ORIGINAL ARTICLE

Tofacitinib or Adalimumab versus Placebo for Psoriatic Arthritis

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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 previously had an inadequate response to conventional synthetic disease-modifying antirheumatic drugs (DMARDs).

METHODS

In this 12-month, double-blind, active-controlled and placebo-controlled, phase 3 trial, we randomly assigned patients in a 2:2:2:1:1 ratio to receive one of the following regimens: tofacitinib at a 5-mg dose taken orally twice daily (107 patients), tofacitinib at a 10-mg dose taken orally twice daily (104), adalimumab at a 40-mg dose administered subcutaneously once every 2 weeks (106), placebo with a blinded switch to the 5-mg tofacitinib dose at 3 months (52), or placebo with a blinded switch to the 10-mg tofacitinib dose at 3 months (53). Placebo groups were pooled for analyses up to month 3. Primary end points were the proportion of patients who had an American College of Rheumatology 20 (ACR20) response (≥20% improvement from baseline in the number of tender and swollen joints and at least three of five other important domains) at month 3 and the change from baseline in the Health Assessment Questionnaire–Disability Index (HAQ-DI) score (scores range from 0 to 3, with higher scores indicating greater disability) at month 3.

RESULTS

ACR20 response rates at month 3 were 50% in the 5-mg tofacitinib group and 61% in the 10-mg tofacitinib group, as compared with 33% in the placebo group ($P=0.01$ for the comparison of the 5-mg dose with placebo; $P<0.001$ for the comparison of the 10-mg dose with placebo); the rate was 52% in the adalimumab group. The mean change in the HAQ-DI score was −0.35 in the 5-mg tofacitinib group and −0.40 in the 10-mg tofacitinib group, as compared with −0.18 in the placebo group ($P=0.006$ for the comparison of the 5-mg dose with placebo; $P<0.001$ for the comparison of the 10-mg dose with placebo); the score change was −0.38 in the adalimumab group. The rate of adverse events through month 12 was 66% in the 5-mg tofacitinib group, 71% in the 10-mg tofacitinib group, 72% in the adalimumab group, 69% in the placebo group that switched to the 5-mg tofacitinib dose, and 64% in the placebo group that switched to the 10-mg tofacitinib dose. There were four cases of cancer, three serious infections, and four cases of herpes zoster in patients who received tofacitinib during the trial.

CONCLUSIONS

The efficacy of tofacitinib was superior to that of placebo at month 3 in patients with psoriatic arthritis who had previously had an inadequate response to conventional synthetic DMARDs. Adverse events were more frequent with tofacitinib than with placebo. (Funded by Pfizer; OPAL Broaden ClinicalTrials.gov number, NCT01877668.)

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A complete list of the investigators in the Oral Psoriatic Arthritis Trial (OPAL) Broaden trial is provided in the Supplementary Appendix, available at NEJM.org.

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Psoriatic arthritis is a chronic, systemic inflammatory arthritis that occurs in 6 to 42% of patients with psoriasis, affecting the peripheral joints, tendons, ligaments, and the axial skeleton.[1] Current treatment guidelines for psoriatic arthritis recommend conventional synthetic disease-modifying antirheumatic drugs (DMARDs), such as methotrexate, as initial therapy, followed by biologic DMARDs (tumor necrosis factor [TNF] inhibitors, interleukin-12 and interleukin-23 inhibitors, and interleukin-17 inhibitors) or apremilast in patients who had an inadequate response to conventional synthetic DMARDs.[2,3]

Tofacitinib is an oral Janus kinase (JAK) inhibitor. JAK inhibitors influence the signaling of a number of cytokines that are implicated in the pathogenesis of psoriatic arthritis, such as common gamma chain–containing cytokines, interferon-γ, interleukin-12, and those involved in the interleukin-23 and interleukin-17 pathway, including interleukin-23, interleukin-6, and interleukin-22.[4,5] JAK inhibition offers the potential to modulate multiple pathways that are implicated in the activation and proliferation of inflammatory cells in articular and extraarticular locations and in the activation and proliferation of cell types associated with joint destruction and psoriatic skin changes in patients with psoriatic arthritis.[4,5] We report the results of the Oral Psoriatic Arthritis Trial (OPAL) Broaden phase 3 trial, which evaluated the efficacy and safety of tofacitinib and an active control, adalimumab, in altering the signs and symptoms of psoriatic arthritis, physical function, and progression of structural damage over a period of 12 months in patients with active psoriatic arthritis who had previously had an inadequate response to at least one conventional synthetic DMARD.

Methods

Patients

Eligible patients were 18 years of age or older, had received a diagnosis of psoriatic arthritis at least 6 months previously, fulfilled the Classification Criteria for Psoriatic Arthritis (CASPAR),[6] had previously had an inadequate response to at least one conventional synthetic DMARD, and had not previously received a TNF inhibitor. Further details regarding the inclusion and exclusion criteria are provided in the Supplementary Appendix, available with the full text of this article at NEJM.org.

Trial Design

This randomized, placebo-controlled, double-blind, phase 3 trial was carried out at 126 centers worldwide from January 2014 through December 2015 (Table S1 in the Supplementary Appendix). Eligible patients were randomly assigned in a 2:2:2:1:1 ratio, by means of an automated Web-based randomization system, to receive one of the following regimens: tofacitinib at a dose of 5 mg taken orally twice daily, tofacitinib at a dose of 10 mg taken orally twice daily, adalimumab at a dose of 40 mg administered subcutaneously once every 2 weeks, placebo with a switch to the 5-mg dose of tofacitinib at month 3, or placebo with a switch to the 10-mg dose of tofacitinib at month 3. Patients were followed through month 12, and blinding regarding the trial regimen was maintained throughout the trial (see the Study Blinding section in the Supplementary Appendix). Patients were required to receive a stable background dose of a single conventional synthetic DMARD — methotrexate, sulfasalazine, or leflunomide (medication choice and dosing details are provided in the Supplementary Appendix).

Trial Oversight

The trial was conducted in accordance with the Good Clinical Practice guidelines of the International Conference on Harmonisation and with 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. Protocol amendments after the commencement of the trial are provided in the Supplementary Appendix. All the patients provided written informed consent.

The trial was sponsored by Pfizer, which provided tofacitinib, adalimumab, and placebo. Employees of the sponsor designed the trial in conjunction with the principal academic investigators. A contract research organization (ICON)

collected the trial data, and employees of the sponsor analyzed, and all the authors jointly interpreted, the data. All the authors vouch for the accuracy of the data and analyses and for the adherence of the trial to the protocol. Drafts of the manuscript were written by Complete Medical Communications, with funding from the sponsor. All the authors participated directly in the writing of the manuscript and made the decision to submit the manuscript for publication.

TRIAL END POINTS

Details regarding the scoring and time points for each trial end point are provided in Table S2 in the Supplementary Appendix. The two primary end points, assessed at month 3, were the proportion of patients who had an American College of Rheumatology 20 (ACR20) response[7] and the change from baseline in the Health Assessment Questionnaire–Disability Index (HAQ-DI) score.[8] The ACR20 response is defined as an improvement of 20% or more from baseline in the number of tender joints (from an analysis of 68 joints), in the number of swollen joints (from an analysis of 66 joints), and in three of the following five domains: a patient's global assessment of arthritis activity, a physician's global assessment of arthritis activity, and a patient's assessment of arthritis pain (with all three evaluations measured on a visual-analogue scale of 0 to 100 mm, with higher scores indicating greater pain or disability); disability as measured by the HAQ-DI (see below); and the level of acute-phase reactants (as measured by the level of high-sensitivity C-reactive protein). The HAQ-DI measures physical function, with the overall score ranging from 0 to 3 and higher scores indicating greater disability. A decrease from baseline of 0.35 points is considered to be the smallest change that is clinically important in patients with psoriatic arthritis.[9]

Secondary efficacy end points included the following: improvement of 50% or more and improvement of 70% or more in the ACR domains (ACR50 and ACR70 responses); components of the ACR response criteria; improvement of 75% or more from baseline in the psoriasis area-and-severity index (PASI75; PASI scores range from 0 to 72, with higher scores indicating more severe disease) among patients who had at least 3% of their body-surface area affected at baseline[10]; and patients who met Psoriatic Arthritis Response Criteria (as defined in Table S2 in the Supplementary Appendix).[11] In patients with enthesitis or dactylitis at baseline, improvements were assessed according to the change from baseline in the Leeds Enthesitis Index score (scores range from 0 to 6, with higher scores indicating more affected sites)[12]; the Spondyloarthritis Research Consortium of Canada enthesitis index score (scores range from 0 to 16, with higher scores indicating more affected sites)[13]; and the Dactylitis Severity Score (scores range from 0 to 60, with higher scores indicating greater severity).[14] The proportion of patients with minimal disease activity[15] and the 28-joint Disease Activity Score on the basis of levels of C-reactive protein (DAS28-CRP)[16] were also assessed as secondary outcomes. Minimal disease activity was defined as meeting five or more of the following criteria: zero or one tender or painful joint; zero or one swollen joint; a PASI score of 1 or less or an affected body-surface area of 3% or less; a patient's assessment of arthritis pain of 15 mm or less on the visual-analogue scale; a patient's global assessment of arthritis activity of 20 mm or less on the visual-analogue scale; a HAQ-DI score of 0.5 or less; or a Leeds Enthesitis Index score of 1 or less.

Radiographs of the hands and feet were obtained at baseline and at month 12 and were scored independently by two central assessors who were unaware of the trial-group assignments. The assessors of radiographs used the van der Heijde–modified total Sharp score for psoriatic arthritis (scores range from 0 to 528, with higher scores indicating greater erosion, joint-space narrowing, or both).[17] Progression was assessed at two thresholds: a change in the modified total Sharp score of more than 0.5 and of more than 0. Nonprogression of disease as assessed radiographically was defined as a change from baseline of 0.5 or less in the modified total Sharp score. For the threshold of 0, nonprogression was defined as no change in the score or as a decrease in the score (indicating fewer erosions and less joint-space narrowing).

Patient-reported outcomes included fatigue, physical function, and health status. Fatigue was assessed with the use of the Functional Assess-

ment of Chronic Illness Therapy–Fatigue (FACIT-F) scale (scores range from 0 to 52, with higher scores indicating less fatigue),[18] impairment in physical function with the use of the physical functioning domain of the Medical Outcomes Study 36-Item Short Form Health Survey (SF-36), version 2 (norm-based scores were used, with higher scores indicating less impairment),[19] and health status with the use of the five EuroQol Group 5-Dimension Health State Profile domains (scores on each domain range from 0 to 3, with higher scores indicating greater impairment).[20]

Safety was assessed by means of spontaneous reporting of adverse events, physical examinations, and clinical laboratory tests. Potential opportunistic infections, cancers, gastrointestinal perforations, cardiovascular events, and hepatic events were adjudicated by independent expert committees whose members were unaware of the trial-group assignments. The incidence of nonmelanoma skin cancer was assessed separately from the incidence of other cancers. Confirmation of changes in laboratory variables was performed by means of two sequential measurements. Details regarding the adjudication and safety monitoring are provided in the Supplementary Appendix.

STATISTICAL ANALYSIS

Details regarding the calculation of the sample size are provided in the Supplementary Appendix. The trial was designed to show the superiority of tofacitinib over placebo. Adalimumab was used as an active control. The trial was not designed and was not powered to evaluate the noninferiority or superiority of tofacitinib as compared with adalimumab.

Efficacy analyses included all the patients who underwent randomization and received at least one dose of tofacitinib, adalimumab, or placebo (full analysis set). To control for type I error at the 5% level, a sequential hierarchical testing method was used: for all end points, the 10-mg dose of tofacitinib was compared with placebo before the 5-mg dose of tofacitinib was compared with placebo (see the Supplementary Appendix). For the two primary end points, the fixed sequence for testing the superiority of each tofacitinib dose versus placebo at month 3 was the following: the ACR20 response rate in the 10-mg tofacitinib group versus the placebo group; the ACR20 response rate in the 5-mg tofacitinib group versus the placebo group; the change from baseline in the HAQ-DI score in the 10-mg tofacitinib group versus the placebo group; and the change from baseline in the HAQ-DI score in the 5-mg tofacitinib group versus the placebo group.

If both the primary end points were significant for each dose of tofacitinib versus placebo, the key secondary end points were tested in the following order: the proportion of patients with PASI75, the change from baseline in the Leeds Enthesitis Index score, the change from baseline in the Dactylitis Severity Score, the change from baseline in the SF-36 physical functioning score, and the change from baseline in the FACIT-F total score. The type I error was controlled globally for the primary end points and for the key secondary end points listed here.

Additional hierarchies were applied to the family of ACR responses at month 3 (ACR20 response, followed by the ACR50 response and then the ACR70 response; the type I error was controlled within the family of ACR responses) and to the ACR20 responses at each trial visit (month 3 followed by month 2, month 1, and week 2; the type I error was controlled within the family of ACR20 response times). Statistical significance was declared if a comparison passed the test according to the prespecified hierarchical testing procedures. All the P values are unadjusted and two-sided. For all the trial end points, 95% confidence intervals for the difference between active treatment and placebo were calculated.

Binary end points were analyzed with the use of the normal approximation for the difference in binomial proportions (i.e., normal approximation for binomial distribution), with an imputation of no response for missing values, and multiple imputations were not used. 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 mixed model for repeated measures with trial group, visit, interaction of the trial group by visit, geographic location, and baseline value as fixed effects, without imputation for missing values. Supportive analyses for the primary end points are described in the Supplementary Appendix.

Two separate mixed models for repeated measures were used: results through month 3 were based on a model with the two placebo–tofacitinib sequences (placebo with a switch to 5 mg or 10 mg of tofacitinib) combined into a single placebo group, with the use of all the data through month 3. Results after month 3 were based on a model with the placebo–tofacitinib sequences kept separate, with the use of all post-baseline data through month 12 (the results through month 3 were discarded). Missing values for end points regarding the modified total Sharp score were imputed by means of linear extrapolation. The response rate or least-squares mean was estimated from the above analyses for each trial group at each visit through month 12. The comparison between each active treatment group and the pooled placebo group was made at each visit through month 3. Safety data are summarized descriptively for all the patients in the full analysis set.

RESULTS

PATIENTS

All 422 patients who had undergone randomization received the assigned trial regimen, and 373 patients completed the trial (Fig. 1). The demographic and disease characteristics of the patients at baseline were similar across groups (Table 1, and Table S4 in the Supplementary Appendix), with the exception of the mean Leeds Enthesitis Index score, the mean swollen-joint count, and the rate of methotrexate use, which were all lower in the adalimumab group than in the other groups, and the rate of glucocorticoid use, which was lower in the 10-mg tofacitinib group than in the other groups. At baseline, 74% of the patients had psoriasis affecting at least 3% of their body-surface area, 66% had enthesitis (as assessed with the use of the Leeds Enthesitis Index), and 56% had dactylitis; 84% of the patients were receiving concomitant methotrexate.

EFFICACY

At 3 months, the rate of ACR20 response was 50% in the 5-mg tofacitinib group and 61% in the 10-mg tofacitinib group, as compared with 33% in the placebo group ($P=0.01$ for the comparison of the 5-mg tofacitinib dose with placebo; $P<0.001$ for the comparison of the 10-mg dose with placebo) (Table 2 and Fig. 2, and Fig. S1 in the Supplementary Appendix). The mean change from baseline in the HAQ-DI score was −0.35 in the 5-mg tofacitinib group and −0.40 in the 10-mg tofacitinib group, as compared with −0.18 in the placebo group ($P=0.006$ for the comparison of the 5-mg dose with placebo; $P<0.001$ for the comparison of the 10-mg dose with placebo). Adalimumab resulted in an ACR20 response rate of 52% and in a mean change in the HAQ-DI score of −0.38.

Changes from baseline through month 12 with tofacitinib and adalimumab were numerically similar to those at month 3 but could not be compared with placebo at month 12 because the patients in the placebo group had switched to tofacitinib at month 3 (Fig. 2). Significantly higher rates of ACR20 response were observed with the two tofacitinib doses than with placebo at week 2 ($P<0.001$ for both comparisons). At month 3, a decrease (indicating clinical improvement) in the HAQ-DI score that was greater than or equal to the minimum clinically important difference (change from baseline, −0.35) occurred in 53% of the patients in the 5-mg tofacitinib group and 55% of those in the 10-mg tofacitinib group, as compared with 31% of those in the placebo group; such a decrease occurred in 53% of the patients in the adalimumab group (Table S5 in the Supplementary Appendix).

At month 3, the rates of ACR50 response were significantly higher in each tofacitinib group (28% in the 5-mg tofacitinib group and 40% in the 10-mg tofacitinib group) than in the placebo group (10%; $P<0.001$ for both comparisons), as were the rates of ACR70 response (17% in the 5-mg tofacitinib group and 14% in the 10-mg tofacitinib group, vs. 5% in the placebo group; $P=0.004$ for the comparison of the 5-mg dose with placebo; $P=0.02$ for the comparison of the 10-mg dose with placebo) (Table 2), and improvements were observed across all ACR components (Fig. S2 and Table S3 in the Supplementary Appendix). Adalimumab resulted in an ACR50 response rate of 33% and an ACR70 response rate of 19% (Table 2).

Sequential hierarchical testing of the key secondary end points at month 3 showed a significantly higher rate of PASI75 response in each

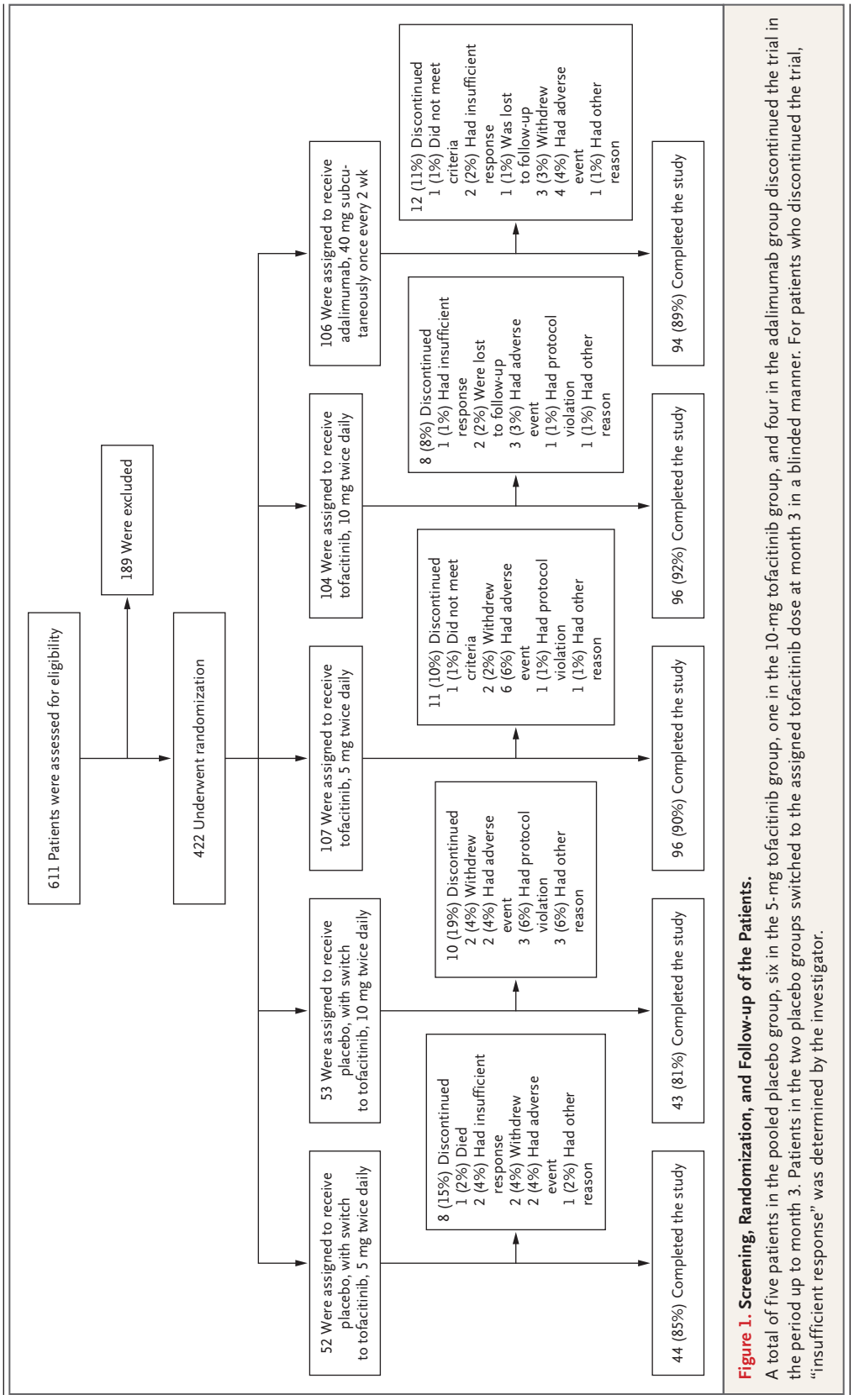


Figure 1. Screening, Randomization, and Follow-up of the Patients.
A total of five patients in the pooled placebo group, six in the 5-mg tofacitinib group, one in the 10-mg tofacitinib group, and four in the adalimumab group discontinued the trial in the period up to month 3. Patients in the two placebo groups switched to the assigned tofacitinib dose at month 3 in a blinded manner. For patients who discontinued the trial, "insufficient response" was determined by the investigator.

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

Characteristic	Placebo (N=105)	Tofacitinib, 5 mg (N=107)	Tofacitinib, 10 mg (N=104)	Adalimumab (N=106)
Age — yr	47.7±12.3	49.4±12.6	46.9±12.4	47.4±11.3
Female sex — no. (%)	56 (53)	57 (53)	62 (60)	50 (47)
White race — no. (%)†	104 (99)	105 (98)	97 (93)	103 (97)
Duration of psoriatic arthritis — yr	6.4±6.4	7.3±8.2	5.4±5.8	5.3±5.3
HAQ-DI score‡	1.1±0.6	1.2±0.6	1.1±0.6	1.1±0.6
Leeds Enthesitis Index§				
Score >0 — no. (%)	65 (62)	75 (70)	64 (62)	76 (72)
Mean score	2.8±1.5	2.5±1.4	3.0±1.6	2.3±1.2
Dactylitis Severity Score¶				
Score >0 — no. (%)	58 (55)	61 (57)	60 (58)	58 (55)
Mean score	9.9±8.4	9.1±8.0	8.5±8.2	8.0±7.4
Swollen-joint count (of 66 joints)	11.5±8.8	12.9±9.9	11.7±7.7	9.8±7.9
Tender- or painful-joint count (of 68 joints)	20.6±14.4	20.5±12.6	20.3±12.9	17.1±11.2
Elevated high-sensitivity CRP level — no. (%)‖	63 (60)	68 (64)	66 (63)	64 (60)
Modified total Sharp score**				
Score >0 — no. (%)	95 (90)	96 (90)	96 (92)	99 (93)
Mean score	17.6±43.4	17.1±28.6	10.4±18.4	14.4±39.2
Affected body-surface area ≥3% — no. (%)	82 (78)	82 (77)	70 (67)	78 (74)
PASI score††				
No. of patients with data (%)	82 (78)	82 (77)	70 (67)	77 (73)
Median PASI score (range)	6.6 (0.8–41.4)	5.6 (0.4–46.0)	7.8 (0.3–24.3)	7.0 (2.0–47.1)
Oral glucocorticoid use on day 1 — no. (%)	18 (17)	29 (27)	11 (11)	23 (22)
Concomitant use of conventional synthetic DMARD up to 3 mo — no. (%)				
Methotrexate‡‡	92 (88)	91 (85)	92 (88)	79 (75)
Sulfasalazine	9 (9)	8 (7)	8 (8)	15 (14)
Leflunomide	4 (4)	7 (7)	3 (3)	10 (9)
Hydroxychloroquine	0	0	0	1 (1)
Other§§	0	1 (1)	1 (1)	1 (1)
Methotrexate dose — mg/wk¶¶	15.5±4.1	16.4±3.8	16.8±11.7	15.8±4.4
Previous use of non–TNF-inhibiting biologic DMARD — no. (%)	3 (3)	3 (3)	4 (4)	1 (1)

* Plus–minus values are means ±SD. Unadjusted P values were determined with the use of chi-square tests for categorical variables and Kruskal–Wallis tests for continuous variables. For the data on baseline characteristics and for the testing of significant differences from the other groups, the two placebo sequences were pooled. Significant differences among the trial groups were found for the mean Leeds Enthesitis Index score (unadjusted P=0.02 for the comparison among all four groups [among patients with baseline score >0; scores range from 0 to 6, with higher scores indicating more affected sites[12]]), the mean number of swollen joints (unadjusted P=0.03 for the comparison among all four groups), oral glucocorticoid use at day 1 (unadjusted P=0.02 for the comparison of the 10-mg tofacitinib group with other groups), and concomitant methotrexate use up to month 3 (unadjusted P=0.02 for the comparison among all four groups); no other significant differences were found. CRP denotes C-reactive protein, DMARD disease-modifying antirheumatic drug, and TNF tumor necrosis factor.

† 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.

§ The presence of enthesitis was defined as a Leeds Enthesitis Index score of more than 0.

¶ The Dactylitis Severity Score is on a scale from 0 to 60, with higher scores indicating greater severity. The presence of dactylitis was defined as a score of more than 0.[14]

‖ An elevated level of high-sensitivity CRP was defined as a level of more than 2.87 mg per liter.

** The van der Heijde–modified total Sharp score ranges from 0 to 528, with higher scores indicating greater erosion, joint-space narrowing, or both.[17]

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

‡‡ For the purpose of analysis, methotrexate includes both methotrexate and methotrexate sodium.

§§ Data included patients who were treated with more than one DMARD.

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

Table 2. Primary and Key Secondary Efficacy End Points at Month 3 and Month 12.*

End Point	At 3 Mo				At 12 Mo				
	Pooled Placebo (N=105)	Tofacitinib, 5 mg (N=107)	Tofacitinib, 10 mg (N=104)	Adalimumab (N=106)	Placebo to Tofacitinib, 5 mg (N=52)	Placebo to Tofacitinib, 10 mg (N=53)	Tofacitinib, 5 mg (N=107)	Tofacitinib, 10 mg (N=104)	Adalimumab (N=106)
Primary efficacy end points									
ACR20 response — no. (%)	35 (33)	54 (50)†‡	63 (61)‡§	55 (52)	35 (67)	31 (58)	73 (68)	73 (70)	64 (60)
Change in HAQ-DI score [no. of patients with data]	−0.18±0.05 [102]	−0.35±0.05 [103]‡¶	−0.40±0.05 [103]‡§	−0.38±0.05 [101]	−0.41±0.08 [44]	−0.46±0.08 [44]	−0.54±0.05 [96]	−0.51±0.05 [96]	−0.45±0.05 [94]
Key secondary efficacy end points									
PASI75 response — no./total no. (%)‖	12/82 (15)	35/82 (43)‡§	31/70 (44)‡§	30/77 (39)	15/42 (36)	21/40 (52)	46/82 (56)	47/70 (67)	43/77 (56)
Change in Leeds Enthesitis Index score [no. of patients with data]**	−0.4±0.2 [63]	−0.8±0.2 [70]	−1.5±0.2 [63]‡§	−1.1±0.2 [73]	−1.4±0.3 [24]	−1.9±0.3 [29]	−1.7±0.2 [67]	−1.6±0.2 [56]	−1.6±0.2 [67]
Change in Dactylitis Severity Score [no. of patients with data]**	−2.0±1.1 [55]	−3.5±1.0 [58]	−5.5±0.9 [60]	−4.0±1.0 [56]	−6.7±0.9 [26]	−7.7±1.0 [24]	−7.4±0.7 [54]	−7.5±0.6 [58]	−6.1±0.7 [52]
Change in SF-36 physical functioning score [no. of patients with data]††	2.1±0.9 [102]	5.2±0.8 [102]	5.2±0.8 [103]	5.2±0.9 [101]	6.5±1.3 [44]	4.8±1.3 [44]	7.7±0.9 [96]	7.1±0.9 [96]	6.8±0.9 [94]
Change in FACIT-F total score [no. of patients with data]‡‡	3.3±0.9 [102]	7.0±0.9 [102]	6.0±0.9 [102]	6.0±0.9 [101]	5.7±1.4 [44]	7.6±1.4 [44]	8.5±1.0 [96]	8.4±1.0 [96]	6.9±1.0 [94]
Secondary efficacy end points									
ACR50 response — no. (%)	10 (10)	30 (28)§,§§	42 (40)§,§§	35 (33)	21 (40)	19 (36)	48 (45)	50 (48)	43 (41)
ACR70 response — no. (%)	5 (5)	18 (17)¶§§	15 (14)†§§	20 (19)	12 (23)	12 (23)	25 (23)	32 (31)	31 (29)
Other secondary efficacy end points									
Nonprogression according to the modified total Sharp score — no./total no. (%)¶¶	—	—	—	—	46/48 (96)	41/45 (91)	94/98 (96)	94/99 (95)	93/95 (98)
Minimal disease activity — no. (%)‖‖	7 (7)	28 (26)	27 (26)	27 (25)	16 (31)	18 (34)	40 (37)	45 (43)	42 (40)

* Plus–minus values are least-squares means ±SE. The primary efficacy end points and key secondary efficacy end points were subject to a hierarchical testing procedure for global type I error control, the secondary efficacy end points regarding the American College of Rheumatology (ACR) response were subject to a hierarchical testing procedure for type I error control within the family of ACR responses, and other secondary efficacy end points were not controlled for type I error. An ACR20 response was defined as a 20% improvement from baseline in the number of tender and swollen joints and at least three other important domains. For the key secondary end points, hierarchical testing failed at the end point of change in the Leeds Enthesitis Index in the comparison of the 5-mg tofacitinib group with the placebo group. Minimal disease activity and nonprogression according to the modified total Sharp score were not included in the prespecified step-down testing procedure. Data on the ACR20 response at month 3 were missing for three patients in the placebo group, for four in the 5-mg tofacitinib group, for two in the 10-mg tofacitinib group, and for six in the adalimumab group. In the repeated-measures analysis for change from baseline in the HAQ-DI score through month 3, data were missing for one patient in the placebo group. Missing values for the assessments of improvements of 20%, 50%, and 70% according to the ACR criteria (ACR20, ACR50, and ACR70 responses, respectively), of a 75% improvement in the PASI score (PASI75), and of minimal disease activity were considered to be no response to treatment.

† Unadjusted P≤0.05 for the comparison with placebo at month 3.

‡ 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.

§ Unadjusted P<0.001 for the comparison with placebo at month 3.

¶ Unadjusted P<0.01 for the comparison with placebo at month 3.

‖ 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 of more than 0.

** Results were assessed among patients who had a baseline score of more than 0.

†† On the physical functioning domain of the Medical Outcomes Study 36-Item Short Form Health Survey (SF-36), version 2, norm-based scores were used, with higher scores indicating less impairment.[19]

‡‡ Scores on the Functional Assessment of Chronic Illness Therapy–Fatigue (FACIT-F) scale range from 0 to 52, with higher scores indicating less fatigue.[18]

§§ 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.

¶¶ The modified total Sharp score was not assessed at month 3, and linear extrapolation applied at month 12.

‖‖ Minimal disease activity was defined as meeting five or more of the following criteria: zero or one tender or painful joint; zero or one swollen joint; a PASI score of 1 or less or an affected body-surface area of 3% or less; a patient's assessment of arthritis pain of 15 mm or less on a visual-analogue scale (range, 0 to 100 mm, with higher scores indicating more pain); a patient's assessment of global arthritis activity of 20 mm or less on a visual-analogue scale (range, 0 to 100 mm, with higher scores indicating greater disability); a HAQ-DI score of 0.5 or less; or a Leeds Enthesitis Index score of 1 or less.

tofacitinib group than in the placebo group (P<0.001 for both comparisons), and a significantly greater decrease in the Leeds Enthesitis Index score in the 10-mg tofacitinib group than in the placebo group (P<0.001) (Table 2). Hierarchical statistical testing failed with regard to the Leeds Enthesitis Index score when the 5-mg dose of tofacitinib was compared with placebo, which prevented the testing of significance for tofacitinib versus placebo with regard to the other key secondary end points that were lower in the testing hierarchy. The mean change from baseline to month 3 in the Dactylitis Severity Score with the 10-mg dose of tofacitinib versus placebo and the mean changes from baseline to month 3 in the FACIT-F total score and the SF-36 physical functioning score with the two tofacitinib doses versus placebo were in the same direction as the primary end points (Table 2, and Figs. S5 and S6 in the Supplementary Appendix); however, these results were not tested for significance because of failure in the hierarchical testing procedure. Changes from baseline in the secondary end points that were observed through month 12 were numerically similar to those at month 3 but could not be compared with placebo because the patients in the placebo group had switched to tofacitinib at month 3 (Table 2, and Figs. S3 through S6 in the Supplementary Appendix). The percentages of patients with minimal disease activity are shown in Table 2, and in Figure S7 in the Supplementary Appendix. The percentages of patients who met the Psoriatic Arthritis Response Criteria over the course of the trial to month 12 are shown in Tables S3 and S5 and Figure S7 in the Supplementary Appendix.

At month 12, the minimal mean changes from baseline in the modified total Sharp score were observed across all the trial groups, including the groups of patients who switched from placebo to tofacitinib at month 3 (range of changes from baseline, −0.07 to 0.09). A total of 91 to 98% of patients across all trial groups met the radiographic criteria for nonprogression (Table 2, and Fig. S8 in the Supplementary Appendix).

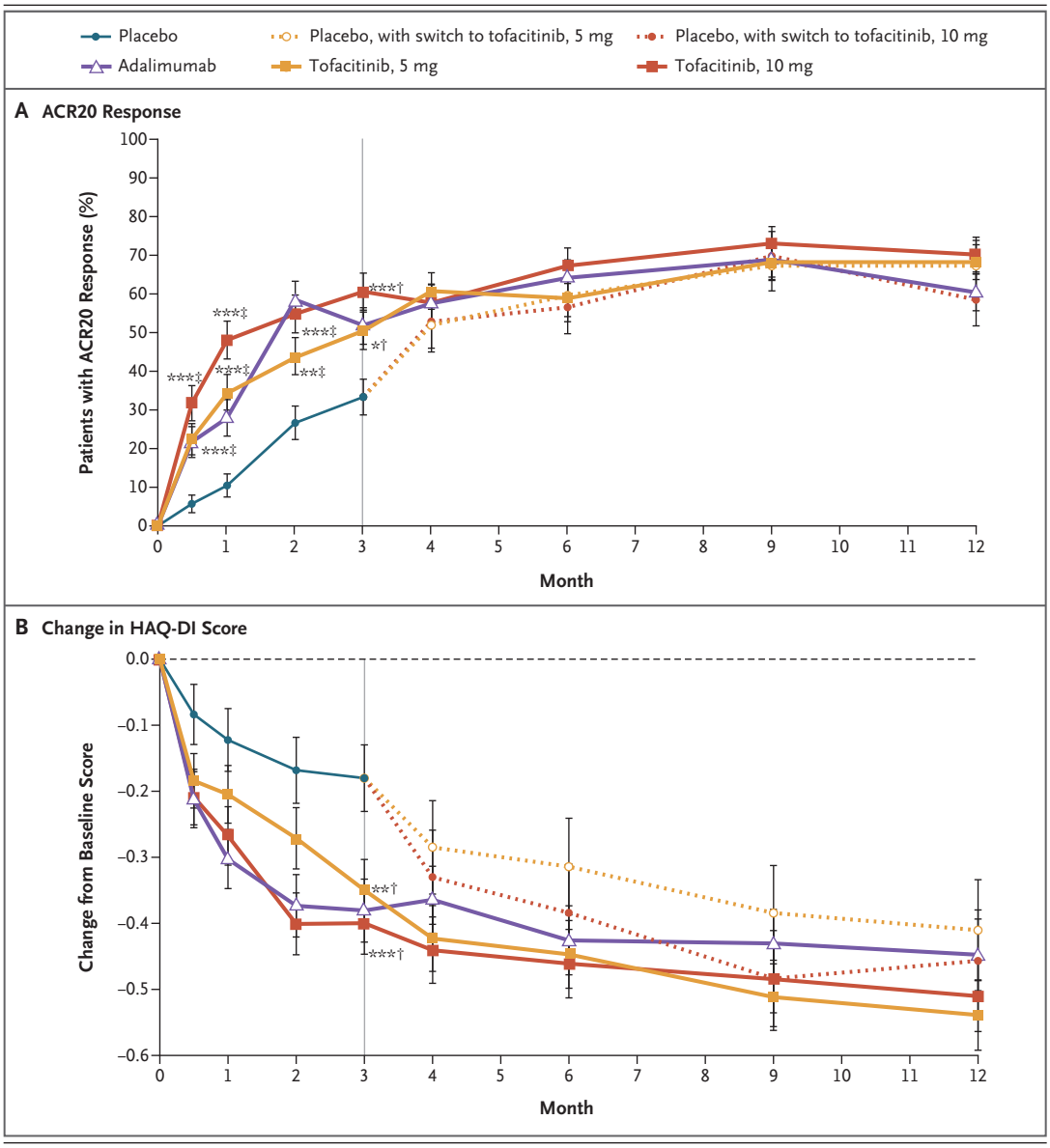
SAFETY

During the 3-month placebo-controlled period, the percentage of patients with adverse events was higher in the 5-mg tofacitinib group (39%), the 10-mg tofacitinib group (45%), and the adalimumab group (46%) than in the placebo group (35%) (Table 3). Serious adverse events occurred in 3% of the patients in the 5-mg tofacitinib group, in 1% of those in the 10-mg tofacitinib group, in 1% of those in the adalimumab group, and in 1% of those in the placebo group.

Over a period of 12 months, serious adverse events occurred in 7% of patients receiving continuous tofacitinib at a dose of 5 mg, 4% of those receiving continuous tofacitinib at a dose of 10 mg, and 8% of those receiving adalimumab, and discontinuations due to adverse events occurred in 6%, 3%, and 4%, respectively (Table 3). The most common adverse events that occurred among patients receiving the 5-mg or 10-mg dose of tofacitinib or receiving adalimumab were nasopharyngitis (in 7%, 12%, and 10%, respectively), upper respiratory tract infection (in 9%, 11%, and 8%), and headache (in 5%, 11%, and 7%) (Table S6 in the Supplementary Appendix). One death due to cardiac arrest occurred during month 4 in a patient in the placebo group that switched to the 5-mg dose of tofacitinib; the death was adjudicated as a major adverse cardiovascular event.

Over a period of 12 months, serious infections were reported in four patients (Table 3), three of whom were receiving tofacitinib (influenza, appendicitis, and pneumonia in one patient each) and one of whom was receiving adalimumab (herpes simplex and streptococcal pyoderma). Herpes zoster was reported in four patients, all of whom were receiving tofacitinib; one case was adjudicated as an opportunistic infection. No cases of tuberculosis were reported. Three cancers (excluding nonmelanoma skin cancer) were reported (bladder transitional-cell carcinoma [with onset on day 1], squamous-cell carcinoma of the vulva [with onset on day 11], and invasive ductal breast carcinoma [with onset on day 232]), and one event of nonmelanoma skin cancer was reported (basal-cell carcinoma [with onset on day 103]); all these events occurred in patients who had received tofacitinib continuously since baseline (Table 3).

At month 3, greater reductions in the neutrophil count were observed with all active treatments than with placebo (Table S7 in the Supplementary Appendix). There were no reported cases of confirmed decreases in lymphocyte counts of less than 0.5×10^9 cells per liter or of neutrophil counts of less than 1.0×10^9 cells per



liter, and there were no confirmed cases of a decrease from baseline in the hemoglobin level of more than 0.8 g per deciliter or more than 30%. Increases from baseline to month 3 in levels of low-density lipoprotein cholesterol and high-density lipoprotein cholesterol were greater in all active treatment groups than in the placebo group, and levels were generally maintained over the 12-month period (Table S7 in the Supplementary Appendix). Over the 12-month period, five patients who received tofacitinib (two of whom had switched from placebo) and three patients who received adalimumab had a confirmed aspartate aminotransferase level of three or more times the upper limit of the normal range, and five patients who received tofacitinib (three of whom had switched from placebo) and nine who received adalimumab had a confirmed alanine aminotransferase level of three or more times the upper limit of the normal range (Table S7 in the Supplementary Appendix).

Figure 2 (facing page). American College of Rheumatology (ACR) 20 Response Rate and Change from Baseline in the Health Assessment Questionnaire–Disability Index (HAQ-DI) Score to Month 12.

Shown are the response rates of a 20% improvement from baseline in the number of tender and swollen joints and at least three other important domains (ACR20 response) (Panel A) and the least-squares mean change in the HAQ-DI score from baseline (Panel B, dashed line) throughout the trial to month 12 among patients who received 5 mg of tofacitinib, 10 mg of tofacitinib, adalimumab, placebo with a switch to the 5-mg tofacitinib dose at month 3, or placebo with a switch to the 10-mg tofacitinib dose at month 3. Data from the placebo groups were pooled for the visits at or before month 3. HAQ-DI scores range from 0 to 3, with higher scores indicating greater disability (minimal clinically important decrease from baseline, 0.35 points). I bars indicate ±1 SE. All the data are shown for the full analysis set, which included all the patients who underwent randomization and received at least one dose of tofacitinib, adalimumab, or placebo. The vertical line at month 3 indicates the end of the placebo-controlled period. Missing data regarding the ACR20 response were imputed as no response (data were missing at 3 months for three patients in the placebo group, for four in the 5-mg tofacitinib group, for two in the 10-mg tofacitinib group, and for six in the adalimumab group). No imputation was applied for missing HAQ-DI data (data were missing at 3 months for three patients in the placebo group, for four in the 5-mg tofacitinib group, for one in the 10-mg tofacitinib group, and for five in the adalimumab group; in a repeated-measures analysis, data were missing for one patient in the placebo 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. The 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.

DISCUSSION

Tofacitinib provides an alternative mechanism of action, as compared with current treatment options for psoriatic arthritis, by targeting multiple stages in the inflammatory pathways by means of JAK inhibition. This trial showed that tofacitinib at a dose of 5 mg or 10 mg was superior to placebo with regard to the two primary efficacy outcomes (rate of ACR20 response and change from baseline in the HAQ-DI score) at 3 months among patients with psoriatic arthritis who had not had a previous response to or could not take conventional synthetic DMARDs. The response rates for the ACR50, ACR70, and PASI75 assessments with the two tofacitinib doses and the change in the Leeds Enthesitis Index score with the 10-mg dose of tofacitinib (but not with the 5-mg dose) were superior to placebo at month 3. Changes from baseline through month 12 were numerically similar to those at month 3 in the two tofacitinib groups and the adalimumab group but could not be compared with the placebo group because of the design of the trial. Statistical significance regarding the changes from baseline in the Dactylitis Severity Score, the SF-36 physical functioning score, and the FACIT-F total score could not be tested under the hierarchical analysis plan, but the observed effects with tofacitinib were in the same direction as the primary end points. As in our trial, a relatively high rate of response in the placebo group with regard to several end points has been observed in other studies involving patients with psoriatic arthritis.[21,22]

There were no observed differences between the tofacitinib doses of 5 mg and 10 mg in efficacy across the disease domains regarding psoriatic arthritis (peripheral arthritis, skin manifestations, enthesitis, and dactylitis). Neither tofacitinib dose differed substantially in a numerical sense from adalimumab in its effects on the main outcomes; however, the trial was not designed and was not powered for statistical comparisons between tofacitinib and adalimumab. This trial also investigated the effect of tofacitinib on changes in psoriatic arthritis that were assessed radiographically. At month 12, the rates of nonprogression of joint damage, as assessed radiographically, were more than 90% among patients who received tofacitinib or adalimumab or who switched from placebo to tofacitinib at month 3.

Up to month 3, more adverse events were reported with the active treatments than with placebo. Over a period of 12 months, herpes zoster occurred in four patients who received tofacitinib continuously, as compared with none of the patients who received placebo or adalimumab. Cancers (excluding nonmelanoma skin

Table 3. Summary of Safety Events.*

Event	Up to 3 Mo				Up to 12 Mo				
	Pooled Placebo (N=105)	Tofacitinib, 5 mg (N=107)	Tofacitinib, 10 mg (N=104)	Adalimumab (N=106)	Placebo to Tofacitinib, 5 mg (N=52)	Placebo to Tofacitinib, 10 mg (N=53)	Tofacitinib, 5 mg (N=107)	Tofacitinib, 10 mg (N=104)	Adalimumab (N=106)
Any adverse event — no. (%)	37 (35)	42 (39)	47 (45)	49 (46)	36 (69)	34 (64)	71 (66)	74 (71)	76 (72)
Serious adverse event — no. (%)	1 (1)	3 (3)	1 (1)	1 (1)	3 (6)	4 (8)	8 (7)	4 (4)	9 (8)
Discontinuation due to adverse event — no. (%)	1 (1)	3 (3)	0	2 (2)	2 (4)	2 (4)	6 (6)	3 (3)	4 (4)
Adverse event of special interest — no. (%) [day of onset]†									
Serious infection	0	0	0	0	2 (4) [days 102 and 331]	0	0	1 (1) [day 132]	1 (1) [day 170]
Herpes zoster infection	0	1 (1) [day 61]	0	0	0	0	2 (2) [days 61 and 173]	2 (2) [days 221 and 317]	0
Opportunistic infection	0	1 (1) [day 61]	0	0	0	0	1 (1) [day 61]	0	0
Cancer, excluding nonmelanoma skin cancer	0	2 (2) [days 1 and 11]	0	0	0	0	3 (3) [days 1, 11, and 232]	0	0
Nonmelanoma skin cancer	0	0	1 (1) [day 103]	0	0	0	0	1 (1) [day 103]	0
Cardiovascular event	0	0	0	0	1 (2) [day 139]	0	0	0	2 (2) [days 263 and 345]
Gastrointestinal perforation	0	0	0	0	1 (2) [day 102]	0	0	0	0

* Analyses were performed with data from the safety analysis set, which was the same as the full analysis set and included all patients who received at least one dose of tofacitinib, adalimumab, or placebo. Adverse events from any cause were included in the analyses.

† Among the adverse events of special interest, the cases of herpes zoster infection were not judged to be serious adverse events, and the events of opportunistic infection, cancer, cardiovascular event, and gastrointestinal perforation were all adjudicated.

cancer) occurred in three patients who received tofacitinib continuously and in none of those who received placebo or adalimumab; two cancers were diagnosed within 30 days after the patient received the first dose of tofacitinib. One patient who had switched from placebo to the 5-mg dose of tofacitinib died as a result of a cardiac arrest during month 4 of the trial.

In conclusion, tofacitinib at a dose of 5 mg or 10 mg showed superior efficacy to placebo in several clinical domains of psoriatic arthritis at 3 months. The rates of nonprogression, as assessed radiographically, were similar across all the trial groups over a period of 12 months. The rates of adverse events were higher in the active treatment groups than in the placebo group. Further studies are required in order to determine the long-term efficacy and safety of tofacitinib in patients with psoriatic arthritis.

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APPENDIX

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