ORIGINAL ARTICLE

Tofacitinib or Adalimumab versus Placebo in Rheumatoid Arthritis

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This article was updated on June 27, 2013, at NEJM.org.

N Engl J Med 2012;367:508-19.
DOI: 10.1056/NEJMoa1112072

Abstract

BACKGROUND

Tofacitinib (CP-690,550) is a novel oral Janus kinase inhibitor that is being investigated for the treatment of rheumatoid arthritis.

METHODS

In this 12-month, phase 3 trial, 717 patients who were receiving stable doses of methotrexate were randomly assigned to 5 mg of tofacitinib twice daily, 10 mg of tofacitinib twice daily, 40 mg of adalimumab once every 2 weeks, or placebo. At month 3, patients in the placebo group who did not have a 20% reduction from baseline in the number of swollen and tender joints were switched in a blinded fashion to either 5 mg or 10 mg of tofacitinib twice daily; at month 6, all patients still receiving placebo were switched to tofacitinib in a blinded fashion. The three primary outcome measures were a 20% improvement at month 6 in the American College of Rheumatology scale (ACR 20); the change from baseline to month 3 in the score on the Health Assessment Questionnaire–Disability Index (HAQ-DI) (which ranges from 0 to 3, with higher scores indicating greater disability); and the percentage of patients at month 6 who had a Disease Activity Score for 28-joint counts based on the erythrocyte sedimentation rate (DAS28-4[ESR]) of less than 2.6 (with scores ranging from 0 to 9.4 and higher scores indicating greater disease activity).

RESULTS

At month 6, ACR 20 response rates were higher among patients receiving 5 mg or 10 mg of tofacitinib (51.5% and 52.6%, respectively) and among those receiving adalimumab (47.2%) than among those receiving placebo (28.3%) ($P<0.001$ for all comparisons). There were also greater reductions in the HAQ-DI score at month 3 and higher percentages of patients with a DAS28-4(ESR) below 2.6 at month 6 in the active-treatment groups than in the placebo group. Adverse events occurred more frequently with tofacitinib than with placebo, and pulmonary tuberculosis developed in two patients in the 10-mg tofacitinib group. Tofacitinib was associated with an increase in both low-density and high-density lipoprotein cholesterol levels and with reductions in neutrophil counts.

CONCLUSIONS

In patients with rheumatoid arthritis receiving background methotrexate, tofacitinib was significantly superior to placebo and was numerically similar to adalimumab in efficacy. (Funded by Pfizer; ORAL Standard ClinicalTrials.gov number, NCT00853385.)

Rheumatoid arthritis is a common autoimmune disease of the musculoskeletal system that is associated with considerable morbidity and diminished quality of life.[1-3] Treatment of rheumatoid arthritis is based on conventional or biologic (or both) disease-modifying drugs, of which methotrexate is the most widely used.[4] For patients who have an inadequate response to methotrexate, anti–tumor necrosis factor (TNF) biologic agents have proved to be effective as second-line treatment.[5-7] Conventional disease-modifying drugs are small, orally active molecules, whereas biologic products are, by definition, large proteins that are available only as parenteral agents. The development of a novel oral antirheumatic agent with safety and adverse-event profiles and efficacy that are similar to those of biologic agents would be of clinical interest.

Tofacitinib (CP-690,550) is being investigated as a targeted immunomodulator and disease-modifying therapy for rheumatoid arthritis. Tofacitinib is a novel, small-molecule, oral selective inhibitor of Janus kinase (JAK) 1 and JAK3 and, to a lesser extent, JAK2. JAKs mediate signal-transduction activity by the surface receptors for multiple cytokines, including interleukins 2, 4, 6, 7, 9, 15, and 21.[8,9] These cytokines are integral to lymphocyte activation, proliferation, and function; inhibition of their signaling may result in the modulation of multiple aspects of the immune response.[8-11]

Methods

The authors who are employees of Pfizer designed the study in collaboration with the academic authors. Data were collected by an employee of Kendle International, a clinical research organization, and were analyzed by an author who is an employee of Pfizer. The first author wrote the initial draft of the manuscript with subsequent revisions provided by all authors; all the authors vouch for the completeness of the data and analyses and made the decision to submit the manuscript for publication. Writing assistance and editorial support were provided by an employee of Complete Medical Communications who was funded by Pfizer. The final protocol, amendments, and informed-consent documentation were approved by a central or local institutional review board or an independent ethics committee. The study was conducted and analyzed according to the protocol, which is available with the full text of this article at NEJM.org. All patients provided written informed consent.

Patients

Patients were eligible for enrollment if they were 18 years of age or older and had received a diagnosis of active rheumatoid arthritis, as defined according to the American College of Rheumatology (ACR) 1987 Revised Criteria.[12] Active disease was defined as the presence of 6 or more tender or painful joints (of 68 joints examined) and 6 or more swollen joints (of 66 joints examined) and either an erythrocyte sedimentation rate (ESR) greater than 28 mm per hour (Westergren method) or a C-reactive protein level exceeding 7 mg per liter. Patients were receiving 7.5 to 25 mg of methotrexate weekly and had an incomplete response (defined as sufficient residual disease activity to meet entry criteria). Key exclusion criteria were current treatment with other antirheumatic agents, including biologic agents; prior treatment with adalimumab; lack of response to prior anti-TNF biologic treatment; and current infection or evidence of active or inadequately treated infection with *Mycobacterium tuberculosis*.

Study Design and Treatment

The Oral Rheumatoid Arthritis Phase 3 Trials Standard (ORAL Standard) study, was a randomized, phase 3 clinical trial conducted in 115 centers worldwide between January 30, 2009, and February 10, 2011, to investigate the clinical efficacy of tofacitinib as compared with placebo. All patients were taking background methotrexate and, by means of an interactive voice-response system, were randomly assigned, in a 4:4:4:1:1 ratio, to one of five regimens: 5 mg of tofacitinib twice daily, 10 mg of tofacitinib twice daily, 40 mg of adalimumab administered by subcutaneous injection once every 2 weeks, placebo for 3 months or 6 months followed by 5 mg of tofacitinib twice daily, and placebo for 3 months or 6 months followed by 10 mg of tofacitinib twice daily. Patients in the placebo group who did not have a 20% reduction in the number of swollen and tender joints after 3 months (considered as not having had a response) were randomly assigned to either 5 mg or 10 mg of tofacitinib. After 6 months, all patients assigned to placebo were switched in a blinded fashion to either 5 mg or 10 mg of tofacitinib. Patients randomly assigned to tofacitinib or adalimumab who did not have a response to treatment continued

with the same regimens for the duration of the trial. All patients self-administered injections of either adalimumab or placebo once every 2 weeks and also took placebo or tofacitinib pills twice daily.

MEASURES OF EFFICACY

The three primary efficacy end points, for which the efficacy of tofacitinib was compared with placebo, were the percentage of patients at month 6 who met the criteria for an ACR response (defined as a 20% reduction in the number of tender and swollen joints, as well as improvement in at least three of the other five ACR components)[13]; the mean change from baseline to month 3 in physical function status, as assessed with the use of the Health Assessment Questionnaire–Disability Index (HAQ-DI) (with higher scores indicating greater disability)[14]; and the percentage of patients who had a Disease Activity Score of less than 2.6 at month 6 (with scores ranging from 0 to 9.4 and higher scores indicating greater disease activity).[15] The Disease Activity Score for the primary efficacy end point is based on a 28-joint count for swollen joints and for tender joints, the patient's global assessment of disease activity, and the erythrocyte sedimentation rate (DAS28-4[ESR]). Secondary end points included comparisons of the two doses of tofacitinib (5 mg and 10 mg) with placebo over time with respect to the percentage of patients who met the criteria for ACR 20, ACR 50, and ACR 70 responses (indicating reductions from baseline of at least 20%, 50%, and 70%, respectively, in the number of tender and swollen joints, as well as improvement in at least three of the other five ACR components) and with respect to changes from baseline in the HAQ-DI score and DAS28-4(ESR).

SAFETY ASSESSMENTS

Another primary objective was to assess the safety of tofacitinib as compared with placebo during the 12-month study period. The incidence and severity of all adverse events were recorded, and clinical laboratory tests, assessment of vital signs, and physical examinations were performed at scheduled visits.

STATISTICAL ANALYSIS

To preserve the type I error rate, the three primary efficacy end points were assessed sequentially as follows: the percentage of patients with an ACR 20 response,[13] the mean change from baseline in the HAQ-DI score, and the percentage of patients with a DAS28-4(ESR) below 2.6 (Fig. S1 in the Supplementary Appendix, available at NEJM.org). The type I error rate was preserved for the primary end points when statistical significance was determined; no preservation of the type I error rate was applied for the secondary end points. P values of 0.05 or less were considered to indicate statistical significance.

The full analysis set for efficacy and safety included all patients who underwent randomization and who received at least one dose of study drug. The normal approximation for the difference in binomial proportions was used to test the superiority of each of the two tofacitinib regimens over placebo with respect to ACR 20 response rates and the percentage of patients with a DAS28-4(ESR) of less than 2.6. Imputation of no response was used to account for missing data in the calculation of these two end points and was applied to patients who discontinued the study drug for any reason (including patients who were lost to follow-up before month 6), as is standard in many clinical trials involving patients with rheumatoid arthritis. However, in this trial, the imputation of no response was also applied to patients who did not have a 20% reduction in the number of tender and swollen joints at month 3, regardless of treatment assignment; patients in the active-treatment groups who did not meet the criteria for this response continued with the same treatment, whereas patients who were receiving placebo were switched to tofacitinib in a double-blind fashion. The imputation-of-no-response analysis assumes that patients who did not have a response to treatment by month 3 will not have a response during the remainder of the trial — even if they subsequently meet the criteria for an ACR 20 response.

Thus, in this trial, the application of imputation of no response (referred to as "imputation of no response with advancement penalty") was more conservative than in prior analyses, because historically the application has not assumed that treatment has failed in patients receiving placebo. An analysis was also performed in which the advancement penalty was removed to allow any new response to active treatment after month 3 to be observed (referred to as "imputation of no response without advancement penalty"). For these analyses, the placebo group at month 6 comprised patients who were still receiving placebo and pa-

Table 1. Demographic and Clinical Characteristics at Baseline, According to Treatment Group.*

Variable	Placebo Followed by Tofacitinib, 5 mg (N=56)	Placebo Followed by Tofacitinib, 10 mg (N=52)	Tofacitinib, 5 mg (N=204)	Tofacitinib, 10 mg (N=201)	Adalimumab, 40 mg (N=204)
Female sex — no. (%)	43 (76.8)	39 (75.0)	174 (85.3)	168 (83.6)	162 (79.4)
White race — no. (%)†	40 (71.4)	35 (67.3)	151 (74.0)	143 (71.1)	148 (72.5)
Age — yr	55.5±13.7	51.9±13.7	53.0±11.9	52.9±11.8	52.5±11.7
Mean duration of rheumatoid arthritis — yr	6.9	9.0	7.6	7.4	8.1
Region of origin — %‡					
North America	28.6	28.8	24.5	24.9	25.5
Latin America	3.6	5.8	3.9	1.5	2.9
Europe	51.8	44.2	53.9	55.7	53.9
Rest of world	16.1	21.1	17.6	17.9	17.6
Tender and swollen joints — mean no.§					
Tender	26.6	28.1	28.5	26.1	26.7
Swollen	16.9	16.4	16.7	15.8	16.4
Mean HAQ-DI score	1.5	1.4	1.5	1.5	1.5
Mean DAS28-4(ESR)	6.6	6.3	6.6	6.5	6.4
Mean ESR — mm/hr	52.7	42.9	48.6	49.9	48.5
Mean DAS28-3(CRP)¶	5.6	5.3	5.4	5.4	5.3
Mean CRP — mg/liter	20.3	11.6	14.9	17.3	17.5
Positive for rheumatoid factor — %	71.4	60.8	66.8	66.2	68.2
Positive for anti-CCP — %	76.4	62.0	71.3	64.0	74.8
Prior therapy — no. of patients (%)					
TNF inhibitor	4 (7.1)	5 (9.6)	12 (5.9)	14 (7.0)	16 (7.8)
Non-TNF inhibitor biologic	4 (7.1)	2 (3.8)	2 (1.0)	4 (2.0)	3 (1.5)
Disease-modifying drug other than methotrexate	30 (53.6)	29 (55.8)	109 (53.4)	115 (57.2)	114 (55.9)
Concomitant therapy — no. of patients (%)					
Glucocorticoids	41 (73.2)	31 (59.6)	126 (61.8)	129 (64.2)	125 (61.3)
Lipid-lowering medication	1 (1.8)	3 (5.8)	8 (3.9)	10 (5.0)	10 (4.9)

* Plus–minus values are means ±SD. There were no significant differences among the groups at baseline. ADA denotes adalimumab, CCP cyclic citrullinated peptide, CRP C-reactive protein, DAS28-4 Disease Activity Score for 28 joint counts, DAS28-3(CRP) DAS28 based on the CRP level, DAS28-4(ESR) DAS28 based on the erythrocyte sedimentation rate (ESR), HAQ-DI Health Assessment Questionnaire–Disability Index, and TNF tumor necrosis factor.

† Race was self-reported.

‡ A total of 21 countries were included in the study; the geographic breakdown is based on the number of patients who had 20% improvement in the American College of Rheumatology scale (ACR 20) at month 1. The percentages of patients in each region were 24.5% in North America, 2.9% in Latin America, 54.2% in Europe, and 18.4% in the rest of the world.

§ A total of 68 specific joints were examined for tenderness or pain, and 66 specific joints were examined for swelling. Higher values indicate greater levels of disease activity.

¶ The DAS28-3(CRP) value is based on three variables: tender-joint counts, swollen-joint counts, and CRP levels. Values range from 0 to 9.4, with higher values indicating greater disease activity.

tients who had been switched from placebo to tofacitinib, 5 mg or 10 mg twice daily, at month 3.

For each efficacy end point, the comparison with placebo was performed with the two-sided alpha level for significance set at 0.05 or, equivalently, the one-sided alpha level set at 0.025. For the ACR 20 analysis, we calculated a sample size that we estimated would give the study more than 90% power to detect a difference in response rates of at least 20%, assuming a response of 30% in the placebo groups. For the analysis of the HAQ-DI, we estimated that the sample size would give the

study more than 90% power to detect a difference of at least 0.3 points, assuming a standard deviation of 0.75.

The change from baseline in HAQ-DI scores was expressed as least-squares means. For this analysis, we used a mixed-effect longitudinal model, which included any effects of treatment and follow-up visits. In addition, variability as a result of patient effect was included. Secondary end points with binary variables were analyzed in the same way as ACR 20 responses, and continuous end points were analyzed in the same way as the changes in HAQ-DI scores.

Safety data were summarized descriptively and as least-squares means for selected variables. Formal testing of the observed differences in safety measures was not part of the statistical analysis plan, in part because such testing is poorly defined and misleading for uncommon events.

RESULTS

PATIENTS

The majority of the 717 patients in the full analysis set were women (range among the five study groups, 75.0 to 85.3%) and white (range, 67.3 to 74.0%) and the mean duration of rheumatoid arthritis ranged from 6.9 to 9.0 years (Table 1). A total of 556 patients (77.5%) completed the 12-month study (Fig. S2 in the Supplementary Appendix).

EFFICACY

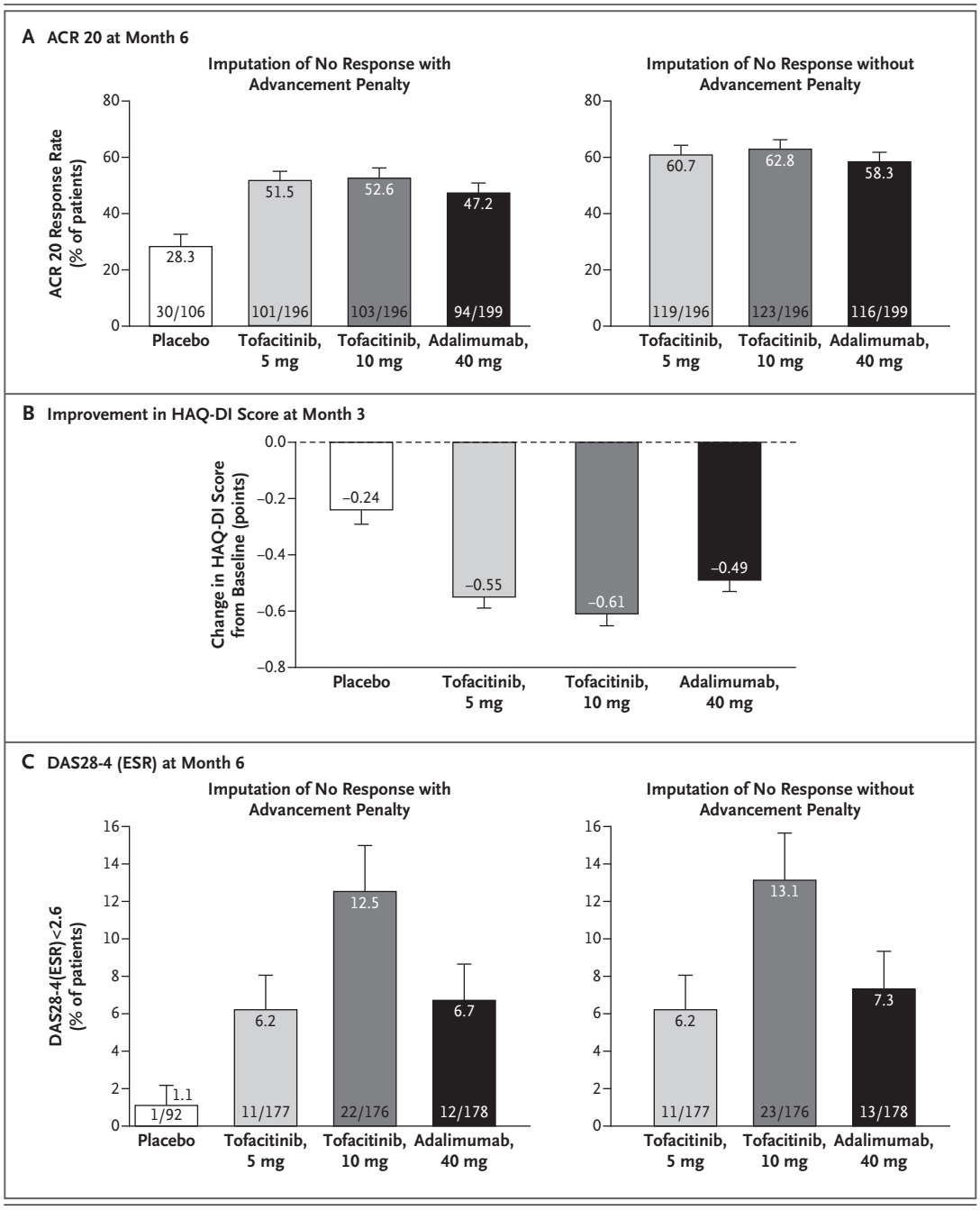
A significantly greater percentage of patients receiving active treatment than those receiving placebo met the criteria for an ACR 20 response at month 6: 51.5% in the 5-mg tofacitinib group, 52.6% in the 10-mg tofacitinib group, and 47.2% in the 40-mg adalimumab group, as compared with 28.3% in the placebo group (P<0.001 for all comparisons) (Fig. 1A). The mean change from baseline in the HAQ-DI score at month 3 (Fig. 1B) and the percentage of patients with a DAS28-4(ESR) below 2.6 at month 6 (Fig. 1C) were also significantly greater with the active treatments than with placebo. With respect to secondary efficacy end points, significantly greater responses were seen with the active treatments than with placebo with respect to ACR 50 and ACR 70 responses and the changes from baseline in DAS28-4(ESR) and HAQ-DI scores over time (P≤0.05 for all comparisons). The magnitude of these responses was sustained to month 12 and was numerically similar among the three active-treatment groups (Fig. S3 and S4 in the Supplementary Appendix). A rapid response to active treatment was observed; a significant difference in ACR 20 and ACR 50 responses with each tofacitinib treatment as compared with placebo was noted after 1 month (P≤0.001 for all comparisons) (Fig. S3 in the Supplementary Appendix).

Figure 1 (facing page). Primary Efficacy Analyses.

Panel A shows the numbers and percentages of patients with at least a 20% improvement in the American College of Rheumatology scale (ACR 20). The bar graph on the left shows the results of the analysis with imputation of no response with the advancement penalty; if patients did not have a response to therapy by month 3, the treatment was considered to be a failure even if they had a response after month 3. P<0.001 for the comparison of each active-treatment group with placebo. The bar graph on the right shows the results of the analysis with imputation of no response without the advancement penalty, which are the actual response rates at month 6 in the active-treatment groups; if patients did not have a response to therapy by month 3 but had a response after month 3, treatment was not considered to be a failure. The response without the advancement penalty in the placebo group cannot be calculated because patients in that group who did not have a response by month 3 were switched to tofacitinib. Panel B shows the change in Health Assessment Questionnaire–Disability Index (HAQ-DI) scores (which range from 0 to 3, with higher scores indicating greater disability) from baseline to month 3. A total of 98 patients in the placebo group, 188 in the 5-mg tofacitinib group, 185 in the 10-mg tofacitinib group, and 190 in the adalimumab group were included in this analysis. P<0.001 for the comparison of each active-treatment group with placebo. Panel C shows the numbers and percentages of patients with a Disease Activity Score for 28-joint counts based on the erythrocyte sedimentation rate (DAS28-4[ESR]) of less than 2.6. Scores on the DAS28-4(ESR) range from 0 to 9.4, with higher scores indicating more disease activity. As in Panel A, the bar graph on the left shows the results of the analysis with imputation of no response with the advancement penalty, and the bar graph on the right shows the results of the analysis with imputation of no response without the advancement penalty. For the bar graph on the left, P<0.05 for the comparison of the 5-mg tofacitinib group and of the adalimumab group with the placebo group, and P<0.001 for the comparison of the 10-mg tofacitinib group with the placebo group. Data are expressed as means, with T bars indicating the standard error.

SAFETY

Table 2 summarizes the changes from baseline in laboratory measurements. After an initial decrease in neutrophil counts at month 3 with all active treatments (decrease of 0.72×10^3 per cubic millimeter with 5 mg tofacitinib, 0.76×10^3 per cu-



bic millimeter with 10 mg tofacitinib, and 1.25×10^3 per cubic millimeter with adalimumab vs. 0.24×10^3 per cubic millimeter with placebo), neutrophil counts remained relatively stable through month 12. The incidence of mild neutropenia (1500 to 1999 neutrophils per cubic millimeter) and moderate-to-severe neutropenia (500 to 1499 neutrophils per cubic millimeter) was low across all treatment groups (Table 2). One patient (in the 5-mg tofacitinib group) had less than 500 neutrophils per cubic millimeter at month 1, a level that was not confirmed on retesting. Levels of low-density lipoprotein (LDL) cholesterol and of high-density lipoprotein (HDL) cholesterol during months 0 to 3 increased from baseline to a greater extent in the tofacitinib groups than in the adalimumab and placebo groups. A total of 3.9% of patients in the 5-mg tofacitinib group, 6.5% in the 10-mg tofacitinib group, 0.1% in the adalimumab group, and 0.93% in the placebo group had

Table 2. Safety and Laboratory Data.*

Variable	Months 0–3				Months 3–6	
	Placebo (N=108)	Tofacitinib, 5 mg (N=204)	Tofacitinib, 10 mg (N=201)	Adalimumab, 40 mg (N=204)	Placebo (N=59)	Tofacitinib, 5 mg, Switched from Placebo (N=28)
Adverse events — no. (%)						
Patients with treatment-emergent adverse events	51 (47.2)	106 (52.0)	94 (46.8)	105 (51.5)	16 (27.1)	7 (25.0)
Patients with serious adverse events	2 (1.9)	12 (5.9)	10 (5.0)	5 (2.5)	2 (3.4)	0
Patients with serious infection events	1 (0.9)	3 (1.5)	4 (2.0)	0	0	0
Discontinuation of study drug owing to adverse event	3 (2.8)	14 (6.9)	10 (5.0)	10 (4.9)	0	1 (3.6)
	Month 3, Mean Change from Baseline				Month 6, Mean Change from Baseline	
Neutrophil count — 10^{-3}/mm^3	−0.24±0.17	−0.72±0.12	−0.76±0.13	−1.25±0.12	NA	−0.51±0.23
Hemoglobin — g/dl	0.04±0.75	0.08±0.91	−0.12±2.38	0.36±0.82	NA	0.26±0.88
Cholesterol level — %						
Low-density lipoprotein	0.26±2.60	12.18±1.94	18.93±1.95	3.62±1.91	NA	10.05±3.61
High-density lipoprotein	−1.55±1.97	12.17±1.48	10.95±1.49	5.64±1.47	NA	5.91±2.77
Serum creatinine — mg/dl	0±0.01	0.04±0.01	0.05±0.01	0.02±0.01	NA	0.04±0.02
	Month 3				Month 6	
	Placebo (N=98)	Tofacitinib, 5 mg (N=186)	Tofacitinib, 10 mg (N=183)	Adalimumab, 40 mg (N=187)	Placebo (N=0)	Tofacitinib, 5 mg, Switched from Placebo (N=52)
Neutropenia — no. of patients (%)†						
Mild, 1500 to 1999 cells/mm^3	2 (2.0)	3 (1.6)	3 (1.6)	5 (2.7)	NA	1 (1.9)
Moderate to severe, 500 to 1499 cells/mm^3	0	2 (1.1)	3 (1.6)	0	NA	0
Decreased hemoglobin, −1.0 to −3.0 g/dl — no. of patients (%)‡	9 (9.2)	15 (8.1)	15 (8.2)	10 (5.3)	NA	3 (5.8)
	Month 0–3				Months 3–6	
	Placebo (N=105)	Tofacitinib, 5 mg (N=203)	Tofacitinib, 10 mg (N=201)	Adalimumab, 40 mg (N=204)	Placebo (N=46)	Tofacitinib, 5 mg, Switched from Placebo (N=28)
Aminotransferase levels — no. of incidents/total no. (%)§						
AST>1× ULN	11/143 (7.7)	48/143 (33.6)	48/143 (33.6)	36/143 (25.2)	3/98 (3.1)	3/98 (3.1)
AST>3× ULN	1/2 (50.0)	1/2 (50.0)	0	0	0	0
ALT>1× ULN	18/173 (10.4)	58/173 (33.5)	49/173 (28.3)	48/173 (27.8)	4/120 (3.3)	7/120 (5.8)
ALT>3× ULN	1/4 (25.0)	2/4 (50.0)	1/4 (25.0)	0	0	0

* Plus–minus values are least-squares means ±SE in all cases except for hemoglobin values, which are means ±SD. A patient may have had more than one adverse event, so the individual totals may not add up to the overall total number of events. To convert the values for creatinine to micromoles per liter, multiply by 88.4. ALT denotes alanine aminotransferase, AST aspartate aminotransferase, NA not assessed, and ULN upper limit of the normal range.

† Potentially life-threatening neutropenia is defined as less than 500 neutrophils per cubic millimeter.

‡ A severe decreased hemoglobin is also defined as an actual level of greater than 7 g per deciliter but less than 8 g per deciliter.

§ For ALT and AST, we recorded the number of incidents in which values were higher than the ULN. More than one incident may be recorded for the same patient.

Months 3–6				**Months 6–12**				
Tofacitinib, 10 mg, Switched from Placebo (N=21)	Tofacitinib, 5 mg (N=204)	Tofacitinib, 10 mg (N=201)	Adalimumab, 40 mg (N=204)	Tofacitinib, 5 mg, Switched from Placebo (N=56)	Tofacitinib, 10 mg, Switched from Placebo (N=52)	Tofacitinib, 5 mg (N=204)	Tofacitinib, 10 mg (N=201)	Adalimumab, 40 mg (N=204)
9 (42.9)	67 (32.8)	62 (30.8)	68 (33.3)	18 (32.1)	21 (40.4)	89 (43.6)	84 (41.8)	83 (40.7)
0	10 (4.9)	7 (3.5)	6 (2.9)	1 (1.8)	4 (7.7)	10 (4.9)	6 (3.0)	7 (3.4)
0	2 (1.0)	1 (0.5)	2 (1.0)	0	1 (1.9)	2 (1.0)	3 (1.5)	1 (0.5)
0	5 (2.5)	11 (5.5)	9 (4.4)	0	2 (3.8)	6 (2.9)	3 (1.5)	4 (2.0)
Month 6, Mean Change from Baseline				**Month 12, Mean Change from Baseline**				
–0.91±0.25	–0.81±0.13	–0.95±0.13	–1.35±0.13	–0.88±0.24	–0.70±0.27	–0.66±0.14	–0.93±0.14	–1.19±0.13
–0.23±0.96	0.15±0.85	–0.04±2.40	0.33±0.97	0.41±0.92	0.09±1.00	0.31±1.06	–0.01±2.65	0.46±1.16
–1.92±3.98	14.12±2.01	21.18±2.00	2.35±1.98	17.38±3.71	12.30±4.16	10.28±2.10	21.12±2.12	1.45±2.05
–2.18±3.01	10.96±1.54	13.32±1.52	2.79±1.52	15.46±2.85	7.83±3.13	15.82±1.62	14.07±1.62	7.73±1.58
0.03±0.02	0.05±0.01	0.06±0.01	0.02±0.01	0.08±0.02	0.08±0.02	0.06±0.01	0.07±0.01	0.03±0.01
Month 6				**Month 12**				
Tofacitinib, 10 mg, Switched from Placebo (N=42)	Tofacitinib, 5 mg (N=170)	Tofacitinib, 10 mg (N=181)	Adalimumab, 40 mg (N=178)	Tofacitinib, 5 mg, Switched from Placebo (N=47)	Tofacitinib, 10 mg, Switched from Placebo (N=37)	Tofacitinib, 5 mg (N=143)	Tofacitinib, 10 mg (N=149)	Adalimumab, 40 mg (N=155)
0	3 (1.8)	7 (3.9)	9 (5.1)	3 (6.4)	0	0	5 (3.4)	9 (5.8)
0	0	2 (1.1)	1 (<1.0)	0	0	0	2 (1.3)	1 (<1.0)
7 (16.7)	17 (10.0)	21 (11.6)	12 (6.8)	2 (4.3)	4 (10.8)	13 (9.1)	18 (12.1)	13 (8.4)
Months 3–6				**Months 6–12**				
Tofacitinib, 10 mg, Switched from Placebo (N=20)	Tofacitinib, 5 mg (N=186)	Tofacitinib, 10 mg (N=183)	Adalimumab, 40 mg (N=187)	Tofacitinib, 5 mg, Switched from Placebo (N=50)	Tofacitinib, 10 mg, Switched from Placebo (N=42)	Tofacitinib, 5 mg (N=167)	Tofacitinib, 10 mg (N=174)	Adalimumab, 40 mg (N=178)
3/98 (3.1)	28/98 (28.6)	37/98 (37.8)	24/98 (24.5)	12/140 (8.6)	10/140 (7.1)	41/140 (29.3)	54/140 (38.6)	23/140 (16.4)
0	2/5 (40.0)	2/5 (40.0)	1/5 (20.0)	0	0	2/6 (33.3)	3/6 (50.0)	1/6 (16.7)
4/120 (3.3)	39/120 (32.5)	38/120 (31.7)	28/120 (23.3)	9/154 (5.8)	9/154 (5.8)	42/154 (27.3)	57/154 (37.0)	37/154 (24.0)
0	3/6 (50.0)	2/6 (33.3)	1/6 (16.7)	0	0	5/14 (35.7)	6/14 (42.9)	3/14 (21.4)

LDL cholesterol levels that were below 100 mg per deciliter (2.6 mmol per liter) at baseline and that increased to 130 mg per deciliter (3.4 mmol per liter) or higher in months 0 to 3. The mean changes from baseline in serum creatinine level were small in magnitude across the treatment groups. The changes at month 6 were 0.06 mg per deciliter (5.3 μmol per liter) with 10 mg of tofacitinib, 0.05 mg per deciliter (4.4 μmol per liter) with 5 mg of tofacitinib, and 0.02 mg per deciliter (1.8 μmol per liter) with adalimumab. Most instances of decreased hemoglobin were mild to moderate in severity; decreased hemoglobin was potentially life-threatening in one patient in the 10-mg tofacitinib group at months 1, 3, 6, and 12, as well as in one patient in the 5-mg tofacitinib group and one patient in the adalimumab group at month 12. A greater percentage of patients in the 5-mg and

Table 3. Serious Adverse and Infection Events Over the Course of 12 Months, According to Treatment Sequence.*

MedDRA System Organ Class	Placebo Followed by Tofacitinib, 5 mg (N = 56)	Placebo Followed by Tofacitinib, 10 mg (N = 52)	Tofacitinib, 5 mg (N = 204)	Tofacitinib, 10 mg (N = 201)	Adalimumab, 40 mg (N = 204)
Blood and lymphatic system disorders					Bone marrow failure
Cardiac disorders		Atrioventricular block complete	Acute myocardial infarction	Cardiac failure congestive, myocardial infarction	Acute myocardial infarction, cardiac arrest, myocardial infarction, myocardial ischemia
Ear and labyrinth disorders				Vertigo	
Endocrine disorders			Autoimmune thyroiditis		
Eye disorders				Retinal detachment	
Gastrointestinal disorders	Salivary-gland calculus	Ileus	Gastroenteritis	Anal polyp, diverticular perforation, peptic ulcer hemorrhage	Abdominal hernia, hematemesis, melena
General disorders and administration site conditions		Liver disorder	Impaired healing	Pyrexia	Chest pain
Hepatobiliary disorders		Cholelithiasis	Cholelithiasis, cholecystitis infective		Cholecystitis acute
Infections and infestations	Sialoadenitis		Cellulitis (two patients), herpes zoster, localized infection, lung abscess, osteomyelitis, pneumonia (two patients), salpingo-oophoritis, septic shock, abscess jaw	Arthritis bacterial, cellulitis, clostridial infection, herpes zoster, labyrinthitis, pneumonia, pulmonary tuberculosis (two patients), urinary tract infection	Breast abscess, breast cellulitis, erysipelas, gallbladder empyema
Injury, poisoning, and procedural complications			Femur fracture, humerus fracture (two patients), tibia fracture, lower-limb fracture, multiple fractures, tendon disorder, tendon rupture	Femur fracture, fibular fracture, tendon rupture	Femur fracture, joint dislocation
Metabolism and nutrition disorders			Diabetes mellitus		
Musculoskeletal and connective tissue disorders				Rheumatoid arthritis,† spinal column stenosis	Bursitis, rheumatoid arthritis,† spondylolisthesis
Neoplasm benign, malignant, and unspecified, including cysts and polyps		Neuroma	Salivary-gland neoplasm, hair follicle tumor benign, metastatic renal-cell carcinoma, non–small-cell lung cancer	Cholesteatoma, cervix carcinoma, ovarian germ-cell teratoma benign	Non–small-cell lung cancer

Nervous system disorders	Dysarthria, ischemic stroke			Headache	
Pregnancy, puerperium, and perinatal conditions					Drug exposure during pregnancy
Reproductive system and breast disorders		Ovarian cyst	Cervix disorder, metrorrhagia, ovarian torsion		
Renal and urinary disorders				Renal failure acute	IgA nephropathy
Respiratory, thoracic, and mediastinal disorders	Pulmonary sarcoidosis	Interstitial lung disease	Chronic obstructive pulmonary disease, pleuritic pain		Hydrothorax
Skin and subcutaneous tissue disorders			Prurigo		
Vascular disorders				Deep-vein thrombosis	

* Events are listed according to the system organ classes in the *Medical Dictionary for Regulatory Activities* (MedDRA), version 13.1, and according to "preferred terms."
† Investigators were at liberty to report rheumatoid arthritis as an adverse event, usually when the disease required that the patient be hospitalized.

10-mg tofacitinib groups than in the adalimumab or placebo group had aspartate aminotransferase levels one or more times the upper limit of the normal range at month 3. Alanine aminotransferase levels that were one or more times the upper limit of the normal range were recorded most frequently in the 10-mg tofacitinib group. Less than 5% of patients in the active-treatment groups had aspartate aminotransferase or alanine aminotransferase levels that were three or more times the upper limit of the normal range (Table 2).

Treatment-emergent adverse events (i.e., adverse events that developed after random assignment) during months 0 to 3 occurred in 52.0% of the patients in the 5-mg tofacitinib group (106 patients), 46.8% in the 10-mg tofacitinib group (94 patients), 51.5% in the adalimumab group (105 patients), and 47.2% in the placebo group (51 patients) (Table 2). During months 6 to 12 (by which time all patients who were initially randomly assigned to placebo had been switched to active treatment), treatment-emergent adverse events occurred in 43.6% of the patients initially assigned to the 5-mg tofacitinib group (89 patients), 41.8% of those initially assigned to the 10-mg tofacitinib group (84 patients), and 40.7% of those in the adalimumab group (83 patients) (Table 2). The most frequently reported system organ class (according to the Medical Dictionary for Regulatory Activities [MedDRA] classification, version 13.1) in which treatment-emergent adverse events occurred from months 0 to 12 was infections and infestations; for months 0 to 3, the rates of treatment-emergent adverse events in this system organ class were 18% in the 5-mg tofacitinib group, 17% in the 10-mg tofacitinib group, 16% in the adalimumab group, and 9% in the placebo group. Treatment-emergent adverse events occurring in more than 2% of patients in any treatment group are summarized according to MedDRA preferred terms in Table S1 in the Supplementary Appendix.

The rates of serious adverse events and serious infectious events in months 0 to 3 were numerically higher with tofacitinib than with placebo or adalimumab (Table 2). In months 6 to 12, the rates of serious adverse events were 4.9% in the 5-mg tofacitinib group, 3.0% in the 10-mg tofacitinib group, and 3.4% in the adalimumab group, and the rates of serious infectious events were 1.0% in the 5-mg tofacitinib group, 1.5% in

the 10-mg tofacitinib group, and 0.5% in the adalimumab group (Table 2). Throughout the trial, serious infections occurred in 7 of 204 patients (3.4%) in the 5-mg tofacitinib group, 8 of 201 patients (4.0%) in the 10-mg tofacitinib group, and 3 of 204 patients (1.5%) in the adalimumab group. All the serious adverse events and serious infectious events recorded during this study are listed in Table 3. Discontinuation of treatment owing to adverse events in months 0 to 3 occurred most frequently in the 5-mg tofacitinib group (6.9% of the patients in that group), as compared with 5.0% of the patients in the 10-mg tofacitinib group, 4.9% of the patients in the adalimumab group, and 2.8% of the patients in the placebo group (Table 2). Two deaths were reported: one in the 5-mg tofacitinib group, 14 days after the patient completed the treatment, and one in the adalimumab group (Table S2 in the Supplementary Appendix). There were two cases of pulmonary tuberculosis (both in the 10-mg tofacitinib group) and no cases of extrapulmonary tuberculosis or other major opportunistic infections (Table S3 in the Supplementary Appendix).

DISCUSSION

The ORAL Standard trial was a phase 3 study in which tofacitinib, a novel, orally available antirheumatic agent, was compared both with placebo and with an anti–TNF biologic agent (adalimumab). This trial is part of a large phase 3 program to study tofacitinib in multiple randomized clinical trials; one other trial is also reported in this issue of the *Journal*.[16] In the trial reported here, results showed that tofacitinib, when administered with background methotrexate, was superior to placebo with respect to all clinical outcomes. The magnitude of the efficacy responses over the 12-month study period was similar with the three active treatments (5 mg and 10 mg of tofacitinib given twice daily and 40 mg of adalimumab given once every 2 weeks). Therefore, in this study population and with respect to the efficacy outcomes reported here, the clinical efficacy of tofacitinib was numerically similar to that observed with adalimumab, an anti–TNF biologic agent. It should be noted that the ACR 20 efficacy data we present were calculated with the use of a more conservative imputation-of-no-response analysis that automatically considered a patient who did not have a response at 3 months to have had no response during the trial, even if that patient later had a response by month 6 without any change in therapy. This analysis was necessary to account for the switch to active treatment in a double-blind fashion of patients initially assigned to placebo. Although the rationale for this type of analysis was agreed on by scientists and regulators, we recognize that it is challenging to compare the results of this trial with those of other trials that used the more usual imputation-of-no-response approach.

The inclusion of adalimumab allowed us to estimate the relative efficacy and safety of tofacitinib. A formal noninferiority comparison among the active treatments, although of obvious interest, was thought to be premature because little was known about the efficacy of tofacitinib at the time the trial was designed. In addition, concern over what constitutes a clinically significant difference (noninferiority margin), as well as the preference of the rheumatology community to use multiple measures to assess the overall efficacy of a compound, made a hypothesis-driven approach difficult.

The risk of adverse events, including serious adverse events and serious infectious events, was greater in patients treated with tofacitinib than in those who received placebo, at month 3. Patients receiving tofacitinib must be monitored by their physician for such events. Notable adverse events included cytopenia, which may be attributable to the inhibition of JAK2; infections (especially respiratory and urinary tract infections); and gastrointestinal side effects. There were two cases of pulmonary tuberculosis (described in detail in Table S3 in the Supplementary Appendix).

Changes in laboratory values that were observed with both doses of tofacitinib, as compared with placebo, included small increases in serum creatinine levels and increases in mean levels of LDL and HDL cholesterol. The effects of tofacitinib on lipid profiles are still not completely understood. Although lipid levels stabilized after 3 months, an unfavorable overall effect cannot be excluded. Given the duration and size of the study, the implications of the elevations in LDL cholesterol for the risk of cardiac events and of neutropenia for the risk of infections could not be assessed. Longer-term monitoring of patients receiving tofacitinib is ongoing. The percentages of patients with adverse events in each MedDRA category were similar across the active treatments, and the percentages of patients who reported se-

rious adverse events, severe adverse events, and either temporary or permanent discontinuations in both tofacitinib groups were similar to those in the adalimumab group.

Patients from our study could continue taking tofacitinib as part of a long-term extension trial. Serious adverse events reported from the long-term study were similar to those reported for this study and were most commonly infection events. To date, one patient from this study reported lymphoma in the long-term extension trial. The rate of lymphomas or other lymphoproliferative disorders in the tofacitinib rheumatoid arthritis program as of April 16, 2012, was 0.07 per 100 patient-years (95% confidence interval, 0.03 to 0.15). This rate for tofacitinib is consistent with the rates reported for all patients with rheumatoid arthritis and for those treated with biologic disease-modifying drugs.[17,18] Close monitoring of the long-term safety of tofacitinib continues to be carried out.

In conclusion, in this randomized, phase 3 trial involving patients with rheumatoid arthritis who had an incomplete response to methotrexate, the efficacy of 5 mg or 10 mg of tofacitinib given twice daily was significantly superior to that of placebo and numerically similar to that of adalimumab. The safety of tofacitinib should be evaluated in a larger number of patients who have received treatment for longer durations.

Supported by Pfizer.

Disclosure forms provided by the authors are available with the full text of this article at NEJM.org.

We thank the patients who were involved in this study; the study team, specifically Jill K. Lundberg, Ann C. Sorrels, Sarah Ripley Jones, Allison G. Brailey, Dr. Richard J. Riese, and Chuanbo Zang; and Martin Goulding, Ph.D., of Complete Medical Communications, who was funded by Pfizer.

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