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Placebo-Controlled Trial of Tofacitinib Monotherapy in Rheumatoid Arthritis

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ABSTRACT

BACKGROUND

Tofacitinib (CP-690,550) is a novel oral Janus kinase inhibitor that is being investigated as a targeted immunomodulator and disease-modifying therapy for rheumatoid arthritis.

METHODS

In this phase 3, double-blind, placebo-controlled, parallel-group, 6-month study, 611 patients were randomly assigned, in a 4:4:1:1 ratio, to 5 mg of tofacitinib twice daily, 10 mg of tofacitinib twice daily, placebo for 3 months followed by 5 mg of tofacitinib twice daily, or placebo for 3 months followed by 10 mg of tofacitinib twice daily. The primary end points, assessed at month 3, were the percentage of patients with at least a 20% improvement in the American College of Rheumatology scale (ACR 20), the change from baseline in Health Assessment Questionnaire–Disability Index (HAQ-DI) scores (which range from 0 to 3, with higher scores indicating greater disability), and the percentage 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 (with scores ranging from 0 to 9.4 and higher scores indicating more disease activity).

RESULTS

At month 3, a higher percentage of patients in the tofacitinib groups than in the placebo groups met the criteria for an ACR 20 response (59.8% in the 5-mg tofacitinib group and 65.7% in the 10-mg tofacitinib group vs. 26.7% in the combined placebo groups, P<0.001 for both comparisons). The reductions from baseline in HAQ-DI scores were greater in the 5-mg and 10-mg tofacitinib groups than in the placebo groups (−0.50 and −0.57 points, respectively, vs. −0.19 points; P<0.001). The percentage of patients with a DAS28-4(ESR) of less than 2.6 was not significantly higher with tofacitinib than with placebo (5.6% and 8.7% in the 5-mg and 10-mg tofacitinib groups, respectively, and 4.4% with placebo; P=0.62 and P=0.10 for the two comparisons). Serious infections developed in six patients who were receiving tofacitinib. Common adverse events were headache and upper respiratory tract infection. Tofacitinib treatment was associated with elevations in low-density lipoprotein cholesterol levels and reductions in neutrophil counts.

CONCLUSIONS

In patients with active rheumatoid arthritis, tofacitinib monotherapy was associated with reductions in signs and symptoms of rheumatoid arthritis and improvement in physical function. (Funded by Pfizer; ORAL Solo ClinicalTrials.gov number, NCT00814307.)

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Rheumatoid arthritis is a chronic autoimmune disease that is characterized by inflammation and destruction of joints. The disease has a major effect on health status and quality of life and imposes a substantial economic burden on patients and society.[1]

Tofacitinib (CP-690,550) is a novel oral Janus kinase (JAK) inhibitor that is being investigated as a targeted immunomodulator and disease-modifying therapy for rheumatoid arthritis. Tofacitinib preferentially inhibits signaling through heterodimeric receptors associated with JAK3, JAK1, or both, with functional selectivity over JAK2-paired receptors.[2] Inhibition of JAK1 and JAK3 by tofacitinib blocks signaling for several cytokines (interleukins 2, 4, 7, 9, 15, and 21) that are integral to lymphocyte function and may thus modulate the immune response.[2] In a 6-week, phase 2a, proof-of-concept study, tofacitinib monotherapy at doses of 5 mg, 15 mg, and 30 mg twice daily, as compared with placebo, showed efficacy in patients with rheumatoid arthritis who had had an inadequate response to disease-modifying drugs.[3] Phase 2b dose-ranging studies of tofacitinib as monotherapy or with background methotrexate therapy showed the efficacy and safety of tofacitinib at doses of 5 mg and 10 mg twice daily, as compared with placebo, over the course of 24 weeks, thus supporting the dose selection for the phase 3 studies.[4,5] In this phase 3 study, we evaluated the efficacy and safety of tofacitinib monotherapy in adults with active rheumatoid arthritis who had had an inadequate response to disease-modifying drugs.

Methods

Patients

Patients were eligible if they were at least 18 years of age; had rheumatoid arthritis that had been diagnosed on the basis of the American College of Rheumatology (ACR) 1987 revised criteria[6]; had active disease, which was defined as the presence of 6 or more tender or painful joints (out of 68 specific joints examined) and 6 or more swollen joints (out of 66 specific joints examined); and had either a Westergren erythrocyte sedimentation rate of more than 28 mm per hour or a C-reactive protein level of more than 7 mg per liter. In addition, eligible patients had had an inadequate response to at least one nonbiologic or biologic disease-modifying drug, owing to a lack of efficacy or the occurrence of toxic effects, and had discontinued all disease-modifying drugs except stable doses of antimalarial agents. The use of nonsteroidal antiinflammatory drugs and glucocorticoids (≤10 mg of a prednisone equivalent per day) was permitted.

The key exclusion criteria were prior treatment with lymphocyte-depleting therapies or alkylating agents; a hemoglobin level of less than 9.0 g per deciliter, a hematocrit of less than 30%, a white-cell count of less than 3.0×10^9 per liter, an absolute neutrophil count of less than 1.2×10^9 per liter, or a platelet count of less than 100×10^9 per liter; an estimated glomerular filtration rate of 40 ml per minute or less (calculated by the method of Cockcroft and Gault); a total bilirubin, aspartate aminotransferase, or alanine aminotransferase level higher than 1.5 times the upper limit of the normal range; a history of another autoimmune rheumatic disease except Sjögren's syndrome; recent, current, or chronic infection, including hepatitis B or hepatitis C infection or human immunodeficiency virus infection; evidence of active, latent, or inadequately treated *Mycobacterium tuberculosis* infection; a history of a lymphoproliferative disorder; and a history of cancer, except adequately treated, nonmetastatic basal-cell or squamous-cell cancer of the skin or cervical carcinoma in situ.

Study Design and Oversight

The study was a phase 3, randomized, double-blind, placebo-controlled, parallel-group trial of a 6-month course of treatment, with primary efficacy end points assessed at month 3. The trial was sponsored by Pfizer and was conducted in 94 centers worldwide from February 2009 through June 2010. Patients were randomly assigned, in a 4:4:1:1 ratio, to one of four regimens: tofacitinib at a dose of 5 mg twice daily for 6 months; tofacitinib at a dose of 10 mg twice daily for 6 months; placebo for 3 months followed by 5 mg of tofacitinib twice daily for 3 months; or placebo for 3 months followed by 10 mg of tofacitinib twice daily for 3 months. Comparisons with placebo for the first 3 months were performed with combined data from the two placebo groups. Randomization was performed with the use of an automated Web-based or telephone-based system (Impala, Pfizer).

The study was conducted in compliance with the provisions of the Declaration of Helsinki,

Good Clinical Practice guidelines of the International Conference on Harmonization, and relevant local country regulations. All patients provided written informed consent. The final protocol, amendments, and consent documentation were reviewed and approved by the institutional review board and independent ethics committee at each participating center. The study protocol, including the statistical analysis plan, is available with the full text of this article at NEJM.org. Under direction from all the authors, the first draft was written by an employee of Complete Medical Communications, who was funded by Pfizer. All the authors revised the manuscript critically for intellectual content. Investigators at the study sites entered data into a Pfizer remote-data-capture system, and the study database was prepared by Pfizer data management. Pfizer programmers generated output specified by the statistical analysis plan that was approved before the database release and under the direction of Pfizer statisticians. All the authors made the decision to submit the manuscript for publication and vouch for the veracity and completeness of the data and analyses and for the fidelity of the study to the protocol.

MEASURES OF EFFICACY

The three primary efficacy end points, for which tofacitinib monotherapy (5 mg or 10 mg twice daily) was compared with placebo at month 3, were the percentage of patients who met the criteria for an ACR 20 response, which is defined as at least a 20% reduction from baseline in the number of both tender and swollen joints and at least a 20% improvement in three or more of the five remaining ACR core set measures (patient's assessment of pain, level of disability, C-reactive protein level, global assessment of disease by the patient, and global assessment of disease by the physician)[7]; the change from baseline in physical function, as measured by the Health Assessment Questionnaire–Disability Index (HAQ-DI, in which scores range from 0 to 3, with higher scores indicating greater disability)[8,9]; and the percentage 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 (with scores ranging from 0 to 9.4 and higher scores indicating more disease activity). The DAS28-4(ESR) is a composite index of four weighted variables: the number of tender joints among 28 specific joints examined; the number of swollen joints among the same 28 joints; the erythrocyte sedimentation rate (range, 0 to 150 mm per hour); and the patient's global assessment of disease activity, assessed with the use of a visual-analogue scale ranging from 0 to 100. The level of disease activity is considered to be low if the DAS28-4(ESR) is 3.2 or less, moderate if the score is greater than 3.2 to 5.1, and high if the score is greater than 5.1. A score of less than 2.6 indicates that the patient is in remission according to these criteria.[10-12] The erythrocyte sedimentation rate was measured at the local study sites, with the treatment assignments of the patients concealed from the study investigators and the sponsor.

Secondary efficacy end points included the percentage of patients who met the criteria for ACR 20, ACR 50, and ACR 70 responses (indicating improvement from baseline of at least 20%, 50%, and 70%, respectively, in the number of tender and swollen joints as well as in at least three of the other five ACR components) at all visits; the change from baseline at all visits in the HAQ-DI score; the change from baseline at all visits in the DAS28-4(ESR) and in the DAS28-3(CRP), in which the C-reactive protein level rather than the erythrocyte sedimentation rate is used in the calculation of the score and the variable of patient's global assessment of disease activity is not included[11]; the percentages of patients with a DAS28-4(ESR) and a DAS28-3(CRP) of less than 2.6 and of 3.2 or less at all visits up to month 6; and scores at month 3 on the Functional Assessment of Chronic Illness Therapy (FACIT)–fatigue instrument, a 13-item questionnaire with scores ranging from 0 to 52 and higher scores indicating less fatigue.[13]

SAFETY ASSESSMENTS

An analysis of the safety of tofacitinib as compared with placebo was also a primary objective. The incidence and severity of all adverse events were recorded. Clinical laboratory tests, assessments of vital signs, and physical examinations were performed at every visit, and electrocardiograms were obtained at the screening visit and at month 6.

STATISTICAL ANALYSIS

To preserve the type I error rate, the primary efficacy end points were assessed sequentially, in

the following order: the percentage of patients with an ACR 20 response, the change from baseline in the HAQ-DI score, and the percentage of patients with a DAS28-4(ESR) of less than 2.6 (see Fig. 1S in the Supplementary Appendix, available at NEJM.org). The type I error rate was protected for these end points when statistical significance was determined. No preservation of type I error rate was applied for the secondary end points; P values of 0.05 or less were considered to indicate statistical significance.

Efficacy and safety analyses included data from all patients who underwent randomization and who received at least one dose of study medication (modified intention-to-treat population). The normal-approximation test for the difference in binomial proportions was used to determine the superiority of each dose of tofacitinib over placebo with respect to two of the primary end points: the percentage of patients with an ACR 20 response 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 (including data from patients who withdrew from the study) in calculating these two end points. The changes in HAQ-DI scores were expressed as least-squares mean changes from baseline, analyzed with the use of a mixed-effect longitudinal model that included effects of treatment and visit. Variation due to changes over time for patients is included in the model. Secondary end points with binary variables were analyzed with the imputation of no response for missing data; 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.

Table 1. Baseline Characteristics of the Patients.*

Characteristic	Placebo (N=122)	Tofacitinib, 5 mg (N=243)	Tofacitinib, 10 mg (N=245)
Female sex — no. (%)	105 (86.1)	207 (85.2)	216 (88.2)
White race — no. (%)†	88 (72.1)	153 (63.0)	168 (68.6)
Age — yr	49.7±12.4	52.2±11.5	52.4±11.7
Duration of rheumatoid arthritis — yr			
Mean	7.7	8.0	8.6
Range	0.2–28.0	0.2–42.3	0.2–49.0
Tender and swollen joints — mean no.‡			
Tender	28.9	29.4	29.1
Swollen	17.3	16.3	17.0
Mean score on HAQ-DI§	1.53	1.53	1.50
DAS28–4(ESR)¶			
Mean score	6.65	6.71	6.70
Score of >5.1 — %	93.0	95.3	95.7
Mean score on DAS28–3(CRP)¶	5.56	5.68	5.60
Erythrocyte sedimentation rate — mm/hr‖	50.9	53.1	52.1
C-reactive protein — mg/liter**	17.8	22.9	19.1
Positive for rheumatoid factor, anti–cyclic citrullinated peptide antibodies, or both — %††	68.0	76.8	74.6
Prior treatment — %			
TNF inhibitor	19.7	14.0	16.7
Other biologic agent	8.2	4.9	7.8
Methotrexate	83.6	86.0	84.5
Nonbiologic disease-modifying drug other than methotrexate‡‡	60.7	54.3	57.6
Prior disease-modifying drugs resulting in inadequate response — mean no./patient	1.81	1.70	1.71

Table 1. (Continued.)

Characteristic	Placebo (N=122)	Tofacitinib, 5 mg (N=243)	Tofacitinib, 10 mg (N=245)
Concomitant treatment — %			
Antimalarial agents	12.3	18.5	16.7
Glucocorticoids§§	63.1	57.4	60.4
Lipid-lowering medication	6.6	11.5	14.7
Low-density lipoprotein cholesterol ≥130 mg/dl (3.4 mmol/liter) — %¶¶	28.1	33.2	33.8

* Plus–minus values are means ±SD. There were no significant differences among the groups at baseline, except with respect to age (P=0.05 for the comparison of the 10-mg tofacitinib group with the placebo group) and concomitant lipid-lowering medication (P=0.01 for the comparison of the 10-mg tofacitinib group with the placebo group). TNF denotes tumor necrosis factor.
† Race was self-reported.
‡ 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.
§ Scores on the Health Assessment Questionnaire–Disability Index (HAQ-DI) range from 0 to 3, with higher scores indicating greater disability.
¶ The Disease Activity Score for 28-joint counts based on the erythrocyte sedimentation rate (DAS28-4[ESR]) and the DAS28-3 based on the C-reactive protein level (DAS28-3[CRP]) range from 0 to 9.4, with higher scores indicating greater levels of disease activity. A score of more than 5.1 on the DAS28-4(ESR) indicates a high level of disease activity.
‖ The erythrocyte sedimentation rate ranges from 0 to 150 mm per hour; the reference range for men is 0 to 15 mm per hour, and the reference rate for women is 0 to 20 mm per hour. Higher values indicate greater inflammation.
** C-reactive protein levels range from 0 to 180 mg per liter; the reference range is less than 10.0 mg per liter. Higher values indicate greater inflammation.
†† Data were available for 242 patients in the 5-mg tofacitinib group and for 244 in the 10-mg tofacitinib group. Positive status for anti–cyclic citrullinated peptide antibodies was defined as a value of 20 units or more.
‡‡ Data were available for 118 patients in the placebo group, 228 in the 5-mg tofacitinib group, and 235 in the 10-mg tofacitinib group.
§§ Data were available for 244 patients in the 5-mg tofacitinib group. One patient who underwent randomization but did not receive any dose of study medication was included for the analysis of this variable only.
¶¶ Data were available for 121 patients in the placebo group, 241 in the 5-mg tofacitinib group, and 240 in the 10-mg tofacitinib group.

Post hoc subgroup analyses were performed to assess ACR 20 response rates in subgroups of interest, including those defined according to age, sex, geographic location, seropositivity status (presence or absence of rheumatoid factor or anti–cyclic citrullinated peptide antibodies[14]), and inadequate response to prior treatment with biologic disease-modifying drugs. The normal-approximation test was applied with no correction for multiple comparisons. The purpose of the post hoc analyses was to assess the general consistency of the estimates of response rates and to confirm that reported P values are descriptive of the magnitude of effect.

RESULTS

PATIENTS

A total of 611 patients underwent randomization, of whom 610 received at least one dose of study medication; 555 patients completed the 6-month study. The rate of discontinuation of study treatment was lowest in the group that received the 5-mg dose of tofacitinib (Fig. 2S in the Supplementary Appendix). The numbers of patients who underwent randomization are listed according to country in Table 1S in the Supplementary Appendix.

Baseline characteristics were similar among the treatment groups (Table 1). The mean age of the patients ranged from 49.7 to 52.4 years; the mean duration of rheumatoid arthritis ranged from 7.7 to 8.6 years. A total of 67.0% of the patients were white, and 86.6% were women.

EFFICACY

Prespecified Analyses

At month 3, a total of 59.8% of the patients in the 5-mg tofacitinib group and 65.7% in the 10-mg tofacitinib group, as compared with 26.7% in the combined placebo groups, met the criteria for an ACR 20 response (P<0.001 for both comparisons). The corresponding percentages of patients who met the criteria for an ACR 50 response at month 3

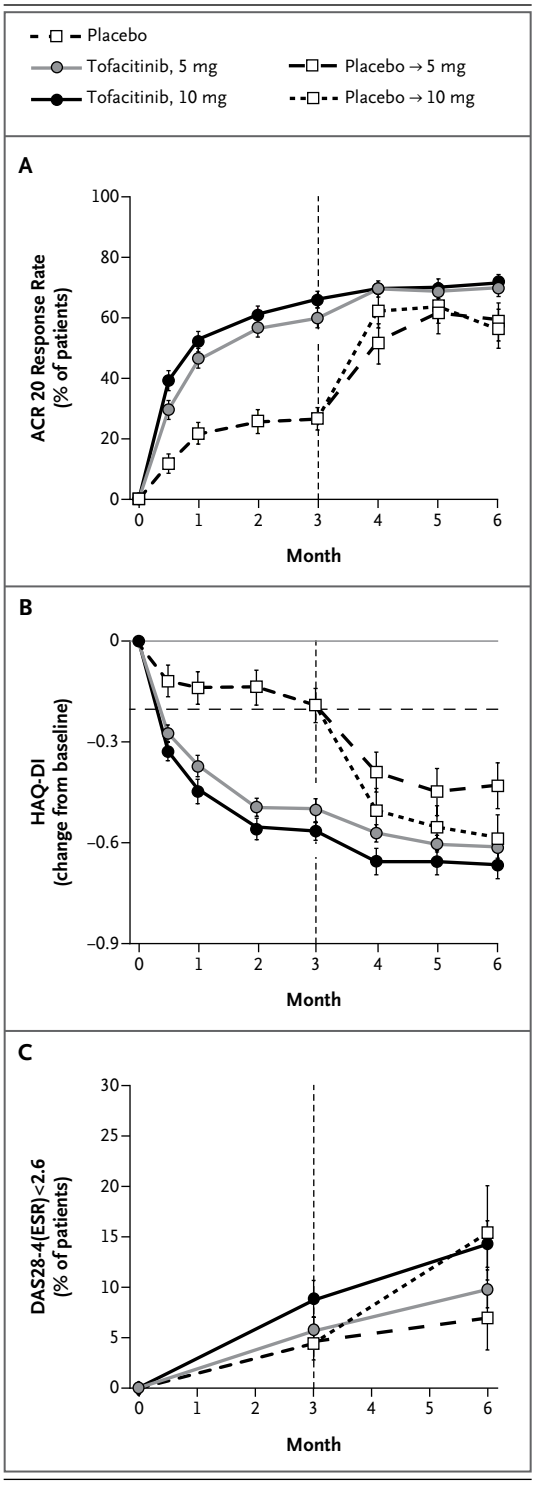

Figure 1. Primary Efficacy Analyses.

The percentage of patients with at least a 20% improvement in the American College of Rheumatology scale (ACR 20) is shown in Panel A; the least-squares mean change from baseline in the score on the Health Assessment Questionnaire–Disability Index (HAQ-DI) (in which scores range from 0 to 3, with higher scores indicating greater disability) is shown in Panel B; and the percentage of patients with a score of less than 2.6 on the Disease Activity Score for 28-joint counts, based on the erythrocyte sedimentation rate (DAS28-4[ESR], in which scores range from 0 to 9.4, with higher scores indicating more disease activity), is shown in Panel C. Analyses were performed in the modified intention-to-treat population (all patients who underwent randomization and who received at least one dose of study medication). The dashed vertical line at the 3-month mark in all three panels shows the time at which all the patients in the placebo group were switched to tofacitinib (either 5-mg or 10-mg dose). The dashed horizontal line in Panel B represents the minimal clinically important difference of −0.22 points for the HAQ-DI score. In Panel A, P<0.001 for the comparison of the 5-mg and 10-mg doses of tofacitinib with placebo at 2 weeks and at months 1, 2, and 3; in Panel B, P<0.001 for the comparisons of the two doses of tofacitinib with placebo at 2 weeks and at months 1, 2, and 3, except P=0.004 for the comparison of the 5-mg dose of tofacitinib with placebo at 2 weeks. I bars indicate standard errors.

were 31.1% and 36.8% versus 12.5% (P<0.001 for both comparisons), and the percentages of patients who met the criteria for an ACR 70 response were 15.4% and 20.3% versus 5.8% (P=0.003 and P<0.001 for the comparison of the 5-mg dose and the 10-mg dose of tofacitinib, respectively, with placebo). Significant increases in the rate of ACR 20, ACR 50, and ACR 70 responses with the 10-mg dose of tofacitinib as compared with placebo were seen by week 2 (P<0.001, P=0.002, and P<0.001, respectively) (Fig. 1, and Fig. 3S in the Supplementary Appendix).

Significant improvements in physical function were observed by week 2. At month 3, the least-squares mean changes from baseline in HAQ-DI scores were −0.50 points with the 5-mg dose of tofacitinib and −0.57 points with the 10-mg dose of tofacitinib, as compared with −0.19 points with placebo (P<0.001 for both comparisons); in addition, the least-squares mean changes were significant with both doses as compared with placebo at all visits up to month 3 (5-mg dose of tofacitinib: P=0.004 at week 2, P<0.001 at all other visits; 10 mg dose of tofacitinib: P<0.001 at all visits) and continued to improve to the end of the study (Fig. 1). Although the minimal clinically important change for the HAQ-DI is 0.22 points,[15] a more conservative measure of 0.30 points was chosen to indicate a significant change in HAQ-DI. A total of 52.9% of the patients in

the 5-mg tofacitinib group and 55.7% in the 10-mg tofacitinib group, as compared with 31.7% in the two placebo groups combined, had reductions in the HAQ-DI score (indicating improvement of physical function) of at least 0.30 points at month 3 (P<0.001 for both comparisons). Patients who switched from placebo to tofacitinib at month 3 had ACR response rates and HAQ-DI scores by month 6 that were similar to the responses seen in patients who received tofacitinib in the first 3 months.

We did not observe significant benefits of tofacitinib over placebo for the third primary outcome measure. At month 3, the percentage of patients with a DAS28-4(ESR) of less than 2.6 was 5.6% with the 5-mg dose of tofacitinib and 8.7% with the 10-mg dose of tofacitinib, as compared with 4.4% with placebo (P=0.62 and P=0.10, respectively) (Fig. 1); at month 6, the percentages in the 5-mg and 10-mg tofacitinib groups had increased to 9.8% and 14.2%, respectively. There were significant differences at month 3 between each of the tofacitinib groups and the combined placebo groups with respect to least-squares mean changes from baseline in DAS28-4(ESR) (P<0.001 for both comparisons) (Fig. 3S in the Supplementary Appendix). A total of 12.5% of the patients in the 5-mg tofacitinib group and 17.0% in the 10-mg tofacitinib group, as compared with 5.3% in the combined placebo groups, had a DAS28-4(ESR) of 3.2 or less by month 3 (P=0.02 for the comparison of the 5-mg group with the placebo group and P<0.001 for the comparison of the 10-mg group with the placebo group). The least-squares mean changes from baseline in the C-reactive protein level, DAS28-3(CRP), erythrocyte sedimentation rate, and DAS28-4(ESR) and the percentage of patients with DAS28-4(ESR) and DAS28-3(CRP) of less than 2.6 and of 3.2 or less at months 3 and 6 are shown in Table 2S in the Supplementary Appendix.

Changes of 3 to 4 points in the FACIT–fatigue score are considered to be clinically meaningful.[13] The least-squares mean changes from baseline at month 3 in FACIT–fatigue scores were 6.7 points with the 5-mg of tofacitinib and 8.0 points with the 10-mg dose, as compared with 2.8 points with placebo (P<0.001).

Post Hoc Subgroup Analyses

Age, sex, and seropositivity status were not associated with meaningful differences in the ACR 20 results, with the 5-mg and 10-mg doses of tofacitinib having similar efficacy (Fig. 4S in the Supplementary Appendix). Among patients who had previously had an inadequate response to tumor necrosis factor (TNF) inhibitors or other biologic agents, 42.9% in the 5-mg tofacitinib group and 62.5% in the 10-mg tofacitinib group, as compared with 17.7% in the combined placebo groups, met the criteria for ACR 20 at month 3 (P=0.06 and P<0.001 for the comparison of the two doses, respectively, with placebo). Significant effects on the rate of ACR 20 response with tofacitinib as compared with placebo were seen in all geographic regions at month 3 (United States: P<0.001 for the comparison of both doses with placebo; Latin America: P=0.002 and P<0.001 for the comparison of the 5-mg dose and the 10-mg dose, respectively, with placebo; Europe: P=0.002 and P=0.005 for the two comparisons; rest of world, P=0.01 and P=0.003, for the two comparisons). The scores for the core components of the ACR assessment are presented in Table 3S in the Supplementary Appendix.

ADVERSE EVENTS

There was an increased rate of serious infections with tofacitinib as compared with placebo. There were seven events involving serious infections in six patients (one case of cellulitis in the 5-mg group; one case each of liver abscess, bronchitis, tuberculous pleural effusion, and pyelonephritis in the 10-mg group; and two cases of cellulitis in one patient in the placebo group, one of which occurred after the switch to 5 mg of tofacitinib at 3 months). The tuberculous pleural effusion occurred in a 47-year-old man from India (see the Supplementary Appendix); a diagnosis of tuberculosis was not confirmed by culture of the pleural fluid (or biopsy).

In months 0 to 3, a total of 330 patients (54.1%) had 701 adverse events, with similar frequencies across the groups (Table 2). The most common of these adverse events were upper respiratory tract infection, headache, and diarrhea (Table 4S in the Supplementary Appendix). Twelve patients (2.0%) discontinued the study drug owing to adverse events in months 0 to 3, with similar frequencies across the groups (Table 2). In months 3 to 6, a total of 244 patients (40.0%) had 471 adverse events. The most common events were upper respiratory tract infection and headache (Table 4S in the Supplementary Appendix). Six

Table 2. Safety and Laboratory Data.*

Variable	Months 0–3			Months 3–6			
	Placebo (N=122)	Tofacitinib, 5 mg (N=243)	Tofacitinib, 10 mg (N=245)	Tofacitinib, 5 mg, Switched from Placebo (N=61)	Tofacitinib, 10 mg, Switched from Placebo (N=61)	Tofacitinib, 5 mg (N=243)	Tofacitinib, 10 mg (N=245)
Adverse events — no.	127	279	295	40	54	170	207
Patients with adverse events — no. (%)	67 (54.9)	124 (51.0)	139 (56.7)	22 (36.1)	24 (39.3)	97 (39.9)	101 (41.2)
Patients with serious adverse events — no. (%)	6 (4.9)	1 (0.4)	5 (2.0)	1 (1.6)	0	5 (2.1)	6 (2.4)
Patients with serious infection events — no. (%)†	0	0	1 (0.4)	1 (1.6)	0	1 (0.4)	3 (1.2)
Discontinuation of study drug due to adverse event — no. (%)‡	5 (4.1)	2 (0.8)	6 (2.4)	0	0	1 (0.4)	5 (2.0)
	Month 3, Mean Change from Baseline			Month 6, Mean Change from Baseline			
	Placebo (N=122)	Tofacitinib, 5 mg (N=243)	Tofacitinib, 10 mg (N=245)	Tofacitinib, 5 mg, Switched from Placebo (N=61)	Tofacitinib, 10 mg, Switched from Placebo (N=61)	Tofacitinib, 5 mg (N=243)	Tofacitinib, 10 mg (N=245)
Neutrophil count — 10^{-3}/mm^3	−0.06±0.17	−0.83±0.11§	−1.35±0.12§	−0.90±0.24	−1.18±0.26	−0.78±0.12	−1.15±0.12
Hemoglobin — g/dl	−0.12±0.76	0.28±0.88	0.03±0.97	0.21±0.97	−0.22±1.05	0.25±0.96	0.15±0.94
Cholesterol — %							
Low-density lipoprotein	3.5±2.28	13.6±1.56§	19.1±1.60§	16.9±3.29	16.8±3.36	12.8±1.60	19.1±1.65
High-density lipoprotein	−0.76±1.93	12.24±1.31§	14.98±1.34§	11.31±2.81	11.02±2.89	10.39±1.37	16.57±1.41
Serum creatinine — mg/dl	0±0.02	0.04±0.01	0.05±0.01	0.06±0.03	0.08±0.03	0.06±0.01	0.08±0.01
	Month 3 Visit			Month 6 Visit			
	Placebo (N=122)	Tofacitinib, 5 mg (N=231)	Tofacitinib, 10 mg (N=227)	Tofacitinib, 5 mg, Switched from Placebo (N=57)	Tofacitinib, 10 mg, Switched from Placebo (N=55)	Tofacitinib, 5 mg (N=231)	Tofacitinib, 10 mg (N=227)
Neutropenia — %							
Mild, 1500–1999 cells/mm^3	<1.0	3.1	3.7	3.8	0	2.2	3.8
Moderate, 1000–1499 cells/mm^3	0	1.3	0	1.9	0	<1.0	<1.0
Severe, 500–999 cells/mm^3	0	0	<1.0	0	0	0	<1.0
Potentially life-threatening, <500 cells/mm^3	0	0	0	0	0	0	0
Decreased hemoglobin, −1.0 to −3.0 g/dl — %	14.6	5.8	14.4	9.4	12.0	8.0	10.5

	Months 0–3			Months 3–6			
	Placebo (N=122)	Tofacitinib, 5 mg (N=242)	Tofacitinib, 10 mg (N=245)	Tofacitinib, 5 mg, Switched from Placebo (N=57)	Tofacitinib, 10 mg, Switched from Placebo (N=52)	Tofacitinib, 5 mg (N=239)	Tofacitinib, 10 mg (N=232)
AST >3×ULN — %¶	<1.0	<1.0	0	1.8	0	<1.0	0
ALT >3×ULN — %¶	<1.0	<1.0	0	1.8	0	<1.0	<1.0

	Months 0–6			
	Placebo followed by Tofacitinib, 5 mg (N=61)	Placebo followed by Tofacitinib, 10 mg (N=61)	Tofacitinib, 5 mg (N=243)	Tofacitinib, 10 mg (N=245)
Serum creatinine — %				
≥33% increase from baseline‖	4.9	8.2	3.3	10.6
>50% increase from baseline**	0	0	<1.0	<1.0

* Plus–minus values are least-squares means ±SE, with the exception of the values for hemoglobin, which are means ±SD. To convert the values for creatinine to micromoles per liter, multiply by 88.4. ALT denotes alanine aminotransferase, AST aspartate aminotransferase, and ULN upper limit of the normal range.

† The incidence rates per 100 patient-years to month 6 were 0 in the placebo group, 0.85 (95% confidence interval [CI], 0.12 to 6.06) in the 5-mg tofacitinib group, and 3.52 (95% CI, 1.32 to 9.37) in the 10-mg tofacitinib group.

‡ For months 3 to 6, data were available for 56 participants in the group that switched from placebo to 5 mg of tofacitinib, 53 in the group that switched from placebo to 10 mg of tofacitinib, 238 in the group that received 5 mg of tofacitinib for all 6 months, and 229 in the group that received 10 mg of tofacitinib for all 6 months.

§ P<0.001 for the comparison with placebo.

¶ The incidence is shown for participants who had normal values at baseline.

‖ The increase from baseline was calculated from the serum creatinine level obtained at the end of the study or at the time of the patient's discontinuation visit.

** Included are participants who had increases from baseline of more than 50% at two or more consecutive visits. In the 5-mg tofacitinib group, two participants met this criterion: one was a 73-year-old man with a baseline serum creatinine level of 0.7 mg per deciliter and a level of 1.1 mg per deciliter at days 120 and 151, the other was a 62-year-old woman with a baseline level of 0.5 mg per deciliter and levels that ranged from 0.4 to 0.8 mg per deciliter throughout the study. In the 10-mg tofacitinib group, one participant met this criterion: a 47-year-old woman with a baseline level of 0.4 mg per deciliter and a level of 0.7 mg per deciliter at days 151 and 179.

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Table 3. Serious Adverse Events over the Course of 6 Months.*

MedDRA System Organ Class	Placebo followed by Tofacitinib, 5 mg (N=61)†	Placebo followed by Tofacitinib, 10 mg (N=61)†	Tofacitinib, 5 mg (N=243)	Tofacitinib, 10 mg (N=245)
Blood and lymphatic system disorders			Thrombocytopenia	
Cardiac disorders				Atrial fibrillation, cardiac arrest, cardiac failure congestive,‡ myocardial infarction§
Ear and labyrinth disorders				Vertigo
Gastrointestinal disorders				Vomiting
General disorders and administrative site conditions				Asthenia, multiorgan failure
Hepatobiliary disorders				Cholecystitis
Infections and infestations	Cellulitis§		Cellulitis	Bronchitis; liver abscess; pleural effusion; pyelonephritis, chronic
Injury, poisoning, and procedural complications			Lower limb fracture, humerus fracture, patella fracture	
Metabolic and nutrition disorders			Hypoglycemia	Diabetes mellitus, hyponatremia, hyperkalemia
Musculoskeletal and connective tissue disorders	Rheumatoid arthritis¶			
Neoplasm benign, malignant, and unspecified (including cysts and polyps)		Uterine leiomyoma§		Non–small-cell lung cancer
Nervous system disorders	Grand mal convulsion, transient ischemic attack			
Reproductive system and breast disorders		Uterine polyp§		
Respiratory, thoracic, and mediastinal disorders	Pulmonary embolism	Sleep apnea syndrome	COPD	COPD,‖ pulmonary fibrosis
Surgical and medical procedures				Abdominoplasty, breast prosthesis user
Vascular disorders	Deep-vein thrombosis			

* Events are listed according to the system organ classes and "preferred terms" in the *Medical Dictionary for Regulatory Activities* (MedDRA), version 13.0. COPD denotes chronic obstructive pulmonary disease.
† All the events in these groups occurred before the switch from placebo to tofacitinib (i.e., during months 0 to 3), except for one instance each of cellulitis, uterine leiomyoma, and uterine polyp, which occurred during months 3 to 6.
‡ There was a total of four events of cardiac failure congestive in three patients.
¶ This event refers to worsening rheumatoid arthritis.
§ In each case, two instances occurred in one patient.
‖ There was a total of three events of COPD in three patients.

patients (1.0%) discontinued the study drug owing to adverse events in months 3 to 6.

A total of 24 patients (3.9%) had 32 serious adverse events (Table 3). Two patients in the 10-mg tofacitinib group had congestive heart failure: a 59-year-old woman had two episodes (on day 140 and day 158) and recovered, and a 79-year-old woman with a history of cardiovascular disease and diabetes had diarrhea followed by renal failure and congestive heart failure, hyperkalemia, and, finally, asystole that resulted in her death on day 107.

Changes in laboratory test results are shown in Table 2 and Figure 2, and in Figure 5S in the Supplementary Appendix. During months 0 to 3, mean low-density lipoprotein (LDL) cholesterol levels increased by 3.5% with placebo (an increase of 1.8 mg per deciliter [0.05 mmol per liter]), as compared with 13.6% with the 5-mg dose of tofacitinib (an increase of 11.4 mg per deciliter [0.29 mmol per liter]) and 19.1% with the 10-mg dose (an increase of 17.2 mg per deciliter [0.44 mmol per liter]). Elevations of aspartate aminotransferase or alanine aminotransferase levels occurred infrequently. Neutrophil counts declined in the tofacitinib groups, and neutropenia occurred more frequently among patients receiving tofacitinib than among those receiving placebo. No serious infections were reported in patients with moderate-to-severe neutropenia. The mean increases from baseline to month 6 in serum creatinine levels were 0.08 mg per deciliter (7.1 μmol per liter) or less in all groups. Two patients in the 5-mg tofacitinib group and one in the 10-mg group had a confirmed increase in serum creatinine levels of 50% or more from baseline; in all three patients, the highest creatinine level was within the normal range.

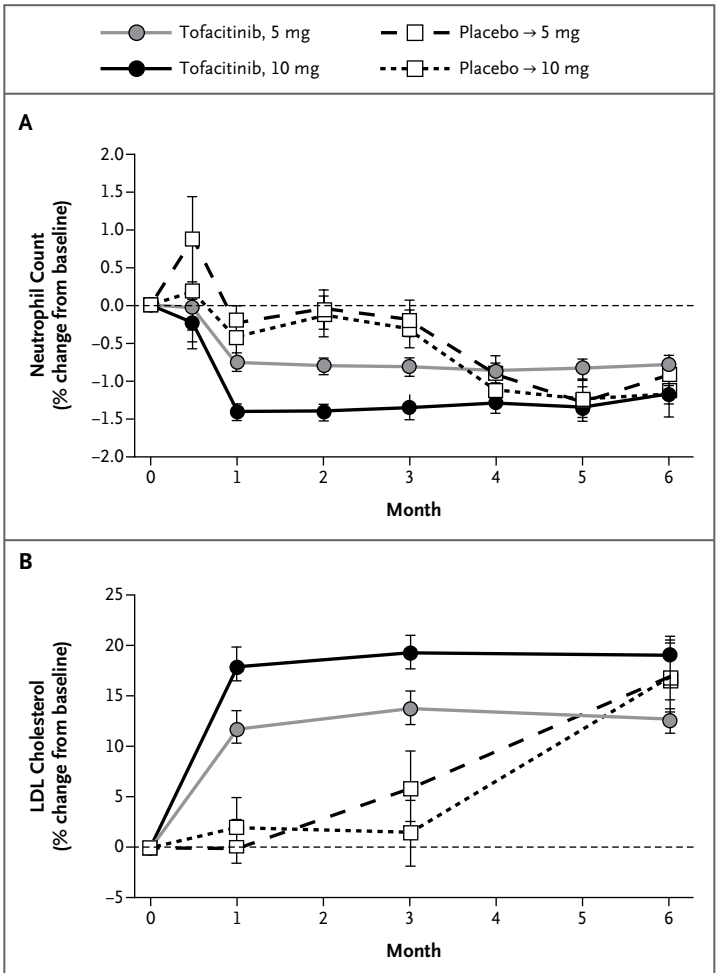

Figure 2. Changes from Baseline in Laboratory Values.

The least-squares mean changes in neutrophil counts are shown in Panel A, and the least-squares mean percent changes in low-density lipoprotein (LDL) cholesterol levels are shown in Panel B. In Panel A, P<0.001 for the changes from baseline values in both tofacitinib groups at months 1, 2, and 3 and in all four groups at months 4, 5, and 6. In Panel B, P<0.001 for the changes from baseline values in both tofacitinib groups at months 1 and 3 and in all four groups at month 6. I bars indicate standard errors.

DISCUSSION

Although the outcome for patients with rheumatoid arthritis has improved in recent years, owing to earlier and more aggressive use of nonbiologic disease-modifying drugs and the introduction of biologic therapies, unmet needs remain. Parenteral biologic therapies represent a considerable contribution to our therapeutic armamentarium, but only approximately half of patients who receive these therapies meet the criteria for low disease activity (≤3.2 on the DAS28-4[ESR]) or remission (<2.6 on the DAS28-4[ESR]), and there are unacceptable risks in certain patient populations.[16] In addition, many biologic therapies are routinely administered in combination with nonbiologic disease-modifying drugs, especially methotrexate, which have their own side-effect profiles. There is an unmet need for an oral agent that can be used as monotherapy and that acts as rapidly as a TNF inhibitor.

This phase 3 study showed that tofacitinib monotherapy, as compared with placebo, had efficacy in reducing signs and symptoms of rheumatoid arthritis and in improving physical

function in patients with active rheumatoid arthritis who had had an inadequate response to previous treatment with disease-modifying drugs. However, the percentage of patients in the tofacitinib groups who met the criterion for disease remission (a score of <2.6 on the DAS28-4[ESR]) was not significantly greater than the percentage in the placebo groups. With regard to secondary end points related to disease activity, clinically meaningful and statistically significant reductions from baseline in DAS28-4(ESR) scores (indicating decreased disease activity) were observed in both tofacitinib groups, as compared with placebo, at month 3; in addition, significantly greater percentages of patients met the criteria for low disease activity (≤3.2 on the DAS28-4[ESR]) in both tofacitinib groups than in the placebo groups at month 3. Patients receiving tofacitinib also had significant reductions in levels of fatigue and pain. Significant differences between the tofacitinib groups and the placebo groups in both ACR and HAQ-DI responses were seen by week 2. These results are consistent with the findings in previous trials of tofacitinib in patients with rheumatoid arthritis.[4,5,17,18] Biomarkers were not assessed in this study, and prior research has not identified any biomarkers, including serum cytokine concentrations, that robustly correlate with clinical efficacy.

Tofacitinib resulted in increases in LDL cholesterol levels, elevations in liver aminotransferase levels, declines in neutrophil counts, and small increases in serum creatinine levels. These adverse events in patients receiving 5-mg or 10-mg doses of tofacitinib twice daily were also observed in phase 2 studies.[3-5,18] The implications of the increases in LDL cholesterol levels with respect to rates of cardiovascular adverse events and of the decreases in neutrophil counts with respect to rates of infectious adverse events will need to be assessed in larger numbers of patients treated for longer periods.

There was an increased rate of serious infections with tofacitinib as compared with placebo. One case of presumed tuberculous pleural effusion and one case of nondisseminated herpes zoster were reported. Larger trials of longer duration are necessary to assess the risk of infections associated with tofacitinib and to compare the safety of this drug with that of other available treatments for rheumatoid arthritis.

Serious adverse events that were observed in patients from this study who continued taking tofacitinib in a long-term extension trial were reported to the Food and Drug Administration and were summarized in the New Drug Application that recently underwent comprehensive and public review. The reported events were similar in type and frequency to those reported for this study. The most common serious adverse events were infection events. To date, neither lymphoma nor other lymphoproliferative disorders have been reported in any of the patients from this study who enrolled in the long-term extension trial. As of April 16, 2012, the rate of lymphomas or other lymphoproliferative disorders in the tofacitinib rheumatoid arthritis clinical studies was 0.07 per 100 patient-years (95% confidence interval, 0.03 to 0.15). This rate is consistent with the rates of lymphoma among all patients with rheumatoid arthritis and among those treated with biologic disease-modifying drugs.[19,20] In compliance with regulatory requirements, the long-term safety of tofacitinib continues to be monitored closely.

Overall, the results of the current study tend to confirm the findings in previous phase 2 studies of tofacitinib, as monotherapy or in combination with background methotrexate therapy, in patients with rheumatoid arthritis who had had an inadequate response to disease-modifying drugs.[4,5] The results of the ORAL Standard study in this issue of the *Journal*[21] suggest that the efficacy and safety of tofacitinib in patients with rheumatoid arthritis who are receiving background methotrexate are generally similar to those in our study, although the populations in the two studies are different. In this study, continued use of background treatment with disease-modifying drugs was not necessary to achieve improvements in ACR responses and physical function over the course of 3 months. These clinical benefits will need to be weighed against the risk of serious infections and adverse effects on lipid, aminotransferase, and serum creatinine levels associated with tofacitinib therapy.

In conclusion, this phase 3 study showed that tofacitinib monotherapy at a dose of 5 mg or 10 mg twice daily was associated with reductions in signs and symptoms of rheumatoid arthritis and improvement in physical function in patients who had had an inadequate response to disease-modifying drugs. The safety of tofacitinib must be evaluated in a larger number of patients who have received treatment for longer periods.

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

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