 4, 6, and 8; and approximately every 4 weeks thereafter. Patients' conditions were evaluated until the determination of treatment failure or the completion of 80 weeks of treatment. The trial was ended when a prespecified number of treatment-failure events — 138 events, as defined below — were recorded (144 actual treatment failures were included, because six patients had treatment failure during the patient rollout period, which was the time after 138 treatment failures had occurred during which all patients still participating in the trial were required to report for the final clinic visit). The maximum duration of treatment was 80 weeks or until the 138th treatment failure occurred. The primary efficacy end point was the time to treatment failure at or after week 6. At week 6, patients were considered to have treatment failure if they met any one of the following criteria in at least one eye: new inflammatory lesions relative to baseline, anterior chamber cell or vitreous haze grade that did not decrease to 0.5+ or lower, or worsening of best corrected visual acuity by 15 or more letters on the Early Treatment Diabetic Retinopathy Study chart, relative to the best state previously achieved. After week 6, patients were considered to have treatment failure if they had new active, inflammatory lesions relative to baseline, a two-step increase in anterior chamber cell or vitreous haze grade, or a worsening of best corrected visual acuity by 15 or more letters on the Early Treatment Diabetic Retinopathy Study chart, relative to the best state previously achieved, in at least one eye.

Nine ranked secondary end points related to disease state were tested for significance in the comparison between the adalimumab group and the placebo group in the following hierarchical order (from first to last): change in anterior chamber cell grade in each eye, change in vitreous haze grade in each eye, change in best corrected visual acuity (logarithm of the minimum angle of resolution) in each eye, time to optical coherence tomographic (OCT) evidence of macular edema in at least one eye, percent change in central retinal thickness in each eye, change in NEI Visual Functioning Questionnaire–25 (VFQ-25) composite score, change in VFQ-25 distance vision subscore, change in VFQ-25 near vision subscore, and change in VFQ-25 ocular pain subscore. All ranked secondary end points, with the exception of the time to OCT evidence of macular edema in at least one eye, were analyzed by a comparison of the best state achieved before week 6 with the value at the final study visit.

All patients who received at least one dose of adalimumab or placebo were included in the safety analysis. Adverse events were monitored and reported from the time the first dose of adalimumab or placebo was administered until 70 days after the last dose was administered or until patients were moved into a separate extension study. Data on serious adverse events were collected starting from the time of informed consent. Adverse events were tabulated with the use of system organ classes and preferred terms from the Medical Dictionary for Regulatory Activities, version 17.0. The immunogenicity of adalimumab was evaluated at baseline and at weeks 12, 27, 36, and 52, or at the termination visit for patients who discontinued treatment before week 52.

PROCEDURES

The schedule of trial procedures is available in Table S3 in the Supplementary Appendix. The presence or absence of inflammatory chorioretinal or retinal vascular lesions was determined by dilated indirect ophthalmoscopy. Anterior chamber cell counts were assessed by slit-lamp biomicroscopy and were graded according to Standardization of Uveitis Nomenclature Working Group criteria.[20] Vitreous haze was assessed by means of dilated indirect ophthalmoscopy and was graded with the use of Standardization of

Uveitis Nomenclature Working Group–adapted NEI criteria.[20,21] The determination of whether macular edema was present was based on the OCT-measured thickness of the macula (measured with a Stratus OCT [Carl Zeiss Meditec], Cirrus HD-OCT [Carl Zeiss Meditec], or Spectralis [Heidelberg Engineering] system).

STATISTICAL ANALYSIS

Efficacy end points were analyzed in the intention-to-treat data set. For all patients, the time to treatment failure (the primary end point) and the time to OCT evidence of macular edema (a secondary end point) were based on the first eye to meet the criteria for treatment failure or macular edema; the change in anterior chamber cell grade in each eye, change in vitreous haze grade in each eye, change in best corrected visual acuity (logarithm of the minimum angle of resolution) in each eye, and percent change in central retinal thickness in each eye were analyzed with the use of data from each eye individually. The time to treatment failure was compared between the study groups with a log-rank test. A proportional-hazards model with study group as a factor was fitted to estimate the hazard ratio with its 95% confidence interval. The time to treatment failure due to each component of the primary end point and the time to macular edema were analyzed in the same way. Other ranked secondary end points were evaluated by analysis of variance. The analysis of variance was adjusted for clustered observations because data from both individual eyes were included. Testing of ranked secondary end points was conducted in hierarchical order. In the case of a nonsignificant test result, the confirmatory multiple-testing procedure was stopped, and P values for secondary end points further down in the hierarchy were considered to be exploratory and descriptive in nature. We also performed exploratory analyses of the results to determine whether there was an association between the efficacy of adalimumab and the underlying condition causing uveitis or the status of baseline immunomodulatory therapy.

Patient information was summarized descriptively, continuous variables were compared by analysis of variance, and discrete variables were analyzed with the use of chi-square tests. Adverse events that occurred during treatment were summarized descriptively and were tabulated as events per 100 patient-years to avoid confounding by between-group differences in the duration of exposure to adalimumab or placebo. All statistical tests were two-sided, and P values of less than 0.05 were considered to indicate statistical significance. Analyses were performed by the trial sponsor with SAS software, version 9.2 (SAS Institute). The data reported here reflect the final trial data.

Because the inclusion of eyes with macular holes or retinal detachment could confound the measurement of uveitic macular edema and central retinal thickness, a post hoc analysis of two secondary end points (time to OCT evidence of macular edema and percent change in central retinal thickness) was performed that excluded patients with these conditions. For these analyses, OCT-determined thickness values were used to quantify new macular edema.

RESULTS

PATIENTS

Of the 223 patients who were randomly assigned to a study group, 217 were included in the intention-to-treat analyses (110 in the adalimumab group and 107 in the placebo group); 6 patients were excluded because of a lack of compliance with Good Clinical Practice guidelines at the study site. The enrollment of patients started on August 10, 2010, and was completed on August 29, 2014. Most patients were female (57%) and white (80%), and 45% of patients had a diagnosis of panuveitis. The mean age of the patients was 42.7 years, and the mean duration of uveitis was 46 months. There were no significant between-group differences in demographic or baseline characteristics (Table 1). The duration of exposure to topical glucocorticoids before discontinuation of this therapy (at approximately week 9) was similar in the two groups (Table S4 in the Supplementary Appendix). A total of 18 patients who received adalimumab and 7 patients who received placebo discontinued participation in the trial; in both groups, adverse events were the most common cause of discontinuation (Fig. S1 in the Supplementary Appendix).

EFFICACY

The median time to treatment failure was 24 weeks in the adalimumab group and 13 weeks in the placebo group; there was early and sustained separation of the treatment-failure curves (Fig. 1A). Patients who received adalimumab

Table 1. Demographic and Baseline Clinical Characteristics of Patients in the Intention-to-Treat Population.*

Characteristic	Placebo Group (N=107)	Adalimumab Group (N=110)	P Value
Age — yr†			0.97
Mean	42.6±14.2	42.7±15.6	
Range	18–79	18–81	
Race — no. (%)‡§			
White	86 (80)	88 (80)	0.95
Black	12 (11)	11 (10)	
Asian	2 (2)	4 (4)	
Other	7 (7)	7 (6)	
Type of uveitis — no. (%)§			0.96
Panuveitis	47 (44)	50 (45)	
Posterior uveitis	37 (35)	36 (33)	
Intermediate uveitis	23 (21)	24 (22)	
Diagnosis — no. (%)			NT
Idiopathic uveitis	45 (42)	36 (33)	
Birdshot choroidopathy	20 (19)	24 (22)	
Vogt–Koyanagi–Harada disease	14 (13)	11 (10)	
Sarcoidosis	8 (7)	10 (9)	
Behçet's disease	4 (4)	12 (11)	
Multifocal choroiditis and panuveitis	3 (3)	8 (7)	
Other	13 (12)	9 (8)	
Duration of uveitis — mo†			0.20
Mean	51.0±72.2	40.2±51.2	
Range	1.2–554.9	1.5–305.9	
No. of flares in the past 12 mo — no. (%)§			0.66
1	19 (18)	18 (16)	
2	46 (43)	54 (49)	
≥3	42 (39)	38 (35)	
Concomitant immunomodulatory treatment — no. (%)			NT
Azathioprine	4 (4)	4 (4)	
Cyclosporine	3 (3)	10 (9)	
Methotrexate	12 (11)	9 (8)	
Mycophenolate mofetil or equivalent	14 (13)	11 (10)	
Affected eye — no. (%)§			0.46
Both	99 (93)	98 (89)	
Left only	5 (5)	5 (5)	
Right only	3 (3)	7 (6)	

* Plus–minus values are means ±SD. NT denotes not tested.
† P value for between-group difference was based on a one-way analysis of variance.
‡ Race was self-reported.
§ P value for between-group difference was based on a chi-square or Fisher's exact test.

were significantly less likely than those who received placebo to have treatment failure (hazard ratio, 0.50; 95% confidence interval [CI], 0.36 to 0.70; P<0.001). Patients who received adalimumab had a significantly lower risk of treatment failure caused by vitreous haze (hazard ratio, 0.32; 95% CI, 0.18 to 0.58; P<0.001), new active inflammatory lesions (hazard ratio, 0.38; 95% CI, 0.21 to 0.69; P=0.001), anterior chamber cell grade (hazard ratio, 0.51; 95% CI, 0.30 to 0.86; P=0.01), or a worsening of best corrected visual acuity (hazard ratio, 0.56; 95% CI, 0.32 to 0.98; P=0.04) (Fig. 1B). Similar results were found in subgroup analyses (see the Supplementary Appendix). There were significantly more reasons for treatment failure in the placebo group than in the adalimumab group (P=0.002) (Fig. S2 in the Supplementary Appendix). An increase in vitreous haze grade was the most frequent reason for treatment failure in the placebo group (36%) and the least frequent reason in the adalimumab group (15%) (Fig. 2). An increase in anterior chamber cell grade was the most frequent reason for treatment failure in the adalimumab group (22%); a worsening of best corrected visual acuity was the least frequent reason for treatment failure in the placebo group (25%).

We performed exploratory analyses of the results to determine whether there was an association between the efficacy of adalimumab and the type of diagnosis or status of baseline immunomodulatory therapy. Diagnosis-defined subgroups with 20 or more patients per study group were analyzed. Only two subgroups — idiopathic uveitis and birdshot choroidopathy — met this criterion. We found that the efficacy of adalimumab was significantly greater than that of placebo among patients who had a diagnosis of idiopathic uveitis (hazard ratio, 0.50; 95% CI, 0.31 to 0.80; P=0.003) but not among patients with birdshot choroidopathy (hazard ratio, 0.49; 95% CI, 0.21 to 1.14; P=0.09). We also found the efficacy of adalimumab to be significantly greater than that of placebo in the subgroup of patients who were not using immunomodulatory therapies at baseline (hazard ratio, 0.49; 95% CI, 0.33 to 0.73; P<0.001) but not among patients who were using immunomodulatory therapies at baseline (hazard ratio, 0.55; 95% CI, 0.30 to 1.01; P=0.05). Given the small number of patients in each subgroup and the exploratory nature of these analyses, the results must be considered as tentative.

Hierarchical testing of the ranked secondary outcomes showed that worsening of anterior chamber cell grade, worsening of vitreous haze grade, and worsening of best corrected visual acuity were significantly less common among patients who received adalimumab than among those who received placebo (P≤0.01 for all three end points). The difference between the groups in the time to OCT evidence of macular edema was not significant (Table 2); therefore, no further confirmatory statistical testing of secondary end points was performed. An exploratory post hoc analysis showed that, among patients with no macular edema, macular holes, or retinal detachment at baseline, the risk of development of new macular edema defined by retinal thickening was 67% lower with adalimumab than with placebo (P=0.02). Exploratory analyses of the percent change in central retinal thickness in each eye, the change in VFQ-25 composite score, the change in VFQ-25 distance vision subscore, the change in VFQ-25 near vision subscore, and the change in VFQ-25 ocular pain subscore, which were performed for hypothesis-generating purposes, showed that the results favored adalimumab for each outcome with the exception of the change in VFQ-25 distance vision subscore (Table S5 in the Supplementary Appendix).

SAFETY

The incidence of adverse events was 971.7 per 100 person-years in the placebo group (430 events), and 1052.4 per 100 person-years in the adalimumab group (657 events) (Table 3). The potential relationship of adverse events to the trial intervention (adalimumab or placebo) was judged while investigators were unaware of the study-group assignments. Among the adverse events reported, 124.3 per 100 person-years (55 events) in the placebo group and 257.9 per 100 person-years (161 events) in the adalimumab group were judged by investigators to have been possibly related to the trial intervention. Serious adverse events were more common in the adalimumab group; the incidence was 28.8 per 100 person-years (18 events) in the adalimumab group and 13.6 per 100 person-years (6 events) in the placebo group (Table 3); of these, 9.6 per 100 person-years (6 events) in the adalimumab group and

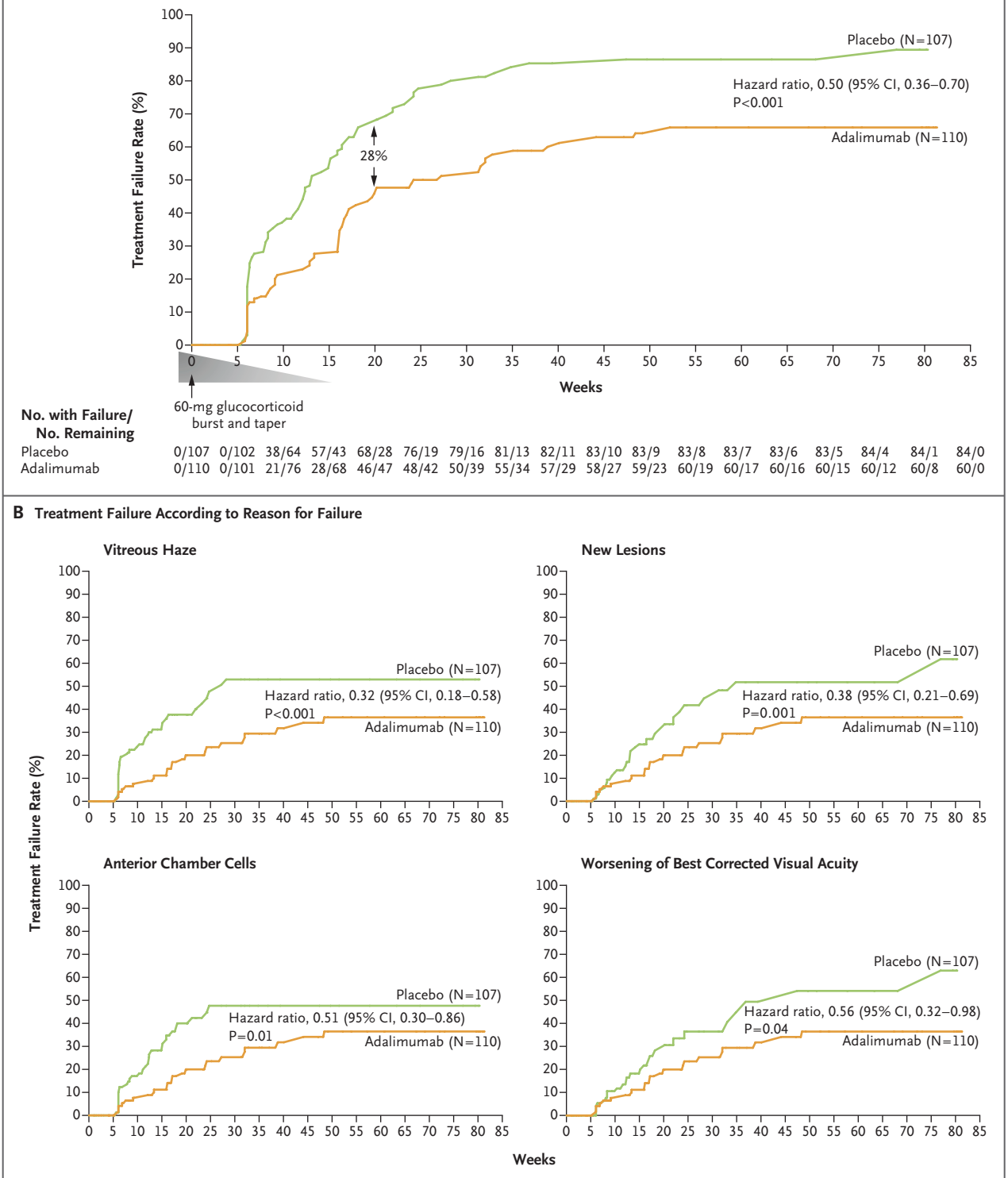

Figure 1. Kaplan–Meier Curves of the Rate of Treatment Failure.

Table 2. Ranked Secondary Efficacy Variables in the Intention-to-Treat Population.

Ranked Secondary Variable	Placebo Group (N=107)		Adalimumab Group (N=110)		Mean Between-Group Difference (95% CI)	P Value
	No. of Patients	Value*	No. of Patients	Value*		
Mean change in anterior chamber cell grade†					−0.29 (−0.51 to −0.07)	0.01‡
Left eye	102	0.59	101	0.35		
Right eye	102	0.69	101	0.36		
Mean change in vitreous haze grade§					−0.27 (−0.43 to −0.11)	<0.001‡
Left eye	103	0.33	101	0.11		
Right eye	103	0.45	101	0.13		
Mean change in best corrected visual acuity — logarithm of the minimum angle of resolution					−0.07 (−0.11 to −0.02)	0.003‡
Left eye	103	0.12	101	0.07		
Right eye	103	0.13	101	0.04		
Median time to OCT evidence of cystoid macular edema on or after week 6 — mo¶	45	6.2	55	11.1		0.23

* With the exception of the time to optical coherence tomographic (OCT) evidence of macular edema, data reflect the change from the best state achieved before week 6 to the state at the final or early termination visit.
† Anterior chamber cell grades range from 0 to 4+, with higher scores indicating more cells visible in the anterior chamber and greater severity of uveitis.
‡ The P value for the between-group difference was calculated by analysis of variance, with treatment as a factor, and was adjusted for clustered observations.
§ Vitreous haze grades range from 0 to 4+, with higher scores indicating greater severity of uveitis.
¶ Cystoid macular edema was included only for patients who did not have cystoid macular edema at baseline. The P value for the between-group comparison was calculated by log-rank test. The hazard ratio for development of macular edema on or after week 6 in the adalimumab group, as compared with the placebo group, was 0.70 (95% CI, 0.39 to 1.26).

6.8 per 100 person-years (3 events) in the placebo group were judged by investigators to have been possibly related to the trial intervention. The most frequently reported adverse events were injection-site reactions and allergic reactions. Serious infections occurred at a similar rate in the two groups. Two cancers (carcinoid tumor of the gastrointestinal tract and glioblastoma multiforme) and 1 event each of active tuberculosis, latent tuberculosis, lupus or lupuslike reaction, and demyelinating disorder were reported in the adalimumab group.

Adverse events leading to discontinuation of participation in the trial were more common in the adalimumab group and included choroidal neovascularization, blurred vision, reduced visual acuity, fatigue, malaise, and suicidal ideation. We detected anti-adalimumab antibodies in 3 of 110 patients in the adalimumab group (2.7%) during the trial. The 3 patients in whom anti-adalimumab antibodies were detected had treatment failure at 16, 44, and 48 weeks; the median time to treatment failure among the 107 patients in whom anti-adalimumab antibodies were not detected was 24 weeks.

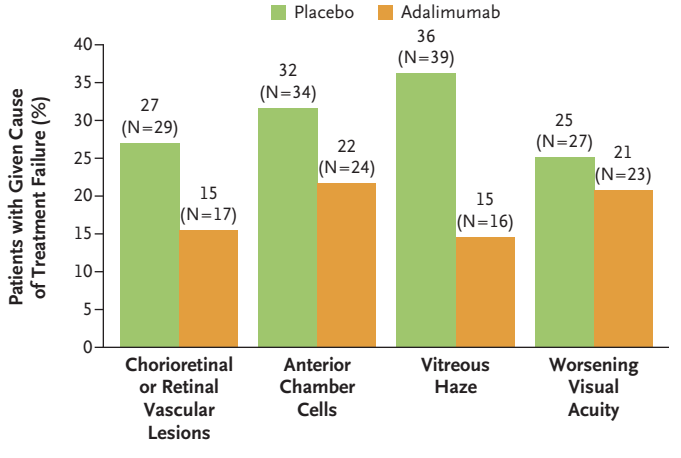

Figure 2. Reasons for Treatment Failure in Each Study Group.

Table 3. Adverse Events in the Safety Population.*

Adverse Event	Placebo Group (N=112)		Adalimumab Group (N=111)	
	no. of events	*events/100 patient-years*	*no. of events*	*events/100 patient-years*
Any adverse event	430	971.7	657	1052.4
Adverse event leading to death	0	0	1†	1.6
Serious adverse event	6	13.6	18	28.8
Accidental overdose	0	0	1	1.6
Anaphylactic reaction	0	0	1	1.6
Angle-closure glaucoma	0	0	1	1.6
Carcinoid tumor of the gastrointestinal tract	0	0	1	1.6
Chronic renal failure	0	0	1	1.6
Demyelination	0	0	1	1.6
Fluid overload	0	0	1	1.6
Glioblastoma multiforme	0	0	1	1.6
Ligament rupture	0	0	1	1.6
Lupuslike syndrome	0	0	1	1.6
Neovascularization	0	0	1	1.6
Pilonidal cyst	0	0	1	1.6
Pneumonia	0	0	1	1.6
Tendon rupture	0	0	1	1.6
Tuberculosis	0	0	1	1.6
Upper respiratory tract infection	0	0	1	1.6
Urinary tract infection	0	0	1	1.6
Urticaria	0	0	1	1.6
Abortion induced	1	2.3	0	0
Acute hepatitis	1	2.3	0	0
Acute pyelonephritis	1	2.3	0	0
Sepsis	1	2.3	0	0
Viral gastroenteritis	1	2.3	0	0
Wrist fracture	1	2.3	0	0
Adverse event leading to discontinuation of the trial intervention	5	11.3	13	20.8
Adverse event possibly related to the trial intervention‡	55	124.3	161	257.9
Serious adverse event possibly related to the trial intervention‡	3	6.8	6	9.6
Injection-site reaction	7	15.8	28	44.9
Allergic reactions	6	13.6	14	22.4
Treatment-related allergic reaction	1	2.3	4	6.4
Serious infection	3	6.8	5	8.0
Opportunistic infection (excluding oral candidiasis and tuberculosis)	0	0	0	0
Cancer§	0	0	2	3.2
Active tuberculosis	0	0	1	1.6
Latent tuberculosis	0	0	1	1.6

Table 3. (Continued.)

Adverse Event	Placebo Group (N=112)		Adalimumab Group (N=111)	
	no. of events	*events/100 patient-years*	*no. of events*	*events/100 patient-years*
Lupus or lupuslike reaction	0	0	1	1.6
Demyelinating disorder	0	0	1	1.6

* The total numbers of patient-years were 44.3 in the placebo group and 62.4 in the adalimumab group.
† The death was due to end-stage chronic renal disease and occurred on day 37 (post-treatment day 3); it was judged by the investigators not to be related to the trial intervention.
‡ The assessment of whether an event was related to the trial intervention was made by the investigator. The investigator was unaware of the study-group assignment at the time of the assessment.
§ The two cases of cancer included one carcinoid tumor of the gastrointestinal tract (detected on day 244 and surgically removed and reported as resolved on day 251; adalimumab treatment was not interrupted) and one case of glioblastoma multiforme (detected on day 242; adalimumab was discontinued because of this event; the last adalimumab dose was administered on day 248).

DISCUSSION

In this trial involving patients with active, vision-threatening, noninfectious intermediate or posterior uveitis or panuveitis, treatment with adalimumab was associated with a significantly lower risk of treatment failure than was placebo; there was an early and sustained separation of adalimumab and placebo treatment-failure curves regardless of whether patients were receiving nonadalimumab immunomodulatory treatment at baseline. Without glucocorticoid support, adalimumab treatment controlled multiple aspects of uveitic inflammation and was associated with a lower risk of uveitic flare and a longer time to a flare than was placebo.

Posterior manifestations of uveitis, such as vitreous haze and retinal lesions, are more closely associated with vision loss than is anterior inflammation (as indicated, for example, by the number of anterior chamber cells).[22] Vitreous haze was the most common reason for treatment failure in the placebo group and was the least common cause of treatment failure in the adalimumab group; patients who received adalimumab were approximately one third as likely to have treatment failure caused by a worsening grade of vitreous haze. Treatment failure due to newly active chorioretinal lesions was also more common with placebo than with adalimumab. These observations are consistent with an effect of adalimumab on posterior segment inflammation. Clinically relevant outcomes associated with uveitic inflammation (e.g., grades of anterior chamber cells and vitreous haze, best corrected visual acuity, and central retinal thickness) were significantly better with adalimumab than with placebo.

The efficacy results of this controlled trial are supported by the results of previous uncontrolled studies. In a prospective, multicenter, open-label trial of adalimumab involving patients with refractory noninfectious uveitis, 68% of the patients met prespecified criteria for clinical success after 10 weeks of treatment.[17] In a retrospective case series of patients with chronic noninfectious uveitis, sustained inflammation control and glucocorticoid sparing were achieved in 38% of the patients after 12 weeks and in 57% of the patients after 1 year.[23] In a prospective study involving 131 patients with refractory noninfectious uveitis, nearly half of whom had panuveitis and 31% of whom had cystoid macular edema at baseline, adalimumab treatment was associated with a significant reduction in macular thickness relative to baseline and with resolution of macular edema.[15] Likewise, in a retrospective, multicenter study involving 60 patients with active noninfectious uveitis, adalimumab reduced macular edema in 53% of the 32 patients who had had macular edema before treatment; visual acuity and anterior chamber cells were also improved.[16]

The low immunogenicity of adalimumab that was observed in our trial was within the range of rates observed with adalimumab in other disease states.[12] No new safety signals were detected.[13,24] The overall rate of adalimumab-associated adverse events exceeded that of placebo-associated adverse events, as did the rate of adalimumab-

associated serious adverse events and adverse events leading to discontinuation of treatment, possibly because of the immunomodulatory action of the drug. This notion is supported by the greater frequency of respiratory tract infections (e.g., nasopharyngitis and bronchitis) related to adalimumab, as assessed by investigators, and of adalimumab-related adverse events, such as infections and allergic reactions, leading to discontinuation; these adverse events have been described previously.[12] All serious adverse events were unique, and no pattern was identified among the adverse events that led to the discontinuation of adalimumab treatment.

Randomized, controlled trials of immunosuppressive therapies for noninfectious uveitis are generally lacking. The design, large patient population, diversity of uveitis diagnoses, four-component primary end point, and hierarchical statistical analysis of secondary end points were strengths of our trial. The composite primary end point assessed multiple facets of the disease, spanning from anterior to posterior segments of the eye, and enabled broader assessment of the response to treatment.

The extent to which we can interpret the trial data is limited. In patients receiving adalimumab, the time to treatment failure may have been underestimated and rates of treatment failure may have been overestimated, as compared with these measures in a nontrial setting, because all the patients rapidly discontinued glucocorticoid treatment. In clinical practice, patients receive oral or topical glucocorticoids as needed to maintain control of their uveitis.[5] Regardless, because more than half the patients had treatment failure by 80 weeks, adalimumab delayed uveitic flares in the majority of eyes but, as expected, did not "cure" the patients' uveitis.

Treatment with adalimumab effectively achieved early and sustained disease control after discontinuation of glucocorticoid treatment by both markedly reducing inflammation and decreasing visual impairment in patients with active noninfectious intermediate uveitis, posterior uveitis, or panuveitis. There were more treatment-related adverse events and more serious adverse events in the adalimumab group than in the placebo group in the trial. Adalimumab reduced the worsening of several clinically relevant inflammatory measures and significantly lowered the risk of uveitic flare or visual impairment.

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CLINICAL TRIAL REGISTRATION

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