Annals of Internal Medicine | ORIGINAL RESEARCH

Tofacitinib in Combination With Nonbiologic Disease-Modifying Antirheumatic Drugs in Patients With Active Rheumatoid Arthritis

A Randomized Trial

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Background: Many patients with rheumatoid arthritis (RA) do not achieve adequate and safe responses with disease-modifying antirheumatic drugs (DMARDs). Tofacitinib is a novel, oral, Janus kinase inhibitor that treats RA.

Objective: To evaluate the efficacy and safety of tofacitinib in combination with nonbiologic DMARDs.

Design: 1-year, double-blind, randomized trial (ClinicalTrials.gov: NCT00856544).

Setting: 114 centers in 19 countries.

Patients: 792 patients with active RA despite nonbiologic DMARD therapy.

Intervention: Patients were randomly assigned 4:4:1:1 to oral tofacitinib, 5 mg or 10 mg twice daily, or placebo advanced to tofacitinib, 5 mg or 10 mg twice daily.

Measurements: Primary end points were 20% improvement in American College of Rheumatology (ACR20) criteria; Disease Activity Score for 28-joint counts based on the erythrocyte sedimentation rate (DAS28-4[ESR]) of less than 2.6; DAS28-4(ESR)–defined remission, change in Health Assessment Questionnaire Disability Index (HAQ-DI) score, and safety assessments.

Results: Mean treatment differences for ACR20 response rates (month 6) for the 5-mg and 10-mg tofacitinib groups compared with the combined placebo groups were 21.2% (95% CI, 12.2% to 30.3%; $P < 0.001$) and 25.8% (CI, 16.8% to 34.8%; $P < 0.001$), respectively. The HAQ-DI scores (month 3) and DAS28-4(ESR) less than 2.6 response rates (month 6) were also superior in the tofacitinib groups versus placebo. The incidence rates of serious adverse events for patients receiving 5-mg tofacitinib, 10-mg tofacitinib, or placebo were 6.9, 7.3, or 10.9 events per 100 patient-years of exposure, respectively. In the tofacitinib groups, 2 cases of tuberculosis, 2 cases of other opportunistic infections, 3 cardiovascular events, and 4 deaths occurred. Neutrophil counts decreased, hemoglobin and low- and high-density lipoprotein cholesterol levels increased, and serum creatinine levels had small increases in the tofacitinib groups.

Limitations: Placebo groups were smaller and of shorter duration. Patients received primarily methotrexate. The ability to assess drug combinations other than tofacitinib plus methotrexate was limited.

Conclusion: Tofacitinib improved disease control in patients with active RA despite treatment with nonbiologic DMARDs, primarily methotrexate.

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Many nonbiologic disease-modifying antirheumatic drugs (DMARDs) are available for treating active rheumatoid arthritis (RA). Methotrexate, alone or in combination, is most commonly used. However, methotrexate alone is not always appropriate because of inadequate efficacy (1), and approximately 10% to 30% of patients with RA discontinue it because of toxicity (2). Therefore, it is important to investigate whether treatments with novel mechanisms of action are safe and effective when dosed in combination with various nonbiologic DMARDs commonly used for the treatment of RA.

Tofacitinib (CP-690,550) is a novel, oral, Janus kinase (JAK) inhibitor for the treatment of RA. Tofacitinib inhibits JAK1, JAK2, and JAK3 and, to a lesser extent, tyrosine kinase 2 (3, 4). Intracellular pathways for transducing receptor signals that include these kinases are critical to immune cell activation, proinflammatory cytokine production, and cytokine signaling (5) that are thought to mediate RA pathophysiology.

In earlier dose-ranging, randomized, controlled trials, tofacitinib as monotherapy and in combination with background methotrexate was efficacious with a well-defined safety profile in patients with active RA. Safety risks associated with tofacitinib included infection, lipid elevations, anemia, neutropenia, aminotransaminase elevations, and increases in serum creatinine (6, 7). Large-scale trials were subsequently designed to investigate tofacitinib, 5 mg and 10 mg twice daily, as monotherapy and in combination with methotrexate and various other nonbiologic DMARDs.

We report a large-scale clinical trial of tofacitinib in combination with several nonbiologic DMARDs in patients with active RA and an inadequate response to at least 1 nonbiologic or biologic DMARD.

See also:

Print
Summary for Patients I-26

Web-Only
Supplement

Context

The response to disease-modifying drugs may be insufficient in many patients with rheumatoid arthritis (RA).

Contribution

In this randomized trial of patients with active RA despite the use of various disease-modifying regimens, the addition of tofacitinib resulted in improved disease activity compared with placebo.

Caution

Methotrexate, alone or in combination with other drugs, was the most common background therapy, and the ability to assess efficacy with other drugs or combinations is limited.

Implication

Tofacitinib may be an option for some patients with RA and an inadequate response to other treatments.

—The Editors

METHODS

Design Overview

We conducted a randomized, 1-year, double-blind, placebo-controlled, clinical trial conducted at 114 centers in 19 countries from 18 May 2009 (first patient, first visit) to 17 January 2011 (last patient, last visit). The trial involved 2 groups receiving 1 of 2 doses of tofacitinib and 2 groups receiving placebo. Patients randomly assigned to placebo advanced to tofacitinib treatment at month 6 or, if they did not respond at an earlier assessment, at month 3. The study was conducted in compliance with the Declaration of Helsinki and all International Conference on Harmonisation Good Clinical Practice guidelines. The study (Pfizer protocol A3921046) was registered with ClinicalTrials.gov (NCT00856544) and approved by the institutional review boards or independent ethics committees for each study center. All patients provided written informed consent.

Setting and Participants

Enrolled patients were aged 18 years or older with an RA diagnosis consistent with the 1987 American College of Rheumatology (ACR) revised criteria (8). Key inclusion criteria included active RA defined by 4 or more tender or painful joints, 4 or more swollen joints (68- or 66-joint count), and an erythrocyte sedimentation rate (ESR; Westergren method) of 28 mm/h or greater or a C-reactive protein level greater than 66.7 nmol/L. Patients were required to have an inadequate response to treatment with 1 or more stably dosed nonbiologic or biologic DMARDs before baseline and to continue treatment with 1 or more background nonbiologic DMARDs at stable doses throughout the study. Patients receiving background methotrexate (≤25 mg/wk) required at least 4 months of therapy with stable dosing 6 weeks before receiving the study drug. All disallowed DMARDs (defined as biologic DMARDs, potent immunosuppressives [such as cyclosporine and azathioprine], and any DMARD that would be contraindicated according to the local prescribing information) had to be discontinued. Background, low-dose, oral corticosteroid therapy with stable dosing (prednisone, ≤10 mg daily, or equivalent) was permitted.

Key exclusion criteria at screening were previous treatment with lymphocyte-depleting therapies within 1 year of randomization or alkylating agents at any time; hemoglobin level less than 90 g/L, hematocrit less than 30%, leukocyte count less than 3.0×10^9 cells/L, neutrophil count less than 1.2×10^9 cells/L, or platelet count less than 100×10^9 cells/L; estimated glomerular filtration rate of 40 mL/min per 1.73 m^2 or less (Cockcroft–Gault equation); aspartate aminotransferase (AST) or alanine aminotransferase (ALT) levels greater than 1.5 times the upper limit of normal; history of another autoimmune rheumatic disease other than the Sjögren syndrome; history of cancer (except treated nonmelanoma skin cancer and cervical carcinoma in situ); infection that required hospitalization or parenteral antimicrobial therapy within 6 months of randomization, infection requiring antimicrobial therapy within 2 weeks of randomization, recurrent or disseminated herpes zoster infection, or infection with hepatitis B or C virus or HIV; and evidence of *Mycobacterium tuberculosis* infection.

Randomization and Interventions

Patients were randomly assigned 4:4:1:1 at baseline to 1 of 4 twice-daily treatment sequences: 5 mg of tofacitinib, 10 mg of tofacitinib, placebo advanced to 5 mg of tofacitinib, and placebo advanced to 10 mg of tofacitinib. At month 3, placebo recipients who did not respond (not achieving ≥20% reduction from baseline in swollen and tender joint counts) were blindly advanced to tofacitinib, 5 mg or 10 mg twice daily. Tofacitinib recipients who did not respond at month 3 continued the same treatment and dose. At month 6, all patients still receiving placebo were blindly advanced to tofacitinib, 5 mg or 10 mg twice daily. Month 6 was considered an appropriate time to assess the primary end points—20% improvement in ACR (ACR20) criteria and rates of remission, defined by a Disease Activity Score for 28-joint counts based on the ESR (DAS28-4[ESR]) of less than 2.6—because of current understanding of RA and expectations of when full potential treatment benefits probably occurred. The primary end point of the Health Assessment Questionnaire Disability Index (HAQ-DI) score was believed to be sufficiently sensitive to indicate an early treatment difference, and assessment at month 3 enabled a beneficial comparison of active treatment with a "pure" placebo, that is, before a proportion of patients initially receiving placebo were advanced at month 3 to active treatment.

Randomization ratio, rationale for dose selection, and blinding procedures are detailed in the **Supplement** (available at www.annals.org).

Outcomes and Follow-up

Our primary objectives were to compare the efficacy of tofacitinib, 5 mg and 10 mg twice daily, with placebo assessed by the proportion of patients achieving an ACR20 (9) at month 6, the mean change from baseline in physical function status as measured by the HAQ-DI (10) at month 3, and the proportion of patients achieving DAS28-4(ESR)–defined remission (11) at month 6. "Response" was defined as a 20% improvement in the patient's tender or painful and swollen joint count at month 3 compared with baseline values. "Nonresponse" was defined as not achieving such improvement. This contrasts with the ACR's more stringent definition of the ACR20 response criteria, which requires the same 20% or more improvement in both joint counts plus a 20% or more improvement in 3 of the 5 remaining ACR core set measures of patient and physician global assessments, pain, disability, and an acute-phase reactant. An additional primary objective was to assess the safety of tofacitinib versus placebo over 12 months. Secondary objectives were to evaluate the ACR20, ACR50, and ACR70 response rates; change from baseline in HAQ-DI; DAS28-4(ESR) assessments; and Functional Assessment of Chronic Illness Therapy—Fatigue score over time.

The incidence and severity of all adverse events and clinical laboratory abnormalities were recorded, and vital sign assessments and physical examinations were routinely performed. To assess safety end points of cardiovascular events, a panel of independent experts (the Cardiovascular Safety Endpoint Adjudication Committee) reviewed all potential cardiovascular events and patient deaths regardless of cause.

Statistical Analysis

To control type I error rates, we assessed the 3 primary end points for efficacy in sequential order: ACR20, HAQ-DI, then DAS28-4(ESR) less than 2.6 (**Figure 1** of the **Supplement**). Doing so prevents the type I error rates (that is, the null hypotheses of no difference from placebo being mistakenly rejected when there is no difference) for the primary end points from becoming greater than 5% when statistical significance was measured. No preservation of type I error was applied for secondary end points, and a P value of 0.050 or less was considered statistically significant. The efficacy and safety analyses included all randomly assigned patients who received 1 or more doses of the study drug. The normal approximation for difference in binomial proportions was used to test the superiority of each tofacitinib dose against placebo with respect to ACR20 and the proportion of patients achieving DAS28-4(ESR) less than 2.6. Prespecified nonresponder imputation that addressed missing data in calculating ACR20 and DAS28-4(ESR) less than 2.6 was also applied to patients who had not achieved 20% improvement in tender and swollen joint counts, regardless of treatment assignment (placebo and active tofacitinib groups) at month 3. Nonresponder imputation analysis assumes that such patients did not respond to treatment for the remainder of the trial, even if they fulfill the ACR20 (or higher) or DAS28-4(ESR) less than 2.6 response criteria after 3 months. The HAQ-DI was expressed as the change from baseline and analyzed using a mixed-effect longitudinal model, with treatment and visit as fixed effects and patient as a random effect (estimates expressed as least-squares means). Comparisons with placebo for the first 6 months were analyzed by combining data from the 2 placebo sequences into 1 group. Secondary end points with binary variables were analyzed by nonresponder imputation, and continuous end points followed the analysis described for HAQ-DI. In addition, a multiple-imputation approach was implemented as a sensitivity analysis for rates of ACR20 and DAS28-4(ESR) less than 2.6 response, specifically to model the placebo response had placebo recipients continued placebo after month 3 and not advanced to tofacitinib treatment. See the **Supplement** for details of analysis and **Appendix Table 1** for results (available at www.annals.org). We used SAS, version 9.2 (SAS Institute, Cary, North Carolina).

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

Role of the Funding Source

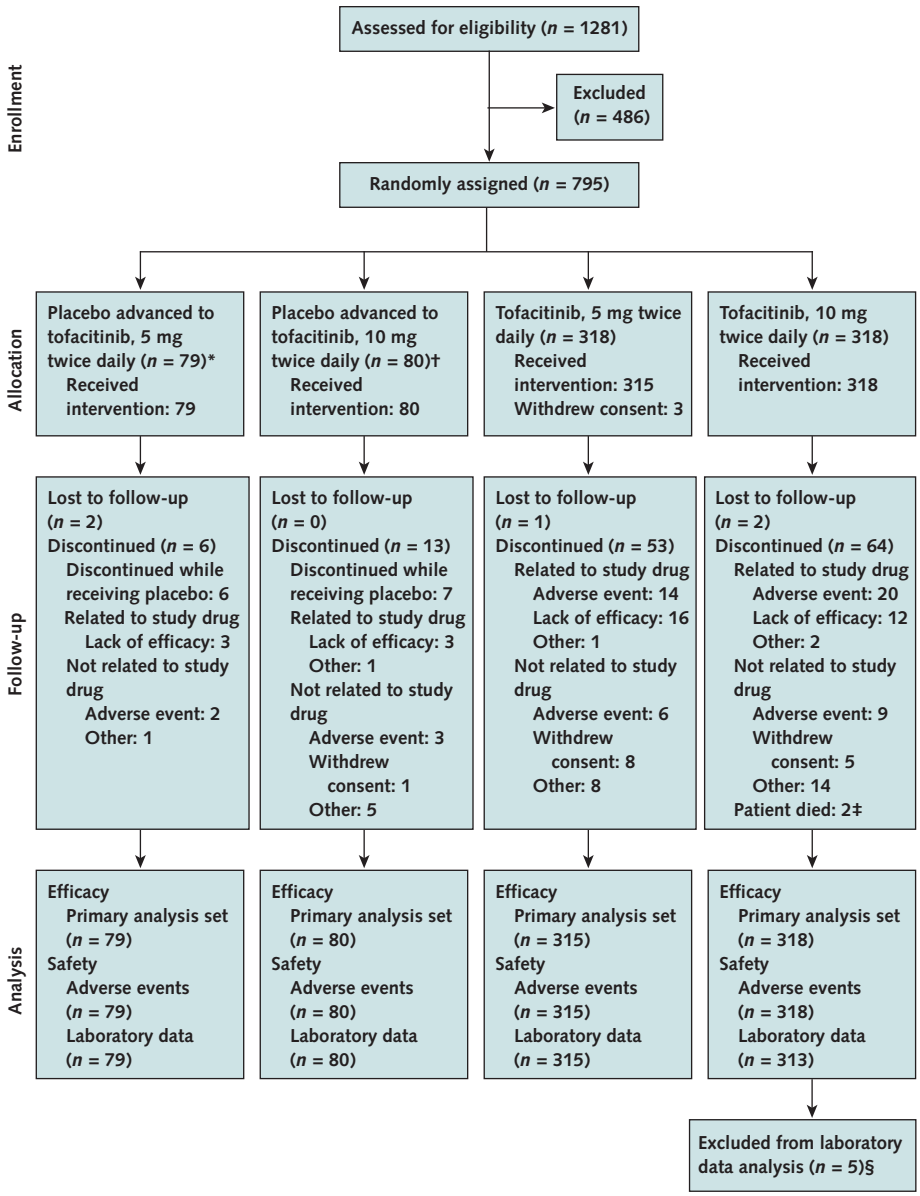
The study design, collection of data, analysis, and interpretation of the results were funded by Pfizer. Pfizer employees participated in the study design and data analysis and interpretation. All authors had full access to all study data, and the corresponding author had final responsibility for the decision to submit the manuscript for publication.

RESULTS

Patient Disposition and Demographic Characteristics

Patients ($n = 795$) were randomly assigned; 792 (99.6%) received 1 or more doses of study medication (the primary analysis set), and 651 (82.2%) completed the study (**Figure 1**). Seven patients at 2 sites were identified to have site-specific violations of the Good Clinical Practice guidelines. Demographic and baseline characteristics are shown in **Table 1**. Across treatment sequences, the mean age ranged from 50.8 to 53.3 years, 75.0% to 83.8% of patients were female, and the mean disease duration ranged from 8.1 to 10.2 years. During the study, 62.5% to 73.4% of patients continued to receive 1 background DMARD and 25.3% to 37.5% continued to receive 2 or more DMARDs. Methotrexate was the most frequently prescribed background DMARD (79.0% of all patients). The

Figure 1. **Study flow diagram.**



Three patients were randomly assigned but did not receive treatment, so they were not included in the efficacy analyses.
* Patients randomly assigned to receive placebo for months 0 to 6 and then tofacitinib, 5 mg twice daily, for months 6 to 12.
† Patients randomly assigned to receive placebo for months 0 to 6 and then tofacitinib, 10 mg twice daily, for months 6 to 12.
‡ Deaths are included in the "Discontinued" count.
§ Exclusion due to no laboratory data after baseline.

number of patients per background DMARD is shown in **Table 1** of the **Supplement**.

Efficacy

Seventy-eight patients (49.1%) receiving placebo did not have a response at month 3 and advanced to tofacitinib, 5 mg ($n = 38$) and 10 mg ($n = 40$) twice daily; 80 (25.4%) and 58 (18.2%) patients randomly assigned to 5-mg and 10-mg twice-daily tofacitinib, respectively, also had no response at month 3. Forty-three patients (27%) receiving placebo met the ACR20 criteria at month 3.

The ACR20 response rates (month 6) were greater for the 5-mg twice-daily tofacitinib (treatment difference, 21.2% [95% CI, 12.2% to 30.3%]; $P < 0.001$) and 10-mg twice-daily tofacitinib (25.8% [CI, 16.8% to 34.8%]; $P < 0.001$) groups compared with the combined placebo group (**Figure 2**). Improvements from baseline in HAQ-DI at month 3 were greater ($P < 0.001$) and the

proportions of patients with a DAS28-4(ESR) less than 2.6 at month 6 were greater for the 2 tofacitinib groups compared with placebo ($P = 0.005$ for 5-mg twice-daily tofacitinib; $P < 0.001$ for 10-mg twice-daily tofacitinib) (**Figure 2**).

Results from an analysis of the primary end points that excluded the 7 patients identified to have site-specific violations of the Good Clinical Practice guidelines are shown in **Figure 2** of the **Supplement**.

Secondary Efficacy End Points

Over time, statistically significant response rates were observed for ACR20 and ACR50 by week 2 in both tofacitinib groups (**Figure 3** [panels *A* and *B*] of the **Supplement**) and for ACR70 by week 2 (tofacitinib, 10 mg twice daily) and month 1 (tofacitinib, 5 mg twice daily) (**Figure 3** [panel *C*] of the **Supplement**). Mean treatment differences in changes from baseline in HAQ-DI, DAS28-4(ESR), DAS28-3(C-reactive protein), DAS28-4(ESR) less

Table 1. **Baseline Characteristics and Concomitant Treatment**

Variable	Placebo Advanced to Tofacitinib, 5 mg Twice Daily (*n* = 79)	Placebo Advanced to Tofacitinib, 10 mg Twice Daily (*n* = 80)	Tofacitinib, 5 mg Twice Daily (*n* = 315)	Tofacitinib, 10 mg Twice Daily (*n* = 318)
Female, %	79.7	75.0	83.8	81.1
White, %	60.8	55.0	54.9	54.7
Mean age (SD), *y*	50.8 (11.2)	53.3 (10.8)	52.7 (11.7)	51.9 (11.8)
Region of origin, %*				
North America (17.4%)	22.8	18.8	16.0	17.0
Latin America (13.7%)	13.9	13.8	14.2	13.2
Europe (27.8%)	31.7	28.8	28.9	25.5
Rest of world (41.1%)†	31.7	38.8	40.9	44.3
Mean disease duration (range), *y*	9.5 (0.3–39.3)	10.2 (0.3–49.0)	8.1 (0.2–39.9)	9.2 (0.2–41.0)
Mean tender joint count (SD), *n*	27.2 (16.8)	21.9 (13.0)	25.0 (15.3)	26.6 (16.1)
Mean swollen joint count (SD), *n*	14.6 (9.7)	13.9 (8.6)	14.5 (10.3)	14.4 (9.7)
Mean HAQ-DI score (SD)	1.45 (0.64)	1.24 (0.66)	1.44 (0.69)	1.43 (0.68)
Mean DAS28-4(ESR) (SD)	6.44 (1.0)	6.14 (1.0)	6.27 (1.0)	6.36 (1.1)
Mean ESR (SD), *mm/h*	51.0 (23.7)	49.3 (27.7)	50.5 (28.7)	51.9 (28.5)
Mean C-reactive protein level (SD), *nmol/L*	160.8 (156.9)	157.5 (173.3)	168.4 (204.2)	168.9 (208.4)
RF-positive, %	73.1	72.2	73.9	72.8
Anti-CCP–positive, %	69.2	67.5	69.6	66.5
Previous treatment				
TNF inhibitor, %‡§	6.3	6.3	7.3	6.0
Non–TNF inhibitor biologic agents, %‡‖	7.6	0	2.2	3.1
Mean failed DMARDs, *n*	1.3	1.4	1.4	1.4
DMARDs other than methotrexate taken before screening, %				
Auranofin	0	0	0	0.3
Chloroquine	6.3	6.3	4.1	4.7
Gold salts	0	0	0.6	1.6
Hydroxychloroquine	17.7	22.5	18.1	15.1
Leflunomide	25.3	23.8	31.4	31.1
Penicillamine	0	1.3	1.3	0.6
Sulfasalazine	20.3	23.8	18.1	23.0
Total	69.6	77.5	73.7	76.1
Methotrexate taken before screening, %	83.5	82.5	86.7	82.7
Mean methotrexate dose (SD), *mg/wk*	14.5 (4.8)	14.6 (5.1)	14.2 (4.8)	13.6 (4.8)
Concomitant treatment				
Background DMARDs, %				
1	73.4	62.5	66.7	64.8
≥2	25.3	37.5	33.3	34.9
Methotrexate, %	77.2	80.0	79.4	78.9
Oral corticosteroids, %	59.5	58.8	61.9	57.2
Mean prednisone dose (SD), *mg*	7.4 (2.8)	7.1 (3.0)	6.4 (2.8)	6.6 (3.1)
NSAIDs, %	72.2	63.8	75.9	74.2

CCP = cyclic citrullinated protein; DAS28-4(ESR) = Disease Activity Score for 28-joint counts based on the erythrocyte sedimentation rate; DMARD = disease-modifying antirheumatic drug; ESR = erythrocyte sedimentation rate; HAQ-DI = Health Assessment Questionnaire Disability Index; NSAID = nonsteroidal anti-inflammatory drug; RF = rheumatoid factor; TNF = tumor necrosis factor.

* 19 countries were included in the study.

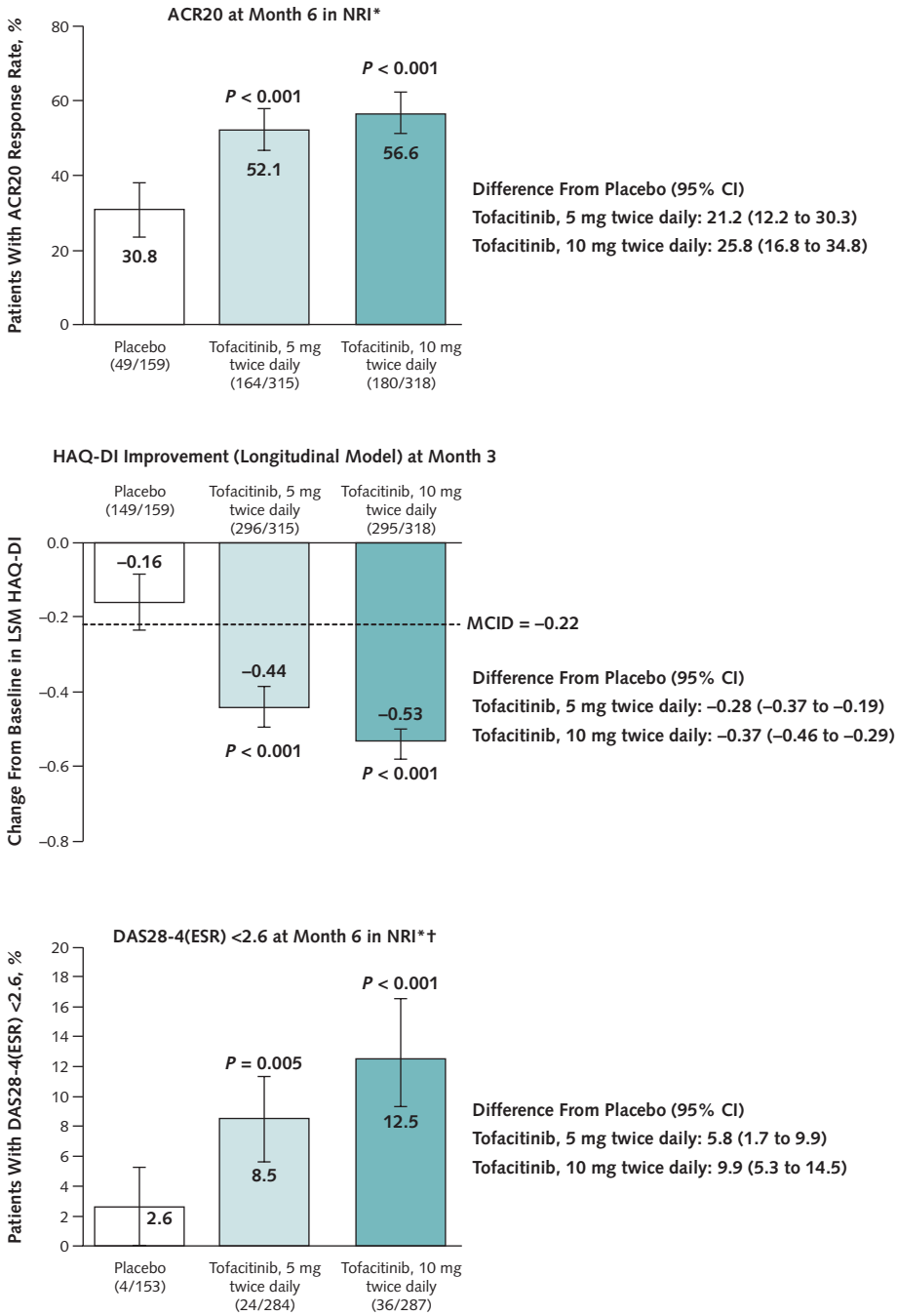
† China, 218 (27.4%); Australia, 52 (6.5%); Thailand, 32 (4.0%); and Malaysia, 25 (3.1%).

‡ Wash-out periods: anakinra and etanercept must have been discontinued for 4 wk, adalimumab for 6 wk, infliximab for 8 wk, and abatacept and tocilizumab for 12 wk before the first dose of study drug. Rituximab or other selective B-lymphocyte–depleting agents (marketed or investigational) must have been discontinued for 1 y before the first dose of study drug and the CD19/20+ cell counts were normal by fluorescence-activated cell-sorting analysis.

§ Adalimumab, certolizumab pegol, etanercept, golimumab, and infliximab.

‖ Abatacept, baminercept, canakinumab, rituximab, and tocilizumab.

Figure 2. **Primary efficacy end points.**



Patients who did respond at 3 mo were considered not to have responded to treatment for the remainder of the trial, even if they subsequently achieved response after month 3. Error bars represent 95% CIs. ACR20 = 20% improvement in American College of Rheumatology criteria; DAS28-4(ESR) = Disease Activity Score for 28-joint counts based on the erythrocyte sedimentation rate; HAQ-DI = Health Assessment Questionnaire Disability Index; LSM = least-squares mean; MCID = minimum clinically important difference; NRI = nonresponder imputation.

* Patients who did not respond at month 3 were considered not to have responded to treatment for the remainder of the trial, even if they subsequently achieved response after month 3.

† The numbers are different for DAS28-4(ESR) <2.6 because ESR was measured locally and some study sites were not able to collect these data.

than 2.6, and Functional Assessment of Chronic Illness Therapy—Fatigue response rates for both tofacitinib groups compared with placebo were also statistically significant over time (**Figure 4** of the **Supplement**). The differences in ACR20 response rates between the tofacitinib groups and placebo groups over time categorized by back-

ground nonbiologic DMARD therapy are illustrated in **Figure 5** of the **Supplement**.

Safety and Tolerability

During months 0 to 12, the incidence rate (events per 100 patient-years) of adverse events was 171.9 (CI, 152.5 to 193.8) in the 5-mg twice-daily tofacitinib group, 175.7 (CI, 155.8 to 198.2) in the 10-mg twice-daily tofacitinib group, and 342.3 (CI, 281.1 to 416.9) in the combined placebo group. The corresponding incidence rates for serious adverse events were 6.9 (CI, 4.6 to 10.5), 7.3 (CI, 4.8 to 11.0), and 10.9 (CI, 4.9 to 24.2). These data, along with the incidence rates of adverse events leading to discontinuation, are shown in **Table 2**. The most common adverse events during months 0 to 12 in the 5-mg and 10-mg twice-daily tofacitinib groups were upper respiratory tract infections (exposure-adjusted event rate [new events per 100 patient-years of exposure] of 12.3 and 14.6, respectively, vs. 12.6 in the combined placebo group), followed by nasopharyngitis (7.1 and 5.6, respectively, vs. 21.6 in the combined placebo group) (**Table 2** of the **Supplement**). Adverse events across groups in months 0 to 3, 4 to 6, and 7 to 12 and the incidence of adverse events, infectious events, and discontinuations are summarized in **Appendix Table 2** (available at www.annals.org). We found no observable trends (no statistical analysis was done) in the type or severity of adverse events when the events were presented by background nonbiologic DMARD therapy (**Table 3** of the **Supplement**).

Four opportunistic infections occurred in patients receiving tofacitinib and were considered related to treatment by the investigators: disseminated (multidermatomal) herpes zoster, cryptococcal pneumonia, and 2 cases of pulmonary tuberculosis (**Table 4** of the **Supplement**). In months 0 to 3, serious infections occurred most frequently ($n = 4$ [1.3%]) in the 10-mg twice-daily tofacitinib group (pneumonia [$n = 2$], diabetic foot infection, and bronchiectasis) compared with the 5-mg twice-daily tofacitinib group ($n = 2$ [0.6%]; bronchitis and disseminated herpes zoster) and the combined placebo group (0%). During months 6 to 12, only patients ($n = 3$ [0.9%]) in the 10-mg twice-daily tofacitinib group reported serious infections (pulmonary tuberculosis [$n = 2$], peritonitis, and cryptococcal pneumonia). Four deaths occurred (**Table 5** of the **Supplement**): 2 during the study (acute heart failure and respiratory failure in the 10-mg twice-daily tofacitinib group) and 2 after treatment discontinuation (traumatic brain injury 22 days after discontinuation and worsening RA 42 days after discontinuation in the 5-mg twice-daily tofacitinib group). One of the deaths, respiratory failure, was assessed by the investigator to be treatment-related.

Three patients had a potential cardiovascular event adjudicated by the Cardiovascular Safety Endpoint Adjudication Committee to meet criteria for ischemic and congestive heart failure events: transient ischemic attack (5-mg twice-daily tofacitinib), cerebrovascular accident (5-mg twice-daily tofacitinib), and congestive heart failure (10-mg twice-daily tofacitinib; patient subsequently died) (**Table 5** of the **Supplement**).

Mean changes from baseline in laboratory values over 12 months of treatment are shown in **Appendix Table 2**. Mean neutrophil counts at month 3 decreased with tofacitinib versus placebo but stabilized thereafter to month 12. Increases in high- and low-density lipoprotein cholesterol levels versus placebo at month 3 were sustained until month 12. Cholesterol levels also increased in placebo recipients after they advanced to tofacitinib. Changes in AST and ALT levels did not differ among tofacitinib recipients who were also receiving various background nonbiologic DMARD therapy combinations, although the relatively small numbers of patients in the nonmethotrexate groups

Table 2. **Overall Incidence Rates of Adverse Events, Serious Adverse Events, and Discontinuation Due to Adverse Events***

Variable	Placebo	Tofacitinib, 5 mg Twice Daily	Tofacitinib, 10 mg Twice Daily
Total patients, *n*	159	388	391
Total exposure, *patient-years*	55.6	324.6	321.7
Adverse events			
Incidence rate† (95% CI)	342.3 (281.1–416.9)	171.9 (152.5–193.8)	175.7 (155.8–198.2)
Patients, *n*	99	267	266
Exposure, *patient-years*	28.9	155.3	151.4
Serious adverse events			
Incidence rate† (95% CI)	10.9 (4.9–24.2)	6.9 (4.6–10.5)	7.3 (4.8–11.0)
Patients, *n*	6	22	23
Exposure, *patient-years*	55.2	318.2	315.8
Discontinuation due to adverse events			
Incidence rate† (95% CI)	5.4 (1.8–16.8)	6.2 (4.0–9.6)	9.7 (6.8–13.8)
Patients, *n*	3	20	31
Exposure, *patient-years*	55.4	323.3	320.5

* Overall incidence rates refer to 0 to 12 mo.
† Events per 100 patient-years of exposure.

limit the strength of these investigations. The incidence of increased AST and ALT levels categorized by background nonbiologic DMARD are shown in **Table 6** of the **Supplement**.

Thirteen tofacitinib recipients discontinued therapy because of laboratory findings: increased AST or ALT levels ($n = 3$), increased creatinine levels ($n = 4$), and decreased neutrophil counts ($n = 2$) (**Table 7** of the **Supplement**). No discontinuations occurred because of anemia.

DISCUSSION

The treatment of RA has improved in recent years because of the more aggressive use of nonbiologic DMARDs, either with a single DMARD or a combination, and the introduction of biologic therapies that may be used in combination with nonbiologic DMARDs. However, because treatment regimens are not effective in all patients and biologic agents are unavailable to some and require parenteral administration (12–15), a safe, effective, and tolerable oral DMARD is needed. Despite the common practice of prescribing nonbiologic DMARDs in combination, few randomized, prospective studies have investigated a new therapy in combination not only with methotrexate but also with other nonbiologic DMARDs.

Our study showed that when used in combination with various nonbiologic DMARDs, tofacitinib, 5 mg and 10 mg twice daily, compared with placebo rapidly reduced the signs and symptoms of RA and improved physical function. However, small sample sizes for patients receiving combinations of nonmethotrexate DMARDs lacked statistical power, and results should be interpreted cautiously.

These results support the findings of previous studies that demonstrated tofacitinib's efficacy in combination with methotrexate (16–19). We also observed the same safety events of special interest as seen in previous tofacitinib studies (6, 7, 16, 20): infections, decreases in neutrophil counts, increases in high- and low-density lipoprotein cholesterol levels, and small increases in serum creatinine and aminotransaminase levels.

Of the 4 deaths, 1 (reported as respiratory failure by the investigator and as an infection by the Cardiovascular Safety Endpoint Adjudication Committee) was attributed to the study drug by the investigator. In all 4 deaths, the patients were receiving (or had received) tofacitinib. Four opportunistic infections were reported (all considered by the investigator to be related to the study drug): pulmonary tuberculosis (in 2 patients), disseminated (multidermatomal) herpes zoster, and cryptococcal pneumonia. The 2 patients with pulmonary tuberculosis lived in Thailand and China, countries classified by the World Health Organization as having a high burden of tuberculosis (21).

We saw changes from baseline by month 3 in neutrophil counts, hemoglobin levels, and lipid levels, which stabilized thereafter. The mechanisms responsible for these changes are not fully understood. Mean neutrophil counts are known to decrease with various treatments and had decreased in a trial of adalimumab in patients with RA (19). Changes in hemoglobin are complex and may reflect improvement in the anemia of chronic disease and inhibition of erythropoietin signaling through JAK2. Elevation of lipids has also been reported with several biologic treatments and nonbiologic DMARDs with disease-modifying or anti-inflammatory activity in RA (22, 23). A recent study has shown that for patients with RA treated with tofacitinib, atorvastatin, 10 mg daily, was effective in reducing low-density lipoprotein cholesterol levels to or below pretreatment levels (24). Small increases in mean serum creatinine levels of unknown mechanism were also observed during our study. Neutropenia, anemia, elevated aminotransaminase levels, and elevated creatinine levels often resolved spontaneously, or stabilized to acceptable levels, and infrequently caused discontinuation of therapy. These observations were also consistent with those of earlier studies of tofacitinib (6, 7, 16, 20). Increased AST and ALT levels were not associated with any specific background nonbiologic DMARD therapy, although the small subset of sample sizes necessitates caution when interpreting results. Separate trials with longer-term monitoring of patients receiving tofacitinib are ongoing.

The limitations of this study include a smaller placebo group of relatively short duration compared with the tofacitinib sequences, although the study was powered to show statistically significant differences in efficacy. We did not stratify enrollment on the basis of background nonbiologic DMARD therapy, and patients receiving methotrexate or methotrexate in combination with another nonbiologic DMARD were predominantly enrolled. Sample sizes were therefore much lower for patients receiving combinations of nonmethotrexate DMARDs. In this context, results of the individual background nonbiologic DMARD subsets should be interpreted cautiously.

All patients, assessors, and intervention providers were blinded to therapy and measures of acute-phase reactants. The study investigators were not blinded to neutrophil counts because these had to be monitored for patient safety. Although we believe blinding was successful and there were no incidents of accidental unblinding, a formal analysis of the success of blinding was not done.

In summary, our study demonstrated that tofacitinib in combination with nonbiologic DMARDs, primarily methotrexate, was superior to placebo in rates of ACR20 response and DAS28-4(ESR)–defined remission and in improving HAQ-DI scores in patients with active RA. Safety events identified were consistent with those in previous tofacitinib studies: observed decreases in neutrophil counts, increases in high- and low-density lipoprotein cholesterol levels, and small increases in serum creatinine and aminotransaminase levels. Tofacitinib showed potential as an effective therapeutic agent in patients with RA who are currently receiving treatment with various nonbiologic

DMARDs. Its efficacy and safety should be further evaluated in a larger number of patients receiving concurrent DMARDs other than methotrexate.

From Albany Medical College, Albany, New York; Peking University People's Hospital, Beijing, China; Cabrini Medical Centre, Malvern, Victoria, Australia; Metroplex Clinical Research Center, Dallas, Texas; Stanford University, Stanford, California; Hospital Universitario La Paz, Madrid, Spain; Newcastle Biomedical Research Centre, Newcastle University, and Newcastle upon Tyne Hospitals NHS Trust, Newcastle upon Tyne, United Kingdom; and Pfizer, Groton, Connecticut, and New York, New York.

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References

1. **van der Kooij SM, de Vries-Bouwstra JK, Goekoop-Ruiterman YP, van Zeben D, Kerstens PJ, Gerards AH, et al.** Limited efficacy of conventional DMARDs after initial methotrexate failure in patients with recent onset rheumatoid arthritis treated according to the disease activity score. Ann Rheum Dis. 2007;66:1356-62. [PMID: 17293364]

2. **Alarcón GS, Tracy IC, Blackburn WD Jr.** Methotrexate in rheumatoid arthritis. Toxic effects as the major factor in limiting long-term treatment. Arthritis Rheum. 1989;32:671-6. [PMID: 2735960]

3. **Ghoreschi K, Jesson MI, Li X, Lee JL, Ghosh S, Alsup JW, et al.** Modulation of innate and adaptive immune responses by tofacitinib (CP-690,550). J Immunol. 2011;186:4234-43. [PMID: 21383241]

4. **Meyer DM, Jesson MI, Li X, Elrick MM, Funckes-Shippy CL, Warner JD, et al.** Anti-inflammatory activity and neutrophil reductions mediated by the JAK1/JAK3 inhibitor, CP-690,550, in rat adjuvant-induced arthritis. J Inflamm (Lond). 2010;7:41. [PMID: 20701804]

5. **Ghoreschi K, Laurence A, O'Shea JJ.** Janus kinases in immune cell signaling. Immunol Rev. 2009;228:273-87. [PMID: 19290934]

6. **Fleischmann R, Cutolo M, Genovese MC, Lee EB, Kanik KS, Sadis S, et al.** Phase IIb dose-ranging study of the oral JAK inhibitor tofacitinib (CP-690,550) or adalimumab monotherapy versus placebo in patients with active rheumatoid arthritis with an inadequate response to disease-modifying antirheumatic drugs. Arthritis Rheum. 2012;64:617-29. [PMID: 21952978]

7. **Kremer JM, Cohen S, Wilkinson BE, Connell CA, French JL, Gomez-Reino J, et al.** A phase IIb dose-ranging study of the oral JAK inhibitor tofacitinib (CP-690,550) versus placebo in combination with background methotrexate in patients with active rheumatoid arthritis and an inadequate response to methotrexate alone. Arthritis Rheum. 2012;64:970-81. [PMID: 22006202]

8. **Arnett FC, Edworthy SM, Bloch DA, McShane DJ, Fries JF, Cooper NS, et al.** The American Rheumatism Association 1987 revised criteria for the classification of rheumatoid arthritis. Arthritis Rheum. 1988;31:315-24. [PMID: 3358796]

9. **Felson DT, Anderson JJ, Boers M, Bombardier C, Furst D, Goldsmith C, et al.** American College of Rheumatology. Preliminary definition of improvement in rheumatoid arthritis. Arthritis Rheum. 1995;38:727-35. [PMID: 7779114]

10. **Fries JF, Spitz P, Kraines RG, Holman HR.** Measurement of patient outcome in arthritis. Arthritis Rheum. 1980;23:137-45. [PMID: 7362664]

11. **Prevoo ML, van 't Hof MA, Kuper HH, van Leeuwen MA, van de Putte LB, van Riel PL.** Modified disease activity scores that include twenty-eight-joint counts. Development and validation in a prospective longitudinal study of patients with rheumatoid arthritis. Arthritis Rheum. 1995;38:44-8. [PMID: 7818570]

12. **Askling J, Bongartz T.** Malignancy and biologic therapy in rheumatoid arthritis. Curr Opin Rheumatol. 2008;20:334-9. [PMID: 18388527]

13. **Khraishi M.** Comparative overview of safety of the biologics in rheumatoid arthritis. J Rheumatol Suppl. 2009;82:25-32. [PMID: 19509327]

14. **Martin-Mola E, Balsa A.** Infectious complications of biologic agents. Rheum Dis Clin North Am. 2009;35:183-99. [PMID: 19481004]

15. **Wolfe F, Michaud K.** Biologic treatment of rheumatoid arthritis and the risk of malignancy: analyses from a large US observational study. Arthritis Rheum. 2007;56:2886-95. [PMID: 17729297]

16. **Tanaka Y, Suzuki M, Nakamura H, Toyoizumi S, Zwillich SH; Tofacitinib Study Investigators.** Phase II study of tofacitinib (CP-690,550) combined with methotrexate in patients with rheumatoid arthritis and an inadequate response to methotrexate. Arthritis Care Res (Hoboken). 2011;63:1150-8. [PMID: 21584942]

17. **Burmester GR, Blanco R, Charles-Schoeman C, Wollenhaupt J, Zerbini C, Benda B, et al; ORAL Step investigators.** Tofacitinib (CP-690,550) in combination with methotrexate in patients with active rheumatoid arthritis with an inadequate response to tumour necrosis factor inhibitors: a randomised phase 3 trial. Lancet. 2013;381:451-60. [PMID: 23294500]

18. **van der Heijde D, Tanaka Y, Fleischmann R, Keystone E, Kremer J, Zerbini C, et al; ORAL Scan Investigators.** Tofacitinib (CP-690,550) in patients with rheumatoid arthritis receiving methotrexate: twelve-month data from a twenty-four-month phase III randomized radiographic study. Arthritis Rheum. 2013;65:559-70. [PMID: 23348607]

19. **van Vollenhoven RF, Fleischmann R, Cohen S, Lee EB, García Meijide JA, Wagner S, et al; ORAL Standard Investigators.** Tofacitinib or adalimumab versus placebo in rheumatoid arthritis. N Engl J Med. 2012;367:508-19. [PMID: 22873531]

20. **Kremer JM, Bloom BJ, Breedveld FC, Coombs JH, Fletcher MP, Gruben D, et al.** The safety and efficacy of a JAK inhibitor in patients with active rheumatoid arthritis: results of a double-blind, placebo-controlled phase IIa trial of three dosage levels of CP-690,550 versus placebo. Arthritis Rheum. 2009;60:1895-905. [PMID: 19565475]

21. **World Health Organization.** Tuberculosis country profiles. Accessed at www.who.int/tb/country/data/profiles/en/index.html on 1 November 2011.

22. **Choy E, Sattar N.** Interpreting lipid levels in the context of high-grade inflammatory states with a focus on rheumatoid arthritis: a challenge to conventional cardiovascular risk actions. Ann Rheum Dis. 2009;68:460-9. [PMID: 19286905]

23. **Saiki O, Takao R, Naruse Y, Kuhara M, Imai S, Uda H.** Infliximab but not methotrexate induces extra-high levels of VLDL-triglyceride in patients with rheumatoid arthritis. J Rheumatol. 2007;34:1997-2004. [PMID: 17787045]

24. **McInnes IB, Kim HY, Lee SH, Mandel D, Song YW, Connell CA, et al.** Open-label tofacitinib and double-blind atorvastatin in rheumatoid arthritis patients: a randomised study. Ann Rheum Dis. 2013. [PMID: 23482473]

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25. **Siegel JN, Zhen BG.** Use of the American College of Rheumatology N (ACR-N) index of improvement in rheumatoid arthritis: argument in favor. Arthritis Rheum. 2005;52:1637-41. [PMID: 15934067]
26. **Fitzmaurice GM, Laird NM, Ware JH.** Applied Longitudinal Analysis. New York: J Wiley; 2004.
27. **Hogan JW, Roy J, Korkontzelou C.** Handling drop-out in longitudinal studies. Stat Med. 2004;23:1455-97. [PMID: 15116353]
28. **Little RJ, Rubin DB.** Statistical Analysis with Missing Data. 2nd ed. New York: J Wiley; 2002.

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Appendix Table 1. **Sensitivity Analyses for ACR20, ACR50, and ACR70 Response Rates and DAS28-4(ESR) Less Than 2.6 Remission Rates, by Multiple Imputation**

Variable	Tofacitinib vs. Placebo	Difference (95% CI), *percentage points*	*P* Value
ACR20			
0.5 mo	5 mg	16.2 (9.17–23.2)	<0.001
	10 mg	21.5 (14.3–28.7)	<0.001
1 mo	5 mg	15.2 (6.51–23.8)	<0.001
	10 mg	25.4 (16.6–34.2)	<0.001
2 mo	5 mg	28.4 (19.4–37.5)	<0.001
	10 mg	38.3 (29.4–47.1)	<0.001
3 mo	5 mg	29.1 (19.8–38.4)	<0.001
	10 mg	36.6 (27.4–45.9)	<0.001
4.5 mo	5 mg	25.9 (14.9–36.8)	<0.001
	10 mg	30.4 (19.4–41.3)	<0.001
6 mo	5 mg	28.7 (17.6–39.7)	<0.001
	10 mg	30.3 (19.2–41.3)	<0.001
ACR50			
0.5 mo	5 mg	4.43 (1.22–7.64)	0.007
	10 mg	6.94 (3.30–10.6)	<0.001
1 mo	5 mg	9.32 (4.98–13.7)	<0.001
	10 mg	16.6 (11.5–21.7)	<0.001
2 mo	5 mg	19.0 (13.1–25.0)	<0.001
	10 mg	25.9 (19.6–32.2)	<0.001
3 mo	5 mg	17.8 (10.6–25.1)	<0.001
	10 mg	25.1 (17.6–32.6)	<0.001
4.5 mo	5 mg	18.9 (9.71–28.0)	<0.001
	10 mg	21.9 (12.7–31.1)	<0.001
6 mo	5 mg	22.1 (12.6–31.6)	<0.001
	10 mg	24.8 (15.2–34.4)	<0.001
ACR70*			
2 mo	5 mg	7.63 (3.61–11.7)	<0.001
	10 mg	9.42 (5.18–13.7)	<0.001
3 mo	5 mg	6.92 (2.78–11.1)	0.001
	10 mg	13.8 (8.86–18.8)	<0.001
4.5 mo	5 mg	5.73 (1.14–12.6)	0.102
	10 mg	13.2 (5.91–20.6)	<0.001
6 mo	5 mg	9.05 (2.25–15.9)	0.009
	10 mg	13.5 (6.24–20.8)	<0.001
DAS28-4(ESR) <2.6			
3 mo	5 mg	8.34 (4.13–12.6)	<0.001
	10 mg	9.66 (5.26–14.1)	<0.001
6 mo	5 mg	9.38 (3.96–14.8)	<0.001
	10 mg	12.2 (6.60–17.8)	<0.001

ACR20 = 20% improvement in American College of Rheumatology criteria; ACR50 = 50% improvement in American College of Rheumatology criteria; ACR70 = 70% improvement in American College of Rheumatology criteria; DAS28-4(ESR) = Disease Activity Score for 28-joint counts based on the erythrocyte sedimentation rate.

* Data for ACR70 response rates commence at 2 mo due to a zero placebo response at 0.5 mo and 1 mo.

Appendix Table 2. Incidence of Adverse Events and Laboratory Data*

Variable	Months 0 to 3		
	Placebo	Tofacitinib, 5 mg Twice Daily	Tofacitinib, 10 mg Twice Daily
Adverse events among patients as treated			
Total patients, *n*	159	315	318
Adverse events, *n*	179	400	373
Patients with adverse events, %	61.0	52.7	54.4
Patients with serious adverse events, %	3.8	2.9	2.5
Patients with serious infections, %	0	0.6	1.3
Discontinuations due to adverse events, %	1.3	4.1	4.1
Incidence, *n (%)*			
AST >1 × ULN	22 (13.8)	74 (23.5)	92 (29.4)
AST >3 × ULN	1 (<1.0)	3 (<1.0)	1 (<1.0)
ALT >1 × ULN	28 (17.6)	88 (27.9)	107 (34.2)
ALT >3 × ULN	1 (<1.0)	6 (1.9)	3 (<1.0)
	Month 3		
Among patients as randomly assigned			
Change from baseline (LSM)			
Total patients, *n*	159	315	318
Neutrophil count (95% CI), × 10^9 *cells/L*†	−0.02 (−0.29 to 0.25)	−0.75 (−0.95 to −0.56)	−0.99 (−1.18 to −0.79)
Hemoglobin level (95% CI), *g/L*†	−0.04 (−0.16 to 0.08)	0.27 (0.17 to 0.36)	0.10 (−0.01 to 0.18)
Serum creatinine level (95% CI)†			
μmol/L	1.77 (0.00 to 2.65)	2.65 (1.77 to 3.54)	5.30 (4.42 to 6.19)
mg/dL	0.02 (0.00 to 0.03)	0.03 (0.02 to 0.04)	0.06 (0.05 to 0.07)
Percentage of change in LDL cholesterol level (95% CI)†	−0.61 (−4.21 to 2.99)	15.65 (13.04 to 18.25)	18.26 (15.63 to 20.88)
Percentage of change in HDL lipoprotein cholesterol level (95% CI)†	−0.72 (−3.95 to 2.51)	12.19 (9.85 to 14.54)	14.71 (12.36 to 17.07)
Incidence, *n (%)*			
Neutropenia (≥0.5 to <1.5 × 10^9 cells/L)	1 (<1.0)	1 (<1.0)	8 (2.8)
Decreased hemoglobin level of −10.0 to −30.0 g/L or between 70 and 80 g/L	15 (10.2)	17 (5.8)	24 (8.3)
Decreased hemoglobin level of ≥30 g/d or <70.0 g/L	0	0	0

ALT = alanine aminotransferase; AST = aspartate aminotransferase; HDL = high-density lipoprotein; LDL = low-density lipoprotein; LSM = least-squares mean; ULN = upper limit of normal.

* Adverse events (Medical Dictionary for Regulatory Activities–preferred term) reported by the investigator as treatment-related that led to discontinuation for the 5-mg twice-daily tofacitinib group were increased international normalized ratio, increased aminotransaminases, drug eruption, paronychia, diarrhea, upper respiratory tract infection, bronchitis, vertigo, increased ALT, increased AST, decreased neutrophil count, decreased platelet count, decreased leukocyte count, dermatitis allergic, cholecystitis, and rash. Adverse events for the 10-mg twice-daily tofacitinib group were peritonitis, increased γ-glutamyltransferase, aspergilloma, pneumonia, cryptococcal pneumonia, edema, dysuria, amenorrhea, increased blood creatinine, diabetic foot infection, constipation, herpes zoster, increased blood creatinine kinase, decreased leukocyte count, tuberculosis, sinusitis, bronchopneumonia, vertigo, diarrhea, nausea, and vomiting. No treatment-related adverse events were reported that led to discontinuation for patients randomly assigned to placebo or randomly assigned to placebo advanced to active treatment. Serious adverse events reported by the investigator as treatment-related for 5-mg twice-daily tofacitinib group were disseminated herpes zoster, bronchitis, and cholecystitis. Serious adverse events for the 10-mg twice-daily tofacitinib group were peritonitis, pulmonary hypertension, respiratory failure, pneumonia, cryptococcal pneumonia, diabetic foot infection, breast cancer, tuberculosis, and bronchiectasis. No treatment-related serious adverse events were reported for patients randomly assigned to placebo or randomly assigned to placebo advanced to active treatment.

† The CIs of 0 to 3 mo represent effect of treatment vs. placebo. Once the "pure" placebo group is lost at 3 mo (placebo recipients without were moved to active treatment at 3 mo), CIs for 3 to 6 mo and 6 to 12 mo represent within-treatment effect.

Appendix Table 2—**Continued**

Placebo	Placebo Advanced to Tofacitinib, 5 mg Twice Daily	Placebo Advanced to Tofacitinib, 10 mg Twice Daily	Tofacitinib, 5 mg Twice Daily	Tofacitinib, 10 mg Twice Daily
Months 4 to 6				
81	40	315	315	318
39	32	39	211	238
25.9	42.1	45.0	38.4	39.0
0	0	0	1.6	2.2
0	0	0	0.3	0.3
1.2	0	2.5	1.9	2.5
9 (12.7)	4 (10.5)	9 (22.5)	52 (17.8)	63 (21.2)
0	0	0	1 (<1.0)	0
13 (18.3)	5 (13.2)	4 (10.0)	57 (19.5)	70 (23.6)
1 (1.4)	0	1 (2.5)	3 (1.0)	3 (1.0)
Month 6				
81	79	80	315	318
−0.38 (−0.74 to −0.03)	−0.53 (−0.91 to −0.15)	−0.96 (−1.34 to −0.57)	−0.96 (−1.15 to −0.76)	−1.10 (−1.29 to −0.90)
−0.15 (−0.31 to 0.01)	0.01 (−0.17 to 0.19)	−0.11 (−0.29 to 0.07)	0.26 (0.17 to 0.36)	0.08 (−0.02 to 0.17)
1.77 (0.0 to 3.54)	2.65 (0.88 to 4.42)	5.30 (2.65 to 7.07)	4.42 (3.54 to 5.30)	5.30 (3.54 to 6.19)
0.02 (0.00 to 0.04)	0.03 (0.01 to 0.05)	0.06 (0.03 to 0.08)	0.05 (0.04 to 0.06)	0.06 (0.04 to 0.07)
−2.63 (−7.53 to 2.28)	4.51 (−0.90 to 9.93)	5.66 (0.17 to 11.15)	15.15 (12.35 to 17.96)	17.85 (15.02 to 20.68)
−1.69 (−5.89 to 2.52)	3.90 (−0.93 to 8.73)	10.81 (5.95 to 15.67)	12.33 (9.83 to 14.83)	14.03 (11.52 to 16.54)
0 (0.0)	1 (1.4)	1 (1.4)	1 (<1.0)	8 (2.9)
6 (9.0)	7 (9.9)	11 (15.3)	25 (9.1)	29 (10.4)
1 (1.5)	1 (1.4)	0	0	0

Continued on the following page

Appendix Table 2—**Continued**

Months 7 to 12			
Placebo Advanced to Tofacitinib, 5 mg Twice Daily	**Placebo Advanced to Tofacitinib, 10 mg Twice Daily**	**Tofacitinib, 5 mg Twice Daily**	**Tofacitinib, 10 mg Twice Daily**
79	80	315	318
57	61	208	272
43.0	36.3	33.0	42.5
2.5	0	2.2	2.8
0	0	0	0.9
0	1.3	0.3	2.8
14 (19.4)	17 (24.6)	52 (19.1)	72 (26.7)
0	1 (1.4)	3 (1.1)	1 (<1.0)
16 (22.2)	16 (23.2)	51 (18.8)	74 (27.4)
0	1 (1.4)	7 (2.6)	5 (1.9)
Month 12			
79	80	315	318
−0.72 (−1.11 to −0.34)	−0.66 (−1.06 to −0.26)	−0.73 (−0.94 to −0.53)	−0.90 (−1.11 to −0.69)
0.42 (0.24 to 0.61)	0.23 (0.04 to 0.41)	0.42 (0.32 to 0.52)	0.18 (0.08 to 0.27)
4.42 (1.77 to 6.19)	7.07 (5.30 to 9.72)	5.30 (4.42 to 6.19)	7.07 (5.30 to 7.95)
0.05 (0.02 to 0.07)	0.08 (0.06 to 0.11)	0.06 (0.05 to 0.07)	0.08 (0.06 to 0.09)
7.72 (2.23 to 13.20)	12.85 (7.28 to 18.41)	16.24 (13.36 to 19.12)	19.93 (17.0 to 22.87)
14.08 (9.19 to 18.97)	18.97 (14.02 to 23.91)	15.26 (12.70 to 17.82)	19.04 (16.45 to 21.63)
3 (4.3)	3 (4.7)	2 (<1.0)	4 (1.7)
5 (7.2)	7 (10.9)	19 (7.6)	23 (9.4)
0	0	0	1 (<1.0)