International Journal of
Rheumatic Diseases

International Journal of Rheumatic Diseases 2018; **21:** 402–414

ORIGINAL ARTICLE

Tofacitinib with conventional synthetic disease-modifying antirheumatic drugs in Chinese patients with rheumatoid arthritis: Patient-reported outcomes from a Phase 3 randomized controlled trial

Zhanguo LI,[1] Yuan AN,[1] Houheng SU,[2] Xiangpei LI,[3] Jianhua XU,[4] Yi ZHENG,[5] Guiye LI,[6] Kenneth KWOK,[7] Lisy WANG[8] and Qizhe WU[6]

[1]*Peking University People's Hospital, Beijing,* [2]*Qingdao Municipal Hospital, Qingdao,* [3]*Anhui Provincial Hospital, Hefei, Anhui,* [4]*First Affiliated Hospital of Anhui Medical University, Hefei,* [5]*Beijing Chaoyang Hospital, Chaoyang District, Beijing,* [6]*Pfizer Inc, Beijing, China,* [7]*Pfizer Inc, New York, New York, and* [8]*Pfizer Inc, Groton, Connecticut, USA*

Abstract

Aim: Tofacitinib is an oral Janus kinase inhibitor for the treatment of rheumatoid arthritis (RA). We assess the effect of tofacitinib + conventional synthetic disease-modifying anti rheumatic drugs (csDMARDs) on patient-reported outcomes in Chinese patients with RA and inadequate response to DMARDs.

Methods: This analysis of data from the Phase 3 study ORAL Sync included Chinese patients randomized 4 : 4 : 1 : 1 to receive tofacitinib 5 mg twice daily, tofacitinib 10 mg twice daily, placebo→tofacitinib 5 mg twice daily, or placebo→tofacitinib 10 mg twice daily, with csDMARDs. Placebo non-responders switched to tofacitinib at 3 months; the remaining placebo patients switched at 6 months. Least squares mean changes from baseline were reported for Health Assessment Questionnaire-Disability Index (HAQ-DI), patient assessment of arthritis pain (Pain), patient global assessment of disease activity (PtGA), physician global assessment of disease activity (PGA), Functional Assessment of Chronic Illness Therapy-Fatigue (FACIT-F) scores, Short Form 36 (SF-36), and Work Limitations Questionnaire (WLQ), using a mixed-effects model for repeated measures.

Results: Overall, 216 patients were included (tofacitinib 5 mg twice daily, $n = 86$; tofacitinib 10 mg twice daily, $n = 86$; placebo→tofacitinib 5 mg twice daily, $n = 22$; placebo→tofacitinib 10 mg twice daily, $n = 22$). At month 3, tofacitinib elicited significant improvements in HAQ-DI, Pain, PtGA, PGA and SF-36 Physical Component Summary scores. Improvements were generally maintained through 12 months.

Conclusion: Tofacitinib 5 and 10 mg twice daily + csDMARDs resulted in improvements in health-related quality of life, physical function and Pain through 12 months in Chinese patients with RA.

Key words: HAQ, pain, patient-reported outcomes, rheumatoid arthritis, tofacitinib.

INTRODUCTION

Rheumatoid arthritis (RA) is a chronic autoimmune disease characterized by systemic inflammation, persistent synovitis and joint destruction. The prevalence of RA in mainland China is estimated to range from 0.2% to 0.9%[1–3] and is comparable with worldwide prevalence estimates (0.24%).[4]

Correspondence: Dr Qizhe Wu, Pfizer Inc, 11F, Tower B, Minmetals Plaza, No. 3 Chaoyangmen North Avenue, Dongcheng District, Beijing 100010, China. Email: qizhe.wu@pfizer.com
*The copyright line for this article was changed on 18 January 2018 after original online publication.

RA represents a significant health and socioeconomic burden, and affects all domains of health-related quality of life (HRQoL).[5] In a cross-sectional survey of patients attending a rheumatology center in southwest China, 58.5% were functionally disabled.[6] For patients, improvement in HRQoL, pain, physical function and fatigue are often more meaningful than improvements in underlying disease activity when evaluating therapies.[7] Several patient-reported outcome (PRO) measures, such as the Health Assessment Questionnaire-Disability Index (HAQ-DI), Short Form-36 Health Survey (SF-36), patient global assessment of disease activity (PtGA), and patient assessment of arthritis pain (Pain), can more comprehensively reflect the impact of treatment on patients with RA than physician-reported measures such as swollen/tender joint assessment and physician global assessment of disease activity (PGA).[8,9]

Tofacitinib is an oral Janus kinase inhibitor for the treatment of RA. The efficacy and safety of tofacitinib 5 and 10 mg twice daily administered as monotherapy or in combination with conventional synthetic disease-modifying antirheumatic drugs (csDMARDs), mainly methotrexate (MTX), in patients with moderately to severely active RA, have been demonstrated in global Phase 2[10–14] and Phase 3[15–20] studies of up to 24 months' duration and in long-term extension studies with up to 105 months' observation.[21–23]

The Phase 3 study, ORAL Sync, was a 12-month, randomized controlled trial (ClinicalTrials.gov identifier NCT00856544) assessing tofacitinib treatment in combination with DMARDs in adult patients with active RA who had previously had inadequate responses to DMARD therapy.[17] Tofacitinib 5 and 10 mg twice daily demonstrated rapid, clinically meaningful improvements in symptoms of RA and physical function, with a safety profile consistent with that observed in other Phase 3 studies in the global study population[17] and a Chinese sub-population of ORAL Sync.[24] In a Chinese sub-population analysis using non-responder imputation, patients receiving tofacitinib 5 and 10 mg twice daily achieved significantly higher American College of Rheumatology (ACR) 20 response rates (67.4% and 70.6%, respectively) versus placebo (34.1%) at month 6. Rates of remission (Disease Activity Score in 28 joints, erythrocyte sedimentation rate [DAS28-4(ESR)] < 2.6) were also significantly greater in patients receiving tofacitinib 5 and 10 mg twice daily (7.1% and 13.1%, respectively) versus placebo (2.3%) at month 6. The safety profile of tofacitinib in Chinese patients was consistent with findings from global studies.[24] Significant and clinically meaningful improvements in several PROs have been reported in the global population of a number of Phase 3 trials of tofacitinib.[25–29] The objective of this analysis was to investigate the impact of tofacitinib with background csDMARDs on PROs in Chinese patients enrolled in ORAL Sync, the only Phase 3 study of tofacitinib in patients from China with RA.

MATERIALS AND METHODS

Study design and patient population

PRO data were analyzed from a sub-population of Chinese patients with RA enrolled in the randomized, 12-month, double-blind, placebo-controlled, parallel group, Phase 3 study, ORAL Sync (A3921046 [NCT00856544]).[17] In ORAL Sync, patients with an inadequate response to treatment with one or more csDMARDs or biologic DMARDs (bDMARDs) at a stable dose were randomized 4 : 4 : 1 : 1 to receive tofacitinib 5 mg twice daily, tofacitinib 10 mg twice daily, placebo switched to tofacitinib 5 mg twice daily (placebo→tofacitinib 5 mg twice daily), or placebo switched to tofacitinib 10 mg twice daily (placebo→tofacitinib 10 mg twice daily), respectively, all in combination with csDMARDs. Patients receiving background MTX (maximum dose 25 mg/week) required at least 4 months of therapy with stable dosing 6 weeks before receiving the study drug. Patients receiving placebo who did not respond at 3 months were switched blindly to tofacitinib 5 or 10 mg twice daily; response was defined as a reduction of at least 20% from baseline in swollen and tender joint counts. At month 6, all remaining placebo patients were switched to tofacitinib.[17]

Detailed inclusion criteria have been previously reported.[17] Briefly, eligible patients were aged ≥ 18 years and had active RA based on the ACR 1987 revised criteria.[30] Key inclusion criteria included ≥ 4 tender or painful joints, ≥ 4 swollen joints (68- or 66-joint count), and an ESR of ≥ 28 mm/h or a C-reactive protein level of >7 mg/L. Key exclusion criteria included: serious chronic or recurrent infections; evidence of active or inadequately treated latent tuberculosis infection; history of recurrent herpes zoster (HZ), disseminated HZ or herpes simplex, hepatitis B or C, human immunodeficiency virus or other opportunistic infections; history of lymphoproliferative disorder and malignancy (except adequately treated or excised non-metastatic basal or squamous cell skin cancer or cervical carcinoma *in situ*).

The study was conducted in accordance with the Declaration of Helsinki and the International Conference on Harmonisation Good Clinical Practice

Guidelines, and was approved by the Institutional Review Boards and/or Independent Ethics Committees at each investigational center. All patients provided written informed consent.

Outcomes

Physical functioning was assessed by HAQ-DI, a generic patient-reported questionnaire assessing mobility and physical function. The HAQ-DI includes 20 questions across eight categories, each scored 0–3, with 0 indicating that the respondent is able to undertake the activity without any difficulty, and 3 indicating that the respondent is unable to perform the activity.[31] Change from baseline in HAQ-DI score and the proportion of patients achieving a minimal clinically important difference (MCID) in HAQ-DI, defined as an improvement from baseline ≥ 0.22, were analyzed.

PtGA, PGA and Pain were each assessed by 100 mm visual analogue scales, on which the patient indicated their subjective opinion of their current disease activity or arthritis pain severity.[32] Change from baseline in PtGA, PGA and Pain were analyzed.

Fatigue was assessed by the Functional Assessment of Chronic Illness Therapy-Fatigue (FACIT-F) scale, a 13-item questionnaire used extensively to assess fatigue in chronic diseases. Each item has five response options, scored 0–4; the total FACIT-F scale score ranges 0–52, with 0 being the worst possible score and 52 the best.[33] Change from baseline in total FACIT-F score was analyzed.

General aspects of HRQoL were assessed using the SF-36 questionnaire, which consists of a series of simple, generic questions regarding quality of life across eight domains: physical functioning, role-physical, bodily pain, general health, vitality, social functioning, role-emotional and mental health, each scored 0–100.[34] These eight items can be aggregated into two summary measures: the Physical and Mental Component Summary scores (PCS and MCS, respectively). The Chinese version of the SF-36 questionnaire has been validated in Chinese patients.[35] Change from baseline in each of the domains, PCS and MCS of the SF-36 were analyzed.

The Work Limitations Questionnaire (WLQ) measured the extent, over the last 2 weeks, to which health problems interfered with specific aspects of job performance and the productivity impact of work limitations. The WLQ consists of 25 items across four domains (physical demands, time management, mental/interpersonal demands and output demands), with each item rated on a five-point scale.[36] A Work Loss Index was also calculated from the WLQ scores. Change from baseline in each of the domains of the WLQ and the Work Loss Index were analyzed.

Statistical analysis

This exploratory analysis was based on the Chinese subpopulation of the full analysis set (FAS; all patients who received at least one dose of study treatment and for whom data were available from at least one post-baseline assessment). No imputation for missing values was performed. Statistical significance was declared at $P \leq 0.05$ with no correction for multiple comparisons.

All endpoints were summarized as least squares mean (LSM) changes from baseline at week 2, months 3, 6, 9 or 12, and analyzed using a linear mixed-effects repeated-measures model. For comparison with placebo, data from patients receiving each dose of tofacitinib were compared with combined data from placebo→tofacitinib 5 mg twice daily and placebo→tofacitinib 10 mg twice daily at 3 and 6 months. Data from 6 to 12 months are presented with no formal statistical comparisons between treatment groups.

RESULTS

A total of 216 patients were enrolled in China and received study treatment. Eighty-six patients received tofacitinib 5 mg twice daily and tofacitinib 10 mg twice daily, and 22 received placebo→tofacitinib 5 mg twice daily and placebo→tofacitinib 10 mg twice daily. A total of 17 patients discontinued, four from the tofacitinib 5 mg twice daily group, eight from the tofacitinib 10 mg twice daily group, three from the placebo→tofacitinib 5 mg twice daily group, and two from the placebo→tofacitinib 10 mg twice daily group (Fig. 1).

Patients

For the total Chinese patient population, the mean age of patients was 48.1 years (range: 20–78 years), the mean body mass index was 22.4 kg/m^2 (range: 15.1–32.5 kg/m^2), and the majority of patients (85.2%) were female. There were no major differences in demographics between treatment groups. Baseline HAQ-DI indicated moderate to severe RA, with no clear differences between treatment groups (Table 1).

A total of 184 patients had previously received DMARD therapy with MTX (tofacitinib 5 mg twice daily: $n = 75$; tofacitinib 10 mg twice daily: $n = 71$; placebo→tofacitinib 5 mg twice daily: $n = 19$; placebo→tofacitinib 10 mg twice daily: $n = 19$). Tumor necrosis

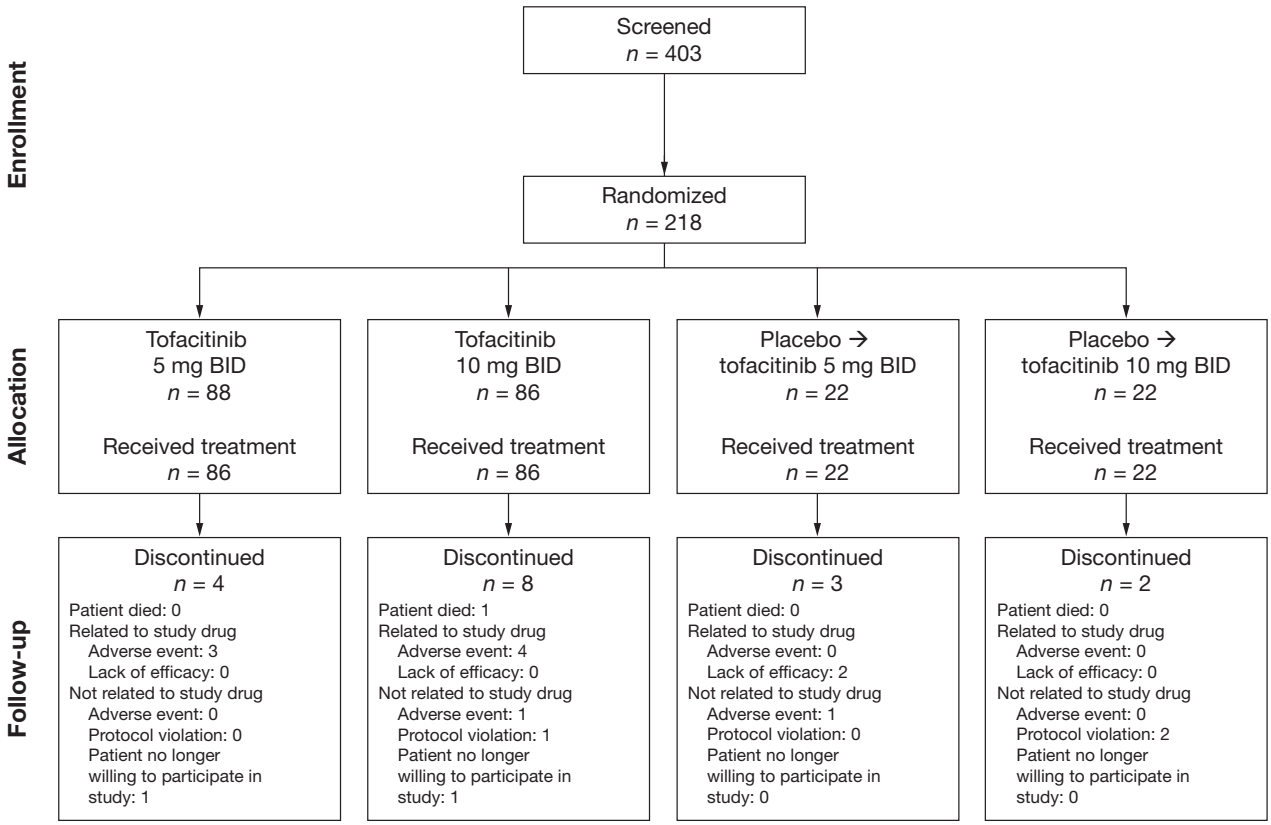

Figure 1 Patient disposition and study attrition.

Table 1 Patient baseline demographics and disease characteristics

	Tofacitinib 5 mg twice daily *N* = 86	Tofacitinib 10 mg twice daily *N* = 86	Placebo→tofacitinib 5 mg twice daily *N* = 22	Placebo→tofacitinib 10 mg twice daily *N* = 22
Age, years				
Mean (SD)	49.2 (10.1)	47.1 (12.3)	47.2 (11.6)	48.7 (10.1)
Range	21–70	20–78	22–66	28–67
Female, *n* (%)	75 (87.2)	71 (82.6)	21 (95.5)	17 (77.3)
BMI, kg/m^2				
Mean (SD)	22.3 (3.4)	22.9 (3.1)	20.7 (3.2)	23.0 (3.1)
Range	16.0–32.5	15.1–30.5	15.8–30.1	16.7–29.7
Disease duration, years				
Mean (SD)	6.6 (6.2)	7.6 (7.5)	9.5 (9.5)	7.1 (6.4)
Range	0.3–29.2	0.3–41.0	0.3–39.3	0.5–25.0
DAS28-4 (ESR)				
Mean (SD)	6.23 (1.08)	6.34 (1.03)	6.71 (1.09)	6.17 (0.94)
Range	2.52–8.52	3.55–8.46	4.46–8.74	4.97–7.57
HAQ-DI				
Mean (SD)	1.28 (0.68)	1.24 (0.71)	1.20 (0.75)	1.14 (0.70)[†]
Range	0–2.63	0–2.88	0–2.38	0–2.25

[†]Baseline HAQ-DI score was not available for one patient. BMI, body mass index; DAS28-4 (ESR), Disease Activity Score in 28 joints, erythrocyte sedimentation rate; HAQ-DI, Health Assessment Questionnaire-Disability Index; SD, standard deviation.

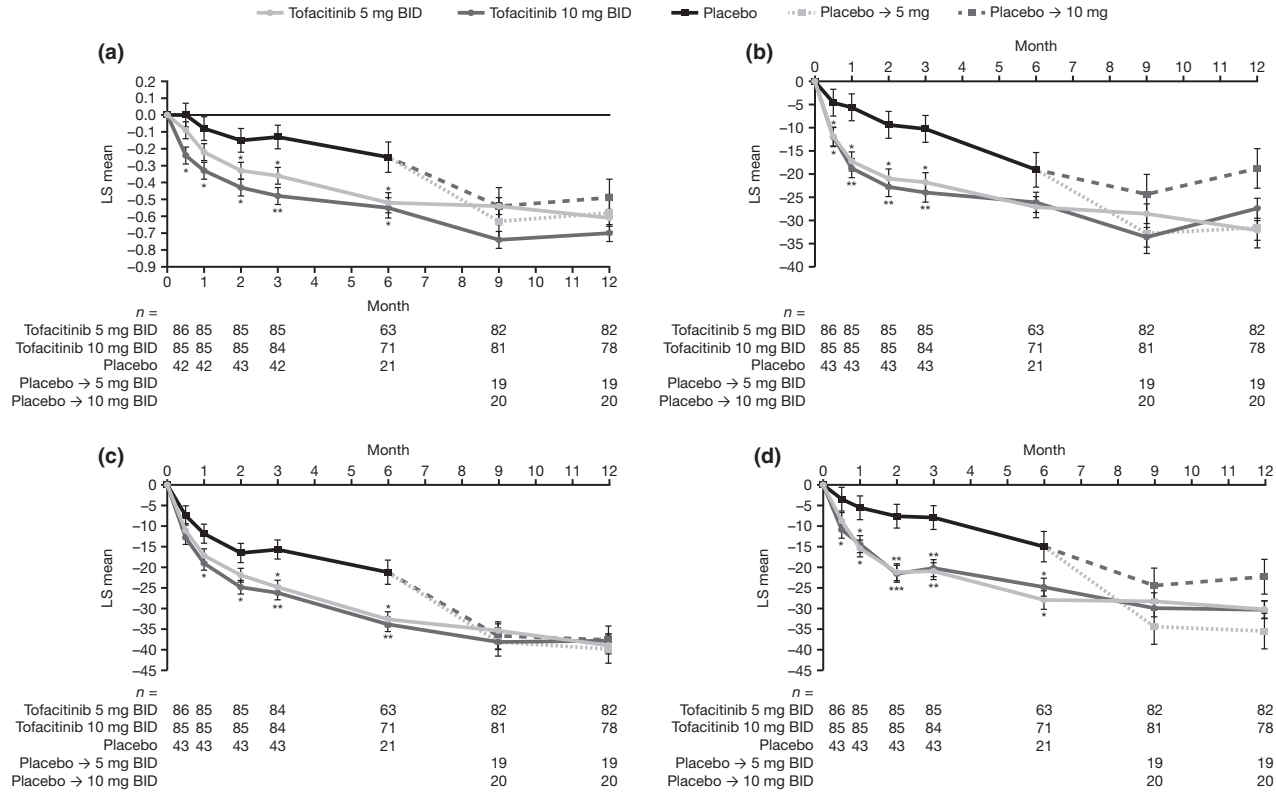

Figure 2 Least squares mean (LSM) (±SE) changes from baseline over 12 months in (a) Health Assessment Questionnaire-Disability Index (HAQ-DI), (b) patient global assessment of disease activity (PtGA), (c) physician global assessment of disease activity (PGA), (d) Pain.

factor inhibitor (TNFi) therapy was previously received by four patients in the tofacitinib 5 mg twice daily group (three received etanercept and one infliximab), and two patients in the tofacitinib 10 mg twice daily group (one received etanercept and one infliximab).

Of the 216 patients who received treatment, 111 (51.4%) received a single background csDMARD, and 105 (48.6%) received a combination of background csDMARDs. The most common background csDMARD was MTX (as a single background csDMARD: 37.5% [81/216]; in combination with other csDMARDs: 43.1% [93/216]). Other background csDMARDs included chloroquine, hydroxychloroquine, leflunomide, penicillamine and sulfasalazine.

HAQ-DI

Both tofacitinib doses resulted in significantly greater changes from baseline in HAQ-DI scores (indicating improvement in physical functioning) at 3 months (5 mg twice daily: −0.36, $P < 0.05$; 10 mg twice daily: −0.48, $P < 0.001$) compared with placebo (−0.13) (Fig. 2a). At 6 months, HAQ-DI for patients in both tofacitinib dose groups remained significantly improved (5 mg twice daily: −0.52, $P < 0.05$; 10 mg twice daily: −0.55, $P < 0.05$) compared with the placebo group (−0.25). At 12 months, all treatment groups showed similar improvements in HAQ-DI relative to baseline (Fig. 2a).

A significant difference in change from baseline in HAQ-DI scores was observed as early as 2 weeks for tofacitinib 10 mg twice daily compared with placebo (−0.24 *vs.* 0.0; $P < 0.05$) and 2 months for tofacitinib 5 mg twice daily compared with placebo (−0.33 *vs.* −0.15; $P < 0.05$).

The proportion of patients achieving improvement in HAQ-DI score ≥ 0.22 from baseline (defined as MCID) at 3 months was significantly higher in the tofacitinib groups (5 mg twice daily: 60.0%, $P < 0.01$; 10 mg twice daily: 59.5%, $P < 0.01$) compared with placebo (35.7%). At 12 months, the proportion of patients achieving MCID was 76.8%, 73.1%, 73.7% and 65.0% for tofacitinib 5 mg twice daily, tofacitinib 10 mg twice

daily, placebo→tofacitinib 5 mg twice daily, and placebo→tofacitinib 10 mg twice daily, respectively. A significantly higher proportion of patients receiving tofacitinib 10 mg twice daily compared with patients receiving placebo achieved MCID as early as 2 weeks (45.9% *vs.* 28.6%; $P < 0.05$); the earliest significant difference from placebo for patients receiving tofacitinib 5 mg twice daily was 2 months (62.4% *vs.* 44.2%; $P < 0.05$).

PtGA

Changes from baseline in PtGA at 3 and 6 months were greater in the tofacitinib groups (5 mg twice daily: −21.8 at 3 months and −27.1 at 6 months; 10 mg twice daily: −24.0 at 3 months and −26.1 at 6 months) compared with placebo (−10.3 at 3 months and −19.1 at 6 months) (Fig. 2b); however, the differences were statistically significant only at 3 months ($P < 0.05$). At 12 months, the tofacitinib 5 mg twice daily, tofacitinib 10 mg twice daily, and placebo→tofacitinib 5 mg twice daily groups showed similar improvements from baseline in PtGA (−32.1, −29.4 and −31.6, respectively), with the placebo→tofacitinib 10 mg twice daily group showing an improvement of −18.8 (Fig. 2b).

Significantly greater changes from baseline in PtGA were observed as early as 2 weeks for both tofacitinib groups (5 mg twice daily: −11.9, $P < 0.05$; 10 mg twice daily: −12.0, $P < 0.05$) compared with placebo (−4.6) (Fig. 2b).

PGA

Changes from baseline in PGA at 3 months were significantly greater in the tofacitinib groups (5 mg twice daily: −24.8, $P < 0.05$; 10 mg twice daily: −26.2, $P < 0.001$) than with placebo (−15.7) (Fig. 2c). At 6 months, changes from baseline were significantly greater in the tofacitinib groups (5 mg twice daily: −32.6, $P < 0.05$; 10 mg twice daily: −33.8, $P < 0.001$) than with placebo (−21.2). At 12 months, the tofacitinib 5 mg twice daily, tofacitinib 10 mg twice daily, placebo→tofacitinib 5 mg twice daily, and placebo→tofacitinib 10 mg twice daily groups showed similar improvements from baseline in PGA (−39.0, −37.8, −39.8 and −37.6, respectively).

Significant improvements in change from baseline in PGA for either tofacitinib group compared with placebo were first observed after 1 month for the tofacitinib 10 mg twice daily group (−19.1 *vs.* −11.8, $P < 0.05$) and after 3 months for the tofacitinib 5 mg twice daily group (−24.8 *vs.* −15.7, $P < 0.05$).

Pain

Decreases from baseline in Pain scores (indicating reduction of pain) at 3 months were significantly greater in both tofacitinib groups (5 mg twice daily: −20.9, $P < 0.001$; 10 mg twice daily: −20.2, $P < 0.001$), compared with placebo (−7.9) (Fig. 2d). Significant decreases compared with placebo (−15.0) were also observed at 6 months in both tofacitinib groups (5 mg twice daily: −27.9, $P < 0.05$; 10 mg twice daily: −24.8, $P < 0.05$). At 12 months, the tofacitinib 5 mg twice daily, tofacitinib 10 mg twice daily, and placebo→tofacitinib 5 mg twice daily groups showed similar decreases from baseline in Pain scores (−30.2, −30.3 and −35.5, respectively), with the placebo→tofacitinib 10 mg twice daily group showing a decrease of −22.3 (Fig. 2d).

Significantly greater change from baseline in Pain for tofacitinib 10 mg twice daily compared with placebo (−10.9 *vs.* −3.5; $P < 0.05$) was observed as early as 2 weeks, and for tofacitinib 5 mg twice daily compared with placebo (−15.4 *vs.* −5.5; $P < 0.05$) as early as 1 month (Fig. 2d).

FACIT-F

There were no significant differences between the tofacitinib (5 mg twice daily: 3.3; 10 mg twice daily: 3.6) and placebo (1.5) groups in change from baseline in FACIT-F scores at 3 months (Fig. 3a). At 6 months, patients receiving tofacitinib 10 mg twice daily demonstrated statistically significant improvement in FACIT-F scores compared with placebo (4.0 *vs.* 0.6; $P < 0.05$). Improvements in FACIT-F scores were maintained in the tofacitinib groups between 6 and 12 months (Fig. 3a).

SF-36

SF-36 domain scores in bodily pain, vitality and social functioning were significantly improved in both tofacitinib groups at 3 months, compared with placebo; additionally, physical functioning was improved in patients receiving tofacitinib 10 mg twice daily and general health perception was improved in patients receiving tofacitinib 5 mg twice daily at 3 months (Table 2). At 6 months, improvements were significant in general health perception score in patients receiving 5 mg twice daily, and vitality and role-emotional scores in patients receiving 10 mg twice daily. Improvements in SF-36 domain scores were generally maintained at 12 months (Table 2).

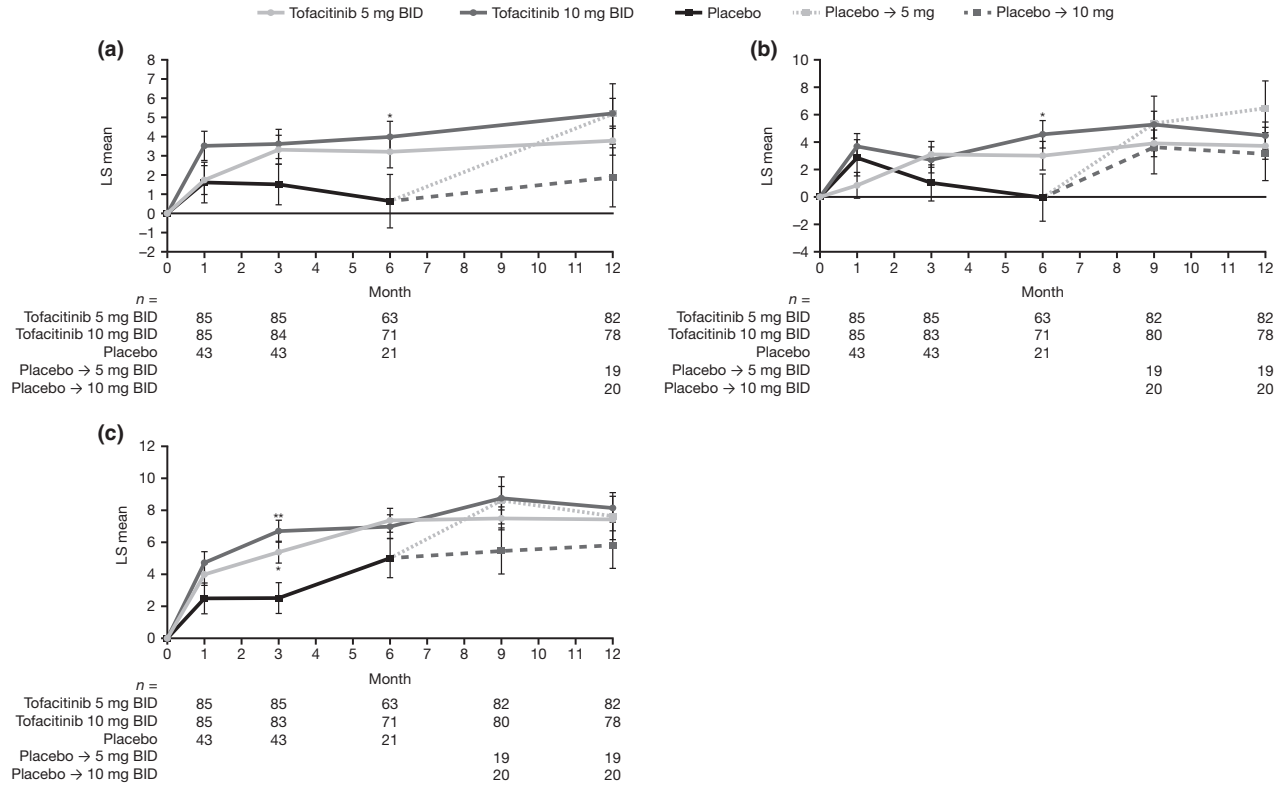

Figure 3 Least squares mean (LSM) (±SE) changes from baseline over 12 months in (a) Functional Assessment of Chronic Illness Therapy-Fatigue (FACIT-F), (b) Short Form 36 (SF-36) Mental Component Summary (MCS), (c) SF-36 Physical Component Summary (PCS).

At 3 months, changes from baseline in PCS scores were significantly higher with both tofacitinib doses (5 mg twice daily: 5.4, $P < 0.05$; 10 mg twice daily: 6.7, $P < 0.001$) than with placebo (2.5) (Fig. 3c). At 6 months, change from baseline in MCS score was significantly greater compared with placebo in the tofacitinib 10 mg twice daily group (4.6 *vs*. 0.0; $P < 0.05$). Improvements in MCS scores were maintained at 12 months in all treatment groups (Fig. 3b).

Work Limitations Questionnaire

The improvements in changes from baseline at months 3 and 6 with tofacitinib versus placebo in all domains of the WLQ (physical demands, time management, mental/interpersonal demands and output demands), and in WLQ Work Loss Index (Fig. 4a–d and Fig. S1), were not statistically significant.

DISCUSSION

This analysis evaluated the effect of tofacitinib in combination with csDMARDs on PROs in a Chinese subgroup of patients from a Phase 3 randomized study who had previously had an inadequate response (lack of efficacy or toxicity) to at least one csDMARD or bDMARD.

Improvements in physical functioning, that is, changes from baseline in HAQ-DI, were statistically greater for both tofacitinib doses compared with placebo at 3 and 6 months, and appeared to be sustained over the 12-month duration of the study. After 3 months, ~60% of all patients receiving tofacitinib achieved the MCID in HAQ-DI, significantly higher than in the placebo group (~36%). HAQ-DI is a commonly used instrument for assessing physical functioning in patients with RA, and scores have been reported to reflect HRQoL in patients with RA.[37] HAQ-DI scores have also been reported in China to be predictive of RA total costs, and it has been suggested that reduction in HAQ-DI score should be a treatment target, with the potential to reduce the total societal costs of RA.[38]

Significantly greater reductions in PtGA, PGA and Pain were reported at 3 months, and in PGA and Pain at 6 months, in patients receiving tofacitinib compared

Table 2 LSM (±SE) changes from baseline over 12 months in SF-36 domain scores

	Tofacitinib 5 mg twice daily *N* = 86	Tofacitinib 10 mg twice daily *N* = 86	Placebo→tofacitinib 5 mg twice daily *N* = 22	Placebo→tofacitinib 10 mg twice daily *N* = 22
Physical functioning				
Month 1	2.97 (0.86)	4.60 (0.86)	1.48 (1.81)	2.85 (1.78)
Month 3	5.19 (0.86)	6.01 (0.87)*	4.80 (1.81)	0.16 (1.78)
Month 6	6.37 (0.96)	7.55 (0.92)	2.62 (1.88)	5.68 (1.81)
Month 9	7.57 (0.91)	9.32 (0.92)	8.00 (1.88)	4.00 (1.84)
Month 12	6.27 (0.91)	8.59 (0.93)	5.96 (1.88)	4.72 (1.84)
Role-physical				
Month 1	3.96 (0.97)	5.02 (0.97)	6.61 (1.95)	3.92 (1.92)
Month 3	5.65 (0.97)	7.14 (0.98)	5.78 (1.95)	2.29 (1.92)
Month 6	6.97 (1.07)	7.75 (1.03)	7.71 (2.02)	6.12 (1.95)
Month 9	7.40 (0.98)	9.19 (0.99)	9.21 (2.02)	6.52 (1.97)
Month 12	7.32 (0.98)	8.81 (1.00)	9.97 (2.02)	6.88 (1.97)
Bodily pain				
Month 1	3.69 (0.65)	4.08 (0.65)	1.97 (1.38)	2.51 (1.36)
Month 3	4.97 (0.65)*	6.38 (0.65)**	2.60 (1.38)	1.66 (1.36)
Month 6	6.88 (0.73)	6.11 (0.70)	5.41 (1.44)	4.81 (1.38)
Month 9	7.22 (0.70)	8.09 (0.70)	8.44 (1.44)	7.56 (1.40)
Month 12	7.97 (0.70)	7.51 (0.71)	7.58 (1.44)	7.94 (1.40)
General health perception				
Month 1	2.80 (0.81)	4.14 (0.81)	1.01 (1.66)	2.20 (1.63)
Month 3	4.01 (0.81)*	3.30 (0.81)	2.34 (1.66)	−0.32 (1.63)
Month 6	5.67 (0.89)*	4.17 (0.86)	5.58 (1.72)	3.14 (1.66)
Month 9	4.82 (0.84)	5.76 (0.84)	7.24 (1.72)	3.24 (1.68)
Month 12	4.96 (0.84)	4.88 (0.85)	6.50 (1.72)	2.19 (1.68)
Vitality				
Month 1	2.69 (0.92)	6.38 (0.93)*	1.95 (1.83)	3.42 (1.80)
Month 3	4.85 (0.92)*	5.40 (0.93)*	1.52 (1.83)	1.43 (1.80)
Month 6	4.86 (1.03)	6.33 (0.99)*	4.92 (1.90)	4.45 (1.83)
Month 9	6.70 (0.92)	7.41 (0.93)	7.91 (1.90)	4.53 (1.86)
Month 12	6.52 (0.92)	6.62 (0.94)	8.70 (1.90)	5.28 (1.86)
Social functioning				
Month 1	1.88 (0.91)	3.65 (0.91)	2.88 (1.79)	1.05 (1.76)
Month 3	4.31 (0.91)*	4.57 (0.91)*	1.91 (1.79)	0.07 (1.76)
Month 6	6.34 (1.00)	6.83 (0.96)	5.30 (1.86)	3.25 (1.79)
Month 9	5.38 (0.91)	6.53 (0.91)	5.02 (1.86)	4.55 (1.82)
Month 12	6.17 (0.91)	5.63 (0.92)	7.28 (1.86)	3.21 (1.82)
Role-emotional				
Month 1	1.28 (1.14)*	3.53 (1.14)	7.00 (2.26)	3.87 (2.22)
Month 3	3.84 (1.14)	4.56 (1.15)	4.25 (2.26)	1.98 (2.22)
Month 6	4.35 (1.26)	6.70 (1.21)*	4.15 (2.35)	5.70 (2.26)
Month 9	5.48 (1.14)	7.82 (1.15)	7.74 (2.35)	4.82 (2.29)
Month 12	4.24 (1.14)	6.94 (1.16)	7.74 (2.35)	5.58 (2.29)
Mental health				
Month 1	1.61 (0.90)	3.59 (0.90)	1.87 (1.90)	1.46 (1.86)
Month 3	3.38 (0.90)	2.24 (0.90)	1.83 (1.90)	−0.08 (1.86)
Month 6	2.96 (1.01)	3.40 (0.96)	0.29 (1.97)	1.33 (1.89)
Month 9	4.10 (0.96)	4.97 (0.96)	5.69 (1.97)	3.84 (1.93)
Month 12	4.03 (0.96)	4.60 (0.98)	5.40 (1.97)	3.01 (1.93)

*$P < 0.05$; **$P < 0.001$ versus placebo (before placebo switch to tofacitinib at months 1–6). LSM, least squares mean; SE, standard error; SF-36, Short Form-36 Health Survey.

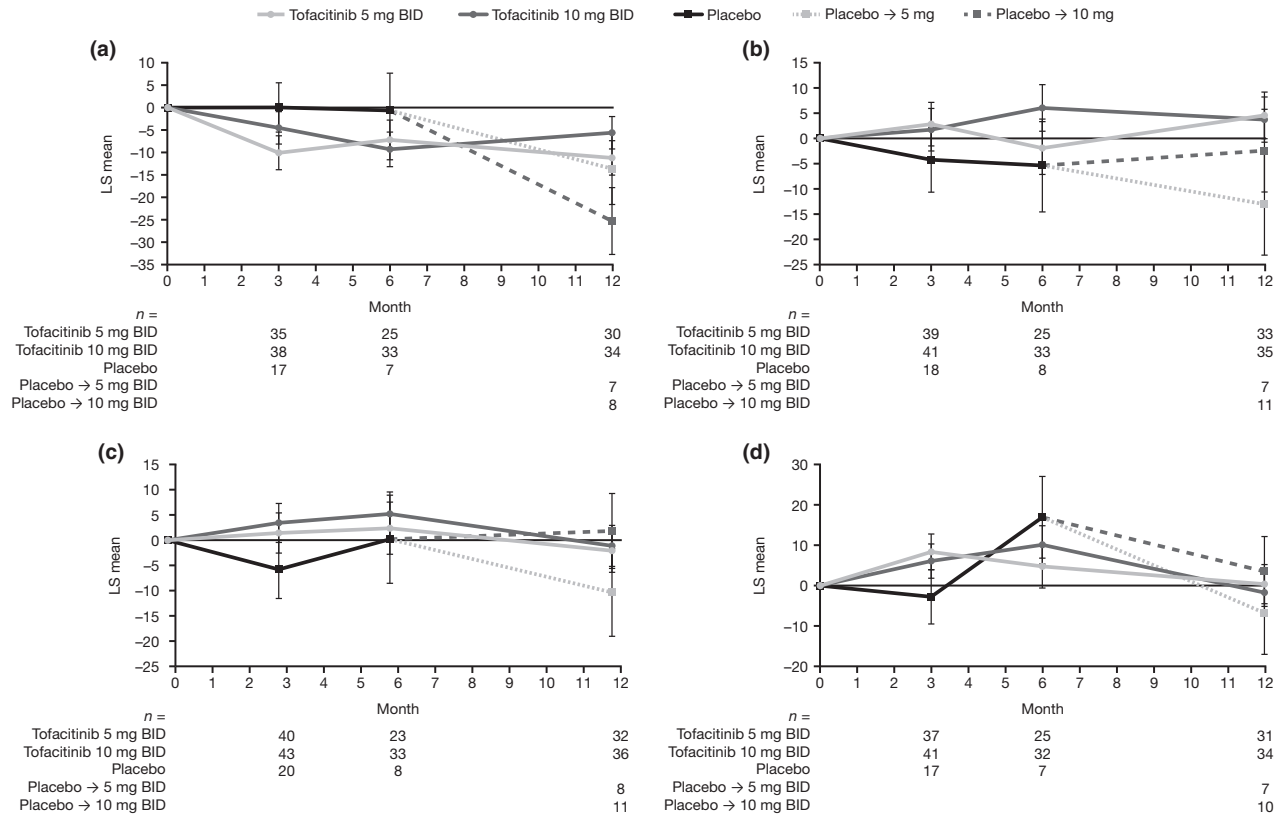

Figure 4 Least squares mean (LSM) (±SE) changes from baseline over 12 months in Work Limitations Questionnaire (WLQ) (a) physical demands, (b) time management, (c) mental/interpersonal demands, (d) output demands.

with placebo; changes at 6 months were of a similar magnitude to those reported for TNFi monotherapy, but somewhat lower than for TNFi/MTX combination therapy, in a global population.[39] Improvements in PtGA and Pain in patients receiving tofacitinib compared with placebo appeared to manifest earlier than improvements in PGA; this observation is in line with recent reports of discordance between PtGA and PGA from a meta-analysis of global studies.[40]

Generic HRQoL measures, such as the SF-36, allow comparison with population norms.[5] SF-12 MCS and PCS have been demonstrated to be substantially reduced in a survey of an urban population with RA in China.[41] Treatment-related improvements in HRQoL can be important for patients, and such data may also be considered when making formulary and reimbursement decisions.[42]

The SF-36 questionnaire used in the present study has been validated in Chinese patients.[35] Patients receiving tofacitinib at either dose had significantly greater improvement at 3 months in SF-36 PCS scores than those receiving placebo; however, improvements in SF-36 MCS were not statistically significantly different. Improvements in SF-36 PCS and MCS scores were maintained at 6 and 12 months. In the global ORAL Sync population, SF-36 PCS and MCS were both significantly improved at 3 months in patients receiving tofacitinib compared with patients receiving placebo;[29] the lack of statistical significance for SF-36 MCS at 3 months in Chinese patients might reflect the reduced sample size in the current analysis. Increases in SF-36 PCS and MCS scores reported here were of a similar magnitude to those reported for Asian patients with RA receiving etanercept plus MTX.[43]

A rapid onset of action is considered a positive feature of RA treatment.[44] Significant improvements at 2 weeks, the earliest time point for data collection, were observed in PtGA for both tofacitinib groups and in HAQ-DI and Pain for tofacitinib 10 mg twice daily.

RA has been identified as having a substantial impact on work capacity in Chinese patients,[45] however, no significant changes were observed in any of the

individual domains or the Work Loss Index of the WLQ. Significantly greater changes at 3 months in the Physical Demands domain of the WLQ were seen for patients receiving tofacitinib than those receiving placebo in the global population in the ORAL Sync study (unpublished data). Although the employment status of patients in the Chinese sub-population was not captured during the study, the instructions in the WLQ asked patients to consider how their health may have affected them at work during the past 2 weeks. This instruction led to a relatively smaller number of patients answering the questionnaire (e.g., Work Loss Index was calculated for 42, 44 and 21 patients receiving tofacitinib 5 mg twice daily, tofacitinib 10 mg twice daily and placebo, respectively, at 3 months). This may also have contributed to the lack of statistical significance in WLQ domains and WLQ Work Loss Index at 3 and 6 months.

These findings are consistent with those reported in other Phase 3 trials of tofacitinib, which report significant and clinically meaningful improvements in several PROs.[25–28] Overall, findings obtained with PRO measures in a Chinese sub-population of the ORAL Sync study were consistent with those observed in the global population, in which patients receiving tofacitinib reported statistically significant improvements in PtGA, Pain, HAQ-DI, SF-36 MCS and PCS scores, and FACIT-F compared with patients receiving placebo.[29] These findings are also consistent with those reported in trials reporting PROs during bDMARD therapy in patients who have previously had an inadequate response to csDMARDs.[46,47] The improvements in HAQ-DI at 6 months reported in Chinese patients in the present study were comparable to those observed after 24 weeks treatment with TNFi as monotherapy or in combination with MTX in a network meta-analysis.[39] They were also comparable to those reported for treatment with etanercept for 16 weeks in 197 Asian patients with RA.[43]

Currently, six bDMARDs are approved for RA treatment in China, and a recent large-scale, real-world study of RA patients in China reported bDMARD usage in routine clinical practice in accordance with treatment guidelines.[48] Interestingly, this study also reported that a lower proportion of patients (10.5%) were prescribed bDMARD monotherapy in China than in the USA (30%),[49] which suggests better compliance with international treatment guidelines that recommend bDMARDs in combination with csDMARDs, rather than as monotherapy.[50]

A number of limitations of the current analysis are acknowledged. The study was not designed specifically for analysis of PRO data from the Chinese sub-population, which was exploratory. Furthermore, the limited number of patients in this sub-population necessitates caution when interpreting these results. Also, owing to patients who received placebo being switched to tofacitinib therapy at either 3 or 6 months, a direct comparison of tofacitinib and placebo cannot be undertaken across the full 12-month duration of the study. However, HAQ-DI, PtGA, Pain, SF-36 MCS, SF-36 PCS and FACIT-F scores all showed numerical improvements from 6 months onward for patients initially receiving placebo (i.e., after they had been switched to tofacitinib). As enrollment was not stratified by background DMARD therapy and most patients (approximately 85%) were receiving MTX prior to enrollment, analysis of the effect of different csDMARDs on PRO response to tofacitinib was not possible. The employment status of patients was also not captured during the study. Finally, missing data were not imputed in this analysis; however, LSM change from baseline, as used presently, is generally considered to be less sensitive to such missing data than when analysis is based on arithmetic means.

In conclusion, in this analysis in Chinese patients, tofacitinib 5 and 10 mg twice daily in combination with csDMARDs appeared to provide benefit across a range of PROs in patients who had previously had an inadequate response to csDMARD therapy, reflecting improvements in HRQoL, physical function and pain, which were maintained for up to 12 months.

AUTHOR CONTRIBUTIONS

Zhanguo Li, Yuan An, Houheng Su, Xiangpei Li, Jianhua Xu, and Yi Zheng made substantial contributions to the acquisition of data; substantial contributions to the analysis and interpretation of data; were involved in drafting the article or revising it critically for important intellectual content; and approved the version of the article to be published. Guiye Li, Lisy Wang, and Qizhe Wu made substantial contributions to the analysis and interpretation of data; were involved in drafting the article or revising it critically for important intellectual content; and approved the version of the article to be published. Kenneth Kwok made substantial contributions to study conception and design; substantial contributions to the analysis and interpretation of data; was involved in drafting the article or revising it critically for important intellectual content; and approved the version of the article to be published.

FUNDING SOURCES

This study was sponsored by Pfizer Inc. Yingchun Luo, of Eliassen Group, provided statistical support. Medical writing support, under direction from the authors, was provided by Martin Bell, PhD, at Complete Medical Communications, Glasgow, UK, and Carole Evans, PhD, on behalf of Complete Medical Communications, Macclesfield, UK, and was funded by Pfizer Inc, New York, NY, USA in accordance with Good Publication Practice (GPP3) guidelines (*Ann Intern Med* 2015, 163, 461–4).

CONFLICTS OF INTEREST

Zhanguo Li and Yuan An are employees of Peking University People's Hospital, Beijing, China. Houheng Su is an employee of Qingdao Municipal Hospital, Qingdao, China. Xiangpei Li is an employee of Anhui Provincial Hospital, Hefei, Anhui, China. Jianhua Xu is an employee of First Affiliated Hospital of Anhui Medical University, Hefei, China. Yi Zheng is an employee of Beijing Chaoyang Hospital, Chaoyang District, Beijing, China. Guiye Li is an employee of Pfizer Inc. Kenneth Kwok, Lisy Wang, and Qizhe Wu are employees and shareholders of Pfizer Inc.

NCT trial registration: NCT00856544.

REFERENCES

1 Li R, Sun J, Ren LM *et al.* (2012) Epidemiology of eight common rheumatic diseases in China: a large-scale cross-sectional survey in Beijing. *Rheumatology (Oxford)* **51**, 721–9.
2 Zeng QY, Le Chen R, Darmawan J *et al.* (2008) Rheumatic diseases in China. *Arthritis Res Ther* **10**, R17.
3 Zeng SY, Gong Y, Zhang YP *et al.* (2015) Changes in the prevalence of rheumatic diseases in Shantou, China, in the past three decades: a COPCORD study. *PLoS One* **10**, e0138492.
4 Cross M, Smith E, Hoy D *et al.* (2014) The global burden of rheumatoid arthritis: estimates from the global burden of disease 2010 study. *Ann Rheum Dis* **73**, 1316–22.
5 Strand V, Singh JA (2010) Newer biological agents in rheumatoid arthritis: impact on health-related quality of life and productivity. *Drugs* **70**, 121–45.
6 Zhao S, Chen Y, Chen H (2015) Sociodemographic factors associated with functional disability in outpatients with rheumatoid arthritis in Southwest China. *Clin Rheumatol* **34**, 845–51.
7 Kirwan JR, Hewlett SE, Heiberg T *et al.* (2005) Incorporating the patient perspective into outcome assessment in rheumatoid arthritis–progress at OMERACT 7. *J Rheumatol* **32**, 2250–6.
8 Strand V, Cohen S, Crawford B, Smolen JS, Scott DL, Leflunomide Investigators Groups (2004) Patient-reported outcomes better discriminate active treatment from placebo in randomized controlled trials in rheumatoid arthritis. *Rheumatology (Oxford)* **43**, 640–7.
9 Pincus T, Strand V, Koch G *et al.* (2003) An index of the three core data set patient questionnaire measures distinguishes efficacy of active treatment from that of placebo as effectively as the American College of Rheumatology 20% response criteria (ACR20) or the Disease Activity Score (DAS) in a rheumatoid arthritis clinical trial. *Arthritis Rheum* **48**, 625–30.
10 Fleischmann R, Cutolo M, Genovese MC *et al.* (2012) Phase IIb dose-ranging study of the oral JAK inhibitor tofacitinib (CP-690,550) or adalimumab monotherapy versus placebo in patients with active rheumatoid arthritis with an inadequate response to disease-modifying antirheumatic drugs. *Arthritis Rheum* **64**, 617–29.
11 Kremer JM, Bloom BJ, Breedveld FC *et al.* (2009) The safety and efficacy of a JAK inhibitor in patients with active rheumatoid arthritis: results of a double-blind, placebo-controlled phase IIa trial of three dosage levels of CP-690,550 versus placebo. *Arthritis Rheum* **60**, 1895–905.
12 Kremer JM, Cohen S, Wilkinson BE *et al.* (2012) A phase IIb dose-ranging study of the oral JAK inhibitor tofacitinib (CP-690,550) versus placebo in combination with background methotrexate in patients with active rheumatoid arthritis and an inadequate response to methotrexate alone. *Arthritis Rheum* **64**, 970–81.
13 Tanaka Y, Suzuki M, Nakamura H, Toyoizumi S, Zwillich SH, Tofacitinib Study Investigators (2011) Phase II study of tofacitinib (CP-690,550) combined with methotrexate in patients with rheumatoid arthritis and an inadequate response to methotrexate. *Arthritis Care Res (Hoboken)* **63**, 1150–8.
14 Tanaka Y, Takeuchi T, Yamanaka H, Nakamura H, Toyoizumi S, Zwillich S (2015) Efficacy and safety of tofacitinib as monotherapy in Japanese patients with active rheumatoid arthritis: a 12-week, randomized, phase 2 study. *Mod Rheumatol* **25**, 514–21.
15 Burmester GR, Blanco R, Charles-Schoeman C *et al.* (2013) Tofacitinib (CP-690,550) in combination with methotrexate in patients with active rheumatoid arthritis with an inadequate response to tumour necrosis factor inhibitors: a randomised Phase 3 trial. *Lancet* **381**, 451–60.
16 Fleischmann R, Kremer J, Cush J *et al.* (2012) Placebo-controlled trial of tofacitinib monotherapy in rheumatoid arthritis. *N Engl J Med* **367**, 495–507.
17 Kremer J, Li ZG, Hall S *et al.* (2013) Tofacitinib in combination with nonbiologic disease-modifying antirheumatic drugs in patients with active rheumatoid arthritis: a randomized trial. *Ann Intern Med* **159**, 253–61.

18 Lee EB, Fleischmann R, Hall S *et al.* (2014) Tofacitinib versus methotrexate in rheumatoid arthritis. *N Engl J Med* **370**, 2377–86.
19 van der Heijde D, Tanaka Y, Fleischmann R *et al.* (2013) Tofacitinib (CP-690,550) in patients with rheumatoid arthritis receiving methotrexate: twelve-month data from a twenty-four-month phase III randomized radiographic study. *Arthritis Rheum* **65**, 559–70.
20 van Vollenhoven RF, Fleischmann R, Cohen S *et al.* (2012) Tofacitinib or adalimumab versus placebo in rheumatoid arthritis. *N Engl J Med* **367**, 508–19.
21 Wollenhaupt J, Silverfield J, Lee EB *et al.* (2016) Tofacitinib, an oral Janus kinase inhibitor, in the treatment of rheumatoid arthritis: safety and efficacy in open-label, long-term extension studies over 8 years. *Arthritis Rheumatol* **68**, abs.1647.
22 Yamanaka H, Tanaka Y, Takeuchi T *et al.* (2016) Tofacitinib, an oral Janus kinase inhibitor, as monotherapy or with background methotrexate, in Japanese patients with rheumatoid arthritis: an open-label, long-term extension study. *Arthritis Res Ther* **18**, 34.
23 Wollenhaupt J, Silverfield J, Lee EB *et al.* (2014) Safety and efficacy of tofacitinib, an oral Janus kinase inhibitor, for the treatment of rheumatoid arthritis in open-label, longterm extension studies. *J Rheumatol* **41**, 837–52.
24 An Y, Li Z, Wu Q, Kwok K, Wang L (2015) Efficacy and safety of tofacitinib in Chinese Patients with active rheumatoid arthritis: subgroup analysis from a Phase 3 study of tofacitinib in combination with nonbiologic disease-modifying antirheumatic drugs. *Ann Rheum Dis* **74**, 1071.
25 Strand V, Burmester GR, Zerbini CA *et al.* (2015) Tofacitinib with methotrexate in third-line treatment of patients with active rheumatoid arthritis: patient-reported outcomes from a phase III trial. *Arthritis Care Res (Hoboken)* **67**, 475–83.
26 Strand V, Kremer J, Wallenstein G *et al.* (2015) Effects of tofacitinib monotherapy on patient-reported outcomes in a randomized Phase 3 study of patients with active rheumatoid arthritis and inadequate responses to DMARDs. *Arthritis Res Ther* **17**, 307.
27 Strand V, van Vollenhoven RF, Lee EB *et al.* (2016) Tofacitinib or adalimumab versus placebo: patient-reported outcomes from a Phase 3 study of active rheumatoid arthritis. *Rheumatology (Oxford)* **55**, 1031–41.
28 Strand V, Lee EB, Fleischmann R *et al.* (2016) Tofacitinib versus methotrexate in rheumatoid arthritis: patient-reported outcomes from the randomised phase III ORAL Start trial. *RMD Open* **2**, e000308.
29 Strand V, Kremer JM, Gruben D, Krishnaswami S, Zwillich SH, Wallenstein GV (2017) Tofacitinib in combination with conventional disease-modifying antirheumatic drugs in patients with active rheumatoid arthritis: patient-reported outcomes from a Phase III randomized controlled trial. *Arthritis Care Res (Hoboken)* **69**, 592–8.
30 Arnett FC, Edworthy SM, Bloch DA *et al.* (1988) The American Rheumatism Association 1987 revised criteria for the classification of rheumatoid arthritis. *Arthritis Rheum* **31**, 315–24.
31 Hu H, Luan L, Yang K, Li SC (2016) Psychometric validation of Chinese Health Assessment Questionnaire for use in rheumatoid arthritis patients in China. *Int J Rheum Dis* https://dor.org/10.1111 /1756-185X.12831. [epub ahead of print].
32 Felson DT, Anderson JJ, Boers M *et al.* (1993) The American College of Rheumatology preliminary core set of disease activity measures for rheumatoid arthritis clinical trials. The Committee on Outcome Measures in Rheumatoid Arthritis Clinical Trials. *Arthritis Rheum* **36**, 729–40.
33 Cella D, Yount S, Sorensen M, Chartash E, Sengupta N, Grober J (2005) Validation of the Functional Assessment of Chronic Illness Therapy Fatigue Scale relative to other instrumentation in patients with rheumatoid arthritis. *J Rheumatol* **32**, 811–9.
34 Ware JE Jr, Sherbourne CD (1992) The MOS 36-item short-form health survey (SF-36). I. Conceptual framework and item selection. *Med Care* **30**, 473–83.
35 Li L, Wang HM, Shen Y (2003) Chinese SF-36 Health Survey: translation, cultural adaptation, validation, and normalisation. *J Epidemiol Community Health* **57**, 259–63.
36 Lerner D, Amick BC III, Rogers WH, Malspeis S, Bungay K, Cynn D (2001) The work limitations questionnaire. *Med Care* **39**, 72–85.
37 Kwan YH, Koh ET, Leong KP, Wee HL (2014) Association between helplessness, disability, and disease activity with health-related quality of life among rheumatoid arthritis patients in a multiethnic Asian population. *Rheumatol Int* **34**, 1085–93.
38 Xu C, Wang X, Mu R *et al.* (2014) Societal costs of rheumatoid arthritis in China: a hospital-based cross-sectional study. *Arthritis Care Res (Hoboken)* **66**, 523–31.
39 Jansen JP, Buckley F, Dejonckheere F, Ogale S (2014) Comparative efficacy of biologics as monotherapy and in combination with methotrexate on patient reported outcomes (PROs) in rheumatoid arthritis patients with an inadequate response to conventional DMARDs – a systematic review and network meta-analysis. *Health Qual Life Outcomes* **12**, 102.
40 Desthieux C, Hermet A, Granger B, Fautrel B, Gossec L (2016) Patient-physician discordance in global assessment in rheumatoid arthritis: a systematic literature review with metaanalysis. *Arthritis Care Res (Hoboken)* **68**, 1767–73.
41 Langley PC, Mu R, Wu M, Dong P, Tang B (2011) The impact of rheumatoid arthritis on the burden of disease in urban China. *J Med Econ* **14**, 709–19.
42 Lubeck DP (2002) Health-related quality of life measurements and studies in rheumatoid arthritis. *Am J Manag Care* **8**, 811–20.
43 Bae SC, Gun SC, Mok CC *et al.* (2013) Improved health outcomes with etanercept versus usual DMARD therapy in

an Asian population with established rheumatoid arthritis. *BMC Musculoskelet Disord* **14**, 13.
44 Dougados M, Ripert M, Hilliquin P, Brocq O, Brault Y, Logeart I (2012) Onset of action of etanercept in rheumatoid arthritis based on patient-reported outcomes. *Clin Exp Rheumatol* **30**, 266–8.
45 Zhang X, Mu R, Wang X *et al.* (2015) The impact of rheumatoid arthritis on work capacity in Chinese patients: a cross-sectional study. *Rheumatology (Oxford)* **54**, 1478–87.
46 Genovese MC, Han C, Keystone EC *et al.* (2012) Effect of golimumab on patient-reported outcomes in rheumatoid arthritis: results from the GO-FORWARD study. *J Rheumatol* **39**, 1185–91.
47 van der Heijde D, Klareskog L, Singh A *et al.* (2006) Patient reported outcomes in a trial of combination therapy with etanercept and methotrexate for rheumatoid arthritis: the TEMPO trial. *Ann Rheum Dis* **65**, 328–34.
48 An Y, Liu T, He D *et al.* (2017) The usage of biological DMARDs and clinical remission of rheumatoid arthritis in China: a real-world large scale study. *Clin Rheumatol* **36**, 35–43.
49 Yazici Y, Shi N, John A (2008) Utilization of biologic agents in rheumatoid arthritis in the United States: analysis of prescribing patterns in 16,752 newly diagnosed patients and patients new to biologic therapy. *Bull NYU Hosp Jt Dis* **66**, 77–85.
50 Singh JA, Saag KG, Bridges SL Jr *et al.* (2016) 2015 American College of Rheumatology guideline for the treatment of rheumatoid arthritis. *Arthritis Rheumatol* **68**, 1–26.

Supporting Information

Additional Supporting Information may be found online in the supporting information tab for this article:

Figure S1. LSM (±SE) changes from baseline over 12 months in Work Limitations Questionnaire (WLQ) Work Loss Index.