ORIGINAL ARTICLE

Cardiovascular and Cancer Risk with Tofacitinib in Rheumatoid Arthritis

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ABSTRACT

BACKGROUND

Increases in lipid levels and cancers with tofacitinib prompted a trial of major adverse cardiovascular events (MACE) and cancers in patients with rheumatoid arthritis receiving tofacitinib as compared with a tumor necrosis factor (TNF) inhibitor.

METHODS

We conducted a randomized, open-label, noninferiority, postauthorization, safety end-point trial involving patients with active rheumatoid arthritis despite methotrexate treatment who were 50 years of age or older and had at least one additional cardiovascular risk factor. Patients were randomly assigned in a 1:1:1 ratio to receive tofacitinib at a dose of 5 mg or 10 mg twice daily or a TNF inhibitor. The coprimary end points were adjudicated MACE and cancers, excluding nonmelanoma skin cancer. The noninferiority of tofacitinib would be shown if the upper boundary of the two-sided 95% confidence interval for the hazard ratio was less than 1.8 for the combined tofacitinib doses as compared with a TNF inhibitor.

RESULTS

A total of 1455 patients received tofacitinib at a dose of 5 mg twice daily, 1456 received tofacitinib at a dose of 10 mg twice daily, and 1451 received a TNF inhibitor. During a median follow-up of 4.0 years, the incidences of MACE and cancer were higher with the combined tofacitinib doses (3.4% [98 patients] and 4.2% [122 patients], respectively) than with a TNF inhibitor (2.5% [37 patients] and 2.9% [42 patients]). The hazard ratios were 1.33 (95% confidence interval [CI], 0.91 to 1.94) for MACE and 1.48 (95% CI, 1.04 to 2.09) for cancers; the noninferiority of tofacitinib was not shown. The incidences of adjudicated opportunistic infections (including herpes zoster and tuberculosis), all herpes zoster (nonserious and serious), and adjudicated nonmelanoma skin cancer were higher with tofacitinib than with a TNF inhibitor. Efficacy was similar in all three groups, with improvements from month 2 that were sustained through trial completion.

CONCLUSIONS

In this trial comparing the combined tofacitinib doses with a TNF inhibitor in a cardiovascular risk–enriched population, risks of MACE and cancers were higher with tofacitinib and did not meet noninferiority criteria. Several adverse events were more common with tofacitinib. (Funded by Pfizer; ORAL Surveillance ClinicalTrials.gov number, NCT02092467.)

Rheumatoid arthritis is a systemic, chronic, immune-mediated inflammatory disorder.[1] Treatments include conventional synthetic disease-modifying antirheumatic drugs (DMARDs); biologic DMARDs, such as tumor necrosis factor (TNF) inhibitors; and targeted synthetic DMARDs.[2,3] However, these drugs are associated with potentially serious adverse events.[4-11]

Tofacitinib is a targeted synthetic DMARD that selectively inhibits Janus kinase (JAK)1, JAK3, and, to a lesser extent, JAK2[12,13] and is approved for the treatment of rheumatoid arthritis by the Food and Drug Administration (FDA) at doses of 5 mg twice daily or 11 mg once daily (extended-release formulation). During drug development, increases in serum lipid levels and the incidence of cancers, including lymphoma, were observed,[14-16] which prompted the FDA to require a prospective, head-to-head safety trial comparing tofacitinib with TNF inhibitors.

We report results from the Oral Rheumatoid Arthritis Trial (ORAL) Surveillance, a randomized, postauthorization, noninferiority trial evaluating the safety and efficacy of tofacitinib as compared with a TNF inhibitor in patients with rheumatoid arthritis who were 50 years of age or older and had at least one additional cardiovascular risk factor. This noninferiority trial assessed the hypothesis that the risk of major adverse cardiovascular events (MACE) or cancers, excluding nonmelanoma skin cancer, would not be at least 1.8 times higher with tofacitinib (combined doses of 5 mg and 10 mg twice daily) than with a TNF inhibitor in this patient population.

Methods

Patients

We enrolled patients with active rheumatoid arthritis despite methotrexate treatment who were 50 years of age or older and had at least one additional cardiovascular risk factor (current cigarette smoker, hypertension, high-density lipoprotein cholesterol level of <40 mg per deciliter, diabetes mellitus, family history of premature coronary heart disease, extraarticular rheumatoid arthritis, or history of coronary artery disease). A key exclusion criteria was current or previous cancer, except adequately treated nonmelanoma skin cancer. Full eligibility criteria are provided in the Supplementary Appendix, available with the full text of this article at NEJM.org.

Trial Design

A Quick Take is available at NEJM.org

ORAL Surveillance was a randomized, open-label, noninferiority, phase 3b–4 safety end-point trial. Patients were randomly assigned in a 1:1:1 ratio, with the use of an automated Web and telephone system, to receive open-label oral tofacitinib at a dose of 5 mg or 10 mg twice daily or a subcutaneous TNF inhibitor (adalimumab at a dose of 40 mg every 2 weeks [in North America, including the United States, Puerto Rico, and Canada] or etanercept at a dose of 50 mg once weekly [in the rest of the world]); background methotrexate was continued, unless modification was clinically indicated. Details of concomitant rheumatoid arthritis medications are provided in the Supplementary Appendix. Patients could discontinue the trial drug for less than 2 months for safety issues. All the patients, including those who permanently discontinued the trial drug, were asked to continue to participate in the trial through its completion.

The first patient was enrolled in March 2014. In February 2019, the tofacitinib dose of 10 mg twice daily was reduced to 5 mg twice daily after the data and safety monitoring board noted a higher frequency of pulmonary embolism among patients receiving tofacitinib at a dose of 10 mg twice daily than among those receiving a TNF inhibitor. In addition, the board noted a higher mortality with tofacitinib at a dose of 10 mg twice daily than with tofacitinib at a dose of 5 mg twice daily or with a TNF inhibitor.

Trial Oversight

The trial was conducted in compliance with the Declaration of Helsinki, the Good Clinical Practice guidelines of the International Council for Harmonisation, and local regulations. Patients provided written, informed consent. The protocol, amendments, and consent documentation were approved by the institutional review board or independent ethics committee at each center. The protocol and statistical analysis plan are available at NEJM.org.

The trial was sponsored by Pfizer, which provided the trial medication. Sponsor employees and the academic authors designed the trial with the FDA. An external steering committee whose members were unaware of the trial-group assign-

ments oversaw the conduct of the trial. An external data and safety monitoring board whose members were aware of the trial-group assignments provided recommendations on trial-conduct alterations to the steering committee and sponsor on the basis of ongoing safety monitoring. External committees adjudicated the coprimary end points and other adverse events of special interest (see the Supplementary Appendix). A contract research organization (ICON) collected the data, and sponsor employees and the academic authors analyzed and interpreted the data and vouch for its completeness and accuracy. The first draft of the manuscript was written by the academic authors without input from the sponsor or other writers. Editorial support was subsequently provided by CMC Connect and funded by Pfizer.

TRIAL END POINTS

The coprimary end points were adjudicated MACE (death from cardiovascular causes, nonfatal myocardial infarction, or nonfatal stroke) and cancers, excluding nonmelanoma skin cancer. Secondary safety end points included adverse events of special interest (serious infections; adjudicated opportunistic infections, including herpes zoster and tuberculosis; all herpes zoster [nonserious and serious]; adjudicated hepatic events; adjudicated nonmelanoma skin cancer; adjudicated deaths from any cause; adjudicated venous thromboembolism, including deep-vein thrombosis and pulmonary embolism; all arterial thromboembolism; and adjudicated cardiovascular events other than MACE), all adverse events, serious adverse events, clinically significant laboratory abnormalities, adverse events leading to permanent or temporary discontinuations of a trial medication, serum lipid levels, and blood pressure levels. Additional adverse events of special interest included adjudicated interstitial lung disease and adjudicated gastrointestinal perforations.

Secondary efficacy end points and patient-reported outcomes, including the change from baseline in the Simplified Disease Activity Index (SDAI) score[17-19] and the Health Assessment Questionnaire–Disability Index (HAQ-DI) score[20] and the percentages of patients with SDAI-defined low disease activity (score of ≤11)[21] and remission (score of ≤3.3),[21] were assessed at baseline and scheduled follow-up visits. All secondary efficacy end points and patient-reported outcomes are listed in the protocol. Adverse events were recorded on the adverse-event case-report form and presented according to the system organ class and preferred terms in the *Medical Dictionary for Regulatory Activities*, version 23.1. (For details on the trial end points, see the Supplementary Appendix.)

STATISTICAL ANALYSIS

We calculated that approximately 4000 patients, with 1500 or more patients completing 3 years of follow-up, were required to achieve the prespecified number of events: 103 MACE and 138 cancers to achieve 80% and 90% power, respectively, assuming that the rates were 1.0 and 1.1 events per 100 patient-years, respectively. (For details, see the Supplementary Appendix.) The estimated trial duration was 5 years.

Hazard ratios for each tofacitinib dose relative to a TNF inhibitor were estimated, with two-sided 95% confidence intervals, based on two Cox proportional-hazards models (for comparing the combined tofacitinib doses with a TNF inhibitor and for pairwise comparisons among treatment groups), with treatment as the covariate. Noninferiority would be shown if the upper limit of the two-sided 95% confidence interval for the hazard ratio was less than 1.8 for the combined tofacitinib doses as compared with a TNF inhibitor (primary comparison) or less than 2.0 for tofacitinib at a dose of 10 mg twice daily as compared with a dose of 5 mg twice daily (secondary comparison).[22] Crude incidence rates were expressed in patients with first events per 100 patient-years, with two-sided 95% confidence intervals.[23] According to the protocol, no multiplicity adjustments were applied. P values, without adjustment for multiplicity, were produced for the coprimary end points (post hoc).

Safety end points were analyzed in the safety analysis population, which included all the patients who had undergone randomization and received at least one dose of a trial drug. Patients were analyzed in their originally assigned group, including those required to switch the tofacitinib dose from 10 mg twice daily to 5 mg twice daily in February 2019. In the group assigned to receive tofacitinib at a dose of 10 mg twice daily, the treatment period included the time after

patients had been switched to 5 mg twice daily. For MACE, the primary censoring time was the 60-day on-treatment time, defined as the time from the first dose of a trial drug until the end of the risk period (i.e., last contact date or last trial dose plus 60 days, whichever was earliest). For cancers, the primary censoring time was total time, defined as the time from the first dose of a trial drug until the last contact date. The last contact date was the latest of the following: the start date of an adverse event, the end date of an adverse event, the date of the last trial visit, the withdrawal date, the telephone-contact date, or the date of death.

The number needed to harm was calculated post hoc for each tofacitinib dose. It was defined as the reciprocal of the difference in incidence rates between tofacitinib and a TNF inhibitor and interpreted as the number of patient-years of exposure to tofacitinib required to have one additional adverse event, relative to a TNF inhibitor.[24] Additional details of secondary safety and efficacy end points, the efficacy population, subgroup analyses, supportive and sensitivity analyses for the coprimary end points (including analyses with data censored after patients had switched the tofacitinib dose from 10 mg twice daily to 5 mg twice daily in February 2019), and supportive analyses for the efficacy end points are provided in the Supplementary Appendix.

RESULTS

PATIENTS

The trial was conducted at 323 sites in 30 countries from March 2014 through July 2020. Of 6559 patients screened, 4362 underwent randomization and received a trial drug: 1455 received tofacitinib at a dose of 5 mg twice daily, 1456 received tofacitinib at a dose of 10 mg twice daily, and 1451 received a TNF inhibitor (Fig. S1 in the Supplementary Appendix). Patients received tofacitinib at a dose of 5 mg or 10 mg twice daily or a TNF inhibitor for 5073.49, 4773.41, or 4940.72 patient-years, respectively, up to the last dose of a trial treatment, with a mean (±SD) duration of treatment of 41.14±17.48, 38.53±18.76, and 40.24±18.04 months (Table S1). The demographic and clinical characteristics of the patients at baseline were generally similar across trial groups (Tables 1 and S2). At baseline, 31.0% of the patients were 65 years of age or older, the mean disease duration was more than 10 years, and 48.2% of the patients had ever smoked.

PRIMARY END POINTS

Adjudicated MACE

During a median follow-up of 4.0 years, the incidence of MACE was higher with the combined tofacitinib doses (3.4%; 98 patients) than with a TNF inhibitor (2.5%; 37 patients). Noninferiority was not shown for the combined tofacitinib doses as compared with a TNF inhibitor (hazard ratio, 1.33; 95% confidence interval [CI], 0.91 to 1.94), because the upper boundary of the 95% confidence interval was more than 1.8 (Fig. 1A). In comparisons between tofacitinib doses, noninferiority was shown for tofacitinib at a dose of 10 mg twice daily as compared with 5 mg twice daily (hazard ratio, 1.15; 95% CI, 0.77 to 1.71), because the upper boundary of the 95% confidence interval was less than 2.0. MACE incidence rates are reported in Figure 1B. Per-protocol analyses and analyses that accounted for competing risks supported the findings of the primary and secondary comparisons (Fig. S2A and S2B and Table S3). Sensitivity analyses with follow-up censored after patients receiving tofacitinib at a dose of 10 mg twice daily had been switched to 5 mg twice daily supported the findings of the primary comparison, and noninferiority was not shown for tofacitinib at a dose of 10 mg twice daily as compared with 5 mg twice daily (Fig. S3A and S3B). The most common cases of MACE were nonfatal myocardial infarction with tofacitinib and nonfatal stroke with a TNF inhibitor.

Over a period of 5.5 years, the cumulative estimated probability of MACE was 5.8% with the combined tofacitinib doses and 4.3% with a TNF inhibitor (Fig. S4A). The cumulative estimated probability of nonfatal myocardial infarction was 2.2% and 0.7%, respectively (Fig. S4B).

In subgroup analyses, the incidence rates of MACE were higher across trial groups among patients 65 years of age or older than among those younger than 65 years of age and higher with both tofacitinib doses than with a TNF inhibitor among patients 65 years of age or older (Fig. S5A and S5B). Incidence rates were also higher among patients in North America than

Table 1. Demographic and Clinical Characteristics of the Patients at Baseline (Safety Analysis Population).*

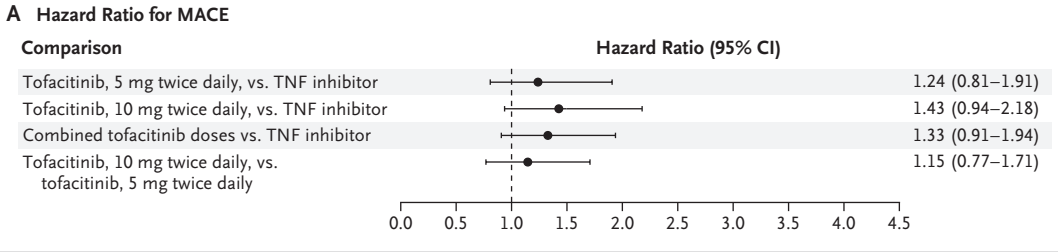
Characteristic	Tofacitinib, 5 mg Twice Daily (N=1455)	Tofacitinib, 10 mg Twice Daily (N=1456)†	TNF Inhibitor (N=1451)	Total (N=4362)
Age				
Mean — yr	60.8±6.8	61.4±7.1	61.3±7.5	61.2±7.1
≥65 yr — no. (%)	413 (28.4)	478 (32.8)	462 (31.8)	1353 (31.0)
Female sex — no. (%)	1169 (80.3)	1124 (77.2)	1117 (77.0)	3410 (78.2)
Race — no. (%)‡				
White	1128 (77.5)	1126 (77.3)	1099 (75.7)	3353 (76.9)
Black	63 (4.3)	65 (4.5)	83 (5.7)	211 (4.8)
Asian	65 (4.5)	56 (3.8)	55 (3.8)	176 (4.0)
Other	199 (13.7)	209 (14.4)	214 (14.7)	622 (14.3)
Smoking status — no. (%)				
Never smoked	735 (50.5)	752 (51.6)	772 (53.2)	2259 (51.8)
Ever smoked	720 (49.5)	704 (48.4)	679 (46.8)	2103 (48.2)
History of hypertension — no. (%)	955 (65.6)	954 (65.5)	969 (66.8)	2878 (66.0)
History of diabetes mellitus — no. (%)	243 (16.7)	261 (17.9)	255 (17.6)	759 (17.4)
History of venous thromboembolism — no. (%)§	19 (1.3)	33 (2.3)	27 (1.9)	79 (1.8)
History of extraarticular disease — no. (%)¶	532 (36.6)	521 (35.8)	552 (38.0)	1605 (36.8)
History of coronary heart disease — no. (%)	161 (11.1)	172 (11.8)	164 (11.3)	497 (11.4)
Family history of coronary heart disease — no. (%)				
First-degree male relative <55 yr of age	154 (10.6)	132 (9.1)	151 (10.4)	437 (10.0)
First-degree female relative <65 yr of age	115 (7.9)	107 (7.3)	100 (6.9)	322 (7.4)
Fasting HDL cholesterol <40 mg/dl — no. (%)	172 (11.8)	195 (13.4)	173 (11.9)	540 (12.4)

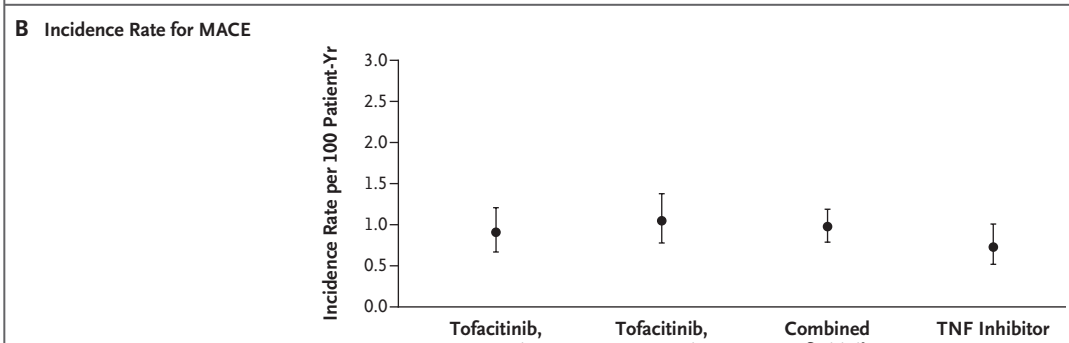
* Plus–minus values are means ±SD. Percentages may not total 100 because of rounding. HDL denotes high-density lipoprotein, and TNF tumor necrosis factor.
† Patients assigned to receive tofacitinib at a dose of 10 mg twice daily who had their dose reduced to 5 mg twice daily or who discontinued the trial drug were counted in the group receiving 10 mg twice daily.
‡ Race was reported by the patient.
§ Venous thromboembolism included deep-vein thrombosis and pulmonary embolism.
¶ Extraarticular disease included nodules, Sjögren's syndrome, anemia of chronic disease, pulmonary manifestations, or other clinical features as identified by the site investigator.

among those in the rest of the world across trial groups (Fig. S5C and S5D), which possibly corresponded with increased risk factors among patients in North America (Table S4).

Adjudicated Cancers

During a median follow-up of 4.0 years, the incidence of cancers (excluding nonmelanoma skin cancer) was higher with the combined tofacitinib doses (4.2%; 122 patients) than with a TNF inhibitor (2.9%; 42 patients). Noninferiority was not shown for the combined tofacitinib doses as compared with a TNF inhibitor (hazard ratio, 1.48; 95% CI, 1.04 to 2.09), because the upper boundary of the 95% confidence interval was more than 1.8 (Fig. 2A). In comparisons between tofacitinib doses, noninferiority was shown for 10 mg twice daily as compared with 5 mg twice daily (hazard ratio, 1.00; 95% CI, 0.70 to 1.43), because the upper boundary of the 95% confidence interval was less than 2.0. Incidence rates of cancers are shown in Figure 2B. Per-protocol, competing-risk, and censoring sensitivity analyses supported the finding of the primary and secondary comparisons (Fig. S2C and S2D, Fig. S3C and S3D, and Table S3). The most common cancers were lung cancer with tofacitinib and breast cancer with a TNF inhibitor.





	Tofacitinib, 5 mg Twice Daily	Tofacitinib, 10 mg Twice Daily	Combined Tofacitinib Doses	TNF Inhibitor
No. of Patients with First Event/Total No. (%)	47/1455 (3.2)	51/1456 (3.5)	98/2911 (3.4)	37/1451 (2.5)
No. of Patient-Yr	5166.32	4871.96	10,038.28	5045.27
Incidence Rate per 100 Patient-Yr (95% CI)	0.91 (0.67–1.21)	1.05 (0.78–1.38)	0.98 (0.79–1.19)	0.73 (0.52–1.01)
NNH (patient-yr) vs. TNF Inhibitor	567	319	—	—
NNH (over 5-yr period) vs. TNF Inhibitor	113	64	—	—

Figure 1. Hazard Ratios and Incidence Rates for Adjudicated MACE (Safety Analysis Population, 60-Day On-Treatment Time).

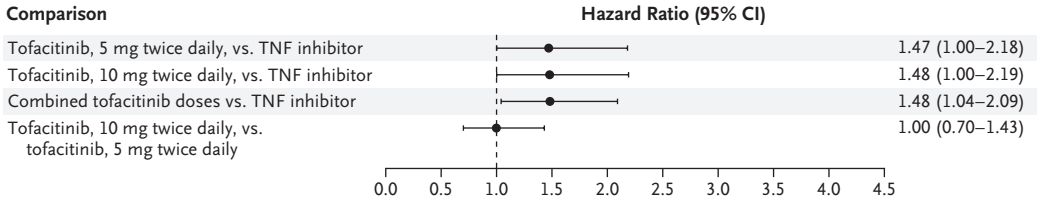
For patients assigned to receive tofacitinib at a dose of 10 mg twice daily who had their dose reduced to 5 mg twice daily, the data collected after patients had been switched to 5 mg twice daily were counted in the group receiving 10 mg twice daily. The number needed to harm (NNH) was the number of patient-years of exposure to tofacitinib required to have one additional major adverse cardiovascular event (MACE), relative to a tumor necrosis factor (TNF) inhibitor; calculations were performed post hoc. The NNH over a period of 5 years was the number of patients who would need to be treated for that duration with tofacitinib rather than with a TNF inhibitor to result in one additional MACE; calculations were performed post hoc. P values for the testing of the null hypotheses of no difference between treatments were for hypothesis generation and descriptive purposes only (post hoc). The P values were 0.14 for the combined tofacitinib doses as compared with a TNF inhibitor, 0.48 for tofacitinib at a dose of 10 mg twice daily as compared with tofacitinib at a dose of 5 mg twice daily, 0.33 for tofacitinib at a dose of 5 mg twice daily as compared with a TNF inhibitor, and 0.10 for tofacitinib at a dose of 10 mg twice daily as compared with a TNF inhibitor. The I bars represent 95% confidence intervals.

Over a period of 5.5 years, the estimated cumulative probability of cancers was 6.1% with the combined tofacitinib doses and 3.8% with a TNF inhibitor (Fig. S4C). The incidence rates of cancer were higher among patients 65 years of age or older than among those younger than 65 years of age and higher among those in North America than among those in the rest of the world (Fig. S6). The incidence rate was higher with tofacitinib than with a TNF inhibitor in North America.

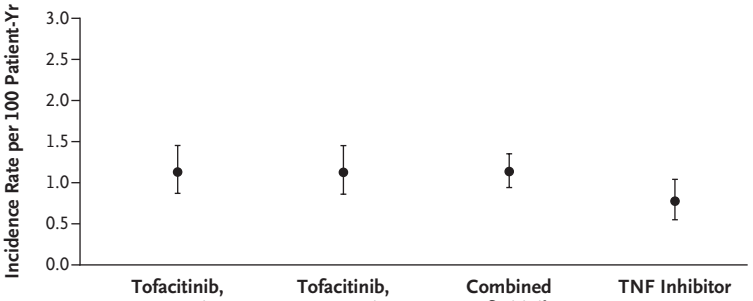
SECONDARY SAFETY END POINTS

The most frequent adverse events and serious adverse events that emerged or worsened during treatment according to system organ class were infections and infestations. Upper respiratory tract infections, bronchitis, and urinary tract infections were the most common adverse events, and pneumonia the most common serious adverse event, across trial groups (Tables S5 and S6). Clinical laboratory abnormalities are described in the Supplementary Appendix, including in Table S7.

A Hazard Ratio for Cancers, Excluding NMSC



B Incidence Rate for Cancers, Excluding NMSC



	Tofacitinib, 5 mg Twice Daily	Tofacitinib, 10 mg Twice Daily	Combined Tofacitinib Doses	TNF Inhibitor
No. of Patients with First Event/Total No. (%)	62/1455 (4.3)	60/1456 (4.1)	122/2911 (4.2)	42/1451 (2.9)
No. of Patient-Yr	5491.48	5311.71	10,803.19	5482.30
Incidence Rate per 100 Patient-Yr (95% CI)	1.13 (0.87–1.45)	1.13 (0.86–1.45)	1.13 (0.94–1.35)	0.77 (0.55–1.04)
NNH (patient-yr) vs. TNF Inhibitor	276	275	—	—
NNH (over 5-yr period) vs. TNF Inhibitor	55	55	—	—

Figure 2. Hazard Ratios and Incidence Rates for Adjudicated Cancers, Excluding NMSC (Safety Analysis Population, Total-Time Analysis).

For patients assigned to receive tofacitinib at a dose of 10 mg twice daily who had their dose reduced to 5 mg twice daily, the data collected after patients had been switched to 5 mg twice daily were counted in the group receiving 10 mg twice daily. The NNH was the number of patient-years of exposure to tofacitinib required to have one additional cancer, relative to a TNF inhibitor; calculations were performed post hoc. The NNH over a period of 5 years was the number of patients who would need to be treated for that duration with tofacitinib rather than with a TNF inhibitor to result in one additional cancer; calculations were performed post hoc. P values for the testing of the null hypotheses of no difference between treatments were for hypothesis generation and descriptive purposes only (post hoc). The P values were 0.03 for the combined tofacitinib doses as compared with a TNF inhibitor, 0.99 for tofacitinib at a dose of 10 mg twice daily as compared with tofacitinib at a dose of 5 mg twice daily, 0.05 for tofacitinib at a dose of 5 mg twice daily as compared with a TNF inhibitor, and 0.05 for tofacitinib at a dose of 10 mg twice daily as compared with a TNF inhibitor. The I bars represent 95% confidence intervals. NMSC denotes nonmelanoma skin cancer.

Serious adverse events and temporary or permanent discontinuations of a trial treatment due to adverse events are shown in Table 2. Adverse events (according to system organ class) leading to permanent discontinuation of a trial treatment are shown in Table S8.

Hazard ratios and incidence rates for adverse events of special interest and additional adverse events of interest are shown in Tables 2, S9, and S10. Serious infections were more frequent with tofacitinib at a dose of 10 mg twice daily than with a TNF inhibitor. Adjudicated opportunistic infections (including herpes zoster and tuberculosis) were more frequent with both tofacitinib doses than with a TNF inhibitor, primarily owing to the incidence of herpes zoster. All herpes zoster (nonserious and serious) and adjudicated herpes zoster were also more frequent with both tofacitinib doses than with a TNF inhibitor. Additional details about herpes zoster cases are provided in the Supplementary Appendix.

Adjudicated hepatic events were more frequent with tofacitinib at a dose of 10 mg twice daily than with a TNF inhibitor, primarily owing

Table 2. Adverse Events (Safety Analysis Population, 28-Day On-Treatment Time).*

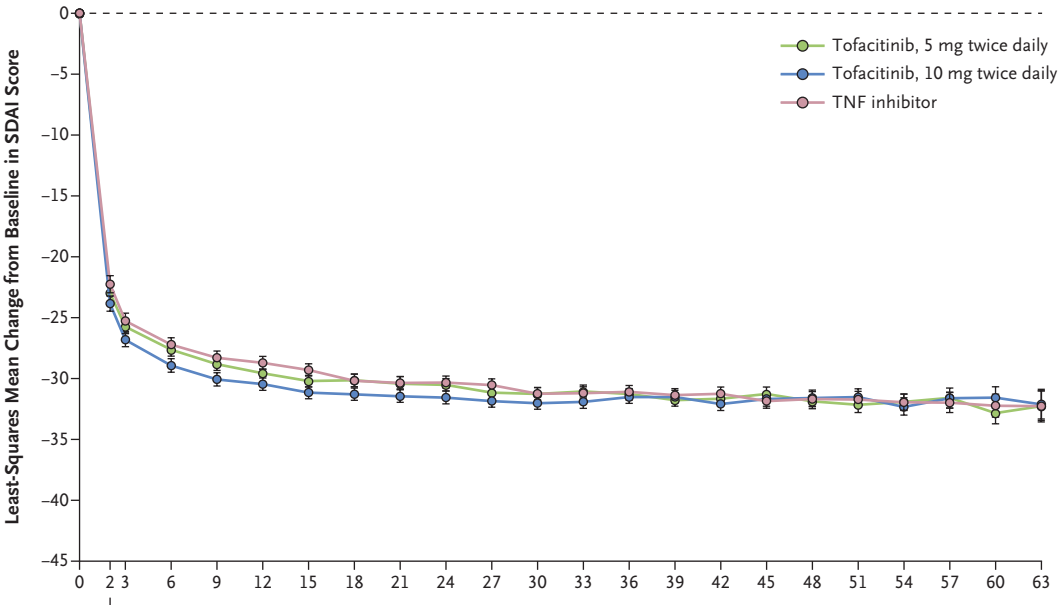
Event	Tofacitinib, 5 mg Twice Daily (N=1455)	Tofacitinib, 10 mg Twice Daily (N=1456)†	TNF Inhibitor (N=1451)
Adverse event — no. (%)	1333 (91.6)	1344 (92.3)	1308 (90.1)
Serious adverse event — no. (%)	351 (24.1)	390 (26.8)	306 (21.1)
Discontinuation of trial treatment due to adverse event — no. (%)			
Permanent discontinuation‡	210 (14.4)	304 (20.9)	210 (14.5)
Temporary discontinuation§	665 (45.7)	736 (50.5)	576 (39.7)
Adverse events of special interest			
Serious infection — no. (%)	141 (9.7)	169 (11.6)	119 (8.2)
Hazard ratio vs. TNF inhibitor (95% CI)	1.17 (0.92–1.50)	1.48 (1.17–1.87)	Referent
Adjudicated opportunistic infection — no. (%)¶	39 (2.7)	44 (3.0)	21 (1.4)
Hazard ratio vs. TNF inhibitor (95% CI)	1.82 (1.07–3.09)	2.17 (1.29–3.66)	Referent
All herpes zoster, serious and nonserious — no. (%)‖	180 (12.4)	178 (12.2)	58 (4.0)
Hazard ratio vs. TNF inhibitor (95% CI)	3.28 (2.44–4.41)	3.39 (2.52–4.55)	Referent
Adjudicated hepatic event — no. (%)	46 (3.2)	72 (4.9)	35 (2.4)
Hazard ratio vs. TNF inhibitor (95% CI)	1.29 (0.83–2.00)	2.14 (1.43–3.21)	Referent
Adjudicated NMSC — no. (%)	31 (2.1)	33 (2.3)	16 (1.1)
Hazard ratio vs. TNF inhibitor (95% CI)	1.90 (1.04–3.47)	2.16 (1.19–3.92)	Referent
Adjudicated pulmonary embolism — no. (%)	9 (0.6)	24 (1.6)	3 (0.2)
Hazard ratio vs. TNF inhibitor (95% CI)	2.93 (0.79–10.83)	8.26 (2.49–27.43)	Referent
Adjudicated DVT — no. (%)	11 (0.8)	15 (1.0)	7 (0.5)
Hazard ratio vs. TNF inhibitor (95% CI)	1.54 (0.60–3.97)	2.21 (0.90–5.43)	Referent
Adjudicated VTE — no. (%)	17 (1.2)	34 (2.3)	10 (0.7)
Hazard ratio vs. TNF inhibitor (95% CI)	1.66 (0.76–3.63)	3.52 (1.74–7.12)	Referent
Adjudicated death from any cause — no. (%)	26 (1.8)	39 (2.7)	17 (1.2)
Hazard ratio vs. TNF inhibitor (95% CI)	1.49 (0.81–2.74)	2.37 (1.34–4.18)	Referent

* Shown are adverse events that emerged or worsened during the 28-day on-treatment period, which was defined as the minimum of the date of last contact or the date of the last dose of a trial treatment plus 28 days. DVT denotes deep-vein thrombosis, NMSC nonmelanoma skin cancer, and VTE venous thromboembolism.
† For patients assigned to receive tofacitinib at a dose of 10 mg twice daily who had their dose reduced to 5 mg twice daily, the data collected after patients had been switched to 5 mg twice daily were counted in the group receiving 10 mg twice daily.
‡ Data are based on the adverse-event and disposition case-report forms.
§ At the discretion of the investigator, discontinuations of trial medication were allowed, not to exceed 2 months, for safety issues.
¶ Also included are opportunistic herpes zoster and tuberculosis events.
‖ Included are herpes zoster adjudicated as an opportunistic infection and nonadjudicated herpes zoster events.

to greater abnormalities on liver-function tests with tofacitinib than with a TNF inhibitor (Tables 2 and S11). No events were adjudicated as being definite or highly likely cases of drug-induced liver injury.

Adjudicated nonmelanoma skin cancer was more frequent with both tofacitinib doses than with a TNF inhibitor. Adjudicated venous thromboembolism and death from any cause were more frequent with tofacitinib at a dose of 10 mg twice daily than with a TNF inhibitor. Hazard ratios for adjudicated pulmonary embolism were more than 1, but 95% confidence intervals were wide. The main cause of adjudicated death across trial groups was cardiovascular events (Table S12).

Adverse events of special interest were generally similar between tofacitinib doses, except for



No. of Patients with Observations																						
Tofacitinib, 5 mg twice daily	1272	1321	1288	1244	1215	1172	1149	1138	1092	1056	1046	1027	994	954	819	692	547	438	347	253	174	102
Tofacitinib, 10 mg twice daily	1257	1280	1245	1204	1168	1128	1085	1040	1010	979	970	947	917	857	733	617	485	406	316	235	179	107
TNF inhibitor	1258	1273	1244	1197	1143	1129	1092	1072	1051	1002	996	997	978	920	800	646	522	400	314	242	161	95

Figure 3. Least-Squares Mean Change from Baseline in SDAI Score (Full Analysis Population, On-Treatment Time).

Simplified Disease Activity Index (SDAI) scores range from 0 to 100, with higher scores indicating more disease activity.[17-19] For patients assigned to receive tofacitinib at a dose of 10 mg twice daily who had their dose reduced to 5 mg twice daily, the data collected after patients had been switched to 5 mg twice daily were counted in the group receiving 10 mg twice daily. Data were derived from a mixed model for repeated measures, with fixed effects for trial group, visit, interaction between trial group and visit, baseline value, and interaction between baseline value and visit, without imputation for missing values. A common heterogeneous compound symmetry covariance matrix was used. The 95% confidence intervals (indicated by I bars) for all efficacy data were not adjusted for multiplicity and therefore should not be used to infer treatment effects. On-treatment time includes data on or before the trial treatment end date. Only visits with more than 50 patients for each treatment group were included.

serious infections, adjudicated hepatic events, pulmonary embolism, and venous thromboembolism, which were more frequent with 10 mg twice daily. Serum lipid levels were higher with both tofacitinib doses than with a TNF inhibitor through trial completion (Figs. S7 and S8); blood pressure values were generally similar across trial groups (Fig. S9).

EFFICACY END POINTS AND PATIENT-REPORTED OUTCOMES

Efficacy was similar across treatments, with decreases (improvements) in the SDAI score and the HAQ-DI score and increases in the incidence of SDAI-defined low disease activity and remission observed from month 2 (first postbaseline assessment) and sustained through trial completion (Figs. 3 and S10). Post hoc supportive analyses that accounted for missing values yielded similar results for the incidence of SDAI-defined low disease activity and remission (Fig. S11). Similar improvements were observed for all other efficacy end points and patient-reported outcomes (data not shown).

DISCUSSION

MACE and cancers occurred more often with tofacitinib than with a TNF inhibitor in this trial that included patients with rheumatoid ar-

thritis who were 50 years of age or older and had at least one additional cardiovascular risk factor. For MACE and cancers (coprimary end points), noninferiority was not shown for the combined tofacitinib doses as compared with a TNF inhibitor. Adjudicated opportunistic infections (including herpes zoster), all herpes zoster (nonserious and serious), and adjudicated nonmelanoma skin cancer occurred more often with both tofacitinib doses than with a TNF inhibitor. The incidences of death from any cause and of pulmonary embolism were higher with tofacitinib at a dose of 10 mg twice daily than with a TNF inhibitor, which led to the switch in the tofacitinib dose from 10 twice daily to 5 mg twice daily during the trial.

In terms of age and sex, patients in our trial were generally representative of the broader population of patients participating in rheumatoid arthritis trials (Tables S4 and S13), with underrepresentation of Black patients with rheumatoid arthritis, as has been observed for other trials.[25] In prespecified subgroup analyses, differences in the risk of MACE and cancers between tofacitinib and a TNF inhibitor were more pronounced in patients 65 years of age or older than in younger patients.

Patients with rheumatoid arthritis are at higher risk for MACE and cancers than are persons in the general population.[26,27] For MACE, this may be due to systemic inflammation and traditional risk factors,[28] whereas for cancers, potential factors include chronic inflammation, common environmental and genetic factors between cancer and rheumatoid arthritis, or immunosuppressive treatments for rheumatoid arthritis.[29] In patients without rheumatoid arthritis who have a high inflammatory risk, targeting inflammation has been shown to reduce the incidence of cardiovascular events; similarly, TNF inhibitors appear to decrease the risk of cardiovascular events among patients with rheumatoid arthritis.[30,31] This trial showed increased lipid levels with tofacitinib, which are caused by reduced cholesterol ester catabolism[14] that has not previously been associated with an increased risk of MACE.[32] Because there were no other control groups in ORAL Surveillance, the incidences of MACE and cancers could not be compared with the incidences with conventional synthetic DMARDs, other biologic DMARDs, or no treatment.

Efficacy was similar across trial groups, with improvements from month 2 and sustained through trial completion, findings that raise the question of the risk–benefit assessment. In this trial, the number needed to harm for tofacitinib at a dose of 5 mg twice daily (FDA-approved dose for rheumatoid arthritis) relative to a TNF inhibitor was 567 patient-years for MACE and 276 patient-years for cancers, which meant that during 5 years of treatment, 113 and 55 patients would need to be treated with tofacitinib at a dose of 5 mg twice daily rather than with a TNF inhibitor to result in one additional MACE and cancer, respectively.

Strengths of this trial included a large patient cohort followed for up to 6 years, with 16,448 patient-years of exposure; up to 50% of the patients across treatments were followed for at least 48 months. These data provide a better understanding of the safety and efficacy of tofacitinib and TNF inhibitors in patients with rheumatoid arthritis who are 50 years of age or older and have at least one additional cardiovascular risk factor.

Limitations of the trial include the open-label design, high rates of discontinuation of trial treatment, a lack of other control groups, and the use of adalimumab in North America and etanercept in the rest of the world. This trial was not powered to compare the risk of venous thromboembolism across treatments. It is also unclear whether the risks are specific to this patient population and to tofacitinib as compared with other JAK inhibitors and whether the relative risk differed between adalimumab and etanercept. Analyses were not adjusted for multiple comparisons.

Taken together, these results show the higher risk of MACE and cancers with tofacitinib than with TNF inhibitors. The efficacies of tofacitinib and TNF inhibitors were similar across multiple outcomes.

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A data sharing statement provided by the authors is available with the full text of this article at NEJM.org.

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