Tofacitinib (CP-690,550) in combination with methotrexate in patients with active rheumatoid arthritis with an inadequate response to tumour necrosis factor inhibitors: a randomised phase 3 trial

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Summary

Background Rheumatoid arthritis is a heterogeneous chronic disease, and no therapeutic agent has been identified which is universally and persistently effective in all patients. We investigated the effectiveness of tofacitinib (CP-690,550), a novel oral Janus kinase inhibitor, as a targeted immunomodulator and disease-modifying therapy for rheumatoid arthritis.

Methods We did a 6-month, double-blind, parallel-group phase 3 study at 82 centres in 13 countries, including North America, Europe, and Latin America. 399 patients aged 18 years or older with moderate-to-severe rheumatoid arthritis and inadequate response to tumour necrosis factor inhibitors (TNFi) were randomly assigned in a 2:2:1:1 ratio with an automated internet or telephone system to receive twice a day treatment with: tofacitinib 5 mg (n=133); tofacitinib 10 mg (n=134); or placebo (n=132), all with methotrexate. At month 3, patients given placebo advanced to either tofacitinib 5 mg twice a day (n=66) or 10 mg twice a day (n=66). Primary endpoints included American College of Rheumatology (ACR)20 response rate, mean change from baseline in Health Assessment Questionnaire-Disability Index (HAQ-DI), and rates of disease activity score (DAS)28-4(ESR) less than 2·6 (referred to as DAS28<2·6), all at month 3. The full analysis set for the primary analysis included all randomised patients who received at least one dose of study medication and had at least one post-baseline assessment. This trial is registered with www.ClinicalTrials.gov, number NCT00960440.

Findings At month 3, ACR20 response rates were 41·7% (55 of 132 [95% CI *vs* placebo 6·06–28·41]; p=0·0024) for tofacitinib 5 mg twice a day and 48·1% (64 of 133; [12·45–34·92]; p<0·0001) for tofacitinib 10 mg twice a day versus 24·4% (32 of 131) for placebo. Improvements from baseline in HAQ-DI were −0·43 ([−0·36 to −0·15]; p<0·0001) for 5 mg twice a day and −0·46 ([−0·38 to −0·17]; p<0·0001) for 10 mg twice a day tofacitinib versus −0·18 for placebo; DAS28<2·6 rates were 6·7% (eight of 119; [0–10·10]; p=0·0496) for 5 mg twice a day tofacitinib and 8·8% (11 of 125 [1·66–12·60]; p=0·0105) for 10 mg twice a day tofacitinib versus 1·7% (two of 120) for placebo. Safety was consistent with phase 2 and 3 studies. The most common adverse events in months 0–3 were diarrhoea (13 of 267; 4·9%), nasopharyngitis (11 of 267; 4·1%), headache (11 of 267; 4·1%), and urinary tract infection (eight of 267; 3·0%) across tofacitinib groups, and nausea (nine of 132; 6·8%) in the placebo group.

Interpretation In this treatment-refractory population, tofacitinib with methotrexate had rapid and clinically meaningful improvements in signs and symptoms of rheumatoid arthritis and physical function over 6 months with manageable safety. Tofacitinib could provide an effective treatment option in patients with an inadequate response to TNFi.

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Introduction

Rheumatoid arthritis is a chronic and debilitating autoimmune disease characterised by persistent synovitis, systemic inflammation, and ultimately joint destruction.[1] Non-biological disease-modifying antirheumatic drugs (DMARDs), such as methotrexate, remain the cornerstone of rheumatoid arthritis therapy.[2–4] Patients with an inadequate response to methotrexate are often treated with biological DMARDs, such as tumour necrosis factor inhibitors (TNFi). However, 41–58% of patients receiving TNFi do not achieve an American College of Rheumatology (ACR)20 response[5–7] and additional patients lose their clinical response[8] or have adverse events during the course of therapy. Therefore, an unmet need exists for rheumatoid arthritis therapies with alternative mechanisms of action.

Tofacitinib (CP-690,550) is a novel oral Janus kinase (JAK) inhibitor that is under investigation as a targeted immunomodulator and disease-modifying therapy in rheumatoid arthritis. The phase 3 programme includes a broad range of therapeutic scenarios that assess the use of tofacitinib as monotherapy or combined with non-biological DMARDs, mainly methotrexate. In a phase 3 study, we assessed the efficacy and safety of tofacitinib

with methotrexate in adult patients with active moderate-to-severe rheumatoid arthritis and an inadequate response to TNFi.

Methods

Study design and patients

We did a phase 3, randomised, 6-month, double-blind, placebo-controlled parallel-group study in 82 centres in 13 countries worldwide. Eligible patients were aged 18 years or older with a diagnosis of active moderate-to-severe rheumatoid arthritis based on the ACR 1987 revised criteria. Active disease was defined as six or more tender or painful joints (of 68-joint count) and six or more swollen joints (of 66-joint count) and either ESR (Westergren method) higher than 28 mm/h or C-reactive protein (CRP) of more than 66·67 nmol/L (7 mg/L). Patients had previous inadequate response or intolerance to one or more approved TNFi, as established by the investigator, administered in accordance with its label. Patients must have taken oral or parenteral methotrexate continuously for 4 months or more before the first study dose and be on a stable dose of 7·5–25 mg per week (7·5–20 mg per week in Republic of Ireland) for 6 weeks or more before the first study dose.

See Online for appendix

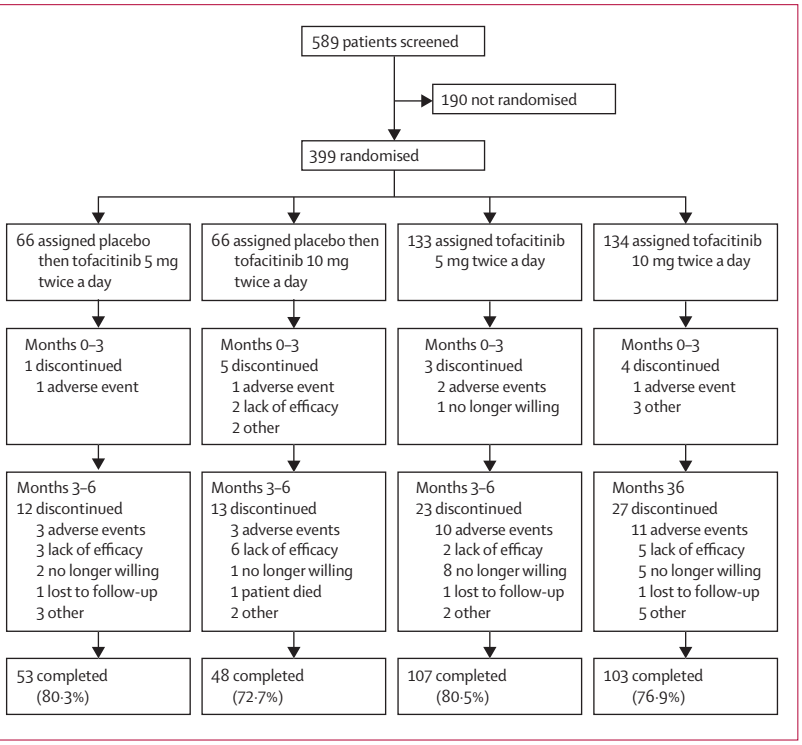

Figure 1: **Study design**

Placebo then 5 mg twice a day=patients randomised to receive placebo months 0–3 and tofacitinib 5 mg twice a day months 3–6. Placebo then 10 mg twice a day=patients randomised to receive placebo months 0–3 and tofacitinib 10 mg twice a day months 3–6. All randomised patients received the assigned treatment. The full analysis set for efficacy included all randomised patients who received at least one dose of study drug and had at least one post-baseline assessment. The safety analysis set was defined as those patients who received at least one dose of tofacitinib or placebo.

Key exclusion criteria included: haemoglobin less than 90·0 g/L, haematocrit less than 30%, white blood cell count lower than $3·0\times10^9$/L, absolute neutrophil count less than $1·2\times10^9$/L, or platelet count less than 100×10^9/L; estimated glomerular filtration rate less than 40 mL/min (Cockcroft-Gault calculation); total bilirubin, aspartate aminotransferase (AST), or alanine aminotransferase (ALT) more than 1·5 times the upper limit of normal (ULN) at screening; chronic or recurrent infections, including latent or inadequately treated *Mycobacterium tuberculosis* infection; or malignancy or history of malignancy, with the exception of adequately treated or excised non-metastatic basal-cell or squamous-cell cancer of the skin or cervical carcinoma in situ.

This study was done in compliance with the Declaration of Helsinki and Good Clinical Practice Guidelines established by the International Conference on Harmonisation. The final protocol, amendments, and informed consent documentation were reviewed and approved by the institutional review board and the independent ethics committee of each investigational centre. All patients provided written informed consent.

Randomisation and masking

Patients were randomly assigned in a 2:2:1:1 ratio to tofacitinib 5 mg twice a day; tofacitinib 10 mg twice a day; placebo for 3 months then advanced to 5 mg tofacitinib twice a day; or placebo for 3 months then advanced to 10 mg tofacitinib twice a day (appendix), all with stably dosed methotrexate. For analyses of tofacitinib versus placebo for months 0–3, data from the two placebo sequences were combined into one group. Randomisation was done with an automated internet or telephone randomisation system (Impala, Pfizer, New York, NY, USA). Treatment was masked to patients, investigators, and sponsors (appendix).

Procedures

Patients had to remain on stable background methotrexate therapy and were allowed to remain on antimalarial therapy, which had to be stable for 8 weeks or more before first study dose. No other DMARDs (non-biological or biological) were permitted and were discontinued before first study dose (appendix). The appendix shows wash-out periods for DMARDs. Non-steroidal anti-inflammatory drugs, selective cyclooxygenase-2 inhibitors, or glucocorticoids (≤10 mg per day prednisone or equivalent) were allowed but had to be stably dosed for 4 weeks or more before the first study dose and remain stable through month 3.

The three co-primary efficacy endpoints (assessed at month 3) were: (1) ACR20 response rates, showing 20% or more improvement in tender and swollen joint counts and in three of five remaining ACR core set measures (pain, disability, CRP, patient and physician global assessment);[9] (2) mean change from baseline in physical function measured by the Health

Assessment Questionnaire-Disability Index (HAQ-DI) score range 0–3, with 0–1 generally representing mild-to-moderate physical difficulty, 1–2 representing moderate-to-severe disability, and 2–3 representing severe-to-very-severe disability;[10,11] and (3) Disease Activity Score (DAS) less than 2·6 rate in 28 joints based on ESR (DAS28-4[ESR] <2·6, also known as DAS-defined remission).[12,13] The co-primary endpoint of DAS28-4(ESR) <2·6 (referred to as DAS28<2·6) was added to the study in a protocol amendment on May 10, 2010, after discussions with the US Food and Drug Administration. The full analysis set for the primary analysis included all randomised patients who received at least one dose of study medication and at least one post-baseline assessment.

Secondary efficacy endpoints included the proportion of patients achieving ACR20, ACR50, and ACR70 (defined as ≥20%, 50%, or 70% improvement from baseline, respectively); mean change from baseline in HAQ-DI and rates of improvement in HAQ-DI of 0·5 units or more; mean change from baseline in DAS28-4(ESR) and DAS28-3(CRP), and rates of DAS28-4(ESR) and DAS28-3(CRP) <2·6 and ≤3·2; pain (patient assessment of arthritis pain; 100-mm visual analogue scale of severity of arthritis pain from 0 [no pain] to 100 [most severe pain]); and fatigue (functional assessment of chronic illness therapy-fatigue [FACIT-F]; a 13-item questionnaire with a score range 0–52; higher scores represent less fatigue).[14] Secondary efficacy endpoints were measured at all visits to month 6 (baseline, week 2, and months 1, 3, 4·5, and 6), except month 4·5 for FACIT-F, and week 2 and months 1 and 4·5 for ESR rate. Outcomes not reported in this paper but included in the protocol are shown in the appendix.

Remission data were also analysed according to the Boolean-based[15] and index-based (simplified disease activity index [SDAI] ≤3·3) criteria recently recommended by the American College of Rheumatology and the European League Against Rheumatism.

The incidence and severity of adverse events were recorded and clinical laboratory tests, vital sign assessments, and physical examinations were done at every visit (baseline, week 2, and months 1, 3, 4·5, and 6). The safety analysis set was defined as those patients who received at least one dose of tofacitinib or placebo.

Statistical analysis

To control for type I error, each of the three co-primary endpoints was assessed in a sequential manner (appendix): ACR20 response rates, then mean change from baseline in HAQ-DI, then DAS28<2·6 rates. Type I error was controlled for the co-primary endpoints when statistical significance was determined. No control for type I error was applied for secondary endpoints and post-hoc analyses, and statistical significance was defined as $p<0·05$. Sample size calculations were made separately for each endpoint: a sample size of 396 patients yielded more than 90% power for each of the three primary endpoints (appendix). We used SAS version 9.2 for all statistical analyses.

This study (A3921032) is registered with ClinicalTrials.gov, number NCT00960440).

	Placebo (n=132)	Tofacitinib 5 mg twice a day (n=133)	Tofacitinib 10 mg twice a day (n=134)
Women	106 (80·3%)	113 (85·0%)	116 (86·6%)
White	112 (84·8%)	108 (81·2%)	112 (83·6%)
Age (years)	54·4 (11·3)	55·4 (11·5)	55·1 (11·3)
Disease duration (years)	11·3 (0·4–47·0)	13·0 (1·2–55·0)	12·6 (0·7–42·0)
Tender joints	28·2 (16·7)	28·4 (18·3)	27·6 (15·7)
Swollen joints	17·2 (10·7)	16·2 (10·1)	16·6 (9·9)
HAQ-DI	1·6 (0·7)	1·6 (0·7)	1·5 (0·6)
DAS28-4(ESR)	6·4 (1·1)	6·5 (1·1)	6·4 (0·9)
DAS28-3(CRP)	5·4 (1·0)	5·4 (1·0)	5·3 (0·9)
ESR (mm/h)	46·7 (24·6)	47·8 (26·1)	45·2 (22·9)
CRP (nmol/L)	159·1 (186·7)	183·8 (261·9)	149·5 (205·6)
RF positive	86 (65·6%)*	80 (60·6%)*	83 (61·9%)
Anti-CCP (ACPA) positive	97 (75·8%)†	89 (68·5%)†	90 (69·8%)†
Previous TNFi	132 (100%)	132 (99·2%)‡	132 (98·5%)§
Adalimumab	78 (59·1%)	65 (48·9%)	74 (55·2%)
Certolizumab	11 (8·3%)	9 (6·8%)	9 (6·7%)
Etanercept	57 (43·2%)	65 (48·9%)	57 (42·5%)
Golimumab	7 (5·3%)	5 (3·8%)	8 (6·0%)
Infliximab	43 (32·6%)	56 (42·1%)	42 (31·3%)
Previous failed TNFi	1·5 (0·7)	1·5 (0·7)	1·4 (0·7)
Number of previous TNFi			
One	86 (65·2%)¶	84 (63·2%)¶	90 (67·2%)
Two	37 (28·0%)	37 (27·8%)	30 (22·4%)
Three or more	9 (6·8%)	11 (8·3%)	12 (9·0%)
Previous non-TNFi biologicals	14 (10·6%)	21 (15·8%)	11 (8·2%)
Abatacept	11 (8·3%)	15 (11·3%)	8 (6·0%)
Anakinra	1 (0·8%)	0	0
Canakinumab	0	1 (0·8%)	0
Rituximab	2 (1·5%)	6 (4·5%)	2 (1·5%)
Tocilizumab	3 (2·3%)	5 (3·8%)	4 (3·0%)
Previous methotrexate	132 (100%)	131 (98·5%)‖	134 (100%)
Previous DMARDs other than methotrexate	33 (25·0%)	53 (39·8%)	37 (27·6%)
Concomitant antimalarials	5 (3·8%)	12 (9·0%)	7 (5·2%)
Concomitant corticosteroids	83 (62·9%)	85 (63·9%)	81 (60·4%)
Concomitant lipid-lowering medication	4 (3·0%)	2 (1·5%)	3 (2·2%)
LDL ≥3·37 mmol/L	33 (25·6%)**	36 (27·9%)**	33 (25·2%)**

Data are number (%), mean (SD), or mean (range). HAQ-DI=health assessment questionnaire-disability index. DAS=disease activity score. CRP=C-reactive protein. RF=rheumatoid factor. CCP=cyclic citrullinated peptide antibody. ACPA=anticitrullinated protein antibodies. TNFi=tumour necrosis factor inhibitor. DMARD=disease-modifying antirheumatic drug. *Placebo n=131; tofacitinib 5 mg twice a day n=132. †Placebo n=128; tofacitinib 5 mg twice a day n=130; tofacitinib 10 mg twice a day n=129. ‡One patient assigned to the 5 mg twice a day treatment group had been previously treated with a biosimilar version of etanercept. §Two patients assigned to the 10 mg twice a day treatment sequence had no previous treatment with TNFi (methotrexate, n=1; methotrexate plus sulfasalazine, n=1). ¶One patient in the 5 mg twice a day treatment group and two patients in the 10 mg twice a day treatment group had no treatment failures. ‖Two patients assigned to the 5 mg twice a day treatment sequence were on methotrexate before screening. This information was erroneously not entered into the database. **Placebo n=129; tofacitinib 5 mg twice a day n=129; tofacitinib 10 mg twice a day n=131.

Table 1: **Demographic and baseline characteristics**

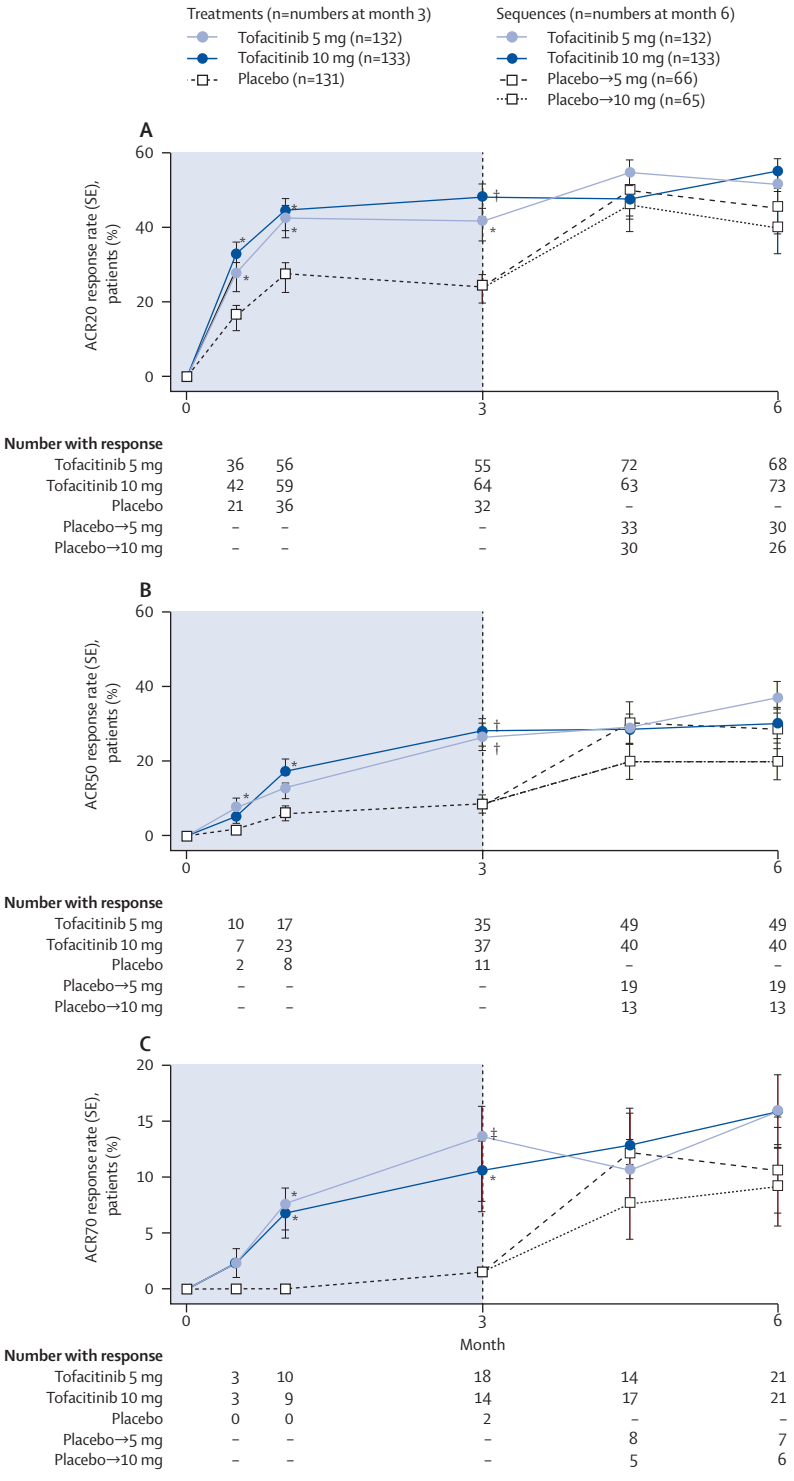

***Figure 2*: ACR response rates over time**

ACR20 (A), ACR50 (B), and ACR70 (C) over time (FAS, NRI). All treatments were given twice a day. Shaded region represents the placebo-controlled study period. ACR=American College of Rheumatology. ACR20/50/70=at least 20%, 50%, or 70% improvement in tender or swollen joint counts as well as at least 20%, 50%, or 70% improvement in three of the other five ACR components. FAS=full analysis set. NRI=non-responder imputation. SE=standard error. *p≤0·05 *vs* placebo; †p<0·0001 *vs* placebo; ‡p<0·001 *vs* placebo.

Role of the funding source

Employees of the sponsor were involved in study conception, design, and conduct, and in data collection and data analysis. The corresponding author had full access to all the data in the study and had final responsibility for the decision to submit for publication.

Results

Between October, 2009, and March, 2011, 399 patients were randomly assigned to receive tofacitinib 5 mg twice a day (n=133), tofacitinib 10 mg twice a day (n=134), placebo for 3 months then tofacitinib 5 mg twice a day (n=66), and placebo for 3 months then tofacitinib 10 mg twice a day (n=66). 311 (77·9%) patients completed the study (figure 1), and follow-up was completed in March, 2011.

Baseline demographic characteristics were similar between treatment groups (table 1). Most patients were white and women. The mean age was 54·4–55·4 years, mean duration of rheumatoid arthritis was 11·3–13·0 years, and mean number of previous TNFi treatments was 1·4–1·5. 257 of 399 patients (64%) had previously received one TNFi, 104 (26%) had received two, and 32 (8%) had received three or more. TNFi use was discontinued because of lack of efficacy (n=260; 65·2%), lack of efficacy and intolerance (78 of 399; 19·5%), or intolerance alone (55 of 399; 13·8%). 46 (12%) patients had also received biological DMARDs other than TNFi. Baseline mean HAQ-DI and DAS28-4(ESR) score ranges were 1·5–1·6 and 6·4–6·5, respectively (table 1). Patients had a substantial burden of concomitant illness at screening, including hypertension (n=161; 40%), hypercholesterolaemia (28; 7%), osteoporosis (64; 16%), diabetes mellitus (17; 4%), and chronic obstructive pulmonary disease (11; 3%).

At month 3, ACR20 response rates for tofacitinib 5 and 10 mg twice a day were 41·7% (55 of 132; [95% CI *vs* placebo 6·06–28·41]; p=0·0024) and 48·1% (64 of 133; [12·45–34·92]; p<0·0001), respectively, versus placebo, 24·4% (32 of 131; figure 2A). Time to onset of a significant ACR20 response was 2 weeks for both tofacitinib groups (figure 2A). ACR20 response rate at month 3 by the number of previous TNFi is shown in the appendix. ACR50 response rates at month 3 were 26·5% (35 of 132; [9·21–27·02]; p<0·0001) for 5 mg twice a day and 27·8% (37 of 133 [10·44–28·39]; p<0·0001) for 10 mg twice a day, versus placebo (8·4%; 11 of 131), with significant improvements also observed as early as week 2 (figure 2B). Response rates at month 3 for ACR70 were 13·6% (18 of 132; [5·89–18·32]; p<0·0001) for tofacitinib 5 mg twice a day and 10·5% (14 of 133; [3·37–14·62]; p=0·0017) for tofacitinib 10 mg twice a day versus placebo, 1·5% (two of 131; figure 2B). Significant improvements in ACR70 response rates for both tofacitinib doses versus placebo were reported at month 1 (figure 2C). Modest continued improvement in ACR response rate was seen beyond month 3, with the greatest

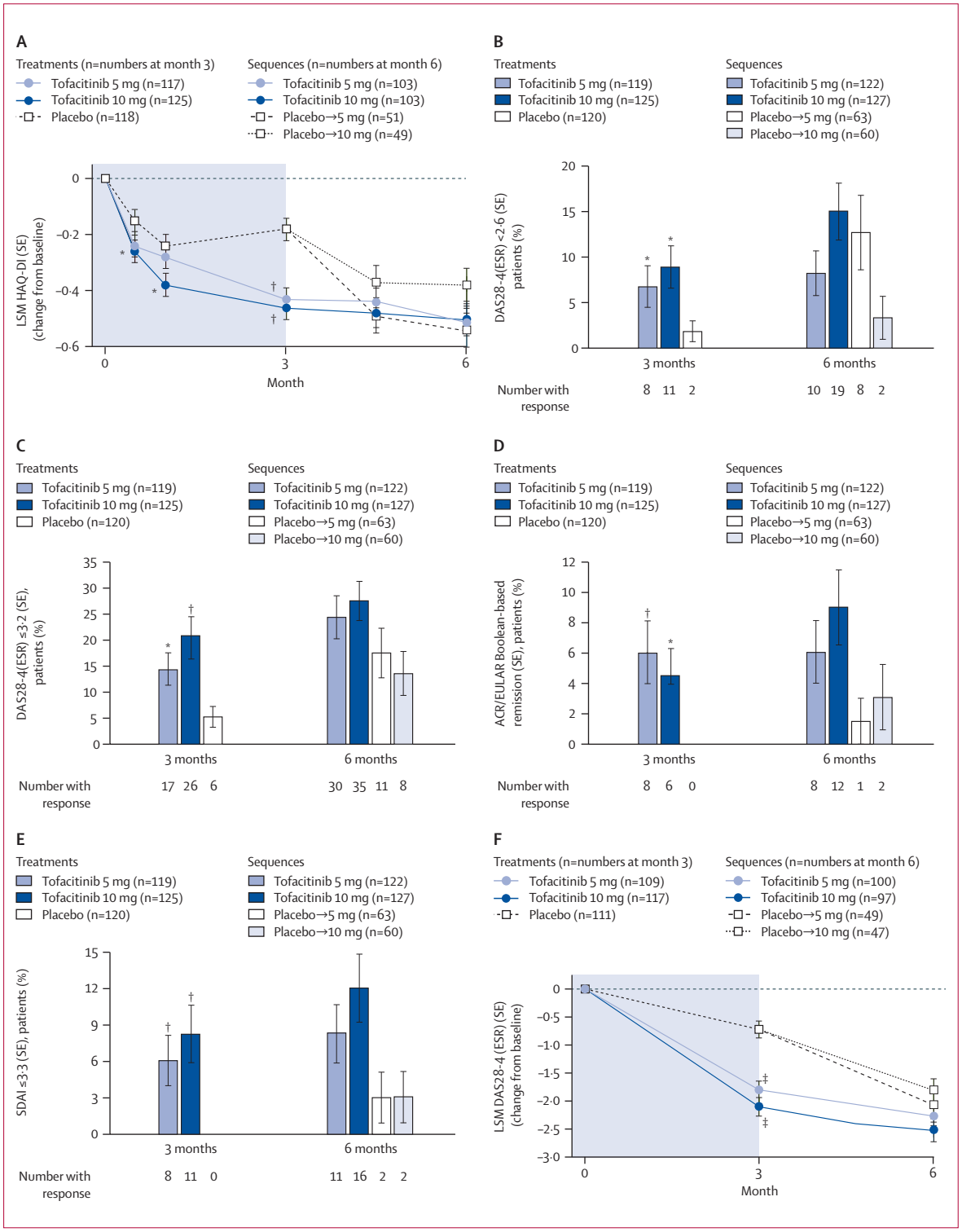

Figure 3: **Assessments of disease activity and physical function over time**
HAQ-DI (FAS, longitudinal model) (A); DAS28-4(ESR) <2·6 (FAS, NRI) (B); DAS28-4(ESR) ≤3·2 (FAS, NRI) (C); ACR/EULAR Boolean-based remission (D); SDAI ≤3.3 (E); and DAS28-4(ESR) (FAS, longitudinal model) (F). All treatments were given twice a day. *p≤0·05 *vs* placebo; †p<0·0001; ‡p<0·01 *vs* placebo. Shaded region represents the placebo-controlled study period. HAQ-DI=Health Assessment Questionnaire-Disability Index. FAS=full analysis set. NRI=non-responder imputation. ACR=American College of Rheumatology. DAS=disease activity score. EULAR=European League Against Rheumatism. LSM=least squares mean. SDAI=simplified disease activity index. SE=standard error.

continued improvement noted in ACR70 response rate. ACR component scores are shown in the appendix.

At month 3, least squares mean (LSM) changes from baseline in HAQ-DI were –0·43 ([95% CI –0·36 to –0·15]; p<0·0001) for tofacitinib 5 mg twice a day and –0·46 ([–0·38 to –0·17]; p<0·0001) for tofacitinib 10 mg twice a day versus placebo, –0·18 (figure 3A). LSM changes from baseline in HAQ-DI were significant for 10 mg twice a day versus placebo at all visits up to month 3 and continued to improve through month 6 (figure 3A). For 5 mg twice a day tofacitinib, LSM changes from baseline were significant at month 3 and were maintained through to month 6 (figure 3A). Improvement in HAQ-DI of 0·5 units or more was seen in 35·9% (47 of 131; [4·52–26·01]; p=0·0053) of patients receiving tofacitinib 5 mg twice a day and 39·9% (53 of 133; [8·41–30·06]; p=0·0004) receiving tofacitinib 10 mg twice a day, versus placebo, 20·6% (27 of 131; month 3). Improvement in HAQ-DI of 0·22 units or more was seen in 54·2% (71 of 131; [1·76–25·71]; p=0·0245) of patients receiving tofacitinib 5 mg twice a day and 58·7% (78 of 133; [6·32–30·05]; p=0·0026) receiving tofacitinib 10 mg twice a day versus placebo, 40·5% (53 of 131; month 3).

The proportions of patients with DAS28<2·6 at month 3 were 6·7% (eight of 119; [0–10·10]; p=0·0496) for tofacitinib 5 mg twice a day and 8·8% (11 of 125; [1·66–12·60]; p=0·0105) for tofacitinib 10 mg twice a day versus placebo (1·7%; two of 120), which increased to 8·2% (ten of 122) with tofacitinib 5 mg twice a day and 15·0% (19 of 127) with tofacitinib 10 mg twice a day at month 6 (figure 3B). At month 3, DAS28-4(ESR)≤3·2 was achieved by 14·3% (17 of 119; [1·88–16·68]; p=0·0138) of patients in the tofacitinib 5 mg twice a day group and 20·8% (26 of 125; [7·68–23·91]; p=0·0001) of patients in the 10 mg twice a day group versus placebo, 5·0% (six of 120; figure 3C). At month 3, Boolean-based defined remission was achieved by 6·1% (eight of 132; [1·99–10·13]; p=0·0035) of patients in the tofacitinib 5 mg twice a day group and 4·5% (six of 133; [0·98–8·03]; p=0·0121) of patients in the 10 mg twice a day group versus 0% in the placebo group; at month 6, remission was achieved by 6·1% (eight of 132 [1·99–10·13]) of patients in the 5 mg twice a day group and 9·0% (12 of 133 [4·15–13·89]) of patients in the 10 mg twice a day group (figure 3D). At month 3, the proportion of patients achieving index-based defined remission (SDAI ≤3·3) was 6·1% (eight of 132; [1·99–10·13]; p=0·0035) for tofacitinib 5 mg twice a day and 8·3% (11 of 133; [3·58–12·95]; p=0·0005) for tofacitinib 10 mg twice a day versus 0% for placebo; at month 6, remission was achieved by 8·3% (11 of 132 [3·61–13·04]) of patients in the tofacitinib 5 mg twice a day group and 12% (16 of 133 [6·50–17·55]) of patients in the tofacitinib 10 mg twice a day group (figure 3E).

LSM changes from baseline in DAS28-4(ESR) at month 3 were –1·8 ([–1·43 to –0·72]; p<0·0001) for tofacitinib 5 mg and –2·1 ([–1·72 to –1·03]; p<0·0001) for tofacitinib 10 mg versus placebo, –0·7 (figure 3F). The appendix shows LSM changes from baseline in ESR, CRP, and DAS28-3(CRP), and rates of DAS28-3(CRP)<2·6 and DAS28-3(CRP)≤3·2 at months 3 and 6; the first time-point for measurement was the week 2 visit.

At month 3, LSM changes from baseline in patient assessment of arthritis pain was –27·2 (n=114; [–24·76 to –13·04]; p<0·0001) for tofacitinib 5 mg twice a day and –25·0 (n=119; [–22·49 to –10·89]; p<0·0001) for tofacitinib 10 mg twice a day versus –8·3 (n=115) for placebo. Improvements in FACIT-F at month 3 were 6·3 (n=117; [2·77–7·54]; p<0·0001) for tofacitinib 5 mg twice a day and 4·6 (n=125; [1·09–5·83]; p=0·0043) for tofacitinib 10 mg twice a day versus 1·1 (n=114) for placebo.

In months 0–3, 147 of 267 (55%) patients across tofacitinib groups had 310 treatment-emergent adverse events, with similar frequencies to patients in the placebo group (table 2). The most common adverse events in months 0–3 were diarrhoea (13 of 267; 4·9%), nasopharyngitis (11 of 267; 4·1%), headache (11 of 267; 4·1%), and urinary tract infection (eight of 267; 3·0%) across tofacitinib groups, and nausea (nine of 132; 6·8%) in the placebo group (appendix). Serious adverse events occurred in four of 267 patients (1·5%) treated with tofacitinib and six of 132 patients (4·5%) in the placebo group (table 2). No serious infection events were reported. Discontinuations due to treatment-emergent adverse events occurred in 14 of 267 patients (5·2%) treated with tofacitinib in months 0–3 versus seven of 132 patients (5·3%) receiving placebo.

	Months 0–3			Months 3–6			
	Placebo (n=132)	Tofacitinib 5 mg (n=133)	Tofacitinib 10 mg (n=134)	Placebo then tofacitinib 5 mg (n=66)	Placebo then tofacitinib 10 mg (n=66)	Tofacitinib 5 mg (n=133)	Tofacitinib 10 mg (n=134)
Adverse events	167	145	165	57	59	96	123
Patients with adverse events	75 (56·8%)	71 (53·4%)	76 (56·7%)	24 (36·4%)	28 (42·4%)	57 (42·9%)	58 (43·3%)
Serious adverse events	6 (4·5%)	2 (1·5%)	2 (1·5%)	3 (4·5%)	2 (3·0%)	5 (3·8%)	6 (4·5%)
Serious infections*	0	0	0	1 (1·5%)	0	2 (1·5%)	2 (1·5%)
Discontinuations because of adverse events	7 (5·3%)	8 (6·0%)	6 (4·5%)	1 (1·5%)	2 (3·0%)	4 (3·0%)	7 (5·2%)
Deaths	0	0	0	0	1 (1·5%)	0	0

Data are number or number (%). *No cases of opportunistic infection were reported. All treatments were given twice a day.

Table 2: **Summary of safety data**

In months 3–6, 167 of 399 (41·9%) patients across all groups had 335 treatment-emergent adverse events, and 16 of 399 patients (4·0%) had serious adverse events (table 2). The most common treatment-emergent adverse events in this period were upper respiratory tract infection (13 of 399; 3·3%), nasopharyngitis (11 of 399; 2·8%), and bronchitis (nine of 399; 2·3%; appendix). During months 3–6, serious infection events were reported by two patients in the 5 mg twice a day group (panniculitis [n=1]; bronchopneumonia [n=1]), two patients in the 10 mg twice a day group (pyelonephritis [n=1] and diverticulitis [n=1]), and one patient in the placebo then tofacitinib 5 mg twice a day group (aspiration pneumonia [n=1]). 14 (3·5%) of 399 patients discontinued because of treatment-emergent adverse events in months 3–6. One 51-year-old woman in the placebo plus tofacitinib 10 mg group died on day 132 due to autopsy-confirmed pulmonary embolism. There was no evidence of anti-phospholipid antibodies in this patient. Patient history included obesity, hypertension,

	Month 3			Month 6			
	Placebo (n=132)	Tofacitinib 5 mg (n=133)	Tofacitinib 10 mg (n=134)	Placebo then tofacitinib 5 mg (n=66)	Placebo then tofacitinib 10 mg (n=66)	Tofacitinib 5 mg (n=133)	Tofacitinib 10 mg (n=134)
Neutrophil count, 10⁹/L, LSM change (SE) from baseline	0·13 (0·17)	−0·93 (0·17)	−0·81 (0·17)	−0·77 (0·25)	−0·69 (0·26)	−0·73 (0·18)	−0·77 (0·19)
95% CI *vs* placebo	..	−1·49 to 0·63	−1·37 to −0·52	..	..	..	..
p value *vs* placebo	..	<0·0001	<0·0001	..	..	..	..
Haemoglobin, g/L, mean change (SD) from baseline	−1·00 (7·80)	1·10 (7·00)	0·10 (8·20)	1·10 (7·30)	0·30 (9·70)	1·60 (7·80)	−0·20 (8·80)
95% CI *vs* placebo*	..	−0·19 to 4·01	−0·92 to 3·12	..	..	..	..
p value *vs* placebo*	..	0·03	0·29	..	..	..	..
LDL, LSM % change (SE) from baseline	−0·01 (0·05)	0·29 (0·05)	0·30 (0·05)	0·25 (0·07)	0·42 (0·08)	0·31 (0·05)	0·27 (0·06)
95% CI *vs* placebo	..	0·17 to 0·42	0·19 to 0·43	..	..	..	..
p value *vs* placebo	..	<0·0001	<0·0001	..	..	..	..
HDL, LSM % change (SE) from baseline	0·00 (0·05)	0·35 (0·05)	0·40 (0·05)	0·37 (0·07)	0·45 (0·07)	0·43 (0·05)	0·47 (0·05)
95% CI *vs* placebo	..	0·23 to 0·46	0·28 to 0·51	..	..	..	..
p value *vs* placebo	..	<0·0001	<0·0001	..	..	..	..
Serum creatinine, µmol/L, LSM change (SE) from baseline	3·81 (1·53)	3·05 (1·53)	3·81 (1·53)	3·05 (1·53)	4·58 (2·29)	3·81 (1·53)	4·58 (1·53)
95% CI *vs* placebo	..	−4·58 to 3·05	−3·81 to 3·81	..	..	..	..
p value *vs* placebo	..	0·71	0·90	..	..	..	..
Neutropenia (incidence, n [%])							
n	118	116	124	50	48	100	102
Mild (1·5–1·999×10⁹/L)	2 (1·7)	3 (2·6)	2 (1·6)	2 (4·0)	3 (6·3)	1 (1·0)	0
Moderate (1·000–1·499×10⁹/L) to severe (0·5–0·999×10⁹/L)	0	1 (0·9)	0	0	0	0	1 (1·0)
Potentially life-threatening (<0·5×10⁹/L)	0	0	0	0	0	0	0
Decreased haemoglobin							
Mild to moderate (decrease ≥10 g/L to ≤20 g/L)	12 (10·2)	9 (7·8)	16 (12·9)	4 (8·0)	4 (8·3)	5 (5·0)	15 (14·7)
Severe (decrease >20 g/L to <30 g/L or haemoglobin >70 g/L, but <80 g/L)	0	0	0	0	0	0	0
Potentially life-threatening (decrease of ≥30 g/L or haemoglobin ≤70 g/L)	1 (0·8)	0	0	0	0	0	0
AST/ALT (incidence, n [%])							
n	131	132	133	58	54	116	121
AST >1×ULN	13 (9·9)	18 (13·6)	16 (12·0)	13 (22·4)	8 (14·8)	17 (14·7)	15 (12·4)
AST >3×ULN	0	0	0	0	0	0	0
ALT >1×ULN	17 (13·0)	18 (13·6)	27 (20·3)	10 (17·2)	9 (16·7)	18 (15·5)	23 (19·0)
ALT >3×ULN	0	0	2 (1·5)	0	1 (1·9)	1 (0·9)	1 (0·8)

ALT=alanine aminotransferase. AST=aspartate aminotransferase. LSM=least squares mean. SE=standard error. ULN=upper limit of normal. *95% CI and p values are generated using a paired *t* test for values at month 3. All treatments were given twice a day.

Table 3: **Summary of laboratory data**

and previous or concomitant hormone replacement therapy (ethinylestradiol-norethisterone). In the opinion of the investigator, the event was not related to study drug and was possibly related to concomitant ethinylestradiol-norethisterone. No opportunistic infections and no cases of malignancy were reported.

Differences in mean changes from baseline in laboratory parameters noted for tofacitinib 5 and 10 mg twice a day versus placebo included decreases in neutrophil counts and increases in cholesterol (HDL and LDL) concentrations (table 3, appendix). No patient had a confirmed potential life-threatening absolute neutrophil count of less than $0 \cdot 5 \times 10^9$/L (table 3). All mean laboratory safety values stabilised after month 3.

The proportions of patients with LDL below 2·59 mmol/L at baseline who increased to 3·37 mmol/L or higher in months 0–3 were 10·9% (five of 46) for 5 mg twice a day tofacitinib, 10·0% (five of 50) for 10 mg twice a day tofacitinib, and 7·0% (three of 43) for placebo. Mean increases from baseline in serum creatinine were 5·30 µmol/L or less and similar across all treatment groups through month 6 (table 3).

Hepatic transaminase elevations (>1×ULN) had similar incidences in the placebo and tofacitinib groups overall although the incidence of ALT of more than the ULN was higher in the tofacitinib 10 mg twice a day group during months 0–3; elevations of higher than three times the ULN were uncommon (appendix, table 3). Creatine kinase elevations higher than three times the ULN were few (appendix).

Between baseline and month 3, the mean change in haemoglobin increased by 1·1 g/L in the tofacitinib 5 mg twice a day group, did not change in the tofacitinib 10 mg twice a day (0·01 g/L) group, and declined slightly in the placebo group (–0·10 g/L; appendix). The incidence of decreased haemoglobin from baseline to month 3 was not greater in the active treatment groups (7·8% for 5 mg twice a day and 12·9% for 10 mg twice a day) compared with placebo (10·2%), and most cases of decreased haemoglobin were mild-to-moderate in severity. Changes were seen during months 0–3 of active treatment and stabilised thereafter (appendix). Over the entire 6-month study, two patients in the placebo then tofacitinib 10 mg group discontinued because of decreases in haemoglobin; one of these discontinuations was protocol-mandated and occurred while the patient was receiving placebo.

***Panel:* Research in context**

Systematic review

We did a PubMed literature search in December 2011 with the terms "arthritis", "rheumatoid" [MeSH], "clinical trial", "phase iii" [publication type], "TNFi" (various terms), "inadequate response" OR "refractory" (no date restriction) to identify prospective randomised phase 3 studies of non-TNFi biologicals in patients with previous inadequate response to TNFi. This search yielded 30 papers, of which only three reported phase 3 studies in this specific setting. A phase 3 study of the TNFi golimumab has also been included, as the patient population had a previous inadequate response to TNFi.

Interpretation

Although comparisons across studies cannot be made, similar findings to our study were reported in previous studies in this therapeutic setting: Abatacept Trial in Treatment of Anti-TNF Inadequate Responders (ATTAIN),[24] Randomised Evaluation of Long-Term Efficacy of Rituximab in rheumatoid arthritis (REFLEX),[25] the tocilizumab Research on Actemra Determining Efficacy after Anti-TNF Failures (RADIATE),[26] and the golimumab in patients with active rheumatoid arthritis after treatment with tumour necrosis factor alpha inhibitors (GO-AFTER)[27] studies. The primary efficacy endpoint (ACR20, and also HAQ-DI in ATTAIN) of these studies was reported at week 14 (GO-AFTER) and month 6 (ATTAIN, REFLEX, RADIATE) rather than at month 3 as in our study. ACR20 responses at the time of the primary endpoint were significantly higher with active treatment than with placebo: 50·4% (abatacept) versus 19·5% (placebo) in ATTAIN;[24] 51·0% (rituximab) versus 18·0% (placebo) in REFLEX;[25] 50·0% (tocilizumab 8 mg/kg) and 30·4% (tocilizumab 4 mg/kg) versus 10·1% (placebo) in RADIATE;[26] and 35·3% (golimumab 50 mg) and 37·9% (golimumab 100 mg) versus 18·1% (placebo) in GO-AFTER.[27] As in our study, HAQ-DI was a co-primary endpoint in ATTAIN in which a significant improvement from baseline in the proportion of patients with HAQ-DI improvement 0·3 units or more was seen versus placebo (47·3% abatacept; 23·3% placebo). The data presented herein expand the evidence supporting effective treatment options with alternative mechanisms of action for patients with an inadequate response to TNFi who have high unmet medical need.

Discussion

In this treatment-refractory patient population, in which a third of patients had previously been treated with two or more TNFi, tofacitinib 5 and 10 mg twice a day had rapid, significant, and clinically meaningful improvements compared with placebo. All primary and secondary outcomes improved with both doses versus placebo at month 3, and results are discussed further in the appendix.

The patient population had a substantial burden of concomitant illness at screening; nevertheless, the safety profile of tofacitinib was consistent with previous phase 2 and phase 3 studies (panel);[16–23] no new safety signals were detected. We noted changes in laboratory parameters for tofacitinib 5 and 10 mg twice a day versus placebo, including decreases in mean neutrophil counts, and increases in mean HDL and LDL concentrations. Changes in these parameters were similar between the 5 and 10 mg twice a day doses. Whether changes in lipid levels associated with immune modulatory therapy are necessarily associated with increased cardiovascular risk is unclear. Further studies to achieve a better understanding of the mechanism underlying the lipid changes seen with tofacitinib in patients with rheumatoid arthritis are warranted. Mean changes in serum creatinine and rates of transaminase increases were similar across all groups. The absence of a significant increase in haemoglobin concentrations during tofacitinib treatment is in contrast with the increases commonly seen during treatment with other DMARDs, such as biological therapies. The mean haemoglobin concentration changes in the tofacitinib 5 mg twice a day and 10 mg twice a day groups are probably due to a combination of the attenuation of inflammation-mediated effects on haemoglobin and transient inhibition of signalling by erythropoietin

through JAK2, particularly for the 10 mg twice a day dose. In our study, the incidence of decreased haemoglobin was not greater in active treatment groups than in the placebo groups, and most cases were mild-to-moderate in severity.

Limitations of the study include narrow ethnic and geographic diversity of the patient population. Because of the requirement for previous TNFi treatment, most patients were white (332 of 399; 83%) and from North America or Europe (350 of 399; 88%). Because these patients had severe treatment-refractory rheumatoid arthritis, placebo treatment duration was limited to 3 months; therefore, definitive conclusions about the long-term efficacy and safety of tofacitinib can only be made after additional data are available for longer treatment durations.

In conclusion, in this treatment-refractory population, tofacitinib with methotrexate had rapid and clinically meaningful improvements in signs and symptoms of rheumatoid arthritis and physical function over 6 months with manageable safety. Tofacitinib may provide an effective treatment option in patients with an inadequate response to TNFi.

Contributors

GRB, RB, CC-S, JW, and CZ were involved in the acquisition and analysis of data. BB, DG, GW, SK, SHZ, TK, KS, JB, and CM made substantial contributions to study conception and design, and data analysis. All authors interpreted the data. All authors discussed and agreed the content of the manuscript before writing took place. All authors reviewed and approved the manuscript's content before submission.

Conflicts of interest

GRB is a consultant and member of the Speakers Bureau for Pfizer, Abbott, Bristol-Myers Squibb, MDS Pharma Services, Roche, and UCB, and receives research support from Pfizer, Wyeth, Abbott, Bristol-Myers Squibb, Roche, and UCB, and has received travel support from Pfizer. CC-S is a consultant for, and receives research support from, Pfizer. JW is a consultant and a member of the Speakers Bureau for and has received travel support from Pfizer. BB, DG, GW, SK, SHZ, TK, KS, JB, and CM are employees of Pfizer and hold stock or options in Pfizer. CZ receives research support from Centro Paulista de Investigação Clinica. RB declares that he has no conflicts of interest.

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References

1 Scott DL, Wolfe F, Huizinga TW. Rheumatoid arthritis. *Lancet* 2010; **376:** 1094–108.

2 Smolen JS, Aletaha D, Bijlsma JW, et al. Treating rheumatoid arthritis to target: recommendations of an international task force. *Ann Rheum Dis* 2010; **69:** 631–37.

3 Saag KG, Teng GG, Patkar NM, et al. American College of Rheumatology 2008 recommendations for the use of nonbiologic and biologic disease-modifying antirheumatic drugs in rheumatoid arthritis. *Arthritis Rheum* 2008; **59:** 762–84.

4 Strand V, Singh JA. Improved health-related quality of life with effective disease-modifying antirheumatic drugs: evidence from randomized controlled trials. *Am J Manag Care* 2007; **13** (suppl 9)**:** S237–S251.

5 Klareskog L, van der Heijde D, de Jager JP, et al. Therapeutic effect of the combination of etanercept and methotrexate compared with each treatment alone in patients with rheumatoid arthritis: double-blind randomised controlled trial. *Lancet* 2004; **363:** 675–81.

6 Keystone EC, Kavanaugh AF, Sharp JT, et al. Radiographic, clinical, and functional outcomes of treatment with adalimumab (a human anti-tumor necrosis factor monoclonal antibody) in patients with active rheumatoid arthritis receiving concomitant methotrexate therapy: a randomized, placebo-controlled, 52-week trial. *Arthritis Rheum* 2004; **50:** 1400–11.

7 Lipsky PE, van der Heijde DM, St Clair EW, et al. Infliximab and methotrexate in the treatment of rheumatoid arthritis. Anti-Tumor Necrosis Factor Trial in Rheumatoid Arthritis with Concomitant Therapy Study Group. *N Engl J Med* 2000; **343:** 1594–602.

8 Finckh A, Simard JF, Gabay C, Guerne PA. Evidence for differential acquired drug resistance to anti-tumour necrosis factor agents in rheumatoid arthritis. *Ann Rheum Dis* 2006; **65:** 746–52.

9 Felson DT, Anderson JJ, Boers M, et al. American College of Rheumatology. Preliminary definition of improvement in rheumatoid arthritis. *Arthritis Rheum* 1995; **38:** 727–35.

10 Fries JF, Spitz PW, Young DY. The dimensions of health outcomes: the health assessment questionnaire, disability and pain scales. *J Rheumatol* 1982; **9:** 789–93.

11 Hochberg MC, Chang RW, Dwosh I, Lindsey S, Pincus T, Wolfe F. The American College of Rheumatology 1991 revised criteria for the classification of global functional status in rheumatoid arthritis. *Arthritis Rheum* 1992; **35:** 498–502.

12 Prevoo ML, van 't Hof MA, Kuper HH, van Leeuwen MA, van de Putte LB, van Riel PL. Modified disease activity scores that include twenty-eight-joint counts. Development and validation in a prospective longitudinal study of patients with rheumatoid arthritis. *Arthritis Rheum* 1995; **38:** 44–48.

13 Radboud University Nijmegen Medical Centre. DAS-score.nl: disease activity score in rheumatoid arthritis. http://www.das-score.nl/ (accessed Nov 3, 2011).

14 Cella D, Lai JS, Chang CH, Peterman A, Slavin M. Fatigue in cancer patients compared with fatigue in the general United States population. *Cancer* 2002; **94:** 528–38.

15 Felson DT, Smolen JS, Wells G, et al. American College of Rheumatology/European League Against Rheumatism provisional definition of remission in rheumatoid arthritis for clinical trials. *Arthritis Rheum* 2011; **63:** 573–86.

16 Kremer JM, Bloom BJ, Breedveld FC, et al. The safety and efficacy of a JAK inhibitor in patients with active rheumatoid arthritis: results of a double-blind, placebo-controlled phase IIa trial of three dose levels of CP-690,550 versus placebo. *Arthritis Rheum* 2009; **60:** 1895–905.

17 Kremer JM, Cohen S, Wilkinson B, et al. The oral JAK inhibitor CP-690,550 (CP) in combination with methotrexate (MTX) is efficacious, safe and well tolerated in patients with active rheumatoid arthritis (RA) with an inadequate response to methotrexate alone. *Arthritis Rheum* 2008; **58:** 4030.

18 Tanaka Y, Suzuki M, Nakamura H, Toyoizumi S, Zwillich S. The oral JAK inhibitor CP-690,550 (CP) in combination with methotrexate (MTX) is efficacious, safe and well tolerated in Japanese patients (pts) with active rheumatoid arthritis (RA) with an inadequate response to MTX alone. *Ann Rheum Dis* 2009; **68** (suppl 3)**:** 594.

19 Fleischmann R, Genovese MC, Gruben D, et al. Safety and efficacy after 24 week (wk) dosing of the oral JAK inhibitor CP-690,550 (CP) as monotherapy in patients (pts) with active rheumatoid arthritis (RA). *Arthritis Rheum* 2009; **60** (suppl 10)**:** S718.

20 Fleischmann R, Kremer J, Connell CA, et al. Phase 3 study of oral JAK inhibitor CP-690,550 monotherapy in patients with active rheumatoid arthritis: sub-analysis of efficacy. *Ann Rheum Dis* 2011; **70:** 600, abs SAT0243.

21 Kremer J, Li ZG, Hall S, et al. Tofacitinib (CP-690,550), an oral Janus kinase inhibitor, in combination with traditional DMARDs: a phase 3 efficacy and safety study in patients with active rheumatoid arthritis with an inadequate response to DMARDs. *Ann Rheum Dis* 2011; **70:** 170.

22 van Vollenhoven RF, Fleischmann RM, Cohen SB, et al. Tofacitinib (CP-690,550), an oral Janus kinase inhibitor, or adalimumab versus placebo in patients with rheumatoid arthritis on background methotrexate: a phase 3 study. *Arthritis Rheum* 2011; **63** (suppl 10)**:** S153.

23 van der Heijde D, Tanaka Y, Fleischmann R, et al. Tofacitinib (CP-690,550), an oral Janus kinase inhibitor, in combination with methotrexate reduced the progression of structural damage in patients with rheumatoid arthritis: a 24-month Phase 3 study. *Arthritis Rheum* 2011; **63** (suppl 10): S107.

24 Genovese MC, Becker JC, Schiff M, et al. Abatacept for rheumatoid arthritis refractory to tumor necrosis factor alpha inhibition. *N Engl J Med* 2005; **353:** 1114–23.

25 Cohen SB, Emery P, Greenwald MW, et al. Rituximab for rheumatoid arthritis refractory to anti-tumor necrosis factor therapy: results of a multicenter, randomized, double-blind, placebo-controlled, phase III trial evaluating primary efficacy and safety at twenty-four weeks. *Arthritis Rheum* 2006; **54:** 2793–806.

26 Emery P, Keystone E, Tony HP, et al. IL-6 receptor inhibition with tocilizumab improves treatment outcomes in patients with rheumatoid arthritis refractory to anti-tumour necrosis factor biologicals: results from a 24-week multicentre randomised placebo-controlled trial. *Ann Rheum Dis* 2008; **67:** 1516–23.

27 Smolen JS, Kay J, Doyle MK, et al. Golimumab in patients with active rheumatoid arthritis after treatment with tumour necrosis factor alpha inhibitors (GO-AFTER study): a multicentre, randomised, double-blind, placebo-controlled, phase III trial. *Lancet* 2009; **374:** 210–21.