ORIGINAL ARTICLE

Tofacitinib for Psoriatic Arthritis in Patients with an Inadequate Response to TNF Inhibitors

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ABSTRACT

BACKGROUND

Tofacitinib is an oral Janus kinase inhibitor that is under investigation for the treatment of psoriatic arthritis. We evaluated tofacitinib in patients with active psoriatic arthritis who had previously had an inadequate response to tumor necrosis factor (TNF) inhibitors.

METHODS

In this 6-month randomized, placebo-controlled, double-blind, phase 3 trial, we randomly assigned 395 patients, in a 2:2:1:1 ratio, to four regimens: 5 mg of tofacitinib administered orally twice daily (132 patients); 10 mg of tofacitinib twice daily (132 patients); placebo, with a switch to 5 mg of tofacitinib twice daily at 3 months (66 patients); or placebo, with a switch to 10 mg of tofacitinib twice daily at 3 months (65 patients). Data from the patients who received placebo during the first 3 months of the trial were pooled. The primary end points were the percentage of patients who had at least 20% improvement according to the criteria of the American College of Rheumatology (ACR20 response) and the change from baseline score on the Health Assessment Questionnaire–Disability Index (HAQ-DI; scores range from 0 to 3, with higher scores indicating greater disability) at the month 3 analysis.

RESULTS

At 3 months, the rates of ACR20 response were 50% with the 5-mg dose of tofacitinib and 47% with the 10-mg dose, as compared with 24% with placebo ($P<0.001$ for both comparisons); the corresponding mean changes from baseline in HAQ-DI score were −0.39 and −0.35, as compared with −0.14 ($P<0.001$ for both comparisons). Serious adverse events occurred in 4% of the patients who received the 5-mg dose of tofacitinib continuously and in 6% who received the 10-mg dose continuously. Over the course of 6 months, there were four serious infections, three herpes zoster infections, one myocardial infarction, and one ischemic stroke among the patients who received tofacitinib continuously. Elevations of aspartate and alanine aminotransferase concentrations of three or more times the upper limit of the normal range occurred in more patients who received tofacitinib continuously than in patients who received placebo followed by tofacitinib.

CONCLUSIONS

In this trial involving patients with active psoriatic arthritis who had had an inadequate response to TNF inhibitors, tofacitinib was more effective than placebo over 3 months in reducing disease activity. Adverse events were more frequent with tofacitinib than with placebo. (Funded by Pfizer; OPAL Beyond ClinicalTrials.gov number, NCT01882439.)

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Psoriatic arthritis is a chronic inflammatory disease that is characterized by peripheral arthritis, enthesitis, dactylitis, axial disease, and skin manifestations.[1,2] Depending on the clinical manifestations of the disease, recommended treatments, in addition to topical and systemic treatments for skin manifestations, include nonsteroidal antiinflammatory drugs; conventional synthetic disease-modifying antirheumatic drugs (DMARDs), such as methotrexate, sulfasalazine, and leflunomide; targeted synthetic DMARDs, such as phosphodiesterase-4 inhibitors and apremilast; and biologic DMARDs, such as tumor necrosis factor (TNF) inhibitors, interleukin-12/23 inhibitors, and interleukin-17 inhibitors.[2,3] TNF inhibitors are the current standard of care for severe disease and specific manifestations such as enthesitis and axial disease when conventional synthetic DMARDs are ineffective.[2,3] However, the use of TNF inhibitors is limited in patients who have an inadequate response because of loss of efficacy or adverse events.[4]

Tofacitinib is an oral Janus kinase (JAK) inhibitor that is under investigation for the treatment of psoriatic arthritis. Tofacitinib preferentially inhibits signaling through JAK3 and JAK1 with functional selectivity over JAK2.[5] In psoriatic skin fibroblasts of patients with psoriatic arthritis, tofacitinib significantly decreased expression of phosphorylated signal transducer and activator of transcription 3 (pSTAT3), pSTAT1, and nuclear factor κB p65 and induced expression of suppressor of cytokine signaling-3 and protein inhibitor of activated STAT3.[6] Inhibition of JAKs may result in modulation of psoriatic inflammation in articular and extraarticular locations.[7] We report the results of the Oral Psoriatic Arthritis Trial (OPAL) Beyond, a randomized phase 3 trial of tofacitinib restricted to patients with active psoriatic arthritis who had had an inadequate response to at least one TNF inhibitor.

Methods

Patients

Patients were eligible for participation in the trial if they were 18 years of age or older (≥20 years of age in Taiwan), had received a diagnosis of psoriatic arthritis at least 6 months previously, fulfilled the Classification Criteria for Psoriatic Arthritis (CASPAR),[8] had active plaque psoriasis at screening, had active arthritis (≥3 swollen and ≥3 tender or painful joints) at screening and at baseline, and had had an inadequate response to at least one TNF inhibitor, as determined by a lack of efficacy or the occurrence of an adverse event that was considered by the treating physician to be related to treatment. Further details of inclusion and exclusion criteria are provided in the Supplementary Appendix, available with the full text of this article at NEJM.org.

Trial Design

OPAL Beyond was a 6-month randomized, placebo-controlled, double-blind, multicenter, phase 3 trial that was performed at 98 multinational centers from June 2013 through April 2016 (Table S1 in the Supplementary Appendix). A centralized automated randomization system was used to assign patients, in a 2:2:1:1 ratio, to one of the following regimens: 5 mg of tofacitinib administered orally twice daily for 6 months; 10 mg of tofacitinib twice daily for 6 months; placebo, with a switch to 5 mg of tofacitinib twice daily at 3 months; or placebo, with a switch to 10 mg of tofacitinib twice daily at 3 months. The switch from placebo to the preassigned dose of tofacitinib at 3 months was made in a blinded manner. Tofacitinib or placebo was administered orally at 12-hour intervals; matching placebo tablets were used to maintain the blinding. All the patients received a stable dose of a single conventional synthetic DMARD throughout the trial. The investigators, patients, and sponsor were unaware of the trial-group assignments for the duration of the trial.

Trial Oversight

The trial was conducted in accordance with the International Conference on Harmonisation Good Clinical Practice guidelines and the principles of the Declaration of Helsinki. The trial protocol, available at NEJM.org, and all documentation were approved by the institutional review board or independent ethics committee at each investigational site. All patients provided written, informed consent. The trial was sponsored by Pfizer, which provided the trial medication and placebo. Personnel from Pfizer designed the trial in conjunction with the principal academic investigators. A contract research organization (ICON) collected the trial data; the data on outcomes and adverse events were analyzed by personnel from Pfizer and were interpreted by all the authors. Drafts of the manuscript were

written by an employee of Complete Medical Communications, who was funded by Pfizer; all the authors participated in the writing of the manuscript by jointly evaluating the data at each stage of review and either drafting or critically revising the content. Amendments to the protocol after commencement of the trial are detailed in the Supplementary Appendix. The authors vouch for the completeness and accuracy of the data and for the fidelity of the trial to the protocol. The authors and the sponsor made the decision to submit the manuscript for publication.

TRIAL END POINTS

The two primary end points at 3 months were the percentage of patients who had at least 20% improvement according to the criteria of the American College of Rheumatology (ACR20 response)[9] and the change in Health Assessment Questionnaire–Disability Index (HAQ-DI) score from baseline.[10] An ACR20 response is defined as a 20% or greater reduction from baseline in the numbers of tender or painful joints (of 68 joints assessed) and swollen joints (of 66 joints assessed) and improvement of 20% or more in at least three of the following measures: the patient's global assessment of arthritis (as measured on a visual-analogue scale that ranges from 0 to 100 mm), the physician's global assessment of arthritis (as measured on a visual-analogue scale), the patient's assessment of arthritis pain (as measured on a visual-analogue scale), disability (as measured by the HAQ-DI), or the C-reactive protein level. The HAQ-DI measures physical function; overall scores range from 0 to 3, with higher scores indicating greater disability. A 0.35-point decrease from baseline is considered to be the smallest change that is clinically important for patients with psoriatic arthritis.[11] Primary end points were assessed at baseline, week 2, and months 1, 2, 3, 4, and 6.

Secondary efficacy end points, including patient-reported outcomes, were assessed at multiple trial visits (additional details are provided in the Supplementary Appendix). Secondary efficacy end points included the percentage of patients who had at least 50% and at least 70% improvement according to the ACR (ACR50 and ACR70 response, respectively); scores on the components of ACR response criteria; the percentage of patients who had improvement in the score on the psoriasis area-and-severity index (PASI) of at least 75% (PASI75; PASI scores range from 0 to 72, with higher scores indicating more severe disease),[12] which was assessed among patients who had had, at baseline, at least 3% of their body-surface area affected by psoriasis[13,14] and a PASI score greater than 0; and the percentage of patients who met Psoriatic Arthritis Response Criteria, as defined in the Supplementary Appendix.[15] For patients with dactylitis or enthesitis at baseline, improvements were assessed according to the change from baseline in the Dactylitis Severity Score (scores range from 0 to 60, with higher scores indicating greater severity),[16] Spondyloarthritis Research Consortium of Canada (SPARCC) index score (scores range from 0 to 16, with higher scores indicating more affected sites),[17] and the Leeds Enthesitis Index score (scores range from 0 to 6, with higher scores indicating more affected sites).[18] Patient-reported outcomes included the change from baseline in the physical functioning score on the Medical Outcomes Study 36-Item Short-Form Health Survey version 2 (SF-36; norm-based scores were used, with higher scores indicating better health-related quality of life),[19] in the total score on the Functional Assessment of Chronic Illness Therapy–Fatigue (FACIT-F; scores range from 0 to 52, with higher scores indicating less fatigue),[20] and in scores on the five domains of the European Quality of Life–5 Dimensions (EQ-5D) Health State Profile (scores for each domain range from 0 to 3, with higher scores indicating greater impairment).[21] The percentage of patients with responses that met the criteria for minimal disease activity[22] was also analyzed; minimal disease activity was defined by the presence of at least five of the following seven items: no more than one tender joint, no more than one swollen joint, a PASI score of one or less or a body-surface area covered by psoriasis of 3% or less, a patient's assessment of arthritis pain of 15 mm or less on the visual-analogue scale, patient's global assessment of arthritis of 20 mm or less on the visual-analogue scale, HAQ-DI score of 0.5 or less, and more than one tender enthesitis site.

Safety assessments included adverse-event reporting, physical examinations, and clinical laboratory tests. Adverse events of special interest, as defined in the trial protocol, included serious infection, herpes zoster infection, opportunistic infection, *Mycobacterium tuberculosis* infection, cancers, cardiovascular events, hepatic events, interstitial lung disease, and gastrointestinal perforations. Potential opportunistic infections, cancers,

cardiovascular events, and hepatic events were adjudicated by independent expert committees whose members were unaware of the trial-group assignments (see the Supplementary Appendix).

STATISTICAL ANALYSIS

Details regarding the calculation of the sample size are provided in the Supplementary Appendix. Efficacy analyses included all patients who underwent randomization and received at least one dose of tofacitinib or placebo (full analysis set). To control for type I error at the 5% level, sequential hierarchical testing was performed; for all end points, the comparison of the 10-mg dose of tofacitinib with placebo was performed before the comparison of the 5-mg dose of tofacitinib with placebo (see the Supplementary Appendix). With respect to the primary endpoint analysis at 3 months, testing of the ACR20 response rate was performed for each dose of tofacitinib versus placebo, followed by testing for the change in HAQ-DI score from baseline. If both primary end points were significant, the following key secondary end points at 3 months were tested in hierarchical order: the PASI75 response rate and the change from baseline in the Leeds Enthesitis Index score, Dactylitis Severity Score, SF-36 physical functioning score, and FACIT-F total score. The type I error was controlled globally for the primary end points and the key secondary end points. Testing was planned to stop at the first instance at which statistical significance was not reached in the hierarchical sequence. Additional hierarchies were applied to the ACR family responses at the month 3 analysis (with the 10-mg tofacitinib dose and then the 5-mg dose compared with placebo with respect to the ACR20 response, followed by ACR50 response and then ACR70 response) and to the ACR20 responses at each study visit (with the 10-mg tofacitinib dose and then the 5-mg dose compared with placebo with respect to the ACR20 response at 3 months, followed by 2 months, 1 month, and 2 weeks). Statistical significance was declared if a comparison passed the test according to the prespecified hierarchical testing procedure. All P values are two-sided. For all trial end points, 95% confidence intervals for the difference from placebo are provided in Table S2 in the Supplementary Appendix.

Binary end points were compared with the use of the normal approximation for the difference in binomial proportions, with an imputation of no response for missing values (patients who withdrew from the trial were considered to have no response at any visit after discontinuation). Continuous end points were analyzed with the use of a repeated-measures model that included trial group, visit, interaction of the trial group by visit, geographic location, and baseline value as fixed effects. The model used a common unstructured variance–covariance matrix, without imputation for missing data. Supportive analyses for the primary end points are described in the Supplementary Appendix. In the analyses of results through the first 3 months, the two placebo-to-tofacitinib sequences were combined into a single placebo group (pooled placebo group); the results through month 3 are from this model. In the analyses of results through month 6 (including all postbaseline data through month 6), the placebo-to-tofacitinib sequences were kept separate; the results from month 4 through month 6 are from this model. The response rate or least-squares mean change from baseline was determined for each trial group at each visit through month 6; the comparisons between each active treatment and placebo were made at each visit through month 3 (comparison with placebo was not applicable after month 3, because all patients received active treatment after this visit). Safety data were summarized descriptively for all patients who received at least one dose of tofacitinib or placebo (safety analysis set, which was equivalent to the full analysis set in this trial).

RESULTS

PATIENTS

Of 546 patients screened, 395 underwent randomization, of whom 394 received at least one dose of tofacitinib or placebo; 131 were assigned to receive the 5-mg dose of tofacitinib continuously, 132 to receive the 10-mg dose of tofacitinib continuously, 66 to receive placebo with a switch to the 5-mg dose of tofacitinib after 3 months, and 65 to receive placebo with a switch to the 10-mg dose of tofacitinib after 3 months (Fig. 1). The demographic and disease characteristics of the patients at baseline were similar across the groups, with the exception of the mean number of tender or painful joints, for which a significant difference was seen across trial groups and was highest in the group that was assigned to receive the 10-mg dose of tofaci-

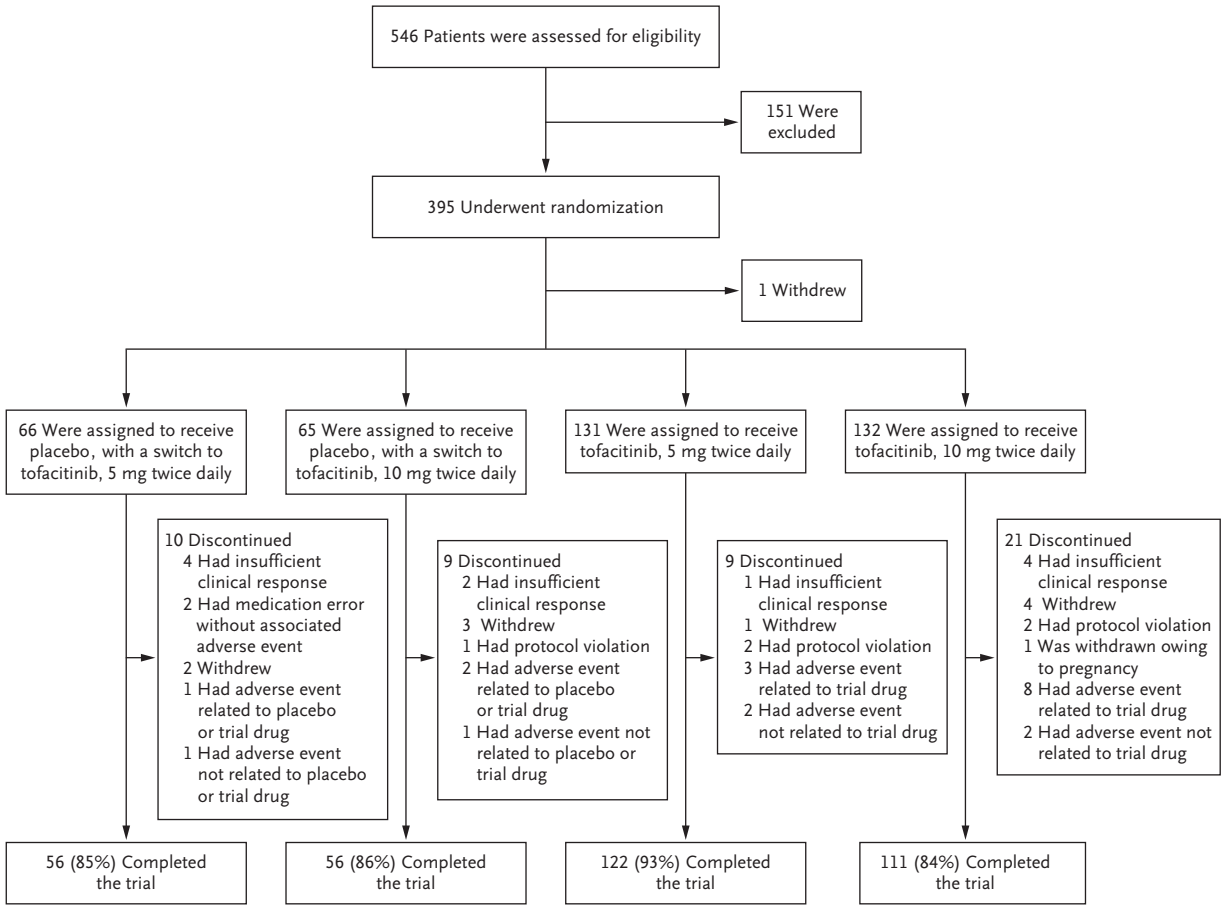

Figure 1. Screening, Randomization, and Follow-up of the Patients.

Patients in the two placebo groups switched to the assigned tofacitinib dose at month 3 in a blinded manner. Numbers of patients who discontinued the trial drug or placebo are shown through the end of the trial at 6 months. Through the first 3 months, the trial drug or placebo was discontinued in 15 patients who received placebo, 5 patients who received the 5-mg dose of tofacitinib, and 10 patients who received the 10-mg dose of tofacitinib.

tinib continuously (Table 1, and Table S3 in the Supplementary Appendix).

EFFICACY

At 3 months, the rates of ACR20 response were 50% with the 5-mg dose of tofacitinib and 47% with the 10-mg dose of tofacitinib, as compared with 24% with placebo ($P<0.001$ for both comparisons), and the corresponding mean changes in HAQ-DI score from baseline were −0.39 and −0.35, as compared with −0.14 ($P<0.001$ for both comparisons) (Table 2 and Fig. 2, and Fig. S1 in the Supplementary Appendix). The rate of ACR20 response was significantly higher with the 5-mg and 10-mg doses of tofacitinib than with placebo at week 2 ($P=0.005$ and $P=0.001$, respectively) (Fig. 2). The changes from baseline in these end points at 6 months were numerically similar to the changes at 3 months in the continuous tofacitinib groups, but the changes could not be compared with placebo at 6 months because all the patients received active treatment after 3 months. The rates of ACR20 response were numerically higher among patients who had had fewer inadequate responses to TNF inhibitors; however, the change from baseline in HAQ-DI score was similar in all subgroups defined according to the number of TNF inhibitors that had failed in the patients owing to an inadequate response. Improvements in ACR component scores at 6 months were consistent with the findings for the primary end point of ACR20 response. (Additional details

Table 1. Baseline Demographics and Clinical Characteristics of Patients.*

Baseline Variable	Placebo (N=131)†	Tofacitinib, 5 mg (N=131)	Tofacitinib, 10 mg (N=132)
Patient demographics			
Age — yr	49.0±12.6	49.5±12.3	51.3±10.9
Female sex — no. (%)	80 (61)	64 (49)	74 (56)
White race — no. (%)‡	118 (90)	121 (92)	124 (94)
Disease characteristics			
Duration of psoriatic arthritis — yr	9.4±8.1	9.6±7.6	9.1±6.8
HAQ-DI score§	1.3±0.8	1.3±0.7	1.4±0.6
Leeds Enthesitis Index¶			
Score >0 — no. (%)	93 (71)	83 (63)	99 (75)
Mean score	2.8±1.6	3.0±1.6	3.4±1.8
Dactylitis Severity Score‖			
Score >0 — no. (%)	63 (48)	66 (50)	65 (49)
Mean score	6.8±5.7	7.8±9.9	9.5±8.2
Swollen-joint count (of 66 joints assessed) — no.	10.5±9.0	12.1±10.6	12.8±11.2
Tender- or painful-joint count (of 68 joints assessed) — no.	19.8±14.9	20.5±13.0	25.5±17.5
Elevated high-sensitivity CRP — no. (%)**	80 (61)	85 (65)	82 (62)
Affected body-surface area ≥3% — no. (%)	86 (66)	80 (61)	81 (61)
Median PASI score (range)††	7.1 (1.6–66.0)	7.6 (0.6–32.2)	8.8 (0.8–41.6)
Day 1 oral glucocorticoid use — no. (%)	31 (24)	37 (28)	25 (19)
Concomitant use of conventional synthetic DMARD up to 3 mo — no. (%)			
Methotrexate	101 (77)	98 (75)	91 (69)
Leflunomide	9 (7)	12 (9)	14 (11)
Sulfasalazine	20 (15)	21 (16)	24 (18)
Other‡‡	1 (1)	2 (2)	1 (1)
Methotrexate dose on day 1 — mg per wk§§	14.1±4.3	14.7±4.4	14.1±4.6
No. of previous TNF inhibitors	1.5±0.8	1.7±1.0	1.6±0.9
Previous use of other biologic agents in addition to TNF inhibitors — no. (%)	11 (8)	11 (8)	14 (11)
SF-36 physical functioning score¶¶	34.0±11.0	33.5±10.4	32.1±9.9
FACIT-F total score‖‖	27.5±11.6	26.1±12.2	26.1±10.3

* Plus–minus values are means ±SD. Analyses were performed in the safety analysis set, which included all patients who received at least one dose of tofacitinib or placebo (equivalent to the full analysis set in this trial). Unadjusted P values were determined with the use of the chi-square test for categorical variables and the Kruskal–Wallis test for continuous variables. A significant difference among trial groups was observed with respect to the mean number of tender or painful joints (unadjusted P=0.03); all other between-group differences were not significant. DMARD denotes disease-modifying antirheumatic drug, and TNF tumor necrosis factor.

† The data in the pooled placebo group were combined from the two groups of patients who received placebo during the first 3 months.

‡ Race was reported by the patient.

§ Scores on the Health Assessment Questionnaire–Disability Index (HAQ-DI) range from 0 to 3, with higher scores indicating greater disability.

¶ Scores on the Leeds Enthesitis Index range from 0 to 6, with higher scores indicating more affected sites. A score greater than 0 indicates the presence of enthesitis. The mean score was determined among the patients who had a score higher than 0.

‖ The Dactylitis Severity Score is on a scale from 0 to 60, with higher scores indicating greater severity. A score greater than 0 indicates the presence of dactylitis. The mean score was determined among the patients who had a score higher than 0.

** An elevated level of high-sensitivity C-reactive protein (CRP) was defined as a level of more than 2.87 mg per liter.

†† Scores on the psoriasis area-and-severity index (PASI) range 0 to 72, with higher scores indicating more severe disease. The median score was determined among patients in whom psoriasis affected at least 3% of the body-surface area at baseline and who had a PASI score higher than 0.

‡‡ Other DMARDs included hydroxychloroquine and chloroquine.

§§ The maximum permitted dose of methotrexate was 20 mg per week.

¶¶ Norm-based scores were used for the physical functioning scores on the Medical Outcomes Study 36-Item Short-Form Health Survey (SF-36) version 2; higher scores indicate better health-related quality of life.

‖‖ Scores on the Functional Assessment of Chronic Illness Therapy–Fatigue (FACIT-F) range from 0 to 52, with higher scores indicating less fatigue.

Table 2. Efficacy End Points and Patient-Reported Outcomes at 3 Months and 6 Months.*

Variable	At 3 Mo			At 6 Mo			
	Placebo (N=131)	Tofacitinib, 5 mg (N=131)	Tofacitinib, 10 mg (N=132)	Placebo to Tofacitinib, 5 mg (N=66)	Placebo to Tofacitinib, 10 mg (N=65)	Tofacitinib, 5 mg (N=131)	Tofacitinib, 10 mg (N=132)
Primary efficacy end points							
ACR20 response — no. (%)	31 (24)	65 (50)†‡	62 (47)†‡	33 (50)	35 (54)	78 (60)	65 (49)
Change in HAQ-DI score from baseline	−0.14±0.05 [117]	−0.39±0.05 [124]†‡	−0.35±0.05 [120]†‡	−0.48±0.07 [56]	−0.42±0.07 [56]	−0.44±0.05 [122]	−0.34±0.05 [112]
Key secondary efficacy end points							
PASI75 response — no./total no. (%)§	12/86 (14)	17/80 (21)	35/81 (43)†‡	11/42 (26)	14/44 (32)	27/80 (34)	37/81 (46)
Change from baseline in Leeds Enthesitis Index score§	−0.5±0.2 [82]	−1.3±0.2 [79]	−1.3±0.2 [86]	−1.4±0.3 [38]	−1.3±0.3 [41]	−1.5±0.2 [77]	−1.6±0.2 [84]
Change from baseline in Dactylitis Severity Score¶	−1.9±0.8 [55]	−5.2±0.7 [64]	−5.4±0.8 [58]	−5.4±1.3 [25]	−5.2±1.3 [26]	−6.0±0.8 [61]	−6.0±0.9 [55]
Change from baseline in SF-36 physical functioning score	1.7±0.7 [117]	5.0±0.7 [124]	4.1±0.7 [120]	5.9±1.2 [56]	5.6±1.1 [56]	5.4±0.8 [121]	3.9±0.8 [112]
Change from baseline in total score on the FACIT-F	3.0±0.8 [117]	7.0±0.8 [124]	5.8±0.8 [120]	7.6±1.3 [56]	8.5±1.3 [56]	7.1±0.9 [122]	6.2±0.9 [113]
Other secondary efficacy end points							
ACR50 response — no. (%)	19 (15)	39 (30)‖**	37 (28)‖**	21 (32)	23 (35)	50 (38)	39 (30)
ACR70 response — no. (%)	13 (10)	22 (17)	19 (14)	10 (15)	12 (18)	28 (21)	19 (14)

* Plus–minus values are least-squares means ±SE. The values in brackets are the number of patients with available data. Analyses were performed in the full analysis set of 394 patients who underwent randomization and received at least one dose of tofacitinib or placebo. The primary efficacy end points and the key secondary efficacy end points were subject to hierarchical testing to control for global type I error. A 20% response according to the criteria of the American College of Rheumatology (ACR20 response) was defined as a 20% or greater reduction from baseline in the numbers of tender or painful joints (of 68 joints assessed) and swollen joints (of 66 joints assessed) and a 20% improvement in at least three of the following measures: the patient's global assessment of arthritis (as measured on a visual-analogue scale), the physician's global assessment of arthritis (as measured on a visual-analogue scale), the patient's assessment of arthritis pain (as measured on a visual-analogue scale), disability (as measured by the HAQ-DI), or C-reactive protein level. Missing data on ACR20 response were imputed as nonresponse to treatment (the numbers of patients with missing data on ACR20 response at 3 months were 15 in the pooled placebo group, 7 in the 5-mg tofacitinib group, and 12 in the 10-mg tofacitinib group). No imputation was applied for missing data on HAQ-DI score; in the repeated-measures analysis of change in HAQ-DI score from baseline through month 3, data were missing for 2 patients in the 5-mg tofacitinib group. The secondary efficacy end points regarding the assessments of improvements of 50% and 70% according to the ACR criteria (ACR50 and ACR70 responses, respectively) were subject to hierarchical testing to control for type I error within the family of ACR responses. Patients with missing values for ACR50 and ACR70 responses and for 75% improvement in the PASI score (PASI75) were considered to have had no response to treatment. Least-squares means were calculated on the basis of a mixed model for repeated measures without imputation for missing values.

† The result was significant at an unadjusted P value of less than 0.001 for the comparison with placebo at 3 months.

‡ The result was significant at a P value of 0.05 or less according to the prespecified step-down testing procedure for global type I error control. Hierarchical testing failed with respect to PASI75 response in the 5-mg tofacitinib group.

§ Results were assessed among patients who had an affected body-surface area of 3% or more at baseline and who had a baseline PASI score higher than 0.

¶ Results were assessed among patients who had a baseline score higher than 0.

‖ The result was significant at an unadjusted P value of less than 0.01 for the comparison with placebo at 3 months.

** The result was significant at a P value of 0.05 or less according to the prespecified step-down testing procedure for type I error control within the family of ACR responses. Hierarchical testing failed with respect to ACR70 response in the 10-mg tofacitinib group.

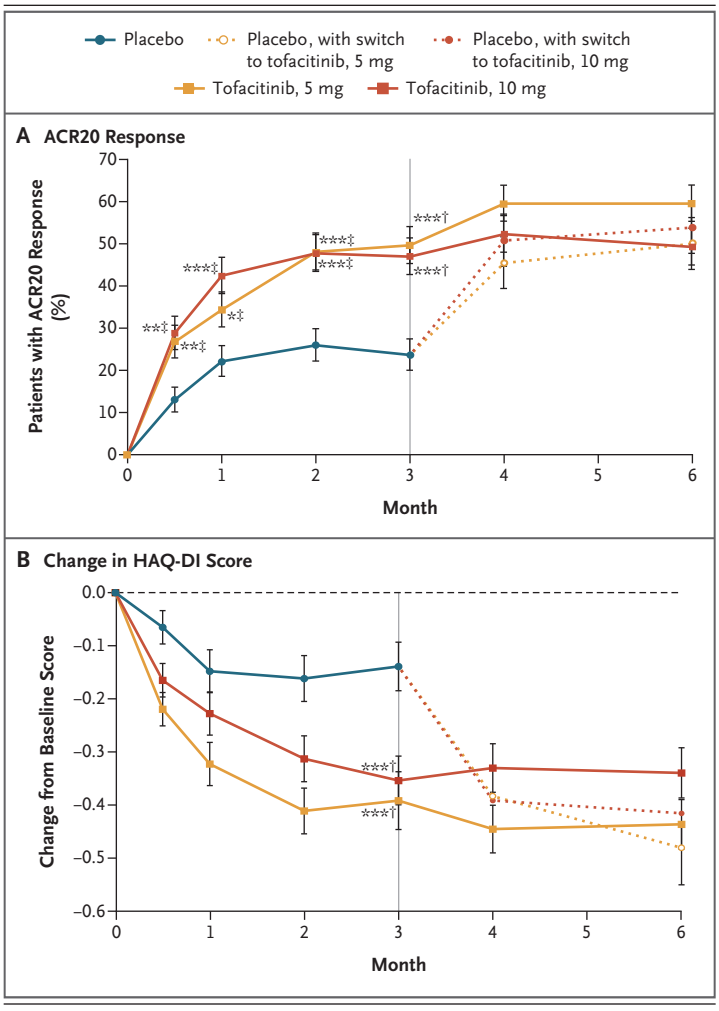

Figure 2. American College of Rheumatology (ACR) 20 Response and Change from Baseline in Health Assessment Questionnaire–Disability Index (HAQ-DI) Score through 6 Months.

Shown are the response rates with respect to ACR20, which is defined as a 20% reduction from baseline in the number of tender or swollen joints and a 20% improvement in at least three other important domains (Panel A), and the least-squares mean change in the HAQ-DI score from baseline (Panel B) through 6 months among patients who received 5 mg of tofacitinib twice daily, 10 mg of tofacitinib twice daily, placebo with a switch to the 5-mg tofacitinib dose at 3 months, and placebo with a switch to the 10-mg tofacitinib dose at 3 months. Data from the placebo groups were pooled for visits at or before 3 months. HAQ-DI scores range from 0 to 3, with higher scores indicating greater disability (minimal clinically important change from baseline, 0.35 points). I bars indicate standard errors. All data shown are for the full analysis set, which included all patients who underwent randomization and received at least one dose of tofacitinib or placebo. The vertical line at 3 months indicates the end of the placebo-controlled period. Missing data regarding the ACR20 response were imputed as no response (at 3 months, data were missing for 15 patients in the pooled placebo group, for 7 patients in the 5-mg tofacitinib group, and for 12 patients in the 10-mg tofacitinib group). No imputation was applied for missing HAQ-DI data (at 3 months, data were missing for 14 patients in the pooled placebo group, for 7 patients in the 5-mg tofacitinib group, and for 12 patients in the 10-mg tofacitinib group; in a repeated-measures analysis, data were missing for 2 patients in the 5-mg tofacitinib group). Asterisks represent the comparison with placebo, with one asterisk (*) indicating an unadjusted P value of 0.05 or less, two asterisks (**) indicating an unadjusted P value of less than 0.01, and three asterisks (***) indicating an unadjusted P value of less than 0.001. A dagger (†) indicates that the P value was 0.05 or less for the comparison with placebo for global type I error control, according to the prespecified step-down testing procedure. A double dagger (‡) indicates that the P value was 0.05 or less, according to the prespecified step-down testing procedure for type I error control within the ACR20 response time course.

are provided in Figs. S2 and S3 in the Supplementary Appendix.)

The 5-mg and 10-mg doses of tofacitinib were superior to placebo at 3 months with respect to the ACR50 (P=0.003 and P=0.007, respectively), but not the ACR70, response rates (Table 2). The 10-mg dose of tofacitinib, but not the 5-mg dose, was superior to placebo with respect to the rate of PASI75 response at 3 months (P<0.001) (Table 2). Because the comparison between the 5-mg dose of tofacitinib and placebo with respect to PASI75 response was not significant, the hierarchical testing scheme dictated that the comparisons between tofacitinib and placebo were not tested for significance with respect to the other key secondary end points that were lower in the testing hierarchy. (Additional details on the ACR50 and ACR70 response rates are provided in Fig. S4, on the PASI75 response rate in Fig. S5, and on the Psoriatic Arthritis Response Criteria response rate in Fig. S5 and Tables S2 and S4 in the Supplementary Appendix.)

At 3 months, the mean changes from baseline in the Leeds Enthesitis Index score, Dactylitis Severity Score, FACIT-F total score, and SF-36 physical functioning score with the two tofacitinib doses versus placebo could not be tested for statistical significance but were in the same direction as the findings for the primary end points (Table 2, and Figs. S6 and S7 in the Supplementary Appendix). The mean changes from baseline in the Leeds Enthesitis Index score, Dactylitis Severity Score, FACIT-F total score, and SF-36

physical functioning score at 6 months among the patients in the continuous tofacitinib groups were numerically similar to the mean changes from baseline at 3 months (Table 2, and Table S4 and Figs. S4 through S6 in the Supplementary Appendix). At 3 months, the percentages of patients who had responses that met the criteria for minimal disease activity were 23% in the 5-mg tofacitinib group, 21% in the 10-mg tofacitinib group, and 15% in the pooled placebo group (Table S4 in the Supplementary Appendix).

SAFETY

During the 3-month placebo-controlled period, the rate of reported adverse events was higher among the patients who received the 5-mg dose of tofacitinib (55%) and among those who received the 10-mg dose of tofacitinib (53%) than among those who received placebo (44%); the corresponding rates of reported serious adverse events were 1%, 2%, and 2% (Table 3). Over the 6-month trial period, adverse events were reported by 71% of the patients who received the 5-mg dose of tofacitinib continuously, by 73% of the patients who received the 10-mg dose of tofacitinib continuously, by 61% of patients who received placebo followed by the 5-mg dose of tofacitinib, and by 58% of the patients who received placebo followed by the 10-mg dose of tofacitinib (Table 3). The rate of serious adverse events and the rate of discontinuation of the trial drug or placebo because of adverse events were higher among the patients who received the 10-mg dose of tofacitinib continuously (6% and 8%, respectively) than among those who received the 5-mg dose of tofacitinib continuously (4% and 4%, respectively), those who received placebo followed by the 5-mg dose of tofacitinib (3% and 3%, respectively), and those who received placebo followed by the 10-mg dose of tofacitinib (2% and 5%, respectively). The most common adverse events among the four trial groups were upper respiratory tract infection (9% in the continuous 5-mg tofacitinib group, 5% in the continuous 10-mg tofacitinib group, 6% in the group that received placebo followed by 5-mg tofacitinib, and 11% in the group that received placebo followed by 10-mg tofacitinib), nasopharyngitis (11%, 9%, 6%, and 2%, respectively), and headache (8%, 9%, 5%, and 6%, respectively) (Table S5 in the Supplementary Appendix). Serious infections were reported by four patients who received tofacitinib. Nonserious cases of herpes zoster infection were reported by three patients who received tofacitinib; one case was adjudicated as an opportunistic infection (three dermatomes affected) (Table 3). Two cardiovascular events were adjudicated as major adverse cardiovascular events — a myocardial infarction in a patient who received the 5-mg dose of tofacitinib continuously and an ischemic stroke in a patient who received the 10-mg dose of tofacitinib continuously (Table 3). No deaths, cancers, gastrointestinal perforations, interstitial lung disease, or cases of *M. tuberculosis* infection were reported.

At 3 months, changes from baseline were similar across all trial groups with respect to hemoglobin and lymphocyte counts; dose-dependent changes with tofacitinib were observed with respect to neutrophil and platelet counts and creatinine, creatine kinase, and lipid values (low-density lipoprotein [LDL] and high-density lipoprotein [HDL] cholesterol and triglycerides) (Table S6 in the Supplementary Appendix). Although early elevations in LDL and HDL cholesterol levels were noted, the levels did not increase further after month 3 through month 6 (except in patients who received placebo during the first 3 months). Overall, three patients were withdrawn from the trial because of laboratory criteria mandated in the protocol — two patients in the continuous 10-mg tofacitinib group (one had a confirmed absolute neutrophil count of $<1.0\times10^9$ cells per liter [withdrawn after month 3] and one had a confirmed positive pregnancy test result [withdrawn before month 3]) and one patient who received placebo during the first 3 months (confirmed absolute lymphocyte count of $<0.5\times10^9$ cells per liter; withdrawn before month 3). Over 6 months, elevations in aspartate and alanine aminotransferase levels greater than the upper limit of the normal range were observed in 30% and 32%, respectively, of the patients who received tofacitinib throughout the trial; elevations in aspartate and alanine aminotransferase levels of 3 or more times the upper limit of the normal range were observed in two and four patients, respectively (Table S6 in the Supplementary Appendix). No cases of drug-induced liver injury were reported.

DISCUSSION

In this phase 3 study of patients with active psoriatic arthritis who had had an inadequate response to one or more TNF inhibitors, tofaci-

Table 3. Summary of Safety Events.*

Event	Up to 3 Mo			Up to 6 Mo			
	Placebo (N=131)	Tofacitinib, 5 mg (N=131)	Tofacitinib, 10 mg (N=132)	Placebo to Tofacitinib, 5 mg (N=66)	Placebo to Tofacitinib, 10 mg (N=65)	Tofacitinib, 5 mg (N=131)	Tofacitinib, 10 mg (N=132)
Adverse event — no. (%)	58 (44)	72 (55)	70 (53)	40 (61)	38 (58)	93 (71)	96 (73)
Serious adverse event — no. (%)	3 (2)	1 (1)	3 (2)	2 (3)	1 (2)	5 (4)	8 (6)
Discontinuation due to adverse event — no. (%)	5 (4)	2 (2)	10 (8)	2 (3)	3 (5)	5 (4)	11 (8)
Adverse event of special interest — no. (%) [day of onset]							
Serious infection	0	0	2 (2) [days 10 and 69]†	0	0	2 (2) [days 166 and 135]‡	2 (2) [days 10 and 69]†
Herpes zoster infection§	0	1 (1) [day 77]	1 (1) [day 8]	0	0	1 (1) [day 77]	2 (2) [days 8 and 156]
Adjudicated opportunistic infection	0	1 (1) [day 77]	0	0	0	1 (1) [day 77]	0
Adjudicated major adverse cardiovascular event¶	0	0	0	0	0	1 (1) [day 245]‖	1 (1) [day 94]**

* Analyses were performed with data from the safety analysis set, which included all patients who received at least one dose of tofacitinib or placebo. Adverse events from any cause were included in the analyses.
† One patient had bilateral pyelonephritis and one had parotitis.
‡ One patient had pneumonia and one had oral candidiasis.
§ The cases of herpes zoster infection were not judged to be serious adverse events.
¶ A major adverse cardiovascular event included any myocardial infarction, cerebrovascular event (nonfatal stroke), or cardiovascular death.
‖ One patient had a myocardial infarction.
** One patient had an ischemic stroke.

tinib was superior to placebo with respect to both primary end points (ACR20 response and change from baseline in HAQ-DI score) at 3 months. Improvements from baseline in ACR20 response with tofacitinib, as compared with placebo, were observed as early as week 2. The heterogeneous nature of psoriatic arthritis requires that multiple clinical end points be assessed, including peripheral arthritis, skin manifestations, enthesitis, and dactylitis. The 10-mg dose of tofacitinib, but not the 5-mg dose, was superior to placebo in treating skin manifestations. The higher rate of PASI75 response observed among the patients who received the 10-mg dose of tofacitinib than among those who received the 5-mg dose was similar to the response observed in two studies of tofacitinib in patients with plaque psoriasis who had not previously received a TNF inhibitor, as well as in those who had.[23] The changes in scores from baseline with respect to enthesitis, dactylitis, physical functioning, and fatigue could not be declared to be statistically significant according to the hierarchical testing scheme, but the observed effects of tofacitinib were in the same direction as the results for the primary end points.

Previous treatment with one or more TNF inhibitors had failed in all trial patients. Patients had previously received, on average, more than one TNF inhibitor or other (non–TNF inhibitor) biologic DMARD, which indicates that they may have had disease that was difficult to treat; however, 50 to 60% of the patients who received tofacitinib had an ACR20 response by the end of the trial, 32 to 38% had an ACR50 response, and 15 to 21% had an ACR70 response. Comparable data for other treatments, such as interleukin-12/23 and interleukin-17 inhibition, showed that the rate of ACR20 response at week 24 was 35.6% with ustekinumab, as compared with 14.5% with placebo,[24] and the rates were 14.7%, 29.7%, and 45.5% with 75-mg, 100-mg, and 150-mg doses of secukinumab, respectively, as compared with 14.3% with placebo.[25]

Over 3 months, serious infections and herpes zoster infections were more common among the patients who received tofacitinib than among the patients who received placebo. Over 6 months, the frequency of serious adverse events and discontinuation because of adverse events were higher among the patients who received the 10-mg dose of tofacitinib than among those who received the 5-mg dose of tofacitinib. Elevations in lipid and liver enzyme levels and cases of herpes zoster infections and serious infections were more common among the patients who received tofacitinib than among those who received placebo; these findings are similar to those in previous trials with tofacitinib.[26-35]

The 6-month duration of this study is not long enough to assess safety and long-term efficacy of tofacitinib in patients with psoriatic arthritis. A 12-month phase 3 trial of tofacitinib in patients with psoriatic arthritis who had not previously received a TNF inhibitor and who had had an inadequate response to conventional synthetic DMARDs has been conducted, and the results are reported in this issue of the *Journal*.[36] An open-label extension study that involves eligible patients from our trial and the trial by Mease et al.[36] is ongoing (ClinicalTrials.gov number, NCT01976364).

In conclusion, among patients with active psoriatic arthritis who had had an inadequate response to TNF inhibitors, the twice-daily doses of 5 mg and 10 mg of tofacitinib were superior to placebo over 3 months in reducing the number of inflamed joints, lowering HAQ-DI scores, and improving physical function. There were, however, higher rates of adverse events among the patients who received tofacitinib than among the patients who received placebo up to 3 months.

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