Efficacy and safety of tofacitinib monotherapy, tofacitinib with methotrexate, and adalimumab with methotrexate in patients with rheumatoid arthritis (ORAL Strategy): a phase 3b/4, double-blind, head-to-head, randomised controlled trial

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Summary

Background **Tofacitinib is an oral Janus kinase inhibitor for the treatment of rheumatoid arthritis. The Oral Rheumatoid Arthritis triaL (ORAL) Strategy aimed to assess the comparative efficacy of tofacitinib monotherapy, tofacitinib plus methotrexate, and adalimumab plus methotrexate for the treatment of rheumatoid arthritis in patients with a previous inadequate response to methotrexate.**

Methods **ORAL Strategy was a 1 year, double-blind, phase 3b/4, head-to-head, non-inferiority, randomised controlled trial in patients aged 18 years or older with active rheumatoid arthritis despite methotrexate therapy. Patients were randomly assigned (1:1:1) to receive oral tofacitinib (5 mg twice daily) monotherapy, oral tofacitinib (5 mg twice daily) plus methotrexate, or subcutaneous adalimumab (40 mg every other week) plus methotrexate at 194 centres in 25 countries. Eligible patients received live zoster vaccine at investigators' discretion. The primary endpoint was the proportion of patients who attained an American College of Rheumatology response of at least 50% (ACR50) at month 6 in the full analysis set (patients who were randomly assigned to a group and received at least one dose of the study treatment). Non-inferiority between groups was shown if the lower bound of the 98·34% CI of the difference between comparators was larger than –13·0%. This trial is registered with ClinicalTrials.gov, number NCT02187055.**

Findings **1146 patients received treatment (384 had tofacitinib monotherapy; 376 had tofacitinib and methotrexate; and 386 had adalimumab and methotrexate). At 6 months, ACR50 response was attained in 147 (38%) of 384 patients with tofacitinib monotherapy, 173 (46%) of 376 patients with tofacitinib and methotrexate, and 169 (44%) of 386 patients with adalimumab and methotrexate. Non-inferiority was declared for tofacitinib and methotrexate versus adalimumab and methotrexate (difference 2% [98·34% CI –6 to 11]) but not for tofacitinib monotherapy versus either adalimumab and methotrexate (–6 [–14 to 3]) or tofacitinib and methotrexate (–8 [–16 to 1]). In total, 23 (6%) of 384 patients receiving tofacitinib monotherapy, 26 (7%) of 376 patients receiving tofacitinib plus methotrexate, and 36 (9%) of 386 patients receiving adalimumab plus methotrexate discontinued due to adverse events. Two (1%) of the 384 patients receiving tofacitinib monotherapy died. No new or unexpected safety issues were reported for either treatment in this study for up to 1 year.**

Interpretation **Tofacitinib and methotrexate combination therapy was non-inferior to adalimumab and methotrexate combination therapy in the treatment of rheumatoid arthritis in patients with an inadequate response to methotrexate in this trial. Tofacitinib monotherapy was not shown to be non-inferior to either combination.**

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Introduction

Rheumatoid arthritis is a chronic, systemic autoimmune disease characterised by inflammation, persistent synovitis, and eventual joint destruction.[1] In patients who have an inadequate response to therapy with conventional synthetic disease-modifying antirheumatic drugs (DMARDs), such as methotrexate, either as monotherapy or in combination with other conventional synthetic DMARDs, the addition of either a biological DMARD, such as a tumour necrosis factor (TNF) inhibitor or a targeted synthetic DMARD, such as a Janus kinase (JAK) inhibitor, is recommended by both the American College of Rheumatology (ACR) and the European League Against Rheumatism (EULAR).[2,3]

Tofacitinib is an oral JAK inhibitor approved for the treatment of rheumatoid arthritis. The efficacy and safety of tofacitinib 5 mg and 10 mg twice daily administered as monotherapy or in combination with conventional synthetic DMARDs (mainly methotrexate) in patients with active rheumatoid arthritis, have been shown in phase 3 studies[4–9] of up to 24 months' duration and in long-term extension studies with up to 105 months of

Research in context

Evidence before this study

We searched PubMed and MEDLINE from Jan 1, 2000, up to Feb 1, 2017 with the terms ("adalimumab"[MeSH Terms] OR "adalimumab"[All Fields]) AND ("tofacitinib"[Supplementary Concept] OR "tofacitinib"[All Fields]) AND Clinical Trial[ptyp] to identify randomised controlled trials published in the English language assessing the efficacy and safety of tofacitinib and adalimumab specifically in patients with rheumatoid arthritis who had an incomplete response to conventional synthetic disease-modifying antirheumatic drugs (DMARDs), either as monotherapy or in combination. Two comparator, but not head-to-head, trials were found. We also searched for head-to-head comparator clinical trials assessing the efficacy and safety of a Janus kinase (JAK) inhibitor and a tumour necrosis factor (TNF) α inhibitor therapy; the RA-BEAM trial suggested JAK inhibition in combination with methotrexate was more efficacious than TNF inhibition in combination with methotrexate in the treatment of rheumatoid arthritis. However, we did not find any comparative randomised controlled trials comparing JAK inhibitor monotherapy versus TNF inhibitor in combination with methotrexate. We also found no comparative randomised controlled trials assessing the efficacy or safety of tofacitinib monotherapy versus tofacitinib in combination with methotrexate.

Added value of this study

To our knowledge, this study is the first head-to-head non-inferiority trial assessing a JAK inhibitor with or without methotrexate directly compared with a TNF inhibitor therapy plus methotrexate in rheumatoid arthritis. Additionally, this study is the first head-to-head non-inferiority comparison of tofacitinib monotherapy versus tofacitinib in combination with methotrexate. Current practice is to add a biological DMARD such as adalimumab to methotrexate, but the 2016 update of the European League Against Rheumatism (EULAR) recommendations propose that the addition of a targeted synthetic DMARD, such as tofacitinib to methotrexate, might be an alternative. If conventional synthetic DMARDs are contraindicated, then EULAR recommends JAK inhibitor or interleukin-6 inhibitor monotherapy as options. Our study, ORAL Strategy, provides evidence that the addition of either a biological DMARD or a targeted synthetic DMARD can be considered as treatment options in patients with rheumatoid arthritis and an inadequate response to methotrexate.

This trial reports that tofacitinib plus methotrexate was non-inferior to adalimumab plus methotrexate when assessing the American College of Rheumatology response of at least 50% at 6 months. The monotherapy tofacitinib group did not show non-inferiority relative to the two combination groups for the primary endpoint.

observation.[10,11] The TNF inhibitor adalimumab is a recombinant human monoclonal antibody approved as a 40 mg dose every other week that has shown efficacy in patients with active rheumatoid arthritis who had an inadequate response to methotrexate[12–16] and an acceptable safety profile shown in long-term extension studies of more than 10 years' duration.[17]

Tofacitinib is approved worldwide either as a monotherapy or in combination with conventional synthetic DMARDs. No randomised clinical trial has compared the clinical efficacy of tofacitinib monotherapy with tofacitinib in combination with a conventional synthetic DMARD; post-hoc analyses suggest similar efficacy between the two approaches.[18] Conversely, as with all biological DMARDs, enhanced clinical efficacy has been shown for adalimumab with concomitant methotrexate compared with adalimumab monotherapy.[19]

Only two studies[9,16] have compared tofacitinib and adalimumab (one with and one without background methotrexate) in patients with active rheumatoid arthritis; neither was appropriately designed as a head-to-head study to compare treatment arms. This phase 3b/4 trial (Oral Rheumatoid Arthritis triaL [ORAL] Strategy) directly compared the efficacy and safety of tofacitinib monotherapy, tofacitinib in combination with methotrexate, and adalimumab in combination with methotrexate in an adequately powered head-to-head trial in patients with active rheumatoid arthritis and an inadequate response to previous methotrexate treatment.

Methods

Study design

ORAL Strategy was a 1 year, double-blind, triple-dummy, phase 3b/4, active comparator, head-to-head controlled trial assessing non-inferiority between treatment groups of tofacitinib 5 mg twice daily monotherapy, tofacitinib 5 mg twice daily in combination with methotrexate, and adalimumab 40 mg every other week with methotrexate, in patients with active rheumatoid arthritis despite methotrexate treatment. The study was done at 194 centres in 25 countries. All procedures were done in accordance with the Declaration of Helsinki and all patients provided written informed consent.

Patients

The study population consisted of individuals aged 18 years or older who met the 2010 ACR and EULAR classification criteria for rheumatoid arthritis[20] with active rheumatoid arthritis defined as having four or more tender or painful joints on motion and four or more swollen joints (based on a 28 joint count) at baseline despite treatment with methotrexate 15–25 mg per week, high-sensitivity C-reactive protein of 3 mg/L or more in a central laboratory, and class I–III functional capacity as classified by the ACR 1991 revised criteria for

global functioning status in rheumatoid arthritis.[21] Patients were required to discontinue all conventional synthetic DMARDs, other than methotrexate, for at least 4 weeks or five half-lives, whichever was longer, before baseline, but could continue to receive stable non-steroidal anti-inflammatory drugs, analgesics, or oral corticosteroids (≤10 mg prednisone or equivalent per day), or a combination, throughout the trial. Patients who had responded inadequately or had an adverse event secondary to treatment with a biological DMARD could be included but had to have discontinued the biological DMARD for a minimum period of time before randomisation (ie, rituximab or other selective B lymphocyte depleting agents 52 weeks; abatacept, certolizumab pegol, and tocilizumab 12 weeks; golimumab 10 weeks; infliximab 8 weeks; and anakinra and etanercept 4 weeks).

Patients were excluded if they had contraindications for any study treatment; a history of infections requiring treatment within 2 weeks, or any admission to hospital within the 6 months before randomisation; had exclusionary morbidities, HIV, hepatitis B or C, inadequately treated or undocumented treatment of tuberculosis; had more than one episode of herpes zoster, one episode of disseminated herpes zoster or herpes simplex; any clinically significant laboratory abnormalities; or were pregnant. Patients who had absence of efficacy or biological DMARD-related adverse events with previous treatment with a TNF inhibitor, or who had previously received tofacitinib, adalimumab, or glucocorticoids (equivalent to >10 mg per day prednisone within the previous 4 weeks), or live attenuated vaccines other than the herpes zoster vaccine (within 6 weeks before study initiation, or planned within 6 weeks after discontinuation of study treatment) were also excluded. A complete list of inclusion and exclusion criteria are provided (appendix).

Randomisation and masking

Patients were randomised (1:1:1) to receive oral tofacitinib (5 mg twice daily) monotherapy, oral tofacitinib (5 mg twice daily) in combination with methotrexate, or subcutaneous adalimumab (40 mg every other week) in combination with methotrexate. All patients enrolled in the study were required to have been treated for a minimum of 4 months with a stable methotrexate dose of 15–25 mg per week for at least 6 weeks before baseline. At the time of randomisation (baseline), patients discontinued their own supply of stable dose of methotrexate and were switched to one of three groups: (1) tofacitinib monotherapy with concomitant placebo methotrexate and placebo adalimumab; (2) tofacitinib plus methotrexate with concomitant placebo adalimumab; or (3) adalimumab plus methotrexate with concomitant placebo tofacitinib. The prestudy stable dose of methotrexate was continued in all patients taking combination therapy.

Randomisation was done by an interactive voice response system: an automated internet-based and telephone-based system with which investigators enrolled patients using minimal identification criteria (such as date of birth and initials), and received a patient identification number that was then used to determine the patient treatment according to a predetermined randomisation schedule. This process ensured blinding of patients, investigators, and sponsor representatives throughout the study.

Procedures

All treatments (except herpes vaccination) were self-administered. To maintain the blinding of treatment in this triple-dummy trial, patients in each treatment group received the appropriate placebo to methotrexate, tofacitinib, or adalimumab, to ensure identical dose burdens between groups. In patients who were eligible (based on vaccine availability at site and age ≥50 years), a live zoster vaccine was administered approximately 4 weeks in advance of study treatment at the investigator's discretion. Physical examinations were done at screening, baseline, and month 12, and laboratory observations and adverse event assessments were done at each visit and at a follow-up visit within 28–42 days after the end of the study treatment period.

Outcomes

The primary endpoint was the proportion of patients attaining an ACR response of at least 50% (ACR50) at 6 months. Secondary efficacy endpoints included the proportion of patients attaining an ACR response of at least 20% (ACR20) and an ACR response of at least 70% (ACR70) at 6 months; the proportion of patients achieving low disease activity (as defined by the Simplified Disease Activity Index [SDAI] ≤11, Clinical Disease Activity Index [CDAI] ≤10, Disease Activity Score in 28 joints, erythrocyte sedimentation rate [DAS28-4(ESR)] <3·2 and Disease Activity Score in 28 joints, C-reactive protein [DAS28-4(CRP)] <3·2), at 6 months; the proportion of patients attaining remission (as defined by SDAI ≤3·3, CDAI ≤2·8, DAS28-4[ESR] <2·6, DAS28-4[CRP] <2·6, and ACR–EULAR Boolean remission criteria) at 6 months; the proportion of patients attaining a Health Assessment Questionnaire-Disability Index (HAQ-DI) response (improvement of ≥0·22 compared with baseline) at 6 months; and least squares mean change from baseline for SDAI, CDAI, DAS28-4(ESR), DAS28-4(CRP), and HAQ-DI at 6 months. Additional secondary outcomes (least square mean change from baseline for 36-Item Short Form Health Survey eight domain scores and two component scores, Work Productivity and Activity Impairment Questionnaire, EuroQol five dimensions questionnaire, and Functional Assessment of Chronic Illness Therapy-Fatigue scale at 6 months; appendix) are not reported in this Article and will be presented elsewhere. Other efficacy endpoints included all outcomes listed as

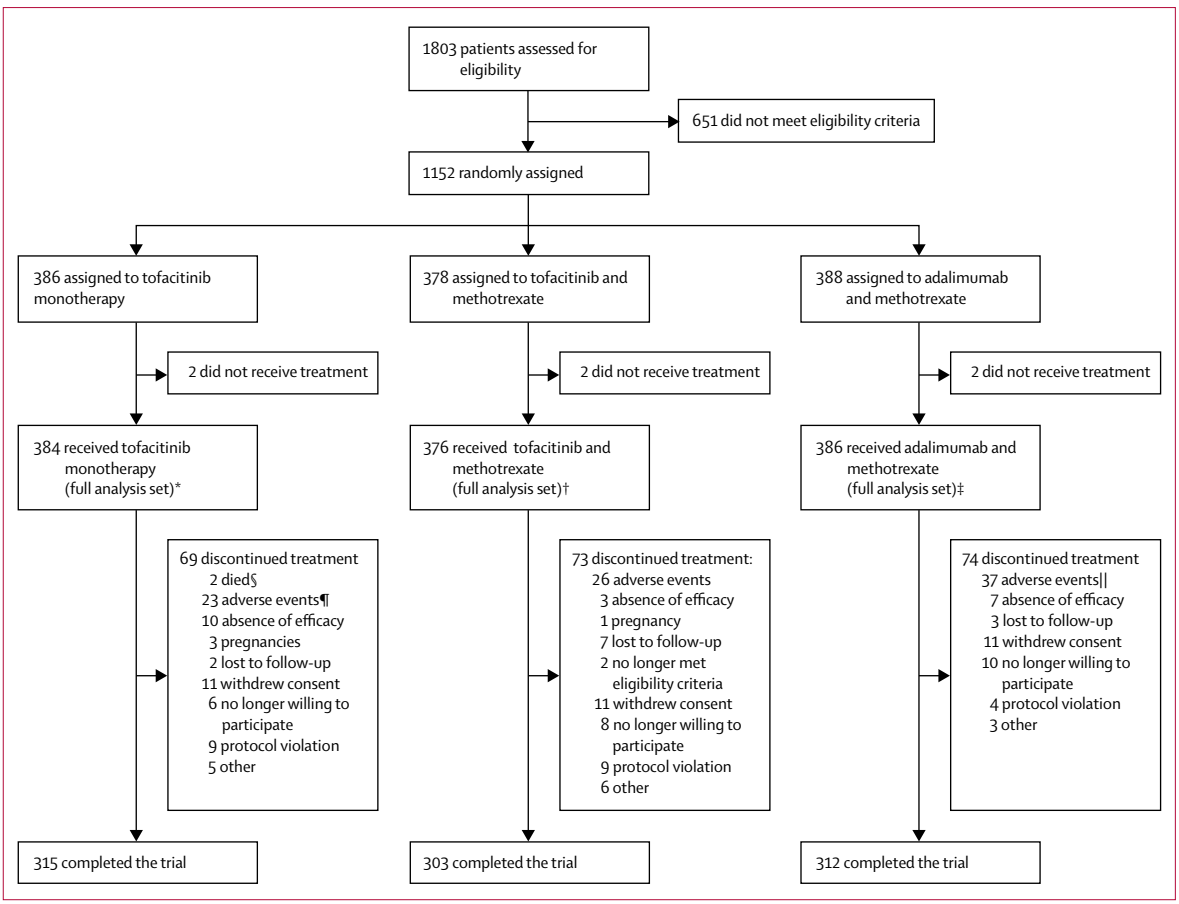

Figure 1: **Trial profile**
*338 had no substantial protocol deviations at 6 months (per-protocol set). †320 had no substantial protocol deviations at 6 months (per-protocol set). ‡330 had no substantial protocol deviations at 6 months (per-protocol set). §One patient died of urosepsis and one patient died of atypical pneumonia and respiratory distress syndrome associated with influenza A. ¶Two patients were recorded as having discontinued due to adverse events, but the reason was listed as "pregnancy". ||One patient was recorded as having discontinued due to adverse events but the reason was listed as "lack of efficacy".

primary and secondary endpoints measured at timepoints other than 6 months.

Safety was assessed with adverse events, serious adverse events, discontinuations due to adverse events, and laboratory observations. A serious adverse event was defined as any medical event that results in death, is life-threatening, requires hospitalisation, causes substantial disability or incapacity, or results in a congenital anomaly or birth defect. A severe adverse event was any adverse event that interferes with the patient's usual function, as deemed by the investigator on the case report form. External adjudication committees were established to standardise the assessment of selected safety events of special interest (ie, cardiovascular events, hepatic events, opportunistic infections, malignancy, and gastrointestinal perforation). An internal adjudication committee identified occurrences of interstitial lung disease.

Statistical analysis

For the primary outcome (non-inferiority in ACR50 at month 6) there were three independent comparisons: tofacitinib and methotrexate was compared with adalimumab and methotrexate; and tofacitinib monotherapy was compared with both adalimumab and methotrexate and with tofacitinib and methotrexate. A sample size calculation, assuming an ACR50 response rate of 35% in all groups, identified that 360 patients in each treatment arm were required to show non-inferiority with a power of 90% in each comparison. A non-inferiority margin of 13% was chosen as it represents approximately half of the observed treatment difference between adalimumab and background methotrexate and placebo (based on a meta-analysis of adalimumab trials[22] supplemented with data from an additional recent trial[9]). For the primary endpoint, an alpha value of 0·0166 was calculated by use of a Bonferroni procedure to preserve the overall type I error rate of 5% for multiple comparisons; non-inferiority was declared if the lower bound of the 98·34% CI for the difference was larger than –13%. For any comparison between primary endpoints, if non-inferiority was shown, superiority could be declared if the lower bound of the 98·34% CI of the difference was greater

than zero. Primary and secondary efficacy endpoints were assessed with the full analysis set, which included all patients who were randomly assigned to a group and received at least one dose of the study treatment; this definition was the same for the safety analysis set. A sensitivity analysis was done to assess the primary endpoint in all patients who completed 6 months with no substantial protocol deviations (the per-protocol set). Non-responder imputation for patient withdrawal and last observation carried forward for patients with missing data before withdrawal were used to handle missing data for binary endpoints, which were then analysed by normal approximation to proportions. Continuous endpoints were analysed with a linear mixed-effects model of repeated measurements including fixed-effect terms (treatment group, visit, treatment group by visit interaction, and geographical region), covariate (baseline value), and patient as a random effect with autoregressive covariance.

This trial is registered with ClinicalTrials.gov, number NCT02187055.

Role of the funding source

The study was sponsored by Pfizer Inc, and was designed by Pfizer Inc in collaboration with the lead author (RF). Pfizer Inc was responsible for the collection of the data. All authors, including those employed by Pfizer Inc, had a role in data analysis, data interpretation, and writing the report. All authors had full access to all the data and the lead author had final responsibility for the decision to submit for publication.

Results

Between Sept 11, 2014, and Dec 28, 2015, a total of 1152 patients were randomly assigned and 1146 were treated in the full analysis set (384 with tofacitinib monotherapy; 376 with tofacitinib and methotrexate; and 386 with adalimumab and methotrexate; figure 1). The proportion of patients who discontinued treatment was similar between all three treatment arms (figure 1). Baseline demographics, disease characteristics, and disease severity for all patients included in the full analysis set were similar between groups (table 1).

At 6 months, ACR50 response was attained in 147 (38%) of 384 patients who received tofacitinib monotherapy, 173 (46%) of 376 patients who received tofacitinib and methotrexate, and 169 (44%) of 386 patients who received adalimumab and methotrexate (figure 2A; table 2). Tofacitinib and methotrexate was deemed non-inferior to adalimumab and methotrexate: the difference in the proportion of patients with an ACR50 response for tofacitinib and methotrexate compared with adalimumab and methotrexate was 2% (98·34% CI −6 to 11), with the lower bound of the CI above the prespecified non-inferiority boundary (−13%; figure 2B). Non-inferiority of the ACR50 response at 6 months was not shown for tofacitinib monotherapy versus tofacitinib and methotrexate (difference −8% [98·34% CI −16 to 1]) or

	Tofacitinib monotherapy (n=384)	Tofacitinib and methotrexate (n=376)	Adalimumab and methotrexate (n=386)
Sex			
Female	319 (83%)	311 (83%)	320 (83%)
Male	65 (17%)	65 (17%)	66 (17%)
Age (years)	49·7 (12·2)	50·0 (13·4)	50·7 (13·4)
Race			
White	296 (77%)	286 (76%)	293 (76%)
Black	11 (3%)	19 (5%)	18 (5%)
Asian	41 (11%)	38 (10%)	40 (10%)
Other	36 (9%)	33 (9%)	35 (9%)
Geographical region			
North America (Canada, USA)	62 (16%)	71 (19%)	73 (19%)
Central and South America (Argentina, Chile, Mexico, Peru)	93 (24%)	91 (24%)	92 (24%)
Eastern Europe, Middle East and Africa (Bosnia and Herzegovina, Bulgaria, Czech Republic, Estonia, Israel, Latvia, Lithuania, Poland, Romania, Russia, South Africa)	170 (44%)	159 (42%)	164 (43%)
Western Europe and Turkey (Spain, Turkey, UK)	13 (3%)	15 (4%)	14 (4%)
Asia and Pacific region (Australia, Korea, Philippines, Taiwan, Thailand)	46 (12%)	40 (11%)	43 (11%)
Duration of disease (years)	6·1 (0·2–41·6)	5·4 (0·0–43·5)	6·0 (0·3–42·8)
Previous drug use			
Conventional synthetic DMARD (excluding methotrexate)	122 (32%)	115 (31%)	142 (37%)
Biological DMARD (excluding TNF inhibitor)	17 (4%)	14 (4%)	20 (5%)
TNF inhibitor	28 (7%)	16 (4%)	19 (5%)
Background weekly methotrexate dose (mg)	0	16·7 (3·7)	16·4 (3·7)
Corticosteroid use at baseline	223 (58%)	214 (57%)	218 (57%)
Daily corticosteroid dose at baseline (mg)	7·3 (13·3)	6·5 (2·5)	6·5 (2·6)
Tender joint count (28)	15·4 (6·5)	15·6 (6·5)	15·2 (6·7)
Swollen joint count (28)	11·2 (5·6)	11·8 (5·7)	11·0 (5·4)
Patient Global Assessment	60·1 (21·4)	61·7 (22·0)	60·2 (23·5)
Physician Global Assessment	59·7 (17·7)	60·7 (18·0)	60·3 (19·6)
Pain*	61·2 (21·7)	60·7 (22·4)	60·6 (22·6)
DAS28-4(ESR)	6·5 (0·9)	6·6 (0·9)	6·5 (1·0)
DAS28-4(CRP)	5·7 (0·9)	5·8 (0·9)	5·7 (1·0)
SDAI	40·2 (13·0)	41·6 (13·2)	39·8 (13·3)
CDAI	38·6 (12·6)	39·7 (12·7)	38·2 (12·9)
HAQ-DI	1·6 (0·6)	1·6 (0·6)	1·6 (0·6)
hsCRP (mg/L)	16·6 (19·3)	18·7 (21·9)	16·7 (21·3)
Patients assessed for rheumatoid factor at screening	275 (72%)	267 (71%)	277 (72%)
Rheumatoid factor in patients assessed (IU/mL)	412·9 (601·0)	439·3 (896·5)	359·3 (565·9)
Anti-CCP-positive	291 (76%)	282 (75%)	299 (78%)
Received live herpes zoster vaccination at screening or baseline	69 (18%)	75 (20%)	72 (19%)

Data are n (%), mean (SD), or median (range). DMARD=disease-modifying antirheumatic drug. TNF=tumour necrosis factor. DAS28-4(ESR)=Disease Activity Score in 28 joints, erythrocyte sedimentation rate. DAS28-4(CRP)=Disease Activity Score in 28 joints, C-reactive protein. SDAI=Simplified Disease Activity Index. CDAI=Clinical Disease Activity Index. HAQ-DI=Health Assessment Questionnaire-Disability Index. hsCRP=high-sensitivity C-reactive protein. CCP=cyclic citrullinated peptide. *By Visual Analogue Scale.

Table 1: **Patient demographics and baseline disease characteristics in the full analysis set**

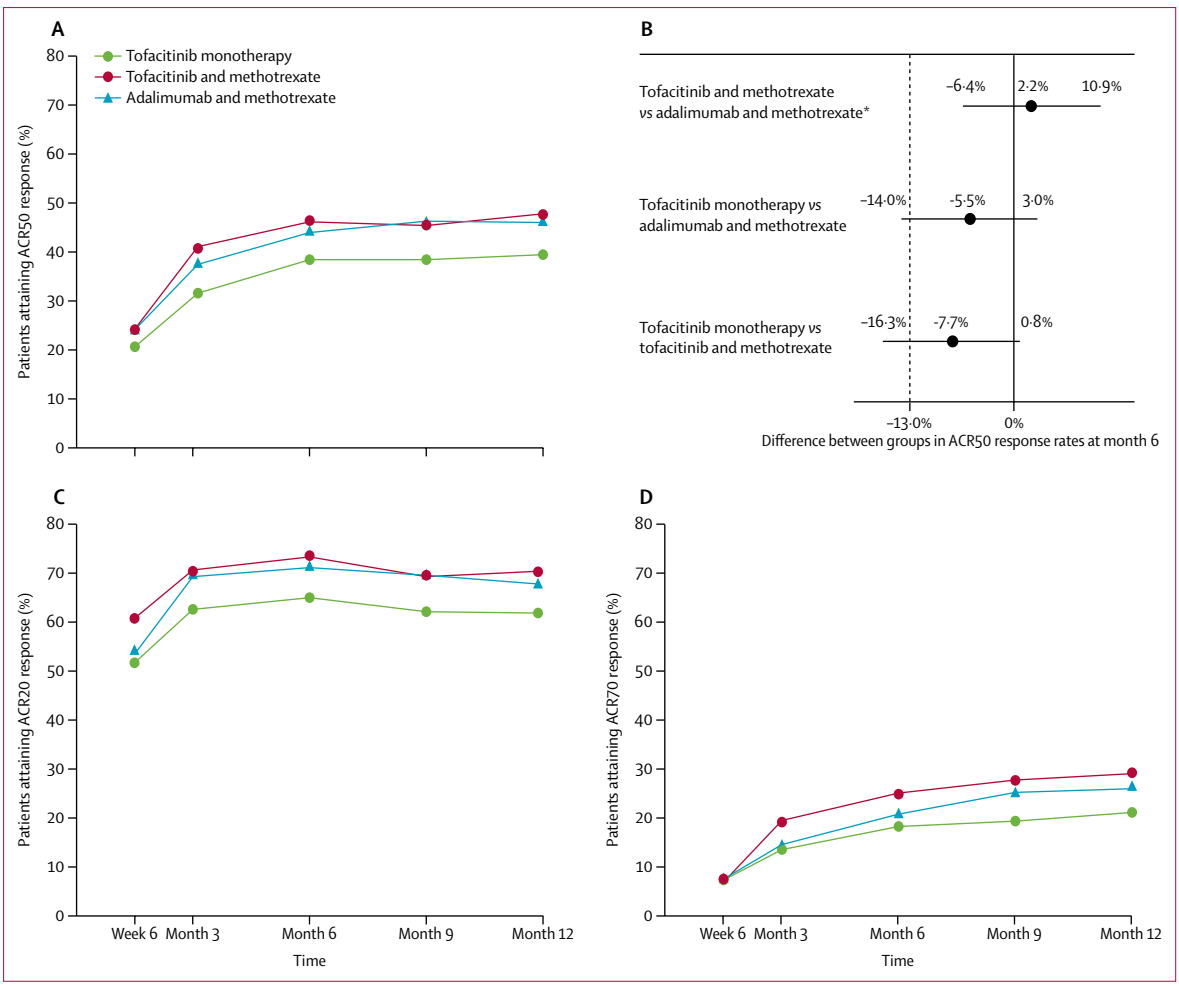

Figure 2: **Results from the full analysis set for (A) ACR50 response rates over 12 months; (B) differences between treatment groups for ACR50 at 6 months; (C) ACR20 response rates over 12 months; and (D) ACR70 response rates over 12 months**

The dotted line represents the −13% non-inferiority margin and error bars represent 98·34% CIs. The number of patients and events for 6 months and 12 months are in table 2. ACR20=the proportion of patients attaining an ACR response of at least 20%. ACR50=the proportion of patients attaining an ACR response of at least 50%. ACR70=the proportion of patients attaining an ACR response of at least 70%.*Criteria for non-inferiority met. The dotted line represents the −13% non-inferiority margin and error bars represent 98·34% CIs.

versus adalimumab and methotrexate (−6% [−14 to 3]); superiority was not shown for any comparison between the treatment groups. ACR50 response was maintained in all treatment groups through month 12 (151 [39%] of 384 in the tofacitinib monotherapy group; 179 [48%] of 376 in the tofacitinib and methotrexate group; and 177 [46%] of 386 in the adalimumab and methotrexate group; figure 2A). ACR20 and ACR70 response rates in each treatment arm showed similar trends to those noted for ACR50, and were maintained over 12 months (figures 2C and 2D). Over 12 months, ACR20, ACR50, and ACR70 response rates were higher in both combination treatment arms compared with the tofacitinib monotherapy group, and were similar between both combination treatment arms (figures 2A, 2C, and 2D; table 2). A sensitivity analysis, assessing non-inferiority of the primary endpoint in the per-protocol set, provided similar observations to the main analysis. The per-protocol ACR50 response rate for tofacitinib monotherapy was 139 (41%) of 338 patients, for tofacitinib and methotrexate was 163 (51%) of 320 patients, and for adalimumab and methotrexate was 156 (47%) of 330 patients. The difference in per-protocol ACR50 response rates for tofacitinib and methotrexate compared with adalimumab and methotrexate was 4% (98·34% CI −6 to 13), with the lower bound above the non-inferiority boundary. Per-protocol comparisons for tofacitinib monotherapy versus tofacitinib and methotrexate (−10% [98·34% CI −19 to −1]) or versus adalimumab and methotrexate (−6% [−15 to 3]) were not shown as non-inferior.

In general, secondary efficacy endpoint responses were similar between combination arms, which were higher than in the tofacitinib monotherapy group. The proportions of patients who had low disease activity at

6 months, as indicated by SDAI (≤11), were similar between combination therapy groups (187 [50%] of 376 in the tofacitinib and methotrexate group and 182 [47%] of 386 in the adalimumab and methotrexate group), which were higher than in the tofacitinib monotherapy group (167 [43%] of 384); these were maintained at 12 months in each treatment group (table 2). The proportions of patients who had low disease activity at 6 months and at 12 months in all treatment groups, as indicated by CDAI, DAS28-4(ESR), and DAS28-4(CRP), were consistent with those reported when assessing low disease activity as indicated by SDAI.

The proportions of patients who had remission at 6 months, as assessed by SDAI (≤3·3), were similar between combination therapy groups (50 [13%] of 376 in the tofacitinib and methotrexate group and 50 [13%] of 386 in the adalimumab and methotrexate group), which were higher than in the tofacitinib monotherapy group (38 [10%] of 384); these were maintained at 12 months in each treatment group (table 2). The proportions of patients who had remission at 6 months and 12 months in all treatment groups, as indicated by CDAI, DAS28-4(ESR), DAS28-4(CRP), and ACR–EULAR Boolean remission criteria, were consistent with those seen when assessing remission as indicated by SDAI. The proportion of patients achieving a HAQ-DI response (ie, improvement from baseline of at least 0·22) at 6 months was similar between treatment arms (254 [66%] of 384 in the tofacitinib monotherapy group; 264 [70%] of 376 in the tofacitinib and methotrexate group; and 260 [67%] of 386 in the adalimumab and methotrexate group); these response rates were broadly maintained at 12 months in each treatment group (241 [63%] of 384 patients; 241 [64%] of 376 patients; and 247 [64%] of 386 patients).

The absolute least squares mean changes from baseline in SDAI, CDAI, DAS28-4(ESR), and DAS28-4(CRP) at months 6 and 12 were greater in patients who received tofacitinib and methotrexate or those who received adalimumab and methotrexate than in those who received tofacitinib monotherapy (figures 3A–D). There was no appreciable difference between the treatment groups in the least squares mean changes from baseline in HAQ-DI, either at months 6 or 12 (figure 3E). For all outcomes and for all study treatment arms, the least squares mean changes from baseline reported at month 6 were maintained through month 12.

Overall, 86 (8%) of 1146 patients discontinued treatment due to adverse events; rates were similar between treatment groups. Although more patients developed serious adverse events in either tofacitinib group, discontinuations due to adverse events were higher in the adalimumab and methotrexate group than in the tofacitinib monotherapy group or the tofacitinib and methotrexate group (table 3). In this limited sample of patients monitored over a year, no new or unexpected safety issues were noted in any treatment arm. A full list of adverse events responsible for discontinuation is provided in the appendix. Most adverse events were mild

	Tofacitinib monotherapy (n=384)	Tofacitinib and methotrexate (n=376)	Adalimumab and methotrexate (n=386)
Proportion of patients achieving ACR criteria			
ACR20			
6 months	249 (65%)	275 (73%)	274 (71%)
12 months	237 (62%)	264 (70%)	261 (68%)
ACR50			
6 months	147 (38%)	173 (46%)	169 (44%)
12 months	151 (39%)	179 (48%)	177 (46%)
ACR70			
6 months	70 (18%)	94 (25%)	80 (21%)
12 months	81 (21%)	109 (29%)	100 (26%)
Proportion of patients who had low disease activity			
SDAI (≤11)			
6 months	167 (43%)	187 (50%)	182 (47%)
12 months	169 (44%)	187 (50%)	204 (53%)
CDAI (≤10)			
6 months	163 (42%)	183 (49%)	179 (46%)
12 months	173 (45%)	188 (50%)	202 (52%)
DAS28-4(ESR) (<3·2)			
6 months	79 (21%)	100 (27%)	106 (27%)
12 months	87 (23%)	102 (27%)	128 (33%)
DAS28-4(CRP) (<3·2)*			
6 months	159 (41%)	174 (46%)	181 (47%)
12 months	157 (41%)	175 (47%)	201 (52%)
Proportion of patients achieving remission			
SDAI (≤3·3)			
6 months	38 (10%)	50 (13%)	50 (13%)
12 months	53 (14%)	61 (16%)	62 (16%)
CDAI (≤2·8)			
6 months	39 (10%)	52 (14%)	51 (13%)
12 months	54 (14%)	70 (19%)	65 (17%)
DAS28-4(ESR) (<2·6)			
6 months	40 (10%)	45 (12%)	48 (12%)
12 months	43 (11%)	55 (15%)	66 (17%)
DAS28-4(CRP) (<2·6)*			
6 months	81 (21%)	115 (31%)	108 (28%)
12 months	92 (24%)	114 (30%)	136 (35%)
ACR–EULAR Boolean criteria			
6 months	27 (7%)	31 (8%)	34 (9%)
12 months	37 (10%)	49 (13%)	47 (12%)

Data are n (%). ACR=American College of Rheumatology. ACR20=the proportion of patients attaining an ACR response of at least 20%. ACR50=the proportion of patients attaining an ACR response of at least 50%. ACR70=the proportion of patients attaining an ACR response of at least 70%. SDAI=Simplified Disease Activity Index. CDAI=Clinical Disease Activity Index. DAS28-4(ESR)=Disease Activity Score in 28 joints, erythrocyte sedimentation rate. DAS28-4(CRP)=Disease Activity Score in 28 joints, C-reactive protein. EULAR=European League Against Rheumatism. *Remission (<2·6) and low disease activity (<3·2) values for DAS28-4(CRP) have not been validated, but are often used in rheumatology.

Table 2: **Proportion of patients in the full analysis set who had an ACR response, low disease activity, or remission**

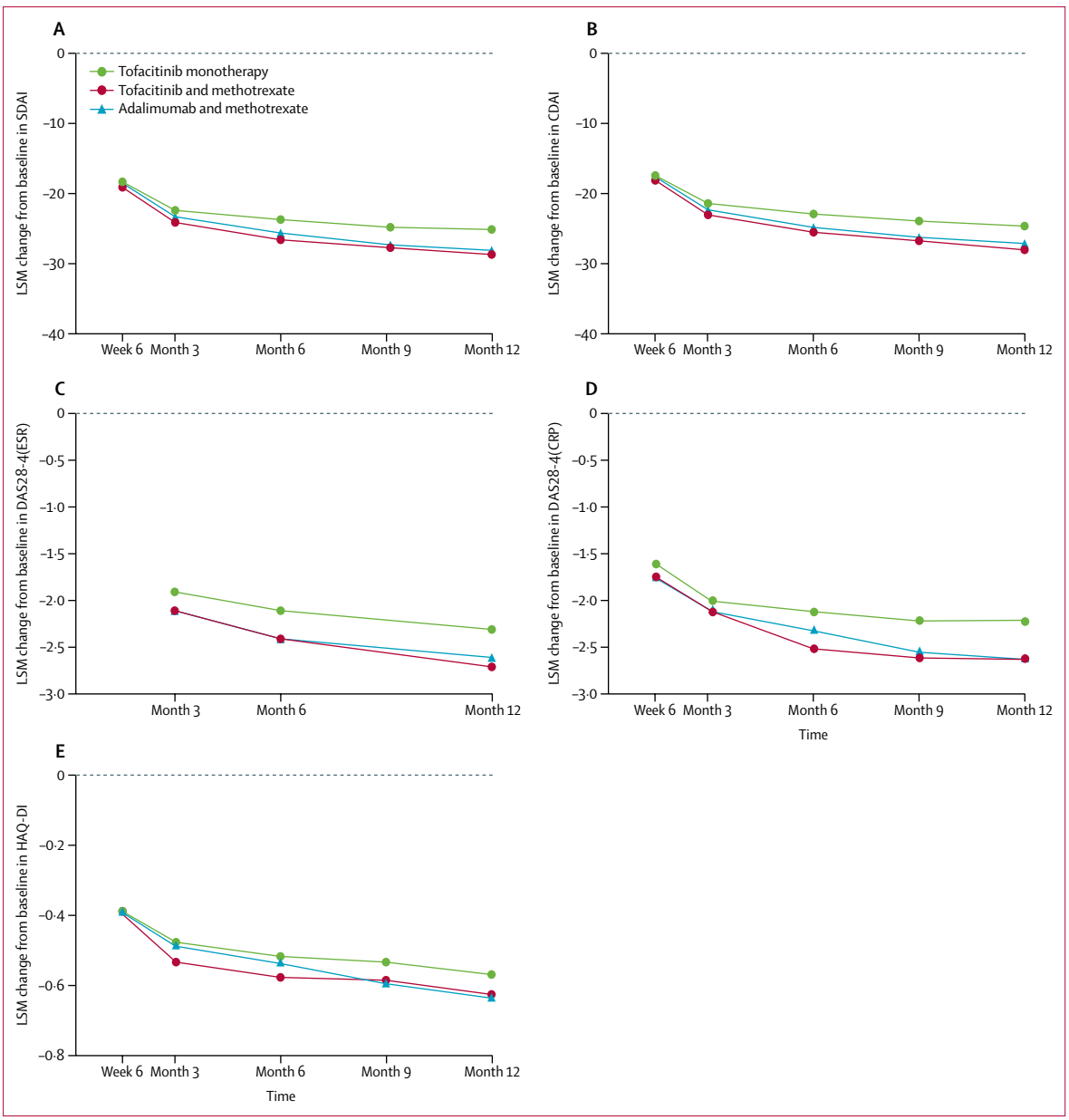

Figure 3: **LSM change from baseline in full analysis set at various timepoints in (A) SDAI, (B) CDAI, (C) DAS28-4(ESR), (D) DAS28-4(CRP), and (E) HAQ-DI**
LSM=least squares mean. SDAI=Simplified Disease Activity Index. CDAI=Clinical Disease Activity Index. DAS28-4(ESR)=Disease Activity Score in 28 joints, erythrocyte sedimentation rate. DAS28-4(CRP)=Disease Activity Score in 28 joints, C-reactive protein. HAQ-DI=Health Assessment Questionnaire-Disability Index.

to moderate, and the most common (occurring in >3·5% of patients overall) investigator-reported adverse events occurring overall across all treatment groups were upper respiratory tract infections (25 [7%] of 384 patients in the tofacitinib monotherapy group *vs* 37 [10%] of 376 patients in the tofacitinib and methotrexate group, *vs* 29 [8%] of 386 patients in the adalimumab and methotrexate group), alanine aminotransferase elevation (eight [2%] *vs* 23 [6%] *vs* 26 [7%]), nasopharyngitis (22 [6%] *vs* 16 [4%] *vs* 18 [5%]), urinary tract infections (11 [3%] *vs* 15 [4%], *vs* 16 [4%]), and nausea (11 [3%] *vs* 13 [4%] *vs* 16 [4%]). Herpes zoster was documented in 18 patients (2%) overall; four (1%) of 384 patients in the tofacitinib monotherapy group, eight (2%) of 376 patients in the tofacitinib and methotrexate group, and six (2%) of 386 patients in the adalimumab and methotrexate group. Of the 216 patients who received herpes zoster vaccination, three (1%) patients developed mild cases of herpes zoster; one (<1%) patient had injection-site erythema in the tofacitinib monotherapy group within 42 days of the vaccination. Of the 930 patients who did not receive a

vaccination, 15 (2%) patients developed herpes zoster. Three multidermatomal cases were reported (two in the tofacitinib monotherapy group and one in the adalimumab and methotrexate group). There was one serious varicella zoster event in the tofacitinib monotherapy group and one serious herpes zoster event in each of the tofacitinib and methotrexate group and adalimumab and methotrexate group. Two cases of tuberculosis were reported, both in the tofacitinib and methotrexate group. One white female patient from Mexico aged 32 years (with a negative QuantiFERON-TB Gold test at screening) experienced headaches and nausea on day 117, after which the study drug was permanently withdrawn. A lumber puncture on day 122 indicated probable bacterial infection, and meningitis tuberculosis was confirmed by the adenosine deaminase test. The patient was admitted to hospital from day 122 until day 144, and went on to recover. Another white female from Mexico aged 45 years, with a history of diabetes and hypertension and receiving isoniazid therapy after a positive QuantiFERON-TB Gold test at screening, developed probable pulmonary tuberculosis on day 233, and the study drug was permanently withdrawn on day 240. Sputum smear microscopy and culture were negative; antituberculosis therapy was initiated based on the judgement of an infectious disease specialist and on radiographic evidence of alveolar infiltrates, and the patient recovered. One (<1%) patient in the tofacitinib monotherapy group and one patient (<1%) in the adalimumab and methotrexate group had probable drug-induced liver injury as determined by adjudication; it was not clear whether this was due to other concomitant therapy or study medication. No gastrointestinal perforations occurred in any treatment group.

Increases from baseline in laboratory parameters, including total cholesterol, low-density and high-density lipoprotein-cholesterol, serum creatinine, haemoglobin, alanine aminotransferase, aspartate aminotransferase, and bilirubin, and decreases from baseline in absolute neutrophil counts were reported in all treatment groups. An increase in absolute lymphocyte count was reported in the adalimumab and methotrexate arm, with no appreciable difference in either of the tofacitinib arms. The incidence of any increase in liver function test was lower in the tofacitinib monotherapy group than in the combination arms (table 4).

Two patients died during the study, both in the tofacitinib monotherapy group. In Chile, a white female aged 71 years completed the study on day 337 and was admitted to an emergency unit with fever and signs of urosepsis on day 363, culminating in her death on day 368, despite antibiotic therapy. No urinary culture was available to confirm this diagnosis. In Mexico, a mixed-race female aged 48 years developed symptoms of an upper respiratory tract infection on day 59, which subsequently deteriorated and the patient was admitted to hospital on day 69. Viral tests confirmed H1N1 influenza and the patient died from septic shock and cardiopulmonary arrest on day 71; an autopsy confirmed influenza A H1N1.

	Tofacitinib monotherapy (n=384)	Tofacitinib and methotrexate (n=376)	Adalimumab and methotrexate (n=386)
Total number of adverse events*	598	652	620
Patients with adverse events	226 (59%)	231 (61%)	253 (66%)
Patients with treatment-related adverse events	101 (26%)	111 (30%)	133 (35%)
Patients with serious adverse events	35 (9%)	27 (7%)	24 (6%)
Patients discontinuing due to adverse events	23 (6%)	26 (7%)	37 (10%)
Patients with severe adverse events (defined by the investigator)	24 (6%)	17 (5%)	23 (6%)
Deaths†	2 (1%)	0	0
Adverse events of special interest			
Serious infections	6 (2%)	10 (3%)	6 (2%)
Herpes zoster (serious and non-serious)	4 (1%)	8 (2%)	6 (2%)
Herpes zoster (serious and non-serious) in patients who were vaccinated	1/69 (1%)	2/75 (3%)	0/72 (0%)
Opportunistic infections (excluding tuberculosis)	2 (1%)	1 (<1%)	2 (1%)
Tuberculosis	0	2 (1%)	0
MACE (non-fatal)	0	0	2 (1%)
Malignancy (excluding non-melanoma skin cancer)	1 (<1%)	0	0
Non-melanoma skin cancer	2 (1%)	0	1 (<1%)

Data are n, n (%), or n/N (%). MACE=major adverse cardiovascular event (includes non-fatal myocardial infarction, fatal cardiovascular event, and non-fatal cerebrovascular accident). *Patients could have had more than one adverse event. †One patient died of urosepsis; one patient died of atypical pneumonia and respiratory distress syndrome associated with influenza A.

Table 3: **Summary of adverse events, serious adverse events, and discontinuations in the safety analysis set**

Discussion

To our knowledge, this study was the first prospective, blinded, head-to-head controlled trial comparing tofacitinib monotherapy versus tofacitinib plus methotrexate, or comparing tofacitinib as monotherapy or combination therapy versus any TNF inhibitor therapy in patients with active rheumatoid arthritis and an inadequate response to methotrexate. The trial assessed clinical and functional measures of efficacy and safety. The primary endpoint, non-inferiority of achieving an ACR50 response at 6 months was met for tofacitinib (5 mg twice daily) and methotrexate compared with adalimumab and methotrexate, with both achieving clinically meaningful responses. This similar efficacy in the tofacitinib and methotrexate and adalimumab and methotrexate groups was not surprising considering previous studies. In ORAL Standard,[9] a phase 3 randomised controlled trial, the proportion of patients who had an ACR20 response at 6 months (the primary endpoint) was similar for those receiving tofacitinib and

	Tofacitinib monotherapy (n=380)	Tofacitinib and methotrexate (n=376)	Adalimumab and methotrexate (n=385)
Alanine aminotransferase			
≥1	110 (29%)	164 (44%)	182 (47%)
≥2	17 (5%)	53 (14%)	62 (16%)
≥3	7 (2%)	29 (8%)	27 (7%)
Aspartate aminotransferase			
≥1	85 (22%)	129 (34%)	143 (37%)
≥2	11 (3%)	33 (9%)	38 (10%)
≥3	3 (<1%)	16 (4%)	15 (4%)
Total bilirubin			
≥1	6 (2%)	15 (4%)	15 (4%)
≥2	1 (<1%)	0	0
≥3	1 (<1%)	0	0

Data are n (%). Data for four patients in the tofacitinib group and one patient in the adalimumab and methotrexate group were not available for liver function tests.

Table 4: **Liver function tests as multiples of upper limit of normal**

methotrexate (101 [52%] of 196 patients) or adalimumab and methotrexate (94 [47%] of 199 patients) for the treatment of rheumatoid arthritis; the ACR50 response was higher with tofacitinib plus methotrexate (37%) compared with adalimumab plus methotrexate (28%) but were not significantly different (NCT00853385). The present analysis suggests that adding tofacitinib (5 mg twice daily) to methotrexate is as effective as adding adalimumab, a TNF inhibitor, to methotrexate.

In a head-to-head trial (RA-BEAM)[23] comparing adalimumab in combination with methotrexate and baricitinib (JAK1/2 inhibitor), in combination with methotrexate, baricitinib plus methotrexate was superior in terms of ACR20 response and change from baseline in DAS28(CRP) at week 12. In this trial, however, baricitinib monotherapy was not tested. Of additional note, the primary endpoint used in RA-BEAM was ACR20, compared with the more conservative use of ACR50 in ORAL Strategy.

In the RA-BEGIN phase 3 trial,[24] baricitinib 4 mg once daily monotherapy was similar to baricitinib 4 mg once daily in combination with methotrexate with respect to clinical and functional outcomes in a methotrexate-naive population. Of note, radiographic progression was significantly attenuated in the baricitinib combination group only. As the population studied in RA-BEGIN was methotrexate-naive (in contrast to the patients included in ORAL Strategy), it is currently unclear whether baricitinib monotherapy is non-inferior to baricitinib in combination with methotrexate in a methotrexate inadequate response population. Additionally, neither RA-BEAM nor RA-BEGIN compared baricitinib monotherapy with adalimumab in combination with methotrexate. Thus, it is unknown whether baricitinib monotherapy is non-inferior to adalimumab plus methotrexate. Taking these studies collectively (ORAL Standard, ORAL Strategy, RA-BEGIN, and RA-BEAM) provides further support for the therapeutic potential of JAK inhibition for the treatment of rheumatoid arthritis. Inferences on the differential efficacy of baricitinib and tofacitinib, however, cannot be made in the absence of a head-to-head comparison of the two therapies.

This trial directly compared tofacitinib monotherapy with tofacitinib in combination with methotrexate. Non-inferiority was not shown for tofacitinib monotherapy compared with either combination arm. In this study, however, tofacitinib monotherapy showed ACR20, ACR50, and ACR70 responses and improvements in composite measures of disease activity and HAQ-DI similar to those previously reported in a phase 3 tofacitinib monotherapy placebo-controlled trial.[5] Of interest, across the tofacitinib phase 3 trial programme, the proportion of patients who attained an ACR20 response was higher in trials of tofacitinib monotherapy[5,7] than in trials of tofacitinib in combination with conventional synthetic DMARDs;[4,6,8,9] this finding was shown not to be true in ORAL Strategy. This observation highlights the importance of comparing efficacy between two treatment strategies only in a powered head-to-head trial, rather than comparing between different source populations, even when baseline demographics seem to be similar.

With treatment for a patient with active rheumatoid arthritis, it is important to not only control clinical symptoms, as measured by ACR responses and change in DAS28-4(ESR), SDAI, and CDAI, but also to improve patient function, which is shown by patient reported outcomes such as the HAQ-DI. Of note, in this trial, improvements in HAQ-DI among the three groups were similar. Taking the clinical and functional results of this trial together, it seems that, in the population assessed, patients generally will respond better to the addition of tofacitinib (5 mg twice daily) or adalimumab (40 mg every other week) to methotrexate than switching from methotrexate directly to tofacitinib (5 mg twice daily) monotherapy. In clinical practice, a conventional synthetic DMARD (or combination of conventional synthetic DMARDs) or a biological DMARD is added to methotrexate in a patient with an inadequate response to methotrexate, consistent with the most recently updated ACR and EULAR recommendations for the treatment of rheumatoid arthritis.[2,3] Thus, in accordance with both sets of recommendations, patients should start treatment with a conventional synthetic DMARD such as methotrexate. If the patient does not reach the desired treatment target with the conventional synthetic DMARD, or combination of conventional synthetic DMARDs, within 6 months, then a targeted synthetic DMARD such as tofacitinib, or a biological DMARD such as adalimumab, can be added with an equal likelihood of attaining the treatment target. The results of this trial also support this concept; in this group of patients, higher efficacy was noted with either

combination therapy arm compared with tofacitinib monotherapy. A missing piece of information is whether methotrexate can be withdrawn in patients treated with tofacitinib in combination with methotrexate who have achieved low disease activity; this question is being assessed in an ongoing clinical trial (NCT02831855).

The patients enrolled in ORAL Strategy had active disease despite methotrexate therapy, with almost 60% also having received glucocorticoids at baseline. Most patients came from countries or regions with low accessibility to biological DMARDs and hence might not have received optimal therapy before enrolment into this trial. The population is quite similar in terms of demographics and disease characteristics to that of other trials of patients with inadequate response to methotrexate.[23,25]

Owing to the active comparator trial design and the absence of a placebo group, ACR50 was selected as the primary endpoint in this study. This composite measure of disease activity has been shown to be a more valid endpoint than ACR20 in head-to-head trials comparing active treatment arms.[26] Most previous clinical trials assessing tofacitinib have contained a placebo group and used an appropriate primary endpoint of ACR20 response.

Although this study was of limited duration and sample size, no new or unexpected safety issues were noted. Data from this trial will be incorporated into the combined safety data for ongoing observational studies to continue to assess the safety of tofacitinib in these patients. Overall proportions of adverse events, including the most common adverse events, were similar between treatment groups; most adverse events were mild to moderate in severity. Rates of serious adverse events and discontinuations due to adverse events were generally similar between treatment arms. Previous studies have shown that the risk of herpes zoster is increased with tofacitinib therapy.[27] In the present analysis, incidence of herpes zoster was similar between the tofacitinib monotherapy group (four [1%] of 384 patients) and the adalimumab and methotrexate group (six [2%] of 386 patients) but was somewhat higher in the tofacitinib and methotrexate group (eight [2%] of 376 patients). These data are in line with previous findings that concomitant conventional synthetic DMARDs augment the risk of herpes zoster with tofacitinib.[27–29] There were 216 patients who received live zoster vaccination; three of these developed mild cases of herpes zoster. There was one case of injection-site erythema in the tofacitinib monotherapy group within 42 days of the vaccination. The incidence of herpes zoster was similar in the groups of patients who did (1%) and did not (2%) receive previous vaccination across all three groups. It is important to note that in the Shingles Prevention Study,[30] the overall efficacy of the live zoster vaccine was 51%. Because vaccination was left to the discretion of the investigators, the present study did not formally assess the efficacy of herpes zoster vaccination. However, with the assumption that patients at high risk of herpes zoster infection might have received the vaccine more frequently than patients with lower risk, then it is possible a channelling bias is present. Thus, further studies are required to assess the risk of herpes zoster infection, and the clinical benefit of herpes vaccination, in patients receiving tofacitinib.

ORAL Strategy was designed to answer clinically relevant questions faced by clinicians in routine clinical practice when presented with a patient with rheumatoid arthritis and an inadequate response to methotrexate who might have also had an inadequate response to other conventional synthetic DMARDs: to either add tofacitinib or a TNF inhibitor, such as adalimumab, to the methotrexate regimen, or to switch methotrexate to tofacitinib monotherapy. The study was sufficiently powered to assess differences in the treatment arms and included clear, prespecified endpoints. The results of ORAL Strategy suggest that the addition of tofacitinib to methotrexate is preferable to switching to tofacitinib monotherapy.

Limitations of this study include the fact that, although TNF inhibitor therapies share a common mechanism of action, the extent to which the observations among patients receiving adalimumab and methotrexate in the present study are generalisable to other TNF inhibitor therapies, or to therapies with another mechanism of action, is unclear. Additionally, radiographic follow-up, which might have assisted clinical interpretation, was not assessed in this trial because all patients had active therapies that inhibited progression of joint damage[12] and no major differences were expected during the short course of the study. The absence of a placebo group precluded a statistical demonstration of the clinically important efficacy of tofacitinib monotherapy in the present study. It is also possible that owing to the lack of a placebo arm, an expectation of efficacy from patients and investigators alike may have been responsible for improved clinical and functional observations in all groups. However, the responses are consistent with those seen in other phase 3 trials[5,7] of tofacitinib as monotherapy or in combination with a conventional synthetic DMARD.[4,6,8,9] This study does not formally answer whether the addition of a targeted synthetic DMARD or biological DMARD is superior to adding combination conventional synthetic DMARDs, even though approximately a third of patients met the inclusion criteria of active disease in spite of previous treatment with combination conventional synthetic DMARDs.

In conclusion, tofacitinib 5 mg twice daily with methotrexate showed efficacy and safety similar to adalimumab with methotrexate in patients with rheumatoid arthritis who had an inadequate response to methotrexate therapy. Tofacitinib monotherapy did not achieve statistical non-inferiority to either combination regimen. These results suggest that in patients with an inadequate response to methotrexate, the addition of tofacitinib or adalimumab is equally efficacious and more effective than switching to tofacitinib monotherapy.

Contributors

All authors were involved in the analysis and interpretation of data and in the writing of the report.

Declaration of interests

RF has received grants and research support from, and has acted as a consultant for, AbbVie, Amgen, Bristol Myers Squibb, Celgene, GlaxoSmithKleine, Eli Lilly, Janssen, Novartis, Pfizer Inc, Sanofi-Genzyme, and UCB Pharma. EM has received research grants, consultancy, and speaking fees from AbbVie, Bristol Myers Squibb, Eli Lilly, Janssen, Medimmune, Pfizer Inc, and Roche. SH has acted as a consultant for AbbVie, Celgene, Eli Lilly, Janssen, Novartis, Pfizer Inc, Roche, and UCB Pharma. RJM has received research grant support or speaking fees from, and has acted as a consultant for, AKL, Biogen, BMS, Chugai, Genzyme, Novartis, Pfizer, Regeneron, Roche, Sandoz, Sanofi, and UCB Pharma. AJK has received research grants, consultancy fees, or speaking fees from AbbVie, Amgen, BMS, Genentech, and Pfizer Inc. ZL, RD, KS, RZ, LT, ST, CM, SK, and SM are all employees and shareholders of Pfizer Inc. JSS has received consultancies, speaking fees, and honoraria from AbbVie, Amgen, AstraZeneca, Astro, Celgene, Celtrion, GlaxoSmithKleine, ILTOO, Janssen, Lilly, MedImmune, MSD, Novartis-Sandoz, Pfizer Inc, Roche, Samsung, Sanofi, and UCB Pharma; and has received institutional grants from AbbVie, Janssen, Lilly, MSD, Pfizer Inc, and Roche.

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