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Trial of Tocilizumab in Giant-Cell Arteritis

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ABSTRACT

BACKGROUND

Giant-cell arteritis commonly relapses when glucocorticoids are tapered, and the prolonged use of glucocorticoids is associated with side effects. The effect of the interleukin-6 receptor alpha inhibitor tocilizumab on the rates of relapse during glucocorticoid tapering was studied in patients with giant-cell arteritis.

METHODS

In this 1-year trial, we randomly assigned 251 patients, in a 2:1:1:1 ratio, to receive subcutaneous tocilizumab (at a dose of 162 mg) weekly or every other week, combined with a 26-week prednisone taper, or placebo combined with a prednisone taper over a period of either 26 weeks or 52 weeks. The primary outcome was the rate of sustained glucocorticoid-free remission at week 52 in each tocilizumab group as compared with the rate in the placebo group that underwent the 26-week prednisone taper. The key secondary outcome was the rate of remission in each tocilizumab group as compared with the placebo group that underwent the 52-week prednisone taper. Dosing of prednisone and safety were also assessed.

RESULTS

Sustained remission at week 52 occurred in 56% of the patients treated with tocilizumab weekly and in 53% of those treated with tocilizumab every other week, as compared with 14% of those in the placebo group that underwent the 26-week prednisone taper and 18% of those in the placebo group that underwent the 52-week prednisone taper ($P<0.001$ for the comparisons of either active treatment with placebo). The cumulative median prednisone dose over the 52-week period was 1862 mg in each tocilizumab group, as compared with 3296 mg in the placebo group that underwent the 26-week taper ($P<0.001$ for both comparisons) and 3818 mg in the placebo group that underwent the 52-week taper ($P<0.001$ for both comparisons). Serious adverse events occurred in 15% of the patients in the group that received tocilizumab weekly, 14% of those in the group that received tocilizumab every other week, 22% of those in the placebo group that underwent the 26-week taper, and 25% of those in the placebo group that underwent the 52-week taper. Anterior ischemic optic neuropathy developed in one patient in the group that received tocilizumab every other week.

CONCLUSIONS

Tocilizumab, received weekly or every other week, combined with a 26-week prednisone taper was superior to either 26-week or 52-week prednisone tapering plus placebo with regard to sustained glucocorticoid-free remission in patients with giant-cell arteritis. Longer follow-up is necessary to determine the durability of remission and safety of tocilizumab. (Funded by F. Hoffmann–La Roche; ClinicalTrials.gov number, NCT01791153.)

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Giant-cell arteritis causes headaches, ischemic visual symptoms, vision loss, claudication of the jaw, claudication of the arms and legs, polymyalgia rheumatica, aortic aneurysm, myocardial infarction, and stroke.[1,2] Giant-cell arteritis generally occurs in adults older than 50 years of age and is 3 times as likely to occur in women as in men.[1] Glucocorticoids are the mainstay of treatment because they control headaches and systemic inflammation, normalize inflammatory markers, and prevent vision loss.[3-5] However, many patients receive long or repeated glucocorticoid courses to prevent disease flares.[3,4,6-9] Long-term use of glucocorticoids is associated with side effects.[3,7,8,10] Therefore, treatments that are capable of maintaining the remission of giant-cell arteritis after the discontinuation of glucocorticoids would be valuable.

The concentrations of C-reactive protein (CRP) and other acute-phase reactants that are increased by elevated serum levels of interleukin-6 correlate with disease activity.[11-17] Case series and a phase 2 trial have suggested that tocilizumab, an interleukin-6 receptor alpha inhibitor, allows for reductions in glucocorticoid doses that are used to control giant-cell arteritis and to maintain remission.[18-26]

We conducted a randomized, double-blind, placebo-controlled, phase 3 trial, the Giant-Cell Arteritis Actemra (GiACTA) trial, to investigate whether tocilizumab resulted in higher rates of sustained glucocorticoid-free remission of giant-cell arteritis than placebo through a period of 52 weeks.[27,28] Results from the 1-year trial are presented.

Methods

Trial Design and Patients

The trial design has been published previously,[27] and the protocol, including the statistical analysis plan, is available with the full text of this article at NEJM.org. We enrolled patients 50 years of age or older who had active giant-cell arteritis within 6 weeks before baseline and who had a history of an elevated erythrocyte sedimentation rate (ESR) attributable to giant-cell arteritis. Disease activity was defined as unequivocal evidence of cranial symptoms of giant-cell arteritis or polymyalgia rheumatica and increased concentrations of serum acute-phase reactants (Section S2 in the Supplementary Appendix, available at NEJM.org). The diagnosis of giant-cell arteritis was based on results of a temporal-artery biopsy showing features of giant-cell arteritis or on evidence of large-vessel vasculitis on angiography, computed tomographic or magnetic resonance angiography, or positron-emission tomography. Patients with newly diagnosed or relapsing disease were eligible.

In this 1-year trial, patients were randomly assigned in a 2:1:1:1 ratio to one of four groups: receipt of weekly subcutaneous tocilizumab, at a dose of 162 mg, plus a 26-week prednisone taper (referred to as the group receiving tocilizumab weekly); receipt of subcutaneous tocilizumab, at a dose of 162 mg, every other week, plus a 26-week prednisone taper (referred to as the group receiving tocilizumab every other week); weekly subcutaneous placebo plus a 26-week prednisone taper (referred to as the placebo group that underwent the 26-week taper); or weekly subcutaneous placebo plus a 52-week prednisone taper (referred to as the placebo group that underwent the 52-week taper). Randomization was stratified according to the baseline prednisone dose (≤30 mg per day vs. >30 mg per day).

Patients were required to adhere to the protocol-defined prednisone taper (Section S3 in the Supplementary Appendix).[28] Glucocorticoid treatment for giant-cell arteritis was initiated or the previously used dose was continued during screening at the discretion of the site investigator, on the basis of the dose that was anticipated to control the patient's disease. The use of intravenous methylprednisolone at doses greater than 100 mg daily within 6 weeks before baseline was not permitted. At baseline, the initial prednisone dose taken orally had to be between 20 mg and 60 mg per day. The prednisone dose was tapered weekly in all the trial groups as determined by the protocol. Doses of 20 mg or more per day were administered in an open-label manner, but when the prednisone dose was less than 20 mg per day, patients and all the trial personnel were unaware of the dose.[28] Once prednisone was tapered from 1 mg per day to 0 mg per day, placebo tablets were used to maintain the blinding.

Disease Assessments and Maintenance of Blinding

To prevent unblinding that could occur because of normalization of the CRP concentration after interleukin-6–receptor blockade with tocilizumab, all the trial personnel were unaware of the patients'

CRP levels.[27] A laboratory assessor monitored all other laboratory variables independently of the efficacy assessor and notified the efficacy assessor of any verified ESR of 30 mm or more per hour. The efficacy assessor evaluated clinical activity of giant-cell arteritis and managed the prednisone taper. Both the laboratory assessor and the efficacy assessor were unaware of the group assignments.

Disease assessment was performed at each visit to determine whether the patient's disease was in remission and whether the patient could safely continue the prednisone taper. Flare of the disease, which was determined by the efficacy assessor, was defined as the recurrence of signs or symptoms of giant-cell arteritis or as an elevation of the ESR to 30 mm or more per hour that was attributable to giant-cell arteritis. The definition of disease flare included the necessity for an increase in the prednisone dose. Remission was defined as the absence of flare and the normalization of the CRP concentration to less than 1 mg per deciliter. Sustained remission was defined as remission from week 12 through week 52 and adherence to the prednisone taper. Patients who had a flare or could not adhere to the prednisone taper switched to open-label escape therapy with prednisone but continued to receive the assigned trial regimen (tocilizumab or placebo). Such patients were considered to have treatment failure with regard to the primary outcome.

TRIAL OVERSIGHT

The trial was conducted in accordance with Good Clinical Practice guidelines and the Declaration of Helsinki. All the patients provided written informed consent. The investigators and sponsor designed the trial and gathered and analyzed the data. The sponsor provided tocilizumab and placebo and participated in the writing and editing of the drafts of the manuscript. All the authors vouch for the fidelity of the trial to the protocol and for the accuracy and completeness of the data and analyses reported. All the authors participated in the writing of every draft of the manuscript, with the assistance of medical writers paid by the sponsor.

END POINTS

The primary efficacy analysis compared the percentages of patients with sustained prednisone-free remission at week 52 between each tocilizumab group and the placebo group that underwent the 26-week taper. The key secondary analysis compared the percentages of patients with sustained remission at week 52 between each tocilizumab group and the placebo group that underwent the 52-week taper. Other secondary efficacy analyses included the cumulative prednisone dose over the 52-week trial period, the incidence of the first flare after remission in a time-to-event analysis, quality-of-life changes from baseline to week 52 (according to the physical and mental component summary scores of the Medical Outcomes Study 36-Item Short-Form Health Survey [SF-36]; on each of these assessments, scores range from 0 to 100, with higher scores representing better function), and a patient's global assessment of disease activity on the basis of a visual-analogue scale (VAS; scores range from 0 to 100 mm, with higher scores indicating greater disease activity).

Safety was assessed as the incidence, nature, and severity of adverse events and laboratory abnormalities in the safety population, which included patients who had received at least one dose of tocilizumab or placebo. Adverse events of giant-cell arteritis that were considered not to be serious by the investigators were reported as efficacy outcomes, not as adverse events.

STATISTICAL ANALYSIS

We calculated that a sample of 100 patients in the group that received tocilizumab weekly and 50 patients in both the group that received tocilizumab every other week and the placebo group that underwent the 26-week taper would provide the trial with more than 90% power to detect a difference in the percentage of patients with sustained remission at week 52 in each tocilizumab group versus the placebo group that underwent the 26-week taper, assuming an effect size of 40 percentage points (i.e., a difference of 40 percentage points in the percentage of patients with the primary outcome). Efficacy was assessed in the intention-to-treat population.

The primary and key secondary efficacy outcomes were tested at a 1% overall significance level (alpha level of 0.01) against two-sided alternatives. Two independent dose hierarchies (for separate comparisons of the two tocilizumab groups vs. placebo) were applied in a fixed sequential order of outcomes to control the type I error for multiple comparisons. Each hierarchy tested the primary outcome for the superiority of tocilizumab

over placebo plus the 26-week taper, followed by the key secondary outcome for the assessment of the noninferiority of tocilizumab versus placebo plus the 52-week taper. The statistical significance for superiority was determined as a P value of less than 0.005 for both the primary outcome and the key secondary outcome and as a P value of less than 0.01 for all other outcomes. No secondary-outcome tests other than for the key secondary outcome were corrected for multiple comparisons.

The comparison of the tocilizumab groups with the placebo group that underwent the 26-week taper for the primary outcome was performed with the use of a Cochran–Mantel–Haenszel test, with adjustment for the baseline prednisone dose (≤30 mg per day vs. >30 mg per day). The tocilizumab groups were also compared for noninferiority with the placebo group that underwent the 52-week taper on the basis of a noninferiority margin of –22.5 percentage points (Section S4 in the Supplementary Appendix). A two-sided 99.5% confidence interval for the difference between the trial groups was used for this comparison, as calculated on the basis of the normal approximation and adjusted for the baseline prednisone dose. A test for superiority was planned if the noninferiority criteria were met. P values were then calculated for the comparisons of superiority.

The time until the first flare was summarized by means of Kaplan–Meier curves. Trial groups were compared with the use of Cox proportional-hazards models, with adjustment for the baseline prednisone dose. Data censoring was used for patients who withdrew from the trial. Between-group differences in the expected cumulative prednisone dose were analyzed with the use of the nonparametric van Elteren test, stratified according to the baseline prednisone dose. Quality-of-life end points were analyzed with the use of repeated-measures analysis, with adjustment for baseline stratification factors, in which data obtained after the use of escape therapy were considered to be missing. No imputation was used for missing prednisone doses, missing mental or physical component summary scores, or missing data on the patient's global assessment of disease activity.

Patients who had a flare, received glucocorticoid treatment beyond that permitted by the protocol, withdrew from the trial, or did not have remission by week 12 were considered not to have had a response. In addition, patients who had two consecutive elevations in the CRP concentration above 1 mg per deciliter or one elevation in the CRP concentration followed by a missing value from week 12 (this last criterion was applied in the analysis phase in order to maintain blinding during the trial) were considered not to have had a response. To minimize bias from the effect of tocilizumab on the CRP concentration, a sensitivity analysis that excluded the requirement for a normalized CRP concentration from the definition of sustained remission was performed on the primary outcome and the key secondary outcome.

RESULTS

PATIENTS

We enrolled 251 patients from July 2013 through April 2015. A total of 100 patients were randomly assigned to the group that received tocilizumab weekly, 50 to the group that received tocilizumab every other week, 50 to the placebo group that underwent the 26-week taper, and 51 to the placebo group that underwent the 52-week taper. The intention-to-treat and safety populations included 250 patients because 1 patient who had been assigned to receive tocilizumab every other week did not receive the trial drug. A total of 216 patients (86%) completed the trial through week 52 (Fig. 1). The demographic characteristics and clinical features of the patients were similar among the four groups (Table 1).[29]

PRIMARY AND KEY SECONDARY OUTCOMES

A total of 56% of the patients in the group that received tocilizumab weekly and 53% of those in the group that received tocilizumab every other week had sustained remission at 52 weeks (the primary outcome), as compared with 14% of the patients in the placebo group that underwent the 26-week taper (P<0.001 for the comparison of each tocilizumab group with placebo) and 18% of those in the placebo group that underwent the 52-week taper (key secondary outcome; P<0.001 for the comparison of each tocilizumab group with placebo) (Table 2). The results of the sensitivity analysis supported those of the primary analysis and the key secondary analysis, except that the comparison of the group that received tocilizumab every other week with the placebo group that underwent the

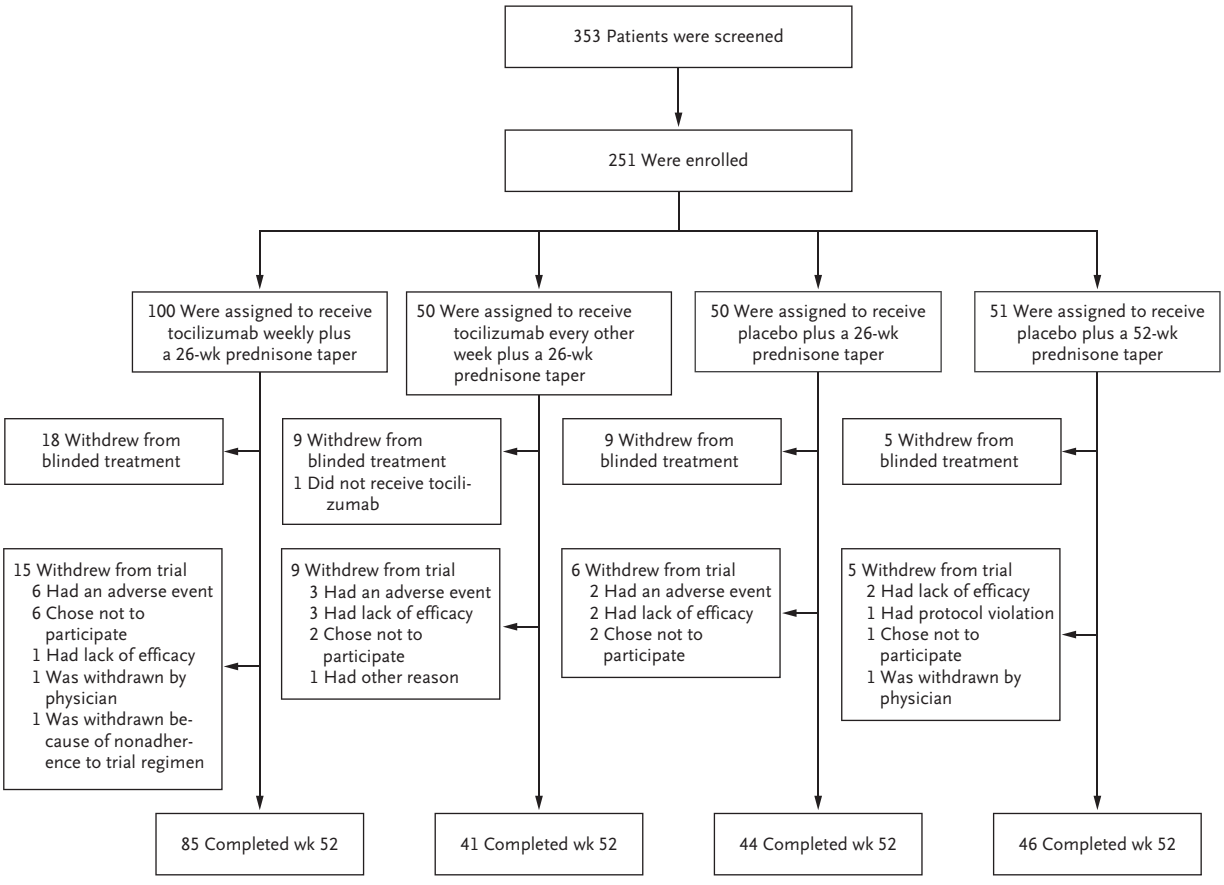


Figure 1. Screening, Randomization, and Follow-up of the Patients.
Not all the patients who withdrew from treatment withdrew from the trial.

52-week taper met the criteria for noninferiority but not for superiority (Table 2).

SECONDARY EFFICACY OUTCOMES

The percentages of patients who had a flare were 23% in the group that received tocilizumab weekly, 26% in the group that received tocilizumab every other week, 68% in the placebo group that underwent the 26-week taper, and 49% in the placebo group that underwent the 52-week taper. As compared with the placebo group that underwent the 26-week taper, the hazard ratios for flare were 0.23 (99% confidence interval [CI], 0.11 to 0.46) in the group that received tocilizumab weekly and 0.28 (99% CI, 0.12 to 0.66) in the group that received tocilizumab every other week ($P<0.001$ for both comparisons). The median value was not reached in the two tocilizumab groups (Fig. 2).

CUMULATIVE PREDNISONE DOSE

The total median cumulative prednisone dose over the 52-week period was 1862 mg (95% CI, 1582 to 1942) in the group that received tocilizumab weekly and 1862 mg (95% CI, 1568 to 2240) in the group that received tocilizumab every other week, as compared with 3296 mg (95% CI, 2730 to 4024) in the placebo group that underwent the 26-week taper and 3818 mg (95% CI, 2818 to 4426) in the placebo group that underwent the 52-week taper ($P<0.001$ for all comparisons of tocilizumab with placebo) (Table 2). In post hoc analyses, the percentages of patients who received open-label prednisone as escape therapy were 23% in the group that received tocilizumab weekly, 33% in the group that received tocilizumab every other week, 74% in the placebo group that underwent the 26-week taper, and 55% in the placebo group that underwent the 52-week taper.

Table 1. Demographic and Disease Characteristics of the Patients at Baseline.*

Characteristic	Tocilizumab Weekly (N=100)	Tocilizumab Every Other Week (N=50)	Placebo +26-Wk Taper (N=50)	Placebo +52-Wk Taper (N=51)
Age — yr	69.5±8.5	69.4±8.2	69.3±8.1	67.8±7.7
Female sex — no. (%)	78 (78)	35 (70)	38 (76)	37 (73)
Race — no. (%)†				
Asian	0	1 (2)	0	0
Black	1 (1)	0	0	2 (4)
Other	1 (1)	1 (2)	0	0
White	97 (97)	47 (94)	50 (100)	49 (96)
Unknown	1 (1)	1 (2)	0	0
Weight — kg	69.8±13.8	70.8±16.1	70.1±15.8	73.1±15.3
Body-mass index‡	26.0±4.4	26.0±6.2	25.7±4.5	25.8±4.1
Giant-cell arteritis — no. (%)				
Newly diagnosed	47 (47)	26 (52)	23 (46)	23 (45)
Relapsing	53 (53)	24 (48)	27 (54)	28 (55)
Prednisone dose — no. (%)				
≤30 mg/day	52 (52)	25 (50)	27 (54)	26 (51)
>30 mg/day	48 (48)	25 (50)	23 (46)	25 (49)
Disease duration — days	307±564	258±501	365±570	255±436
Cranial signs or symptoms — no. (%)§	78 (78)	41 (82)	40 (80)	40 (78)
Symptoms of polymyalgia rheumatica — no. (%)¶	59 (59)	32 (64)	30 (60)	35 (69)
Erythrocyte sedimentation rate — mm/hr	24.6±18.7	20.8±18.1	28.8±25.4	24.2±18.2
Diagnosis — no. (%)‖				
By means of positive temporal-artery biopsy	57 (57)	34 (68)	36 (72)	29 (57)
By means of positive imaging	50 (50)	23 (46)	19 (38)	23 (45)

* Plus–minus values are means ±SD. There were no significant differences among the four trial groups.
† Race was reported by the patients and confirmed by the investigators during screening.
‡ The body-mass index is the weight in kilograms divided by the square of the height in meters.
§ Cranial signs and symptoms were new-onset localized headache, scalp tenderness, temporal-artery tenderness, decreased pulsation, or jaw or mouth claudication.
¶ Symptoms of polymyalgia rheumatica were morning stiffness or pain in the shoulder or hip girdles.
‖ The diagnosis could have been based on either or both types of assessment.

RELAPSING DISEASE VS. NEWLY DIAGNOSED GIANT-CELL ARTERITIS

Prespecified subgroup analyses showed that among 131 patients who had relapsing disease at baseline (1 patient with relapsing disease at baseline was not included in the intention-to-treat population), the risk of flare was lower in the group that received weekly tocilizumab than in the placebo group that underwent the 26-week taper (hazard ratio, 0.23; 99% CI, 0.09 to 0.61; P<0.001) and than in the placebo group that underwent the 52-week taper (hazard ratio, 0.36; 99% CI, 0.13 to 1.00; P = 0.01) (Fig. S1 in the Supplementary Appendix). In this same subgroup of patients with relapsing disease, the patients who were treated with tocilizumab every other week did not have a significantly different risk than those in either placebo group (hazard ratio vs. placebo group with 26-week taper, 0.42; 99% CI, 0.14 to 1.28; P=0.05; hazard ratio vs. placebo group with 52-week taper, 0.67; 99% CI, 0.21 to 2.10; P=0.37). This differential outcome between the tocilizumab dose regimens was not seen in patients who had newly diagnosed disease at baseline (Fig. S1A and S1B in the Supplementary Appendix).

Table 2. Efficacy at Week 52 in the Intention-to-Treat Population.*

Outcome	Tocilizumab Weekly (N=100)	Tocilizumab Every Other Week (N=49)	Placebo +26-Wk Taper (N=50)	Placebo +52-Wk Taper (N=51)
Sustained remission with adherence to protocol-defined prednisone dose at wk 52				
Patients with sustained remission at wk 52 — no. (%)	56 (56)	26 (53)	7 (14)	9 (18)
Primary outcome: unadjusted difference in rate of sustained remission vs. placebo + 26-wk taper (99.5% CI) — percentage points†	42 (18 to 66)	39 (12 to 66)	—	—
P value	<0.001	<0.001		
Key secondary outcome: unadjusted difference in rate of sustained remission vs. placebo + 52-wk taper (99.5% CI) — percentage points†	38 (18 to 59)	35 (10 to 60)	—	—
P value	<0.001	<0.001		
Sustained remission, excluding normalization of CRP concentration, with adherence to protocol-defined prednisone dose at wk 52				
Patients with sustained remission at wk 52, excluding normalization of CRP concentration — no. (%)	59 (59)	27 (55)	10 (20)	17 (33)
Sensitivity analyses				
For primary outcome of unadjusted difference in rate of sustained remission vs. placebo + 26-wk taper (99.5% CI) — percentage points†	39 (15 to 63)	35 (8 to 62)	—	—
P value	<0.001	<0.001		
For key secondary outcome of unadjusted difference in rate of sustained remission vs. placebo + 52-wk taper (99.5% CI) — percentage points†	26 (3 to 49)	22 (−6 to 49)	—	—
P value	0.003	0.03		
Cumulative prednisone dose				
Expected cumulative dose — mg‡				
Median	1337	1442	1337	2608
Range	350 to 2632	332 to 2632	952 to 2632	822 to 3902
Actual cumulative dose — mg§				
Median	1862	1862	3296	3818
Range	630 to 6602	295 to 9912	932 to 9778	822 to 10,698
P value vs. each placebo group	<0.001	<0.001		

* Values are for the patients who had sustained remission while adhering to the protocol-defined prednisone dose at week 52, except as noted. Patients who had a flare, received escape therapy, withdrew from the trial, did not adhere to the protocol-defined prednisone taper, did not have remission by week 12, or had an elevated concentration of C-reactive protein (CRP) followed by an elevated or missing CRP concentration at the next assessment (except for the sensitivity analyses, from which these patients were excluded) were classified as not having had a response with respect to sustained remission.

† P values were calculated by a Cochran–Mantel–Haenszel test for superiority, with adjustment for the baseline prednisone dose (≤30 mg per day vs. >30 mg per day).

‡ The values for the expected cumulative dose were based on a patient's starting prednisone dose in the taper, assuming that the taper was continued without error.

§ The values for the actual cumulative dose were based on actual records of prednisone taken and included all escape therapy and use of commercial prednisone as well as the prednisone used in the tapering process. P values were calculated by a van Elteren test that was stratified according to the baseline prednisone dose (≤30 mg per day vs. >30 mg per day). For any records of missed tablets from the protocol-defined taper of prednisone, the missed tablets were assumed to be the minimum-dose tablets available from that pack. Patients who received an increased dose of prednisone because they entered escape therapy were included in their originally assigned treatment group. No imputation of missing data was implemented.

QUALITY-OF-LIFE ASSESSMENTS

The mean increase (indicating clinical improvement) from baseline to week 52 in the SF-36 physical component summary score was 4.10 in the group that received tocilizumab weekly and 2.76 in the group that received tocilizumab every other week, whereas scores decreased (indicating a worse condition) in the two placebo groups (–0.28 in the placebo group with the 26-week taper and –1.49 in the placebo group with the 52-week taper). The difference between the group that received tocilizumab weekly and the placebo group that underwent the 52-week taper was 5.59 points (99% CI, 0.86 to 10.32; P=0.002). However, the differences between the group that received tocilizumab every other week and each placebo group with respect to the SF-36 physical component summary score did not reach statistical significance. The mean change from baseline in the mental component summary score did not differ significantly between the group that received tocilizumab weekly (score change, 7.28) or the group that received tocilizumab every other week (6.12) and the placebo group that underwent the 26-week taper (6.67) or the placebo group that underwent the 52-week taper (2.84) (Section 5 in the Supplementary Appendix).

The mean decreases (indicating improvement) from baseline to week 52 in the patients' global assessment of disease activity VAS score of –19.0 in the group that received tocilizumab weekly and –25.3 in the group that received tocilizumab every other week were greater than the decrease in either placebo group (–3.4 in the placebo group with the 26-week taper and –7.2 in the placebo group with the 52-week taper; P<0.05 for all comparisons of tocilizumab weekly with placebo; P<0.01 for all comparisons of tocilizumab every other week with placebo) (Section S5 in the Supplementary Appendix).

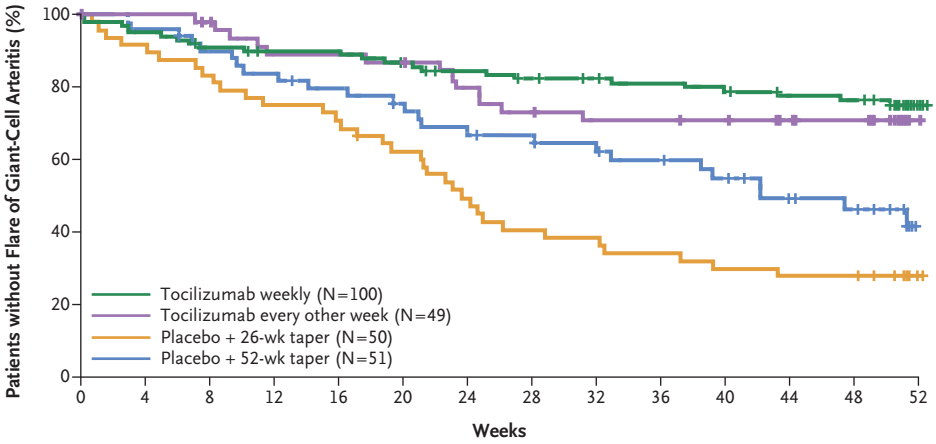
SAFETY

The percentages of patients with adverse events were similar in all the trial groups (Table 3), but fewer patients reported serious adverse events in the group that received tocilizumab weekly (15%) or every other week (14%) than in the placebo group that underwent the 26-week taper (22%) or the placebo group that underwent the 52-week taper (25%). Infection was the most frequently reported adverse event and serious adverse event (Table 3, and Section S6 in the Supplementary Appendix). Serious infections occurred in 7% of the patients in the group that received tocilizumab weekly, 4% of those in the group that received tocilizumab every other week, 4% of those in the placebo group that underwent the 26-week taper, and 12% in the placebo group that underwent the 52-week taper (Table 3).

Withdrawal from the trial due to an adverse event occurred in 6% of the patients in each tocilizumab group, in 4% of those in the placebo group that underwent the 26-week taper, and in no patients in the placebo group that underwent the 52-week taper (Table 3 and Fig. 1). Common reasons for withdrawal from the trial were adverse events (in 11 of 251 patients [4%]), patient's decision (in 11 [4%]), and lack of efficacy (in 8 [3%]). No patients died during year 1. Injection-site reaction occurred in 7% of the patients in the group that received tocilizumab weekly, in 14% of those in the group that received tocilizumab every other week, in 10% of those in the placebo group that underwent the 26-week taper, and in 2% of those in the placebo group that underwent the 52-week taper (Table 3). No gastrointestinal perforations, myocardial infarctions, demyelinating disorders, or anaphylaxis were reported.

One patient in the group that received tocilizumab every other week had a thrombotic stroke on day 254 of the trial. The treating investigator attributed this event to the discontinuation of warfarin for a surgery unrelated to giant-cell arteritis; the stroke was considered by the investigators to be unrelated to the trial drug or to giant-cell arteritis. One episode of anterior ischemic optic neuropathy occurred in the context of a disease flare in one patient in the group that received tocilizumab every other week. The visual loss resolved with glucocorticoid treatment, and the patient was considered to have treatment failure with regard to the primary outcome. Data on vision symptoms at the time of disease flares are shown in Section 8 in the Supplementary Appendix.

Four patients (4%) in the group that received tocilizumab weekly and two (4%) in the group that received tocilizumab every other week had grade 3 neutropenia. A grade 3 elevation of the alanine aminotransferase level occurred in two patients (2%) in the group that received tocilizumab weekly, in one (2%) in the group that received tocilizumab every other week, and in one (2%) in the placebo group that underwent the 52-week taper.



No. at Risk

Tocilizumab weekly	100	93	88	85	85	81	77	74	71	69	67	64	63	5
Tocilizumab every other week	49	47	45	40	40	39	35	32	30	30	29	26	24	2
Placebo + 26-wk taper	50	44	40	36	34	29	23	19	18	16	14	13	13	3
Placebo + 52-wk taper	51	48	44	41	38	35	32	30	28	25	22	17	15	0

Figure 2. Time to First Flare after Clinical Remission of Giant-Cell Arteritis in All Patients.

Patients who never had remission were considered to have had a flare at week 0 (data were censored [tick marks] at that time point). Patients who withdrew from the trial before week 52 had their data censored at the time of withdrawal. The values at week 52 represent patients without flare whose week 52 visit was on day 364 of the trial only for the purpose of plotting time points; the analysis captured all the trial days associated with a week 52 visit, and appropriate censoring was applied. In a comparison with the placebo group that underwent the 26-week taper, the hazard ratio in the group that received tocilizumab weekly was 0.23 (99% CI, 0.11 to 0.46) and the hazard ratio in the group that received tocilizumab every other week was 0.28 (99% CI, 0.12 to 0.66; P<0.001 for both comparisons). Absolute values for the two tocilizumab groups could not be evaluated because the median was not reached.

DISCUSSION

This trial of tocilizumab for the treatment of giant-cell arteritis showed that the two regimens of tocilizumab weekly and of tocilizumab every other week, in combination with a prednisone taper over a period of 26 weeks, were superior to placebo plus a prednisone taper of 26 weeks and to placebo plus a prednisone taper of 52 weeks with regard to sustained remission. The rates of adverse events did not differ across the trial groups, except that neutropenia occurred in 4% of the patients treated with tocilizumab, a rate similar to rates observed in previous trials of tocilizumab.[30] However, one patient who had been assigned to receive tocilizumab every other week had anterior ischemic optic neuropathy and vision loss that resolved after treatment with glucocorticoids. It is important that clinicians treating patients with giant-cell arteritis maintain vigilance for vision complications and other disease-related events, even in patients receiving active therapy.

Patients with giant-cell arteritis are at greater risk for adverse events than the general population, especially in the first year after diagnosis.[7,31] This situation may reflect the receipt of high cumulative glucocorticoid doses. Patients who were assigned to the placebo groups received approximately twice the cumulative glucocorticoid dose as patients assigned to the tocilizumab groups. The numerically higher rates of serious adverse events in the placebo groups might have been the result of the effects of glucocorticoids. In addition, the improvement in the SF-36 physical component summary score in the tocilizumab groups might have reflected disease control and lower cumulative glucocorticoid doses.

There were a number of challenges in designing this trial. First, no validated outcome measures are available to assess giant-cell arteritis in clinical trials. To address this situation, we used stringent definitions of flare and remission. Furthermore, the requirement for escape therapy with prednisone was part of the definition of flare.

Table 3. Safety over the 52-Week Trial Period.*

Variable	Tocilizumab Weekly (N=100)	Tocilizumab Every Other Week (N=49)	Placebo +26-Wk Taper (N=50)	Placebo +52-Wk Taper (N=51)
Duration in trial — patient-yr	92.9	45.6	47.4	48.1
Patients with ≥1 adverse event — no. (%)	98 (98)	47 (96)	48 (96)	47 (92)
Adverse events				
No. of events	810	432	470	486
Rate per 100 patient-yr (95% CI)	872.0 (813.0–934.2)	948.0 (860.7–1041.7)	990.8 (903.2–1084.5)	1011.2 (923.3–1105.3)
Patients with ≥1 infection — no. (%)				
Any	75 (75)	36 (73)	38 (76)	33 (65)
Serious	7 (7)	2 (4)	2 (4)	6 (12)
Patients who withdrew from the trial because of adverse events — no. (%)†	6 (6)	3 (6)	2 (4)	0
Patients with injection-site reaction — no. (%)	7 (7)	7 (14)	5 (10)	1 (2)
Flare of giant-cell arteritis reported as serious adverse event — no. (%)‡	1 (1)	1 (2)§	1 (2)	1 (2)
Patients with ≥1 serious adverse event — no. (%)				
Any	15 (15)	7 (14)	11 (22)	13 (25)
According to system organ class¶				
Infection or infestation	7 (7)	2 (4)	2 (4)	6 (12)
Vascular disorder	4 (4)	2 (4)	2 (4)	1 (2)
Respiratory, thoracic, or mediastinal disorder	2 (2)	1 (2)	2 (4)	2 (4)
Injury, poisoning, or procedural complication	3 (3)	1 (2)	1 (2)	0
Nervous system disorder	1 (1)	1 (2)	2 (4)	1 (2)
Cardiac disorder	2 (2)	0	0	2 (4)
Musculoskeletal or connective-tissue disorder	1 (1)	0	1 (2)	2 (4)
Gastrointestinal disorder	1 (1)	0	2 (4)	0
Cancer	0	0‖	1 (2)	1 (2)

* No gastrointestinal perforations were reported, and no patients died.
† Values are reported for the entire trial population; that is, values were included for 50 patients in the group that received tocilizumab every other week (i.e., including the patient who did not receive tocilizumab).
‡ Values are for flares of giant-cell arteritis that met the protocol-defined criteria for being reported as a serious adverse event.
§ This patient had anterior ischemic optic neuropathy after randomization.
¶ Values were those reported in at least 1% of the patients overall. Patients may have had more than one class of serious adverse event.
‖ One patient in the group that received tocilizumab every other week had a benign ovarian adenoma.

This strategy ensured that symptoms were sufficiently severe to justify an increase in the prednisone dose and created consistency in instituting changes in medications across trial sites. Second, tocilizumab lowers serum CRP concentrations, which poses a risk of unblinding. Consequently, all the investigators and patients were not aware of the CRP concentrations. To address safety concerns, a dual-assessor approach was used in which the laboratory assessor was required to notify the efficacy assessor of clinically significant elevations in the ESR. Only seven flares (all in the placebo groups) were associated with elevations in the ESR without signs or symptoms of giant-cell arteritis. The exclusion of these flares from the analyses did not alter the trial conclusions.

In conclusion, tocilizumab combined with a 26-week prednisone taper was superior to either a 26-week or 52-week prednisone taper plus placebo with regard to the sustained remission of giant-cell arteritis. Tocilizumab treatment was associated with a reduction in the cumulative pred-

nisone dose over the 52-week trial period. Although both the regimen of weekly tocilizumab and the regimen of every-other-week tocilizumab were superior to the 26-week and 52-week prednisone-plus-placebo regimens with regard to sustained remission, weekly treatment with tocilizumab resulted in greater disease control than did treatment with tocilizumab every other week. A 2-year, open-label, follow-up phase of this trial may provide additional information pertaining to the safety and efficacy of tocilizumab beyond 52 weeks. Further studies are required in order to determine the longer-term efficacy and safety of tocilizumab.

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APPENDIX

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