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ORIGINAL ARTICLE

Adalimumab plus Methotrexate for Uveitis in Juvenile Idiopathic Arthritis

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ABSTRACT

BACKGROUND

Adalimumab, a fully human anti–tumor necrosis factor α monoclonal antibody, is effective in the treatment of juvenile idiopathic arthritis (JIA). We tested the efficacy of adalimumab in the treatment of JIA-associated uveitis.

METHODS

In this multicenter, double-blind, randomized, placebo-controlled trial, we assessed the efficacy and safety of adalimumab in children and adolescents 2 years of age or older who had active JIA-associated uveitis. Patients who were taking a stable dose of methotrexate were randomly assigned in a 2:1 ratio to receive either adalimumab (at a dose of 20 mg or 40 mg, according to body weight) or placebo, administered subcutaneously every 2 weeks. Patients continued the trial regimen until treatment failure or until 18 months had elapsed. They were followed for up to 2 years after randomization. The primary end point was the time to treatment failure, defined according to a multicomponent intraocular inflammation score that was based on the Standardization of Uveitis Nomenclature criteria.

RESULTS

The prespecified stopping criteria were met after the enrollment of 90 of 114 patients. We observed 16 treatment failures in 60 patients (27%) in the adalimumab group versus 18 treatment failures in 30 patients (60%) in the placebo group (hazard ratio, 0.25; 95% confidence interval [CI], 0.12 to 0.49; P<0.0001 [the prespecified stopping boundary]). Adverse events were reported more frequently in patients receiving adalimumab than in those receiving placebo (10.07 events per patient-year [95% CI, 9.26 to 10.89] vs. 6.51 events per patient-year [95% CI, 5.26 to 7.77]), as were serious adverse events (0.29 events per patient-year [95% CI, 0.15 to 0.43] vs. 0.19 events per patient-year [95% CI, 0.00 to 0.40]).

CONCLUSIONS

Adalimumab therapy controlled inflammation and was associated with a lower rate of treatment failure than placebo among children and adolescents with active JIA-associated uveitis who were taking a stable dose of methotrexate. Patients who received adalimumab had a much higher incidence of adverse events and serious adverse events than those who received placebo. (Funded by the NIHR Health Technology Assessment Programme and Arthritis Research UK; SYCAMORE EudraCT number, 2010-021141-41.)

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Juvenile idiopathic arthritis (JIA) is the most common rheumatic disease in children. Children with JIA are at risk for inflammation of the uvea (uveitis). Uveitis develops in approximately 12 to 38% of patients with JIA within 7 years after the onset of arthritis.[1,2] Despite current screening and therapeutic options, visual impairment in both eyes may develop in up to 15% of children with JIA-associated uveitis, and they may be certified as legally blind.[3,4]

Experimental models of autoimmune uveitis have shown that tumor necrosis factor α (TNF-α) plays a pivotal role in the pathogenesis,[5] findings that have been borne out in the treatment of uveitis in adults[6-8] and in pediatric case series.[9-17] Adalimumab is a fully humanized anti–TNF-α monoclonal antibody. A multicenter, randomized, double-blind, parallel-group trial showed a significant benefit of adalimumab in children with active rheumatoid arthritis.[18] We carried out the SYCAMORE trial to assess the role of adalimumab in the treatment of methotrexate-refractory JIA-associated uveitis.

Methods

Protocol and Trial Population

In this multicenter, double-blind, randomized, placebo-controlled trial, the primary end point was the efficacy of adalimumab in children with active JIA-associated uveitis, as measured by various scoring systems. All the patients had been receiving a stable weekly dose of methotrexate for at least 12 weeks.

An independent ethics committee and the Medicines for Healthcare Products Regulatory Agency approved the trial protocol (available with the full text of this article at NEJM.org). Each parent or guardian provided written informed consent, and each child gave assent when appropriate. The authors vouch for the fidelity of this report and the trial to the protocol. AbbVie provided the active drug and placebo that were used in the trial. AbbVie had no part in the trial design, the collection or analysis of the data, or the preparation of the manuscript. AbbVie representatives reviewed the final draft of the manuscript. All the authors assume responsibility for the accuracy and completeness of the data and analyses. University Hospitals Bristol NHS Foundation Trust, as the sponsor of this trial, has a data-sharing agreement with AbbVie in support of regulatory purposes.

Children and adolescents 2 years of age or older who had active JIA-associated uveitis were eligible to undergo randomization. Stable methotrexate treatment meant that the dose (10 to 20 mg per square meter of body-surface area; maximum dose, 25 mg) and the method of administration remained constant. Active uveitis was defined as a sustained grade (on at least two occasions) of cellular infiltrate in the anterior chamber of 1+ (indicating 6 to 15 cells in a 1-mm^2 area of the anterior chamber of the eye under a slit-lamp biomicroscope) or higher, according to the Standardization of Uveitis Nomenclature (SUN) criteria,[19] during the 12 weeks before screening despite receipt of methotrexate and glucocorticoid (systemic or topical) therapy. The SUN cell-activity score is proportional to the approximate number of cells per 1 mm^2 in the anterior chamber of the eye under a slit-lamp biomicroscope, with a higher score indicating a greater number of cells.[19] There are no internationally agreed-on minimally important differences for this scale.

Key exclusion criteria were previous exposure to adalimumab, previous exposure to another biologic agent such that the estimated level of the drug in the patient's blood was less than that predicted by 5 half-lives of the drug, receipt of more than six topical glucocorticoid drops per eye per day, and receipt of prednisone (or the equivalent) at a dose exceeding 0.2 mg per kilogram of body weight per day. The full inclusion and exclusion criteria and information regarding the concomitant medications that were and were not permitted are described in the trial protocol.[20]

Randomization and Trial Procedures

Randomization was performed with the use of a Web-based system with random permuted block sizes of 3 and 6, stratified according to trial center. At enrollment, eligible patients were assigned in a 2:1 ratio to receive adalimumab or placebo. Patients were followed for 2 years after randomization. Trial visits were scheduled at 4, 8, and 12 weeks and then every 12 weeks until 18 months or until patients stopped the trial regimen because of treatment failure, after which they were followed for another 6 months.

Ophthalmic assessment of disease activity and ocular complications were measured throughout the trial with the use of slit-lamp biomicroscopy for uveitis activity, according to the SUN criteria[19] (Table S2 in the Supplementary Appendix, avail-

able at NEJM.org). The primary and secondary end points were assessed at each trial visit and at any unscheduled visits.

TRIAL REGIMEN

We recruited patients between October 1, 2011, and April 10, 2015. The first patient underwent randomization on October 27, 2011, and the final patient underwent randomization on March 31, 2015.

All the patients received a stable dose of weekly oral or subcutaneous methotrexate (10 to 20 mg per square meter; maximum dose, 25 mg). No dose reduction or change in the method of administration was allowed. An increase in the dose was acceptable in response to somatic growth (so that the dose per square meter at trial entry was maintained throughout the trial) but not on clinical grounds. Participants received either adalimumab (at a dose of 20 mg in patients weighing <30 kg or 40 mg in patients weighing ≥30 kg), or placebo, administered as a subcutaneous injection every 2 weeks. The volume (0.8 ml) was the same across all doses and groups. AbbVie provided the investigational medicinal product (adalimumab) and matching placebo in identical, prefilled vials.

PRIMARY END POINT

The primary end point was the time to treatment failure (as assessed by means of a multicomponent intraocular inflammation score), which was defined as at least one of the following criteria being met: a two-grade increase from baseline in the SUN cell-activity score (anterior chamber cell count) over a period of two consecutive visits; no change in the SUN cell-activity score in patients with an entry grade of 3 or higher for two consecutive readings (apart from baseline); only partial improvement (decrease of one grade) or no change from baseline, with the development of another ocular coexisting condition that was sustained over a period of two consecutive visits; the worsening of an existing (on enrollment) ocular coexisting condition after 3 months; an entry grade of 1 or 2 that was still present after 6 months of therapy and that had been sustained over a period of two consecutive visits; the use of ineligible concomitant medications (medications not listed in the prespecified acceptable criteria or those that were not allowed); or the intermittent or continuous suspension of the trial regimen for a cumulative period of more than 4 weeks. All the trial assessments were carried out by persons who did not have knowledge of the trial-group assignments.

SECONDARY END POINTS

All the secondary end points were assessed at each trial visit.[20] These end points included the use of topical and systemic glucocorticoids; a flare of uveitis defined according to SUN criteria; control, remission, and duration of inactive disease (uveitis); health-related quality of life, as assessed by means of the Childhood Health Assessment Questionnaire (CHAQ; scores range from 0 to 3, with lower scores indicating better outcomes; minimal clinically important differences, −0.188 for improvement and 0.125 for worsening)[21] and the Child Health Questionnaire (CHQ; scores range from 0 to 100, with higher scores indicating better or more positive health states; no specific minimal clinically important difference is recognized)[22]; flare of JIA; remission while taking medication and remission while not taking medication[23]; minimal JIA disease activity (defined in patients with oligoarticular JIA as a physician's global assessment of ≤2.5 on a 10-cm visual-analogue scale, with higher scores indicating more disease activity, and no swollen joints; or defined in patients with polyarticular JIA as a physician's global assessment of ≤3.4 on the 10-cm visual-analogue scale, the patient's or parent's global assessment of ≤2.1 on the 10-cm visual-analogue scale, and ≤1 swollen joint)[24]; the Juvenile Arthritis Disease Activity Score (JADAS),[25] which was defined as the linear sum of four components: a physician's global assessment on the 10-cm visual-analogue scale, the patient's or parent's global assessment on the 10-cm visual-analogue scale, an active joint count as assessed in one of three ways (with any involved joints up to a maximum of 10 [JADAS 10], with 27 joints including the cervical spine, elbows, wrists, the first to third metacarpophalangeals, proximal interphalangeals, hips, knees, and ankles [JADAS 27], or with all 71 joints [JADAS 71]); and the erythrocyte sedimentation rate (ESR), which was normalized on a scale from 0 to 10 with the use of the following formula to avoid excessive weight in the overall index: (ESR [mm/hr] − 20) ÷ 10; minimal disease activity (defined as a JADAS score of 2 in patients with oligoarticular disease or 3.8 in those with polyarticular disease); and the standard American College of Rheumatology (ACR) pediatric

Table 1. Characteristics of the Patients at Baseline.*

Characteristic	Adalimumab Group (N=60)	Placebo Group (N=30)
Affected eyes — no. (%)		
One eye	43 (72)	22 (73)
Both eyes	17 (28)	8 (27)
Weight <30 kg — no./total no. (%)	33/59 (56)	17/30 (57)
Age — yr	9.07±3.94	8.56±3.79
Female sex — no. (%)	47 (78)	23 (77)
Ophthalmologic characteristics		
No. of eyes assessed	77	38
LogMAR score†	0.04±0.15	0.07±0.12
Anterior chamber cell count — no. (%)‡		
1+	52 (68)	24 (63)
2+	18 (23)	11 (29)
3+	6 (8)	3 (8)
4+	1 (1)	0
Flare score — no. (%)‡		
0	18 (23)	12 (32)
1+	49 (64)	23 (61)
2+	10 (13)	3 (8)
Intraocular pressure — mm Hg	14.76±3.85	14.11±4.27
Vitreous haze grade — no. (%)§		
0	65 (84)	32 (84)
0.5+	8 (10)	4 (11)
1+	3 (4)	2 (5)
2+	1 (1)	0
No. of topical glucocorticoid drops per eye per day	2.31±1.44	2.25±1.54
Ophthalmic complications — no. (%)		
Central band keratopathy	2 (3)	0
Synechia	18 (23)	6 (16)
Iris bombé	0	0
Membrane formation	2 (3)	0
Neovascularization	0	0
Rheumatologic characteristics		
Type of JIA — no. (%)¶		
Extended oligoarthritis	14 (23)	7 (23)
Persistent oligoarthritis	36 (60)	17 (57)
Rheumatoid factor–negative polyarthritis	8 (13)	4 (13)
Rheumatoid factor–positive polyarthritis	1 (2)	1 (3)
Psoriatic arthritis	1 (2)	1 (3)
Time since JIA diagnosis — yr	5.58±3.69	4.81 ±3.19
Physician's global assessment of disease activity‖	0.76±1.48	0.83±1.09
Rheumatoid factor — no./total no. (%)**	1/47 (2)	3/23 (13)
Antinuclear antibody — no./total no. (%)**	33/57 (58)	15/25 (60)

Table 1. (Continued.)

Characteristic	Adalimumab Group (N=60)	Placebo Group (N=30)
Median active-joint count (interquartile range)	0 (0–0)	0 (0–2)
Median swollen-joint count (interquartile range)	0 (0–0)	0 (0–2)

* Plus–minus values are means ±SD.
† Scores for the log of the minimum angle of resolution (logMAR) are on a scale from 0.00 to 2.00, with higher values indicating poorer vision.
‡ The anterior chamber cell count and flare score were assessed according to the Standardization of Uveitis Nomenclature criteria.[19] Scores range from 0 to 4+, with higher scores indicating poorer vision. Grade definitions are provide in Table S2 in the Supplementary Appendix.
§ Vitreous haze grade was assessed on a scale from 0 to 4+, with higher grades indicating poorer vision.[19]
¶ The type of juvenile idiopathic arthritis (JIA) was classified according to the International League of Associations for Rheumatology criteria.[28]
‖ The physician's global assessment of disease activity was assessed on a 10-cm visual-analogue scale, with higher grades indicating more disease activity.
** Data on rheumatoid factor and antinuclear antibody were not available in some patients because repeat blood testing for the purpose of data-set completion was not warranted on the basis of clinical needs.

core outcome set variables.[26] ACR responses of ACR 30, ACR 50, ACR 70, ACR 90, and ACR 100 are defined as 30%, 50%, 70%, 90% and 100% improvement, respectively, in a minimum of three variables in the core set, with worsening of one variable by no more than 30%, as defined in the ACR criteria. The secondary end points and the post hoc analyses are provided in Table S8 in the Supplementary Appendix.

SAFETY

All the participants who received at least one dose of adalimumab or placebo were included in the safety analyses. Adverse events were recorded at each visit and reported from the receipt of the first dose of the trial regimen. Adverse events are reported regardless of severity or perceived association with the trial intervention. Data on serious adverse events were collected from the time of informed consent. Adverse events were tabulated with the use of *Medical Dictionary for Regulatory Activities*, version 18.0, system organ class and preferred terms.

STATISTICAL ANALYSIS

We originally designed the trial with 90% power to detect a 50% relative difference in the rate of treatment failure (estimated at 60% with placebo vs. 30% with adalimumab) at a two-sided 5% significance level. In view of substantial challenges in the early phases of recruitment, the independent data and safety monitoring committee and the trial steering committee, with approval from the trial funders, advised the adoption of a protocol amendment that reduced the power to 80%, required the recruitment of 114 patients (76 patients in the adalimumab group and 38 in the placebo group), and included a 5% inflation for missing data for the primary end point.

In an intention-to-treat analysis of the primary end point, we used the log-rank test to compare the two trial groups and Kaplan–Meier plots to show the distribution of time to treatment failure. Hazard ratios and 95% confidence intervals were estimated after fitting a Cox proportional-hazards model with the assumption of proportional hazards checked by means of the addition of a time-dependent treatment-effect variable to the model. A two-sided P value of less than 0.0001 was used for the Haybittle–Peto stopping boundary for the interim analysis, and a two-sided P value of less than 0.05 was considered to indicate statistical significance for the final analysis.[27] Prespecified sensitivity analyses tested the effects of missing data, participants who stopped their intervention early, and those who had been incorrectly identified as having treatment failure. The statistical analysis plan (see the protocol) includes the full details of the sensitivity analyses. Analyses were performed with the use of SAS software, version 9.3 (SAS Institute).

TRIAL OVERSIGHT AND TRIAL STOPPING

After the second interim analysis, the data and safety monitoring committee noted on March 11, 2015, that the adalimumab group had evidence of a significantly lower risk of treatment

failure than the placebo group. On the basis of formal stopping boundaries,[27] the data and safety monitoring committee recommended that recruitment to the trial should cease, that all participants should be subsequently made aware of their trial-group assignment, that participants in the placebo group should cease taking the trial regimen and enter trial follow-up, and that participants receiving adalimumab should continue per the trial protocol. After consultation with the data and safety monitoring committee, the trial steering committee, and the co-chief investigators (the first and last authors), a decision was made to implement this recommendation, with the support of the trial team (whose members had remained unaware of the trial-group assignments throughout) and with the agreement of the trial sponsor and funders.

Patients were called in for a final assessment of response by investigators who were unaware of the trial-group assignments. Patients in the adalimumab group were asked to continue per the protocol for the duration of the trial in an open-label follow-up until the completion of their 18-month treatment, the occurrence of an adverse event that was attributed to the drug and precluded continued treatment, or treatment failure. All the patients who had received placebo stopped taking the trial regimen and completed the 6-month follow-up phase of the trial. Open-label extension of the trial continues.

RESULTS

PATIENTS

Of 332 patients who underwent screening at 14 sites in the United Kingdom, 242 did not undergo randomization because they did not meet the inclusion criteria. A total of 60 participants were randomly assigned to receive adalimumab and 30 to receive placebo (Table 1, and Fig. S1 in the Supplementary Appendix). Data for the primary end point were available for all the participants who underwent randomization.

Nine patients (15%) in the adalimumab group and seven (23%) in the placebo group discontinued the trial intervention for reasons other than treatment failure (Fig. S1 in the Supplementary Appendix). Seven of these patients in the adalimumab group and six of those in the placebo group agreed to subsequent follow-up.

TREATMENT FAILURE

The addition of adalimumab to methotrexate significantly delayed the time to treatment failure, as compared with placebo (hazard ratio, 0.25; 95% confidence interval [CI], 0.12 to 0.49; P<0.0001 by the log-rank test [the prespecified stopping boundary]) (Fig. 1A). During the 18-month trial period, the median time to treatment failure was not reached in the adalimumab group and was 24.1 weeks (95% CI, 12.4 to 81.0) in the placebo group (Fig. 1A). Treatment failure occurred in a significantly lower percentage of patients in the adalimumab group than in the placebo group (16 patients [27%] vs. 18 [60%]; relative risk, 0.40; 95% CI, 0.22 to 0.73; P=0.002) (Tables S3 and S4 in the Supplementary Appendix). Nine sensitivity analyses confirmed the conclusion found in the primary analysis (Table S5 in the Supplementary Appendix).

SAFETY AND ADVERSE EVENTS

Summary data of the adverse events are listed in Table 2, and serious adverse events are listed in Table 3. A total of 588 adverse events, including minor infections and respiratory disorders, were reported in 53 patients (88%) in the adalimumab group, and 103 adverse events were reported in 25 patients (83%) in the placebo group. The rate of serious adverse events was 0.29 events per patient-year (95% CI, 0.15 to 0.43) in the adalimumab group, as compared with 0.19 events per patient-year (95% CI, 0.00 to 0.40) in the placebo group; the corresponding rates of adverse events per patient-year were 10.07 (95% CI, 9.26 to 10.89) and 6.51 (95% CI, 5.26 to 7.77). Full listings of all the adverse events are provided in Tables S6 and S7 in the Supplementary Appendix.

SECONDARY END POINTS

A full summary of the analyses of the secondary end points is provided in Table S8 in the Supplementary Appendix. At randomization, six participants (five in the adalimumab group and one in the placebo group) were taking systemic glucocorticoids (permitted dose, <0.20 mg per kilogram per day; median dose, 0.14 mg per kilogram per day). Three of the participants in the adalimumab group stopped taking systemic glucocorticoids (median duration of treatment, 18.1 weeks). The patient in the placebo group stopped taking systemic glucocorticoids after 5.6 weeks.

Of 63 participants who were taking two or more drops of topical glucocorticoids per day at randomization, a significantly greater percentage of patients in the adalimumab group than in the placebo group had a reduction to less than two drops (23 of 45 patients [51%] vs. 3 of 18 [17%]; hazard ratio for reduction, 3.72; 95% CI, 1.09 to 12.71; P=0.04) (Fig. 1B). Of 74 participants who were taking one or more drops at randomization, a significantly greater percentage of patients had a reduction to zero drops in the adalimumab group than in the placebo group (23 of 49 patients [47%] vs. 4 of 25 [16%]; hazard ratio, 3.58; 95% CI, 1.24 to 10.32; P=0.02) (Fig. S2 in the Supplementary Appendix).

Patients in the adalimumab group had a significantly longer mean (±SE) duration of sustained inactive disease (zero cells) than did those in the placebo group (179.3±16.9 days vs. 14.5±23.9 days; estimated treatment effect, 164.8 days; 95% CI, 104.4 to 225.2; P<0.0001 [the prespecified stopping boundary]). Patients in the adalimumab group took the trial regimen for twice as long as those in the placebo group (mean [±SD] duration, 315.9±173.8 days vs. 151.6±150.3 days).

Arthritis flare occurred in no patients in the adalimumab group during the trial period, as compared with three patients (10%) in the placebo group (relative risk, 0.07; 95% CI, 0.00 to 1.36; P=0.03). Because most of the children entered the trial with minimal arthritis (Table 1), the ACR 30, ACR 50, ACR 70, ACR 90, and ACR 100 values and the JADAS 10, 27, and 71 values were only minimally affected (Tables S11 and S12 in the Supplementary Appendix). There was no significant difference between the two trial groups with regard to health-related quality of life, as assessed by means of the CHQ and CHAQ, across time (Tables S13 and S14 in the Supplementary Appendix).

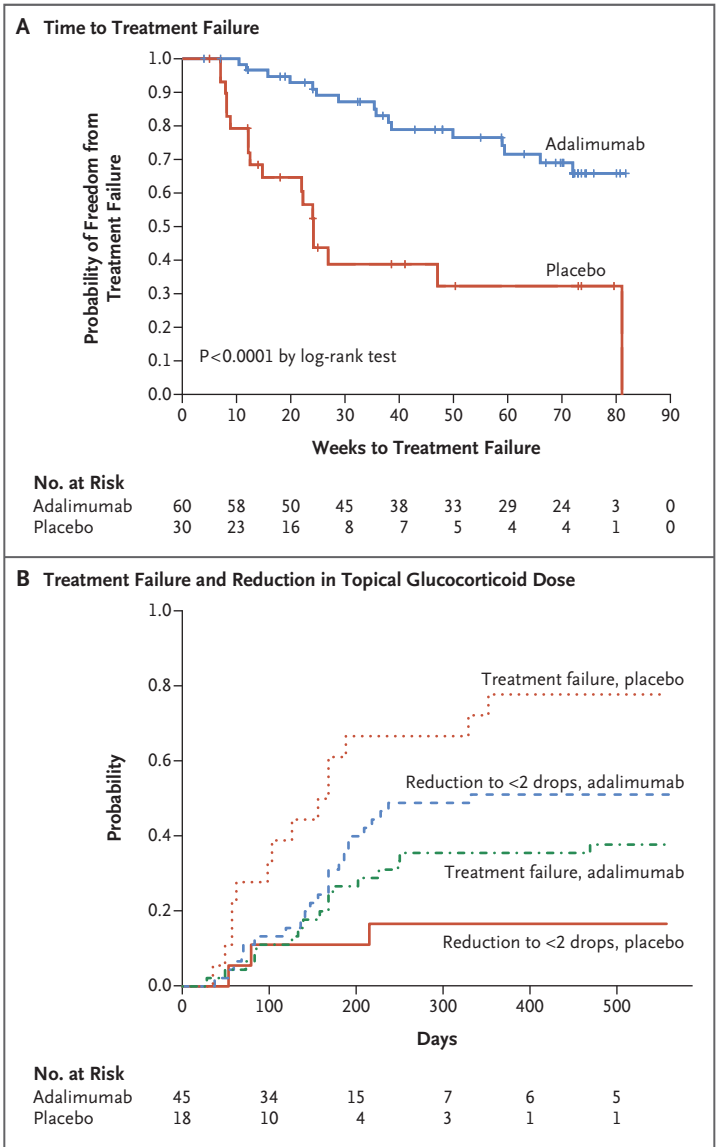

Figure 1. Treatment Failure and Reduction in Topical Glucocorticoid Dose over Time.

In Panel A, the hazard ratio for treatment failure with adalimumab versus placebo was 0.25 (95% CI, 0.12 to 0.49; P<0.0001). Tick marks indicate censored data. In Panel B, the hazard ratio for the dose reduction was 3.72 (95% CI, 1.09 to 12.71; P=0.04).

POST HOC ANALYSES

An exploratory analysis of the time to treatment response showed a difference between the adalimumab group and the placebo group in favor of adalimumab (hazard ratio, 3.15; 95% CI, 1.42 to 7.00; P=0.003 by the log-rank test) (Fig. S3 in the Supplementary Appendix). Another exploratory analysis showed a difference in favor of adalimumab in the percentage of patients with a response at 3 months and at 6 months (P=0.004 for the comparison at each time point). A total of 34 patients (57%) in the adalimumab group and 5 (17%) in the placebo group were classified as having had a response (Table S15 in the Supplementary Appendix).

Table 2. Adverse Events Reported in at Least 5% of the Patients in the Adalimumab Group.

Event	Adalimumab Group (N=60)	Placebo Group (N=30)
	number (percent)	
Blood or lymphatic system disorder: lymphadenopathy	3 (5)	0
Eye disorder: eye pain	4 (7)	0
Gastrointestinal disorder		
Abdominal pain	3 (5)	0
Diarrhea	8 (13)	1 (3)
Nausea	5 (8)	2 (7)
Vomiting	18 (30)	5 (17)
General disorder or injection-site condition		
Injection-site erythema	3 (5)	1 (3)
Injection-site mass	3 (5)	0
Injection-site pain	5 (8)	2 (7)
Injection-site pruritus	3 (5)	0
Injection-site reaction	7 (12)	0
Injection-site swelling	4 (7)	1 (3)
Pyrexia	12 (20)	2 (7)
Infection or infestation		
Ear infection	6 (10)	2 (7)
Impetigo	3 (5)	1 (3)
Lower respiratory tract infection	8 (13)	2 (7)
Nasopharyngitis	15 (25)	7 (23)
Oral herpes	3 (5)	1 (3)
Paronychia	3 (5)	1 (3)
Pharyngitis	4 (7)	0
Tonsillitis	12 (20)	0
Upper respiratory tract infection	4 (7)	1 (3)
Urinary tract infection	9 (15)	3 (10)
Varicella infection	3 (5)	0
Viral infection	13 (22)	1 (3)
Injury, poisoning, or procedural complication: fall	3 (5)	0
Investigation		
Alanine aminotransferase increased	4 (7)	1 (3)
Aspartate aminotransferase increased	3 (5)	1 (3)
Intraocular pressure increased	4 (7)	0
Musculoskeletal or connective-tissue disorder: arthralgia	12 (20)	2 (7)
Neoplasms benign, malignant, or unspecified, including cysts and polyps: skin papilloma	5 (8)	0
Nervous system disorder: headache	12 (20)	4 (13)
Respiratory, thoracic, or mediastinal disorder		
Cough	22 (37)	3 (10)
Epistaxis	3 (5)	0
Oropharyngeal pain	16 (27)	2 (7)
Skin or subcutaneous-tissue disorder: rash	3 (5)	1 (3)

Table 3. Serious Adverse Events, According to Trial Group.

Event	Adalimumab Group (N=60)		Placebo Group (N=30)		All Patients (N=90)	
	no. of events	*no. of patients (%)*	*no. of events*	*no. of patients (%)*	*no. of events*	*no. of patients (%)*
Any serious adverse event	17	13 (22)	3	2 (7)	20	15 (17)
Eye disorder*	1	1 (2)	3	2 (7)	4	3 (3)
Gastrointestinal disorder	2	2 (3)	0	0	2	2 (2)
Infection or infestation	10	8 (13)	0	0	10	8 (9)
Nervous system disorder	1	1 (2)	0	0	1	1 (1)
Respiratory, thoracic, or mediastinal disorder	1	1 (2)	0	0	1	1 (1)
Surgical or medical procedure	2	2 (3)	0	0	2	2 (2)

* One event in the adalimumab group and two events in the placebo group were a flare of uveitis that resulted in hospitalization and treatment. One event in the placebo group was worsening of vision with a flare of uveitis and macular edema.

DISCUSSION

In this randomized, placebo-controlled trial involving patients with JIA-associated uveitis, treatment with adalimumab significantly delayed the time to treatment failure, as compared with methotrexate alone (hazard ratio, 0.25; 95% CI, 0.12 to 0.49; P<0.0001 [the prespecified stopping boundary]). A significantly greater proportion of patients in the adalimumab group than in the placebo group had a reduction in their topical glucocorticoid dose (hazard ratio for reduction, 3.72; 95% CI, 1.09 to 12.71; P=0.04). A significantly greater number of patients in the adalimumab group than in the placebo group discontinued topical glucocorticoids (hazard ratio, 3.58; 95% CI, 1.24 to 10.32; P=0.02).

However, there were many more adverse events and more severe adverse events in the adalimumab group than in the placebo group. The most common adverse events in the adalimumab group were minor infections, respiratory disorders, and gastrointestinal disorders. The rate of adverse events per patient-year was higher in the adalimumab group than in the placebo group (10.07 vs. 6.51 events per patient-year). The number of serious adverse events was also higher in the adalimumab group than in the placebo group. The follow-up period during the course of the trial was not long enough for us to detect events such as cancers and demyelinating diseases. The sample size precludes commentary regarding rarer events.

Limitations of the trial include the use of the anterior chamber cell count (SUN criteria) as a component of the primary end point. Although internationally recognized, the SUN criteria have not been validated for use in children. All the participating clinicians were instructed in the assessment of SUN criteria.

In conclusion, adalimumab in combination with methotrexate was an effective therapy in children and adolescents with JIA-associated uveitis. However, the drug was associated with a higher incidence of adverse and serious adverse events than was placebo plus methotrexate.

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