ORIGINAL ARTICLE

Tofacitinib versus Methotrexate in Rheumatoid Arthritis

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ABSTRACT

BACKGROUND

Methotrexate is the most frequently used first-line antirheumatic drug. We report the findings of a phase 3 study of monotherapy with tofacitinib, an oral Janus kinase inhibitor, as compared with methotrexate monotherapy in patients with rheumatoid arthritis who had not previously received methotrexate or therapeutic doses of methotrexate.

METHODS

We randomly assigned 958 patients to receive 5 mg or 10 mg of tofacitinib twice daily or methotrexate at a dose that was incrementally increased to 20 mg per week over 8 weeks; 956 patients received a study drug. The coprimary end points at month 6 were the mean change from baseline in the van der Heijde modified total Sharp score (which ranges from 0 to 448, with higher scores indicating greater structural joint damage) and the proportion of patients with an American College of Rheumatology (ACR) 70 response (≥70% reduction in the number of both tender and swollen joints and ≥70% improvement in three of five other criteria: the patient's assessment of pain, level of disability, C-reactive protein level or erythrocyte sedimentation rate, global assessment of disease by the patient, and global assessment of disease by the physician).

RESULTS

Mean changes in the modified total Sharp score from baseline to month 6 were significantly smaller in the tofacitinib groups than in the methotrexate group, but changes were modest in all three groups (0.2 points in the 5-mg tofacitinib group and <0.1 point in the 10-mg tofacitinib group, as compared with 0.8 points in the methotrexate group [P<0.001 for both comparisons]). Among the patients receiving tofacitinib, 25.5% in the 5-mg group and 37.7% in the 10-mg group had an ACR 70 response at month 6, as compared with 12.0% of patients in the methotrexate group (P<0.001 for both comparisons). Herpes zoster developed in 31 of 770 patients who received tofacitinib (4.0%) and in 2 of 186 patients who received methotrexate (1.1%). Confirmed cases of cancer (including three cases of lymphoma) developed in 5 patients who received tofacitinib and in 1 patient who received methotrexate. Tofacitinib was associated with increases in creatinine levels and in low-density and high-density lipoprotein cholesterol levels.

CONCLUSIONS

In patients who had not previously received methotrexate or therapeutic doses of methotrexate, tofacitinib monotherapy was superior to methotrexate in reducing signs and symptoms of rheumatoid arthritis and inhibiting the progression of structural joint damage. The benefits of tofacitinib need to be considered in the context of the risks of adverse events. (Funded by Pfizer; ORAL Start ClinicalTrials.gov number, NCT01039688.)

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Rheumatoid arthritis is a chronic autoimmune disease characterized by inflammation and by joint destruction that leads to substantial disability. The predominant first-line treatment is methotrexate, a nonbiologic agent that is associated with acceptable clinical and functional improvements. Although methotrexate prevents progressive joint damage in some patients,[1-3] concerns have been raised regarding its side effects and safety.[4-8] In one study, discontinuation of methotrexate was reported after 2 years of treatment in one third of the patients and after 5 years of treatment in more than half the patients.[9] In combination with methotrexate, biologic disease-modifying antirheumatic drugs (DMARDs), including tumor necrosis factor inhibitors, are efficacious and slow joint damage; however, there are also concerns about the side effects and safety of these agents.[5,7,8,10,11]

Tofacitinib is an oral, small-molecule Janus kinase (JAK) inhibitor for the treatment of rheumatoid arthritis.[12] In phase 3 studies, safety concerns about tofacitinib have included a risk of serious infection and changes in laboratory measurements.[13-17] We report the clinical, structural, and safety outcomes of ORAL Start, a 24-month study of tofacitinib monotherapy as compared with methotrexate monotherapy in patients with active moderate-to-severe rheumatoid arthritis who had not previously received methotrexate or therapeutic doses of methotrexate.

Methods

Patients

Patients were eligible if they were at least 18 years of age; had received a diagnosis of active rheumatoid arthritis according to the American College of Rheumatology (ACR) 1987 revised criteria[18]; had active rheumatoid arthritis, which was defined as the presence of 6 or more joints that were tender or painful (out of 68 joints examined) and 6 or more swollen joints (out of 66 joints examined); and had either an erythrocyte sedimentation rate (ESR) of more than 28 mm per hour (Westergren method) or a C-reactive protein level of more than 7 mg per liter. In addition, eligible patients had three or more distinct joint erosions detected on hand and wrist or foot radiographs, or a positive test for IgM rheumatoid factor or antibodies to cyclic citrullinated peptide. Key exclusion criteria are described in Section 2 in the Supplementary Appendix, available with the full text of this article at NEJM.org.

Study Design and Oversight

We conducted a phase 3, randomized, double-blind, parallel-group study in 151 centers worldwide. The first patient visit was on January 25, 2010; the last patient visit (month 24) was on March 13, 2013. Visits were scheduled at the start of treatment and at months 1, 2, and 3, then every 3 months until the end of the study at month 24. Patients were randomly assigned, in a 2:2:1 ratio, to receive treatment for 24 months with one of three regimens: tofacitinib at a dose of 5 mg twice daily, tofacitinib at a dose of 10 mg twice daily, or methotrexate at a starting dose of 10 mg per week, with increments of 5 mg per week every 4 weeks to 20 mg per week by week 8. Randomization was performed with the use of an interactive Web-based or telephone-based system (Impala, Pfizer)

The study, which was sponsored by Pfizer, was conducted in compliance with the Declaration of Helsinki, International Conference on Harmonisation Guidelines for Good Clinical Practice, and local country regulations. All patients provided written informed consent. The final protocol, amendments, and documentation of consent were approved by the institutional review board of each study center and relevant independent ethics committees. The study protocol is available at NEJM.org. Patients were evaluated by the academic investigators, and the data were collected and analyzed by Pfizer under the direction of both the academic and industry authors. The first draft of the manuscript was written by the second and last authors with the assistance of a writer who was paid by the sponsor, under the direction of the first author. All coauthors revised the manuscript for intellectual content and vouch for the completeness of the data and analyses and the fidelity of the study to the protocol. All the authors made the decision to submit the manuscript for publication.

Measures of Efficacy

The coprimary efficacy end points at month 6 were the mean change from baseline in the van der Heijde modification of the total Sharp score (which ranges from 0 to 448, with higher scores indicating greater structural joint damage)[19] and the proportion of patients with an ACR 70 response (at least a 70% reduction from baseline in the num-

ber of both tender and swollen joints and equivalent improvement in three or more of the five remaining ACR core set measures). These measures are the patient's assessment of pain, level of disability, C-reactive protein level or erythrocyte sedimentation rate, global assessment of disease by the patient, and global assessment of disease by the physician.

Secondary efficacy end points included changes from baseline in modified total Sharp scores at months 12 and 24 and erosion scores (ranging from 0 to 280, with higher scores indicating greater erosive changes in the joints) and joint-space narrowing scores (ranging from 0 to 168, with higher scores indicating greater joint narrowing) at months 6, 12, and 24. The proportion of patients with no radiographic progression (defined by a change from baseline in the modified total Sharp score that was ≤0.5 units) and no new erosion (defined by a change from baseline in the erosion score that was ≤0.5 units)[20] was also assessed at months 6, 12, and 24. Other key secondary end points, such as ACR 20, ACR 50, and ACR 70 responses (at time points other than month 6), rates of low disease activity and remission, and patient-reported outcomes such as fatigue, are defined in Section 2 in the Supplementary Appendix.

SAFETY ASSESSMENTS

The incidence and severity of all adverse events were recorded. Clinical laboratory tests and physical assessments were performed and vital signs were recorded at every visit.

STATISTICAL ANALYSIS

Efficacy and safety analyses included data from all patients who underwent randomization and who received at least one dose of study medication and had a baseline measurement and at least one post-baseline measurement for variables expressed as the change from baseline (the full analysis set). Analyses of coprimary end points (the mean change from baseline in the modified total Sharp score and the ACR 70 response) at month 6 were based on the prespecified interim (year 1) data set; all other analyses were based on the final (year 2) data set. The year 1 data set consisted of data on all patients who were seen at the month 12 visit or had withdrawn from the study previously. No corrections or modifications were made to the year 1 data set after it was established on May 24, 2012.

Preservation of joint structure, as measured by the modified total Sharp score, was used to determine the sample size, which was planned to provide the study with 90% power, assuming a mean (±SD) difference in the modified total Sharp score of at least 0.9±2.8 units. For the ACR 70 response, the given sample size was planned to yield more than 90% power, assuming a difference in response rates of 15 percentage points or higher (with a methotrexate response of approximately 20%).

Analysis of covariance was used to assess the coprimary end point of the modified total Sharp score at month 6; missing values were extrapolated linearly. For the month 6 analysis of the coprimary end point of the ACR 70 response and of other binary end points, the normal approximation for the difference in binomial proportions was used to test the superiority of each dose of tofacitinib over methotrexate; missing values due to withdrawal were imputed with the use of nonresponse imputation, which was also applied to binary, secondary end points that were not based on joint structure. Changes from baseline in the score on the Health Assessment Questionnaire–Disability Index (HAQ-DI) and other continuous end points were expressed as least-squares mean changes and analyzed with the use of a mixed-effect longitudinal model.

Further statistical details, including the step-down approach (Fig. S1 in the Supplementary Appendix) used to assign significance for the coprimary end points, are described in Section 3 in the Supplementary Appendix.

RESULTS

PATIENTS

Overall, 958 patients underwent randomization, of whom 956 patients received tofacitinib at a dose of 5 mg twice daily (373 patients), tofacitinib at a dose of 10 mg twice daily (397 patients), or methotrexate (186 patients) (Fig. S2 in the Supplementary Appendix). Baseline characteristics were similar among the treatment groups (Table 1, and Table S1 in the Supplementary Appendix). The mean dose of methotrexate at month 3 was 18.5 mg per week (10 mg per week in 13 patients, 15 mg per week in 26 patients, and 20 mg per week in 130 patients).

RADIOGRAPHIC FINDINGS

Both baseline and post-baseline radiographs were available for 93.0% of all patients; missing

radiographs accounted for all missing data at month 6. The numbers of patients with modified total Sharp scores that were available at months 6, 12, and 24 are shown in Figure S3 in the Supplementary Appendix. For the year 1 data set, least-squares mean (±SE) changes in the score from baseline to month 6 (the coprimary end point) were 0.2±0.1 points in the 5-mg tofacitinib group (on the basis of data from 346 of 371 patients who were treated) and <0.1±0.1 points in the 10-mg tofacitinib group (on the basis of data from 369 of 395 patients), as compared with 0.8±0.2 points in the methotrexate group (on the basis of data from 166 of 186 patients) (P<0.001 for both comparisons) (Table 2). Likewise, least-squares mean changes from baseline in the modified total Sharp score at months 12 and 24 were significantly smaller in both tofacitinib groups than in the methotrexate group (P<0.001 for all comparisons) (Table 2). Patients in both tofacitinib groups had significantly less radiographic progression from baseline, as reflected by the modified Sharp scores for erosion and joint-space narrowing, than patients in the methotrexate group at months 6, 12, and 24 (Table 2, and Fig. S3C and S3D in the Supplementary Appendix). A longitudinal model in which missing values for the modified total Sharp score were not imputed showed results that were similar to those with the analysis-of-covariance model (Fig. S4 in the Supplementary Appendix).

Table 1. Baseline Characteristics of the Patients.*

Variable	Tofacitinib, 5 mg (N=373)	Tofacitinib, 10 mg (N=397)	Methotrexate (N=186)
Female sex — %	76.7	82.4	78.0
White race — %†	64.1	67.0	68.3
Mean age — yr	50.3	49.3	48.8
Mean duration of rheumatoid arthritis — yr	2.9	3.4	2.7
Tender and swollen joints — mean no.			
Tender	25.7	25.1	25.4
Swollen	16.3	15.6	16.8
Mean HAQ-DI score‡	1.5	1.5	1.5
Mean modified total Sharp score§	19.1	17.9	16.1
Mean erosion score¶	9.1	9.1	8.4
Mean joint-space narrowing score‖	10.0	8.8	7.7
DAS28-4(ESR)**			
Mean score	6.6	6.5	6.6
Score >5.1 — %	94.4	93.7	93.0
Erythrocyte sedimentation rate — mm/hr	55.6	53.4	56.0
Mean C-reactive protein level — mg/liter	22.7	20.3	25.9
Positive for rheumatoid factor — %	82.3	81.6	84.4
Positive for anti-CCP antibodies — %	85.0	81.1	86.6

* There were no significant differences among the groups at baseline. A more detailed version of this table is provided in Table S1 in the Supplementary Appendix. CCP denotes cyclic citrullinated peptide.
† Race was reported by the investigators.
‡ Health Assessment Questionnaire–Disability Index (HAQ-DI) scores of 0 to 1 indicate mild-to-moderate physical difficulty, more than 1 to 2 moderate-to-severe disability, and more than 2 to 3 severe-to-very-severe disability.
§ Modified total Sharp scores range from 0 to 448, with higher scores indicating greater structural joint damage.
¶ Erosion scores range from 0 to 280, with higher scores indicating greater erosive changes in the joints.
‖ Joint-space narrowing scores range from 0 to 168, with higher scores indicating greater narrowing between joints.
** The Disease Activity Score for 28-joint counts based on the erythrocyte sedimentation rate DAS28-4(ESR) ranges from 0 to 9.4, with higher scores indicating greater levels of disease activity (<2.6 indicates remission and ≤3.2 equals low disease activity).

Table 2. Coprimary and Secondary Efficacy End Points.*

Variable	Month 6			Month 12			Month 24		
	Tofacitinib, 5 mg (N=373)	Tofacitinib, 10 mg (N=397)	Methotrexate (N=186)	Tofacitinib, 5 mg (N=373)	Tofacitinib, 10 mg (N=397)	Methotrexate (N=186)	Tofacitinib, 5 mg (N=373)	Tofacitinib, 10 mg (N=397)	Methotrexate (N=186)
ACR 20 response — % of patients†	71.3‡	76.1‡	50.5	67.8‡	71.6‡	51.1	64.2‡	64.2‡	42.4
ACR 50 response — % of patients†	46.6‡	56.4‡	26.6	49.9‡	55.6‡	33.7	49.3‡	49.2‡	28.3
ACR 70 response — % of patients†§	25.5‡	37.7‡	12.0	28.7‡	38.1‡	15.2	34.4‡	37.6‡	15.2
DAS28-4(ESR) <2.6 — % of patients†	14.6¶	21.8‡	7.6	18.7¶	23.4‡	11.7	20.8‡	22.3‡	9.9
DAS28-4(ESR) ≤3.2 — % of patients†	27.8‡	38.2‡	14.0	33.3‡	41.1‡	18.7	34.8‡	36.0‡	15.8
Moderate or good EULAR response — % of patients†	79.0‡	84.1‡	60.8	76.6‡	79.6‡	59.7	68.7‡	69.6‡	49.1
No radiographic progression — % of patients‖	87.1‡	89.3‡	73.7	82.4¶	87.7‡	69.0	79.9‡	83.7‡	64.9
Mean change from baseline — points**‖									
Modified total Sharp score§‖	0.2‡	<0.1‡	0.8	0.4‡	0.2‡	1.2	0.6‡	0.3‡	2.1
Erosion score‖	0.1¶	0.1‡	0.4	0.1‡	0.1‡	0.6	0.2‡	0.2‡	1.0
Joint-space narrowing score‖	0.1¶	0.1¶	0.3	0.2¶	0.1¶	0.6	0.4¶	0.1‡	1.1
DAS28-4(ESR)††	−2.5‡	−2.9‡	−1.9	−2.8‡	−3.1‡	−2.2	−3.0‡	−3.2‡	−2.4
HAQ-DI††	−0.8‡	−0.9‡	−0.6	−0.9‡	−1.0‡	−0.7	−0.9‡	−1.0‡	−0.7

* A more detailed version of this table is provided in Table S2 in the Supplementary Appendix. All data were derived from the full (year 2) data set except for the coprimary end points (mean change from baseline in the modified total Sharp score and ACR 70 response at month 6), which were derived from the prespecified interim (year 1) data set. ACR denotes American College of Rheumatology, and EULAR European League against Rheumatism.

† Missing data were imputed with the use of nonresponse imputation.

‡ P<0.001 for the comparison with methotrexate.

§ Significance at month 6 (for the coprimary end points) was determined with the use of the step-down approach. More information is provided in Section 3 and Figure S1 in the Supplementary Appendix. For secondary end points, no adjustments were made for multiple comparisons; a P value of 0.05 or less was considered to indicate statistical significance.

¶ P≤0.05 for the comparison with methotrexate.

‖ No radiographic progression was defined as a change from baseline in the modified total Sharp score of 0.5 points or less. Missing data were imputed by means of linear extrapolation.

** The least-squares mean change from baseline was derived from an analysis-of-covariance or a mixed-effect longitudinal model.

†† This change was derived from a mixed-effect longitudinal model.

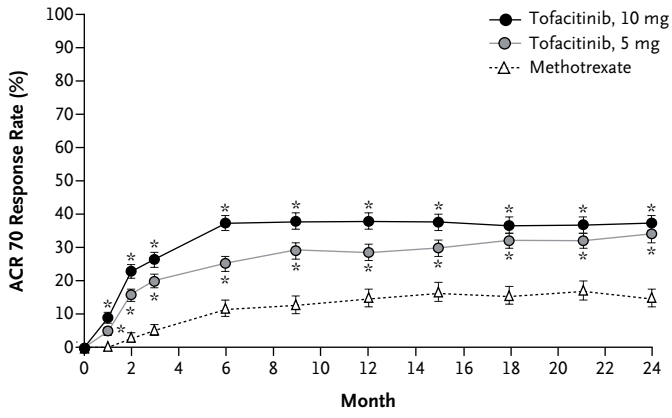

Figure 1. Clinical Responses over Time.

An American College of Rheumatology (ACR) 70 response is defined as at least a 70% reduction from baseline in the number of both tender and swollen joints, as well as at least a 70% improvement in three of five other criteria: the patient's assessment of pain, level of disability, C-reactive protein level or erythrocyte sedimentation rate, global assessment of disease by the patient, and global assessment of disease by the physician. The coprimary end point (the ACR 70 response at month 6) was derived from the prespecified interim (year 1) data set; the ACR 70 response over time was derived from the final (year 2) data set. Missing data were imputed with the use of nonresponse imputation. I bars indicate standard errors. Asterisks denote P<0.001 for the comparison with methotrexate.

The proportions of patients with no radiographic progression or erosion (≤0.5-unit increase from baseline in the modified total Sharp score or erosion score) at months 6, 12, and 24 in the 5-mg and 10-mg tofacitinib groups were significantly larger than the corresponding proportions of patients who received methotrexate (P≤0.05 for all comparisons) (Fig. S5 in the Supplementary Appendix). Cumulative probability plots showed that the distributions for the modified total Sharp score, the erosion score, and the score for joint-space narrowing at months 6, 12, and 24 were similar in the two tofacitinib groups and differed from the distributions in the methotrexate group (Fig. S6 in the Supplementary Appendix).

CLINICAL OUTCOMES

The mean (±SE) proportion of patients who had an ACR 70 response at month 6 (the coprimary end point) was 25.5±2.3% (94 of 369 patients) in the 5-mg tofacitinib group and 37.7±2.4% (148 of 393 patients) in the 10-mg tofacitinib group, as compared with 12.0±2.4% (22 of 184 patients) in the methotrexate group (P<0.001 for either dose vs. methotrexate) (Table 2). Additional data on coprimary and secondary end points at months 6, 12, and 24 are provided in Table S2 in the Supplementary Appendix. Significant improvements over time in the ACR 70 response (Fig. 1), ACR 20 response, and ACR 50 response (Table 2, and Fig. S7B and S7C in the Supplementary Appendix) were also observed with tofacitinib versus methotrexate. Mean changes from baseline in ACR core components at month 6 are shown in Table S3 in the Supplementary Appendix.

Rates of remission and low disease activity, as well as least-squares mean changes (improvements) from baseline, as defined according to the Disease Activity Score for 28-joint counts based on the erythrocyte sedimentation rate (DAS28-4[ESR]), were significantly higher at months 6, 12, and 24 among patients in both tofacitinib groups than among patients in the methotrexate group (Table 2, and Fig. S8 in the Supplementary Appendix). DAS28-4(ESR) scores range from 0 to 9.4, with higher scores indicating more disease activity (<2.6 indicates remission and ≤3.2 indicates low disease activity).

PHYSICAL FUNCTIONING AND OTHER PATIENT-REPORTED OUTCOMES

HAQ-DI scores of 0 to 1 indicate mild-to-moderate physical difficulty, more than 1 to 2 indicate moderate-to-severe disability, and more than 2 to 3 indicate severe-to-very-severe disability. The least-squares mean changes in HAQ-DI scores at month 6 were −0.8 points with the 5-mg dose of tofacitinib and −0.9 points with the 10-mg dose of tofacitinib, as compared with −0.6 points with methotrexate (P<0.001 for both comparisons). At month 12, the least-squares mean changes in HAQ-DI scores were −0.9 points with the 5-mg dose and −1.0 points with the 10-mg dose, as compared with −0.7 points with methotrexate (P<0.001 for both comparisons). At month 24, the least-squares mean changes in HAQ-DI scores were −0.9 points with the 5-mg dose and −1.0 points with the 10-mg dose, as compared with −0.7 points with methotrexate (P<0.001 for both comparisons) (Table 2).

The Functional Assessment of Chronic Illness Therapy (FACIT) fatigue instrument is a 13-item questionnaire with scores ranging from 0 to 52 and higher scores indicating less fatigue.

The least-squares mean changes from baseline at month 6 in FACIT–fatigue scores were 8.7 points with the 5-mg dose of tofacitinib and 9.1 points with the 10-mg dose, as compared with 6.3 points with methotrexate (P=0.003 and P<0.001, respectively). Greater reductions in arthritis pain and disease activity at month 6 were also reported by patients in both tofacitinib dose groups as compared with patients in the methotrexate group at month 6 (Table S3 in the Supplementary Appendix).

SAFETY

The most common category of adverse events was infections and gastrointestinal disorders. Herpes zoster infections occurred in 13 of 373 patients (3.5%) in the 5-mg tofacitinib group and in 18 of 397 patients (4.5%) in the 10-mg tofacitinib group — a total of 31 of 770 patients (4.0%) in the combined tofacitinib groups — as compared with 2 of 186 patients in the methotrexate group (1.1%) (Table S4 in the Supplementary Appendix). A total of 106 patients discontinued the study drug because of adverse events (Table 3), 105 patients (11.0%) had serious adverse events, and 24 patients (2.5%) had serious infections (see Table S5 in the Supplementary Appendix for a summary of serious adverse events observed). Six confirmed cases of cancer were reported: two (non-Hodgkin's lymphoma and chronic lymphocytic leukemia) in the 5-mg tofacitinib group, three (prostate cancer, Burkitt's B-cell lymphoma, and colon cancer) in the 10-mg tofacitinib group, and one (gastric cancer) in the methotrexate group. An adrenal adenoma with cellular atypia, which the local pathologist was unable to confirm as malignant or benign, was also reported in a 38-year-old man who received tofacitinib at a dose of 5 mg twice daily. All cancers are described in detail in Section 4 in the Supplementary Appendix. Four deaths occurred (two during the study and two after the study): one each from non-Hodgkin's lymphoma, cardiac failure, and sudden cardiac causes in the 5-mg tofacitinib group, and one from colon cancer in the 10-mg tofacitinib group. All four deaths are described in detail in Section 5 in the Supplementary Appendix.

Changes in laboratory test results are shown in Table 4 (and Table S6 in the Supplementary Appendix). At 24 months, decreases in mean absolute neutrophil counts and increases in mean serum creatinine levels were seen in all groups.

Table 3. Safety Data from Months 0 to 24.

Variable	Tofacitinib, 5 mg (N=373)	Tofacitinib, 10 mg (N=397)	Methotrexate (N=186)*
Adverse events — no.	1097	1435	561
Patients with adverse events — no. of patients (%)	297 (79.6)	334 (84.1)	147 (79.0)
Patients with serious adverse events — no. (%)	40 (10.7)	43 (10.8)	22 (11.8)
Patients with serious infection — no. (%)	11 (3.0)†	8 (2.0)‡	5 (2.7)§
Discontinuation of study drug because of adverse event — no. (%)	40 (10.7)	41 (10.3)	25 (13.4)
Confirmed cancer — no.¶	2	3	1
Death — no.‖	3	1	0

* The mean dose of methotrexate at the end of the adjustment period (month 3) was 18.5 mg per week.
† In the 5-mg tofacitinib group, serious infection events were pneumonia (in 2 patients), herpes zoster, dengue fever, gastrointestinal infection, gastroenteritis, pleural infection, subcutaneous abscess, tonsillitis bacterial infection, sepsis, and erysipelas.
‡ In the 10-mg tofacitinib group, serious infection events were bronchitis, pneumonia, herpes zoster, disseminated herpes zoster, gastroenteritis (in 2 patients), bone tuberculosis, and lower respiratory tract infection.
§ In the methotrexate group, serious infection events were nasopharyngitis, gastroenteritis, sialoadenitis, chronic hepatitis C, and varicella.
¶ An adrenal adenoma that was unconfirmed as malignant or benign was diagnosed in one additional patient, who received tofacitinib at a dose of 5 mg twice daily.
‖ One death (from colon cancer) in the 5-mg tofacitinib group and one death (from non-Hodgkin's lymphoma) in the 10-mg tofacitinib group occurred after the study.

Table 4. Laboratory Data at Month 24.

Variable	Tofacitinib, 5 mg (N=373)	Tofacitinib, 10 mg (N=397)	Methotrexate (N=186)*
Absolute neutrophil count, change from baseline — per mm³	−1260	−1610†	−1030
Absolute lymphocyte count, change from baseline — per mm³	−350‡	−440†	−220
Hemoglobin, change from baseline — g/dl§	0.57	0.24	0.30
Cholesterol, change from baseline — %			
Low-density lipoprotein	18.6†	21.6†	3.9
High-density lipoprotein	16.8†	17.4†	7.0
Serum creatinine, change from baseline — mg/dl	0.10†	0.10†	0.04
Absolute neutrophil count <1.5×10³/mm³ — no. of patients/total no. (%)	1/256 (<1.0)	5/278 (1.8)	0/102
Absolute lymphocyte count <1.5×10³/mm³ — no. of patients/total no. (%)	117/256 (45.7)	159/278 (57.2)	36/102 (35.3)

* The mean dose of methotrexate at the end of the adjustment period (month 3) was 18.5 mg per week. A more detailed version of this table is shown in Table S6 in the Supplementary Appendix.
† P<0.001 for the comparison with methotrexate.
‡ P≤0.05 for the comparison with methotrexate.
§ No comparison of tofacitinib versus methotrexate was available.

Serum creatinine levels increased from baseline by 33% or more in 37 of 373 patients who received 5 mg of tofacitinib (9.9%) and in 38 of 397 patients who received 10 mg of tofacitinib (9.6%), as compared with 5 of 186 patients who received methotrexate (2.7%). An increase in serum creatinine levels of more than 50% from baseline was confirmed by means of two consecutive tests in 6 patients in the 5-mg tofacitinib group and 11 patients in the 10-mg tofacitinib group, as compared with no patients in the methotrexate group. During months 0 to 24, mean low-density lipoprotein cholesterol levels increased by 18.6%, 21.6%, and 3.9% in the 5-mg tofacitinib group, the 10-mg tofacitinib group, and the methotrexate group, respectively; high-density lipoprotein cholesterol levels increased by 16.8%, 17.4%, and 7.0%, respectively. Increases in aspartate aminotransferase or alanine aminotransferase levels to 3 or more times the upper limit of the normal range were infrequent and similar in frequency across the groups (Table S7 in the Supplementary Appendix).

DISCUSSION

The minimal clinically important difference in the modified total Sharp score is reported to be 4.6 points,[21] which is 1% of the maximum score. In our study, the differences in the modified total Sharp score were smaller than the minimal clinically important difference and less than 1% of the maximum score. The range of changes observed was similar to those observed in other studies of biologic DMARDs.[10,22-24]

The results reported here contrast with the results of two trials of leflunomide at a dose of 20 mg per day as compared with methotrexate (to a maximum dose of 15 mg per week) in patients with long-standing rheumatoid arthritis. In one trial,[24] clinical, functional, and radiographic responses were similar with the two medications. In the second trial,[25] ACR responses were not reported, but improvement in tender and swollen joints, as well as patient's and physician's global assessments, were similar with the two treatments; methotrexate appeared to be more effective in decreasing radiographic progression. In a study of tocilizumab versus methotrexate,[26] tocilizumab monotherapy was associated with superior ACR 20, ACR 50, and ACR 70 responses as compared with methotrexate monotherapy, but radiographs were not obtained.

The structural joint preservation observed with tofacitinib monotherapy in our trial extends the results from the ORAL Scan study, which involved patients who had rheumatoid arthritis and an inadequate response to methotrexate. In that

study, tofacitinib was compared with placebo in patients who were receiving background methotrexate monotherapy.[17] Our findings further establish the structure-preserving effects of tofacitinib at a dose of 5 mg or 10 mg twice daily.

Our study also shows that a targeted small-molecule JAK inhibitor can be more effective clinically, functionally, and radiographically than methotrexate in patients with rheumatoid arthritis who have not previously received methotrexate. Combinations of nonbiologic or biologic DMARDs with methotrexate have been shown to be superior to methotrexate alone.[7,8,27-29] Two prior articles attempted to show the superiority of a biologic DMARD administered as monotherapy over methotrexate.[27,30] In the Early Rheumatoid Arthritis trial of etanercept versus methotrexate, in which a significantly greater proportion of patients who received etanercept at a dose of 25 mg twice weekly had ACR 20, ACR 50, or ACR 70 responses, as compared with patients who received methotrexate within the first 6 months, the differences were not significant at year 1 and thereafter (except for the ACR 20 response at year 2). The change from baseline in the modified total Sharp score at year 1 and year 2, however, was significantly smaller in the group of patients who received etanercept at a dose of 25 mg than in the group of patients who received methotrexate.[27,30]

The benefits of tofacitinib need to be considered in the context of the risks of adverse events. The most common serious adverse events in our study were infections; herpes zoster was reported more frequently in patients receiving tofacitinib than in those receiving methotrexate. Three cases of lymphoma were reported among patients who received tofacitinib. As previously reported and as seen in this study, tofacitinib was associated with decreases in neutrophil and lymphocyte counts and increases in lipid, aminotransferase, and creatinine levels. Although the clinical relevance of the lipid changes is unclear, monitoring of lipids and, when needed, appropriate intervention, including the use of lipid-lowering agents, may be warranted.[31] The mechanism behind the increase in creatinine levels is unknown, but it may involve the effects of tofacitinib on inflammation.[32]

The limitations of this study include an inability to adjust medication more frequently than every 3 months, as has been recommended.[6] Study participants who have not previously received methotrexate are not necessarily patients who have early rheumatoid arthritis (unless the protocol mandates this criterion for inclusion). In our trial, the interval between diagnosis of rheumatoid arthritis and enrollment was less than 2 years for the majority of patients (65.5%) and was less than 6 months (median range, 0.7 to 0.8 years) in 40.0% of the patients. Nonetheless, the mean duration of disease in this trial was approximately 3 years, so a more focused assessment of tofacitinib for the treatment of early rheumatoid arthritis would require a separate trial.

In conclusion, this phase 3 study involving patients with active rheumatoid arthritis who had not previously received methotrexate or therapeutic doses of methotrexate showed that, over a 2-year period of treatment, tofacitinib monotherapy at a dose of 5 or 10 mg twice daily was associated with significant reductions in signs and symptoms of rheumatoid arthritis, improvements in physical functioning, and modest, but larger, reductions in the progression of structural damage, as compared with methotrexate (mean dose, 18.5 mg per week). Tofacitinib was associated with reductions in neutrophil and lymphocyte counts and increases in low-density lipoprotein cholesterol and creatinine levels and infections. Results at 12 and 24 months were similar.

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