Baricitinib in patients with rheumatoid arthritis with inadequate response to methotrexate: results from a phase 3 study

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Abstract

Objective

This study evaluated the efficacy and safety of baricitinib, an oral Janus kinase (JAK)1/JAK2 inhibitor, in patients with moderately to severely active rheumatoid arthritis (RA) and inadequate response to methotrexate (MTX) therapy.

Methods

In this phase 3, double-blind, 52-week, placebo-controlled study, 290 patients with moderately to severely active RA and inadequate response to MTX were randomly assigned 1:1 to placebo or baricitinib 4-mg once daily, stratified by country (China, Brazil, Argentina) and presence of joint erosions. Primary endpoint measures included American College of Rheumatology 20% response (ACR20) at week 12. Secondary endpoints included changes in Health Assessment Questionnaire-Disability Index (HAQ-DI) and Disease Activity Score for 28-joint counts (DAS28)-high-sensitivity C-reactive protein (hsCRP), Simplified Disease Activity Index (SDAI) score ≤3.3, mean duration of morning joint stiffness, severity of morning joint stiffness numeric rating scale (NRS 0-10), worst tiredness NRS, and worst joint pain NRS at week 12.

Results

Most patients (approximately 80%) were from China. More patients achieved ACR20 response at week 12 with baricitinib than with placebo (58.6% vs. 28.3%; p<0.001). Statistically significant improvements were also seen in HAQ-DI, DAS28-hsCRP, morning joint stiffness, worst tiredness, and worst joint pain in the baricitinib group compared to placebo at week 12. Through week 24, rates of treatment-emergent adverse events, including infections, were higher for baricitinib compared to placebo, while serious adverse event rates were similar between baricitinib and placebo.

Conclusion

In patients with RA who had an inadequate response to MTX, baricitinib was associated with significant clinical improvements as compared with placebo.

Key words

disease-modifying anti-rheumatic drugs, rheumatoid arthritis, methotrexate, baricitinib, janus kinase

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Introduction

Rheumatoid arthritis (RA) is a systemic inflammatory autoimmune disease associated with progressive joint destruction, significantly compromised quality of life, and reduced survival (1, 2). Patients experience high levels of pain and disability that affect day-to-day functioning, social interactions, and the ability to work, and are at risk of developing serious comorbidities (3-5). The prevalence of RA ranges from 0.3% to 1% worldwide (6-8).

Management of RA has improved substantially in recent years with the development of new treatments and treatment modalities (2, 7, 9). Currently, for patients with an inadequate response to methotrexate (MTX), the combination of a conventional synthetic disease-modifying anti-rheumatic drug (csDMARD) with biological DMARDs (bDMARDs) or oral targeted synthetic DMARDs (tsDMARDs) is recommended to help reach the treatment target of sustained remission or low disease activity (10, 11). However, despite the clinical improvements in signs and symptoms of RA with biologics, particularly in combination with MTX, many patients do not go into remission or achieve a 50% improvement in American College of Rheumatology (ACR) criteria (ACR50) in clinical trial settings (7, 12). Furthermore, treatment strategies to minimise the risk of disease progression in patients who have achieved remission or low disease activity with bDMARDs are currently under investigation (13, 14). Therefore, a significant unmet need remains for more effective and better tolerated treatments for RA.

Activated Janus kinases (JAKs) play pivotal roles in intracellular signaling from cell-surface receptors for multiple cytokines implicated in the pathologic processes of RA (15). Several JAK inhibitor tsDMARDs (*e.g.* baricitinib, tofacitinib) are approved for treatment of RA or are in development (9, 16). Baricitinib, an orally available JAK inhibitor with selectivity for JAK1 and JAK2 (17), reversibly binds to the JAK adenosine triphosphate (ATP)-binding pocket, which transiently prevents ATP from binding, and thereby reduces cytokine signaling through the JAK-signal transducer and activator of transcription pathway (15). The efficacy and safety of baricitinib have been assessed in several phase 2 and phase 3 clinical trials, conducted predominantly in Caucasian populations (18). Findings from these studies have shown that baricitinib has sustained efficacy with a manageable safety profile in patients with RA who were bDMARD-naïve and had no or minimal csDMARD history (19), and in patients with an inadequate response to csDMARDs (20) or bDMARDs (21), and has demonstrated significant clinical improvements compared to placebo and adalimumab in patients with an inadequate response to MTX (22). However, evidence on the efficacy and safety of baricitinib in China is limited, with only 1 of these studies enrolling a small number of patients (n = 54) from China (22).

The RA-BALANCE trial was a phase 3, double-blind, placebo-controlled study conducted mainly in China and in Brazil and Argentina to assess the efficacy and safety of baricitinib (4-mg, once daily, oral administration) for up to 52 weeks in adult patients with moderately to severely active RA who had had an inadequate response to MTX.

Patients and methods

Patients

The patients were at least 18 years of age with a diagnosis of adult-onset RA as defined by the ACR/EULAR 2010 Classification Criteria (23). Enrolled patients had at least 6 tender joints (of 68 joints examined), at least 6 swollen joints (of 66 joints examined), high-sensitivity C-reactive protein (hsCRP) ≥6 mg/L, had received at least 12 weeks of MTX therapy before study entry, with 8 of these weeks at a stable dose of 7.5- to 25-mg/week, and had an adequate response to MTX. In addition, patients were required to have at least 3 joint erosions in their hand, wrist, or foot joints based on radiographs or have 1 to 2 joint erosions in their hand, wrist, or foot joints based on radiographs and be rheumatoid factor- (RF) or anti-citrullinated peptide antibody- (ACPA) positive. The key exclusion criteria were patients who had previ-

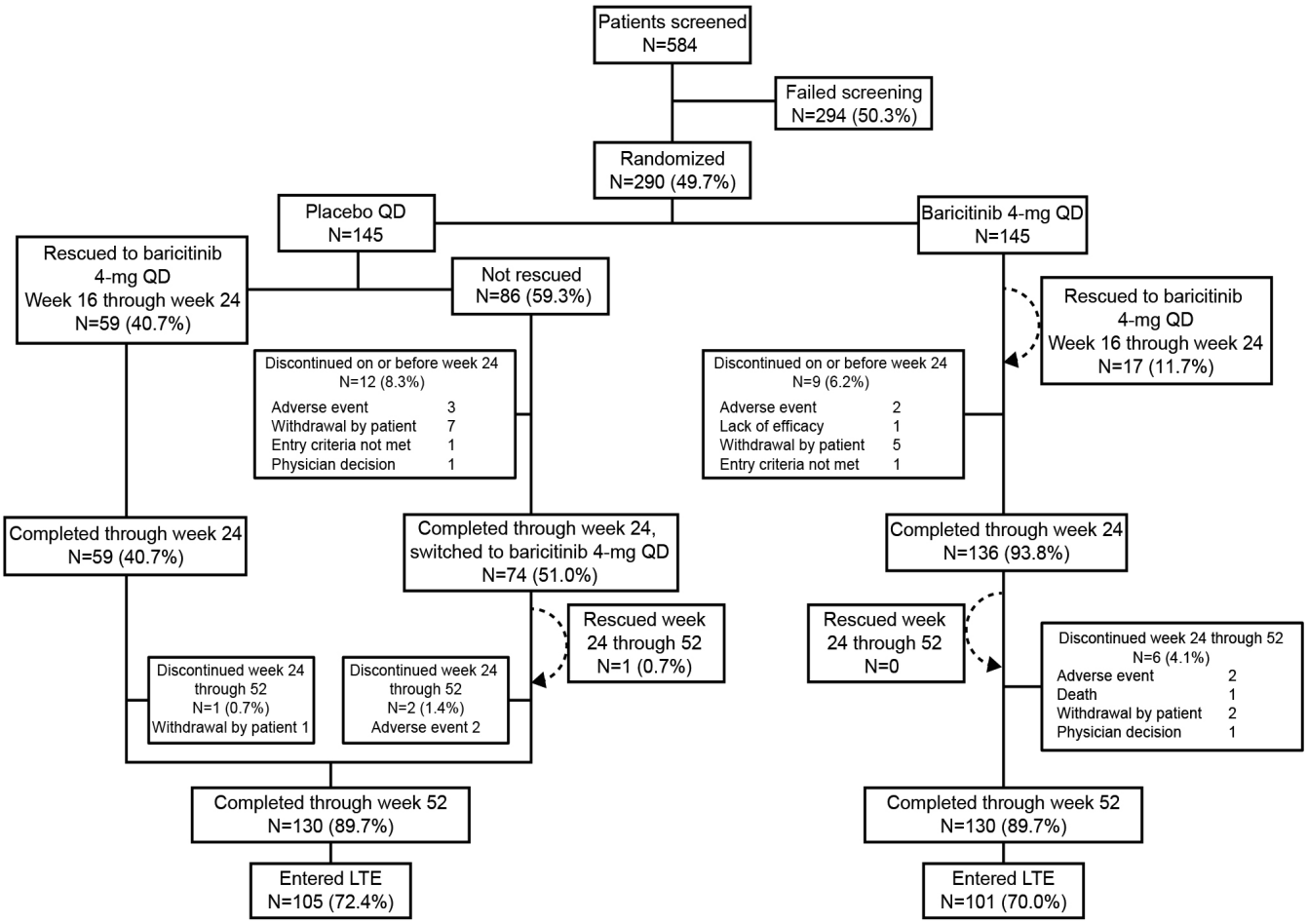

Fig. 1. Patient disposition through 52 weeks. Enrolment: China (79.7%), Central America (20.3%; Argentina 14.8%, Brazil 5.5%). LTE, long-term extension; MTX, methotrexate; QD, once daily.

ously received biologic therapies, had a recent history of infection including active tuberculosis or untreated latent tuberculosis or other serious infections, were immunocompromised, or had selected laboratory abnormalities during screening.

Study protocol and oversight

RA-BALANCE was a phase 3, multicentre, randomised, double-blind study conducted for 52 weeks at 30 centres in 3 countries (China, Brazil, and Argentina) to evaluate the efficacy and safety of baricitinib in comparison with placebo in patients with moderately or severely active RA who had an inadequate response to MTX. Patients were randomised 1:1 to receive once daily doses of placebo or baricitinib 4-mg with concomitant stable doses of background MTX. Randomisation was stratified by country (*i.e.* China, Brazil, and Argentina) and presence or absence of joint erosions on centrally read baseline radiographs. Patients with estimated glomerular filtration rate (eGFR) ≥40 and <60 mL/min/1.73 m^2 who were randomised to baricitinib received 2-mg (with maintenance of blinding *vs.* placebo). Concomitant stable doses of nonsteroidal anti-inflammatory drugs, analgesics, and/or corticosteroids (≤10 mg/day of prednisone or equivalent) were permitted. At week 16, rescue treatment (open-label baricitinib 4-mg) was available for patients whose tender and swollen joint counts improved from baseline by <20% at both week 14 and week 16. At week 24, patients receiving placebo were switched to baricitinib. Blinding to initial randomised treatment was maintained following rescue or switch. Patients who completed the trial were eligible to enter a long-term extension study or were seen for follow-up (up to approximately 28 days after the end of treatment).

The study (NCT02265705) was designed by the sponsor, Eli Lilly and Company. The study was conducted in accordance with ethical principles of the Declaration of Helsinki and Good Clinical Practice guidelines (Peking University People's Hospital, date of approval: 29-Sep-2014, ethics approval/site number: AF/SC-08/03.0) and was approved by each centre's institutional review board and ethics committee (total 30 sites). All patients provided written informed consent. The trial commenced in October 2014 and was completed in May 2017 (patients enrolled from October 2014 through June 2016). Eli Lilly or its representatives provided data, laboratory, and site-monitoring services. All the authors participated in the analysis and interpretation of the data, reviewed the draft and the final manuscript, provided critical comment, and made the decision to submit the manuscript for

Table I. Characteristics of the study patients and disease activity at baseline.

	Placebo (n=145)	Baricitinib 4-mg (n=145)	Total (n=290)
Age, years*	48.9 ± 12.7	49.5 ± 10.6	49.2 ± 11.7
Female, n (%)	106 (73.1)	127 (87.6)	233 (80.3)
Duration of RA, years	9.1 ± 7.0	10.7 ± 8.3	9.9 ± 7.7
ACPA-positive, n (%)†	124 (85.5)	128 (88.3)	252 (86.9)
RF-positive, n (%)‡	130 (89.7)	134 (92.4)	264 (91.0)
Number of cDMARDs previously used			
0	0	0	0
1	107 (73.8)	94 (64.8)	201 (69.3)
2	38 (26.2)	51 (35.2)	89 (30.7)
Methotrexate dose, mg/week	12.9 ± 6.0	12.2 ± 3.5	17.5 ± 4.9
Had ≥3 erosions — no./total no. (%)	116/145 (80.0)	117/144 (81.3)	233/289 (80.6)
mTSS units	48.9 ± 55.5	48.8 ± 47.6	48.8 ± 51.5
Erosion score	27.2 ± 30.6	27.6 ± 25.9	27.4 ± 28.2
Joint space narrowing score	21.7 ± 26.4	21.2 ± 23.1	21.4 ± 24.7
Swollen joint count, of 66 joints	14.8 ± 9.5	14.6 ± 8.6	14.7 ± 9.1
Tender joint count, of 68 joints	25.2 ± 14.7	23.3 ± 13.6	24.2 ± 14.2
Physician's global assessment of disease activity, 0-100 mm, VAS¶	67.8 ± 16.3	66.1 ± 17.8	67.0 ± 17.0
Patient's global assessment of disease activity, 0-100 mm, VAS¶	67.0 ± 19.8	64.8 ± 21.5	65.9 ± 20.7
Patient's assessment of pain, 0- 100 mm, VAS¶	66.6 ± 19.9	65.2 ± 20.3	65.9 ± 20.1
HAQ-DI§	1.52 ± 0.56	1.58 ± 0.58	1.55 ± 0.57
hsCRP level, mg/litre**¶	26.5 ± 31.3	26.0 ± 23.5	26.0 ± 27.3
ESR, mm/hour	60.8 ± 32.5	59.7 ± 28.6	60.2 ± 30.6
DAS28-hsCRP	6.0 ± 0.9	5.9 ± 1.0	5.9 ± 0.9
DAS28-ESR	6.7 ± 0.9	6.6 ± 1.0	6.7 ± 0.9
Simplified Disease Activity Index score	42.5 ± 13.6	40.9 ± 14.4	41.7 ± 14.0
Clinical Disease Activity Index score	39.9 ± 12.7	38.4 ± 13.8	39.2 ± 13.3

ACPA: anti-citrullinated protein antibody; DAS28-CRP: Disease Activity Score for 28-joint counts based on the high-sensitivity C-reactive protein level; DAS28-ESR: DAS28 based on the erythrocyte sedimentation rate; HAQ-DI: Health Assessment Questionnaire-Disability Index; mTSS: modified total Sharp score; RF: rheumatoid factor; VAS: visual analogue scale.
*Data reported as mean ± SD unless otherwise indicated.
†Anti-citrullinated protein antibody (ACPA) positivity. 10 units/ml (upper limit of normal [ULN]).
¶Higher scores indicate greater levels of disease activity or pain.
§Scores on the HAQ-DI range from 0 to 3, with higher scores indicating greater disability.
**ULN 3 mg/litre.

publication. The authors vouch for the veracity and completeness of the data and analyses and for the fidelity of this report to the protocol.

Efficacy

The primary endpoint was the proportion of patients at week 12 with an ACR 20% (ACR20) response (24). Secondary and exploratory endpoints assessed at week 12 included changes in physical function as assessed with Health Assessment Questionnaire-Disability Index (HAQ-DI) (range 0-3); changes in disease activity as assessed with Disease Activity Score for 28-joint counts (DAS28)-hsCRP, with higher scores indicating greater disease activity; remission and low disease activity (LDA) as measured with the Simplified Disease Activity Index (SDAI) and Clinical Disease Activity Index (CDAI) and ACR-50 (ACR50) and ACR-70 (ACR70) response rates. Patient-reported outcomes recorded daily in an electronic diary included morning joint stiffness (measured in minutes and by severity numeric rating scale [NRS] 0-10); severity of tiredness (NRS); and severity of joint pain (NRS). Radiographic structural joint damage was measured using the modified Total Sharp Score (mTSS).

Safety

Clinical laboratory tests, vital signs, and other safety assessments were performed at scheduled visits. The occurrence and severity of all adverse events (AEs) were recorded. The National Institutes of Health Common Terminology Criteria for Adverse Events (CTCAE, v. 3.0) or National Cholesterol Education Program categories were used to describe selected laboratory abnormalities. During the study an independent cardiovascular evaluation committee adjudicated potential cardiovascular events.

Statistical analysis

We estimated that a balanced randomisation of approximately 288 patients (144 assigned to placebo, and 144 to baricitinib) would provide sufficient power (>99%, nQuery® Advisor 7.0) for comparisons of the ACR20 response rates (with assumed rates of 60% and 35%) at week 12 between baricitinib and placebo. Patients who underwent randomisation and received at least 1 dose of the assigned study drug were included in the efficacy analyses on the basis of a modified intent-to-treat (mITT) principle. The safety population was defined as all randomised patients who received at least 1 dose of study drug and who did not discontinue from the study for the reason "lost to follow-up" at the first post baseline visit.

Comparisons of categorical efficacy variables (including proportions of patients achieving ACR20) were made using a logistic regression analysis with region, baseline joint erosion status (1–2 joint erosions plus seropositivity vs. at least 3 joint erosions), and treatment group in the model. A Fisher's exact test was used for any categorical data when the sample size requirements for the logistic regression were not met (*i.e.* <5 responders). Comparisons of continuous efficacy and health outcomes variables were made using analysis of covariance (ANCOVA) with region, treatment group, baseline joint erosion status, and baseline value in the model. Duration of morning joint stiffness was analysed using the Wilcoxon rank-sum test. All statistical tests of treatment effects were performed at 2-sided significance levels ≤0.05.

All patients were included in the analyses. For categorical efficacy outcomes, patients who received rescue treat-

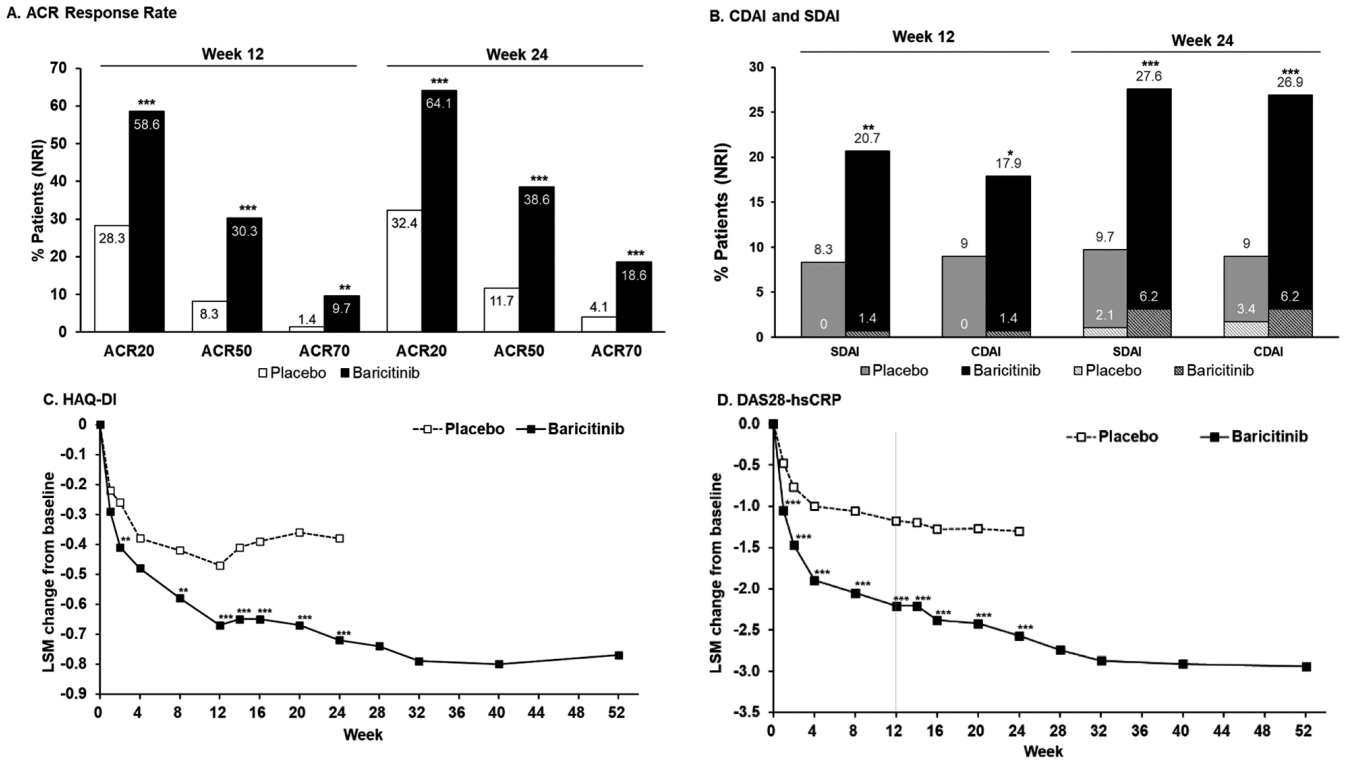

Fig. 2. Primary and secondary efficacy analyses.
A: The proportion of patients achieving ACR20, ACR50 and ACR70 responses at weeks 12 and 24. The proportion of patients with ACR20 at week 12 was the primary endpoint.
B: The proportion of patients with a CDAI score ≤10 or ≤2.8 and proportion of patients with a SDAI score ≤11 or ≤3.3 at weeks 12 and 24. The solid bars represent the proportion of patients with low disease activity (CDAI ≤10 or SDAI ≤11) and the patterned bars represent the proportion of patients achieving remission (CDAI ≤2.8 or SDAI ≤3.3).
C: HAQ-DI: change from baseline through week 52.
D: DAS28-hsCRP: change from baseline through week 52.
* $p \leq 0.05$, ** $p \leq 0.01$, *** $p \leq 0.001$ *vs*. placebo by logistic regression for ACR, CDAI, and SDAI; by ANOVA for HAQ-DI and DAS28-hsCRP.
ANOVA: analysis of variance; ACR: American College of Rheumatology; CDAI: Clinical Disease Activity Index; DAS28-hsCRP: Disease Activity Score for 28-joint counts high-sensitivity C-reactive protein; HAQ-DI: Health Assessment Questionnaire-Disability Index; LSM: least squares means; NRI: non-responder imputation; SDAI: Simplified Disease Activity Index.

ment or discontinued study treatment were defined as non-responders (non-responder imputation [NRI]). For continuous secondary outcomes, patients who discontinued study treatment because of an AE had the baseline observation carried forward; patients who discontinued the study treatment for reason(s) other than an AE had their last observation after baseline and prior to discontinuation carried forward (modified baseline observation carried forward method). For patients who received rescue therapy starting from Week 16, the last non-missing observation at or before rescue was carried forward. For mTSS, scores that were missing at weeks 16 and 24 or obtained subsequent to rescue treatment or a planned switch to baricitinib as defined in the protocol were imputed with the linear extrapolation method.

Results

Patients

Of the 584 patients screened, 290 were included in the study and randomised to placebo (n=145) or baricitinib 4-mg once daily (n=145). All patients were included in the mITT and safety analysis populations (Fig. 1). The most common reason for screen failure was hsCRP <6 mg/L.

Baseline demographic and clinical characteristics were similar between treatment groups (Table I). Most patients (80%) were from China. All patients were receiving background MTX; the majority had previously received one csDMARD. The mean MTX dosages were 12.9 and 12.2 mg/week in the placebo- and baricitinib-treated groups, respectively. Rescue rates for the placebo and baricitinib groups were 41.4% and 11.7%, respectively. Approximately 90% of patients completed the study. Of these, approximately 79% entered the long-term extension study.

Efficacy findings

At week 12, the ACR20 response rate (primary endpoint) for baricitinib was significantly higher compared to placebo (58.6% *vs*. 28.3%, odds ratio [OR] 4.1 [95% CI: 2.5, 6.9], $p \leq 0.001$) (Fig. 2A). In addition, statistically significant improvements in ACR50 and ACR70 response rates were observed at week 12, and ACR20, ACR50, and ACR70 response rates continued to improve through week 24 for baricitinib compared to placebo (Fig. 2A). The ORs (95% CI) or *p*-value for baricitinib compared to placebo at week 12 were 5.7 (2.8, 11.8), $p \leq 0.001$ for ACR50 and $p=0.004$ for ACR70 (OR not applicable); and at week 24 were

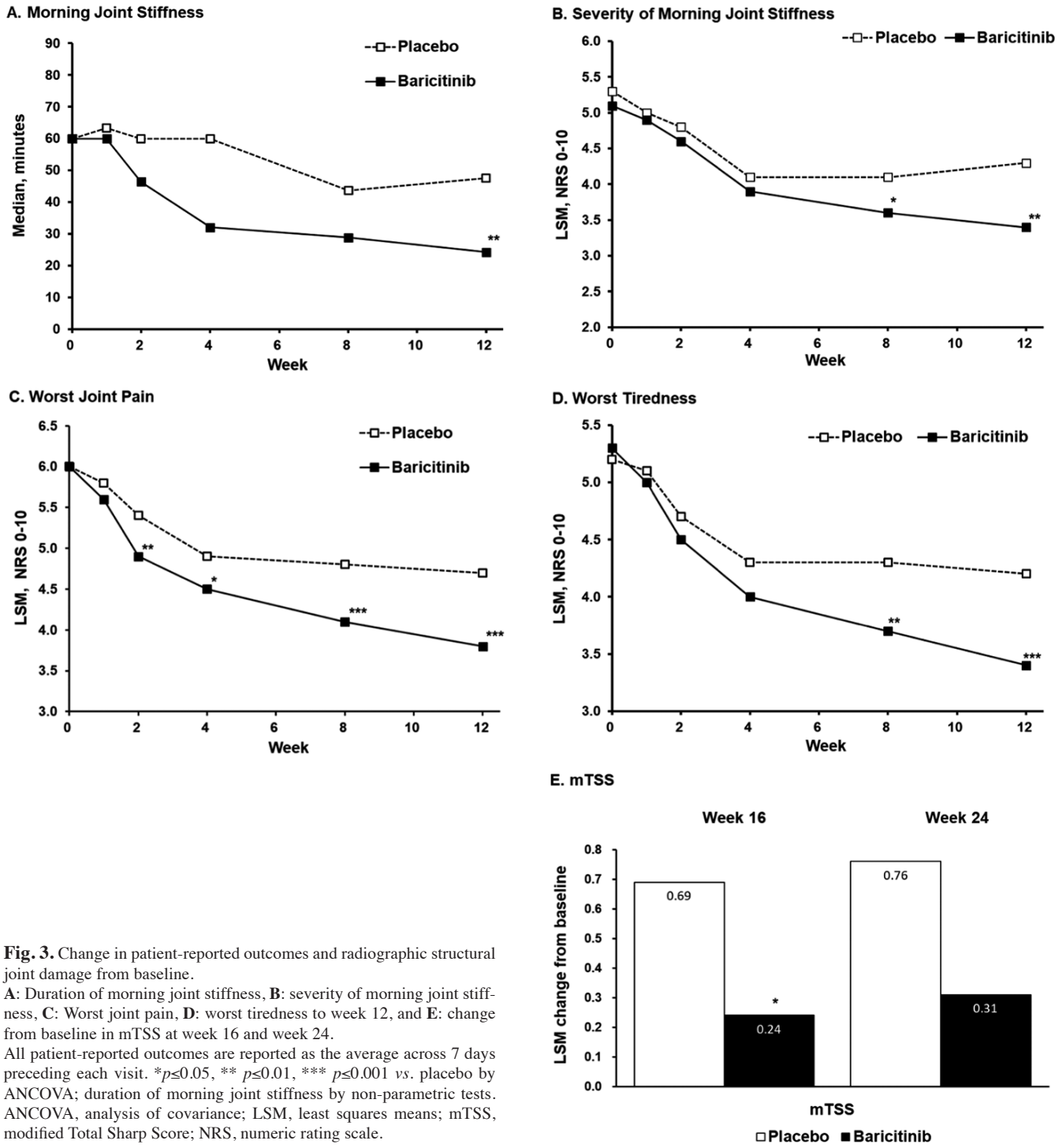

Fig. 3. Change in patient-reported outcomes and radiographic structural joint damage from baseline.
A: Duration of morning joint stiffness, **B**: severity of morning joint stiffness, **C**: Worst joint pain, **D**: worst tiredness to week 12, and **E**: change from baseline in mTSS at week 16 and week 24.
All patient-reported outcomes are reported as the average across 7 days preceding each visit. *$p \leq 0.05$, ** $p \leq 0.01$, *** $p \leq 0.001$ *vs*. placebo by ANCOVA; duration of morning joint stiffness by non-parametric tests. ANCOVA, analysis of covariance; LSM, least squares means; mTSS, modified Total Sharp Score; NRS, numeric rating scale.

4.0 (2.5, 6.7), $p \leq 0.001$ for ACR20, 5.2 (2.8, 9.6), $p \leq 0.001$ for ACR50, and 5.8 (2.3, 14.9), $p \leq 0.001$ for ACR70. Compared to placebo, statistically significant improvements at weeks 12 and 24 were observed for measures of LDA based on CDAI and SDAI (Fig. 2B) and significant improvements with baricitinib were seen at weeks 12 and 24 for the change from baseline in HAQ-DI (Fig. 2C) and DAS28-hsCRP (Fig. 2D) ($p \leq 0.001$ for both comparisons). The ORs (95% CI) for baricitinib compared to placebo for CDAI ≤10 were 2.53 (1.19, 5.36), $p=0.016$ at week 12 and 4.21 (2.08, 8.51), $p \leq 0.001$ at week 24 and for SDAI ≤11 were 3.42 (1.6, 7.3), p=0.002 at week 12 and 3.95 (1.99, 7.81), $p \leq 0.001$ at week 24. The least-squares mean difference (95% CI) for baricitinib compared to placebo for HAQ-DI were -0.20 (-0.31, -0.09), $p \leq 0.001$ at week 12 and –0.34 (-0.46, -0.22), $p \leq 0.001$ at week 24 and for DAS28-hsCRP were -1.03 (-1.26, -0.81), $p \leq 0.001$ at week 12 and -1.27 (-1.54, -1.01), $p \leq 0.001$ at week 24. Only a small proportion of patients achieved remission (CDAI and SDAI) (Fig. 2B) and there were no statistically significant differences between

Table II. Safety and laboratory summary weeks 0-12 and 0-24.

Safety and laboratory data, week 0 to week 12 and 24				
Variable	Weeks 0-12		Weeks 0-24	
	Placebo QD (n=145)	Baricitinib QD 4-mg (n=145)	Placebo QD (n=145)	Baricitinib QD 4-mg (n=145)
Safety data				
Treatment exposure – patient-years	32.7	32.7	56.8	62.4
SAE†,‡	2 (1.4)	1 (0.7)	4 (2.8)	4 (2.8)
TEAE	77 (53.1)	83 (57.2)	90 (62.1)	108 (74.5)*
Discontinuation from study due to AE	1 (0.7)	1 (0.7)	3 (2.1)	2 (1.4)
Infections	32 (22.1)	41 (28.3)	41 (28.3)	61 (42.1)
Herpes zoster	0	1(0.7)	1 (0.7)	3 (2.1)
TB	0	0	0	0
Serious infections	0	1 (0.7)	1 (0.7)	2 (1.4)
Malignancies	0	0	0	0
MACE§	0	0	0	0
GI Perforations	1 (0.7)	0	0	0
Laboratory data (SE)				
LSM change from baseline¥				
Haemoglobin, mmol/L	0.10(0.05)$^{+}$	0.07(0.05)	0.08(0.05)	0.11(0.05)$^{+}$
Neutrophils, 103 cells/µL	-0.10(1.14)	-1.27 (0.14)$^{+++***}$	-0.45(0.13)$^{+++}$	-1.19(0.13)$^{+++***}$
Lymphocytes, 103 cells/µL	0.03(0.04)	0.12(0.04)$^{++}$	0.03(0.04)	0.04(0.04)
Platelets, 103 cells/µL	-7 (5)	1 (5)	-9 (5)	-9 (5)
ALT, U/L	1.3 (0.9)	3.0 (0.9)$^{+++}$	1.0 (0.9)	3.6 (0.9)$^{+++}$
Creatinine, umol/L	0.7(0.6)	4.1(0.6)$^{+++***}$	0.8(0.7)	4.6(0.7)$^{+++***}$
CPK, U/L	3 (11)	70 (11)$^{+++***}$	6 (4)	59 (4)$^{+++***}$
Cholesterol, mmol/L	-0.04 (0.06)	0.54 (0.06)$^{+++***}$	-0.04(0.06)	0.42 (0.06)$^{+++***}$
LDL, mmol/L	-0.02 (0.06)	0.35 (0.05)$^{+++***}$	0.00 (0.05)	0.31 (0.05)$^{+++***}$
HDL, mmol/L	0.005(0.025)	0.285(0.025)$^{+++***}$	0.019(0.024)	0.220(0.024)$^{+++***}$

AE: adverse event; ALT: alanine transaminase; CPK: creatine phosphokinase; HDL: high-density lipoprotein; ICH: International Conference on Harmonization; LDL: low-density lipoprotein; LLN: lower limit of normal; LSM: least squares mean; MACE: major adverse cardiovascular event; n: number of patients randomised and treated; NMSC, non-melanoma skin cancer; PYE: patient-years exposure to treatment; QD: once-daily; SAEs: serious adverse events; SE: standard error; TEAEs: treatment emergent adverse events.

†SAEs reported using conventional ICH definitions. The table does not describe events that were serious for the reason of protocol definition. The protocol required that adverse events or laboratory abnormalities leading to permanent discontinuation of study drug be designated as SAEs.

‡Data displayed are n (%) patients, up to the time of rescue

§MACE was defined as cardiovascular death, myocardial infarction or stroke positively adjudicated by an independent cardiovascular evaluation committee.

¥LSM change from baseline (SE) at Week 12 or at Week 24.

$^{+}p\leq0.05$, $^{++}p\leq0.01$, and $^{+++}p\leq0.001$ *vs*. baseline by ANCOVA

$^{*}p\leq0.05$, $^{**}p\leq0.01$, and $^{***}p\leq0.001$ *vs*. placebo by ANCOVA

groups at weeks 12 or 24 (Fig. 2B). Significant improvements were observed in morning joint stiffness (duration and severity) (Fig. 3A, 3B; $p<0.01$ for both comparisons), worst joint pain (Fig. 3C), and worst tiredness (Fig. 3D) at week 12 for baricitinib compared to placebo ($p\leq0.001$ for both comparisons). Compared to placebo, a statistically significant decrease in progression of mTSS was observed at week 16 but not at week 24 (Fig. 3E).

Clinical measures of efficacy were maintained or improved through week 52 (Fig. 2C and D, Suppl. Fig. S1). Moreover, significant improvement in ACR20, ACR50, and ACR70, response rates (Suppl. Fig. S1A-C), mean change from baseline in SDAI and CDAI scores (Suppl. Fig. S1C-D), and HAQ-DI and DAS28-hsCRP (Fig. 2C and D), and worst joint pain (Fig. 3C) were observed as early as week 1 or week 2 for baricitinib compared to placebo.

Safety findings

The rates of discontinuation resulting from AEs from baseline through week 24 were 2.1% with placebo and 1.4% with baricitinib and rates of serious AEs (SAEs) were the same (2.8%) in both groups (Table II). There were 2 positively adjudicated major adverse cardiovascular events reported in the study; 1 was ischaemic stroke where the patient died in the baricitinib group on day 277 (137 days after rescue), and the other was subarachnoid haemorrhage due to intracranial aneurysm in the follow-up period (placebo rescued to baricitinib). One patient in the placebo group had gastrointestinal perforation.

From baseline through week 24, treatment-emergent adverse events (TEAEs) were more frequent with baricitinib than with placebo (74.5% *vs*. 62.1%) (Table II). Although infections occurred more frequently with baricitinib compared to placebo (42.1% *vs*. 28.3%), few serious infections were reported in either group. Upper respiratory tract infections were the most commonly reported infections (Table II). Few herpes zoster infections (1 with placebo, 3 with baricitinib) or cases of esophageal candidiasis (1 with baricitinib) were reported, and active tuberculosis was not reported in either group. None of the herpes zoster infections were visceral or disseminated beyond the primary or adjacent dermatomes. There was 1 case of a serious lung infection mostly likely arising from cytomegalovirus IgM antibody positive viral infection in a patient 114 days after switching from placebo to baricitinib.

Mean changes from baseline and number of patients with increases in CTCAE grade for selected laboratory analytes through weeks 12 and 24 are reported in Tables II and III, respectively. No imbalance in the number of patients with decreased haemoglobin was seen between the placebo and baricitinib groups (Table III). Compared to placebo, baricitinib was associated with transient increases in alanine aminotransferase levels and lymphocyte grade in some patients (data not shown), modest transient increases in platelet counts during the initial weeks of treatment with baricitinib followed by a return to baseline (data not shown), reductions in neutrophils, and increases from baseline in creatinine levels, serum creatine phosphokinase (CPK), high-density li-

Table III. Summary of laboratory abnormalities of special interest through weeks 12 and 24.

Summary of laboratory abnormalities of special interest through weeks 12 and 24a				
Variable	Weeks 0-12		Weeks 0-24	
	Placebo QD (n=145)	Baricitinib QD 4-mg (n=145)	Placebo QD (n=145)	Baricitinib QD 4-mg (n=145)
Decreased neutrophils, n (%)				
Grade 1: ≥1.5 GI/L to <2 GI/L	4	5	5	4
Grade 2: ≥1.0 GI/L to <1.5 GI/L	1	2	2	5
Grade 3: ≥0.5 GI/L to <1.0 GI/L	0	0	1	0
Decreased lymphocytes, n (%)				
Grade 1: ≥0.8 GI/L to <1.1 GI/L	16	7	18	9
Grade 2: ≥0.5 GI/L to <0.8 GI/L	10	3	14	11
Grade 3: ≥0.2 GI/L to <0.5 GI/L	1	2	2	3
Decreased haemoglobin, n (%)				
Grade 1: ≥6.2 mmol(Fe)/L to <7.27 mmol(Fe)/L for females and <8.18 mmol(Fe)/Lfor males	22	32	23	34
Grade 2: ≥4.9 mmol(Fe)/L to <6.2 mmol(Fe)/L	10	9	15	13
Grade 3: ≥4.0 mmol(Fe)/L to <4.9 mmol(Fe)/L	0	0	1	0
Grade 4: <4.0 mmol(Fe)/L	0	0	0	1
Elevated platelets, n(%)				
Grade 1: ≥75 GI/L to <150 GI/L	6	5	9	8
Grade 2: ≥50 GI/L to <75 GI/L	0	0	0	0
Grade 3: ≥25 GI/L to <50 GI/L	0	0	0	0
Elevated ALT, n(%)				
Grade 1: >ULN to ≤2.5× ULN	5	14	11	17
Grade 2: >2.5× ULN to ≤5× ULN	2	2	2	3
Grade 3: >5× ULN to ≤20×ULN	0	0	0	0
CPK, n(%)				
Grade 1: >ULN and ≤2.5× ULN	2	24	4	32
Grade 2: >2.5× ULN and ≤5× ULN	0	2	0	5
Grade 3: >5× ULN and ≤10× ULN	0	0	0	0
Grade 4: >10× ULN	0	1	0	1
LDL, n (%)b				
Near optimal: ≥2.59 mmol/L and <3.36 mmol/L	9	19	13	27
Borderline high: ≥3.36 mmol/L and <4.14 mmol/L	9	17	10	21
High: ≥4.14 mmol/L and <4.91 mmol/L	4	14	5	16
Very high: ≥4.91 mmol/L	1	5	2	5
HDL, n (%)b				
Normal: ≥1.03 mmol/L and <1.55 mmol/L	15	5	17	9
Low: <1.03 mmol/L	5	3	7	3

ALT: alanine transaminase; CPK: creatine phosphokinase; LDL: Low-density lipoprotein; HDL: cholesterol and high-density lipoprotein; ULN: upper limit of normal.
a Data indicate the worst CTCAE (v. 3.0) grade in patients who experienced a treatment-emergent increase in grade at any time during the treatment period, up to the time of rescue.
b Data indicate the worst National Cholesterol Education Program category in patients who experienced a treatment-emergent worsening in category at any time during the treatment period, up to the time of rescue.

poprotein (HDL) cholesterol, and low-density lipoprotein (LDL) cholesterol (Table II). The ratio of LDL cholesterol to HDL cholesterol did not change over time in either group. One patient in the baricitinib group exhibited grade 4 CPK abnormality but reported physical exertion before being tested. There was no increase in neutropenia or lymphopenia and no imbalance in the number of patients with protocol-defined thrombocytosis (>600,000 cells/mm^3) between the baricitinib and placebo groups (Table III).

Discussion

The RA-BALANCE study was designed to assess the efficacy and safety of baricitinib in adult patients with moderately to severely active RA with inadequate response to MTX and is the first study of a JAK inhibitor to be conducted mainly in a Chinese population. Overall, the efficacy and safety findings from this study were consistent with previous phase 3 clinical trials of baricitinib in other populations (18, 25-27). These findings are particularly relevant for China where RA is estimated to affect approximately 5 million people (8) and use of bDMARD monotherapy is limited or suboptimal compared to other countries (28).

The primary and most secondary efficacy objectives of this study were met. Baricitinib was statistically significantly superior to placebo with regard to ACR20 response rate at week 12 and, compared to placebo, statistically significant improvements in other accepted measures of RA disease activity and physical function were seen. Improvements were seen from the early weeks of treatment and sustained through week 52, including rapid and sustained improvements in a variety of patient-reported outcomes with baricitinib compared to placebo. However, in contrast to some previous phase 3 clinical trials of baricitinib in patients with an inadequate response to csDMARDs/MTX (20, 22, 25), there were no significant differences between baricitinib and placebo in SDAI remission or mTSS at week 24 in the current study. This may be because the relatively small sample size of the current study compared with previous global studies limited the ability to observe significant differences in SDAI remission and structural progression. In addition, differences in management and access of patients to bDMARDs in China compared with other countries (28) may have resulted in a higher proportion of more refractory patients who elsewhere could have accessed and potentially failed bDMARD therapy. A real-world study of 802 patients with RA from China has shown that treatment with bDMARDs (89.5% on csDMARD combination therapy) appears to be suboptimal,

with treatment durations ranging from 4.7 to 34.5 weeks and only 3.5% of patients achieving SDAI remission (28). While it is not clear why patients in China have shorter treatment durations with bDMARDs compared with other countries, the authors of this real-world study speculate that this may be because of poor treatment adherence or limited access. Further study on the rate of remission with bDMARD therapy is required to clarify this issue.

The safety findings in this study were consistent with the safety profile of JAK inhibitors (29) and previous clinical trials with baricitinib (18, 20, 22, 27, 30, 31). Infections were more common with baricitinib compared to placebo, and baricitinib was associated with decreases in neutrophil counts and increases from baseline in laboratory parameters, including levels of aminotransferase, creatinine, CPK, and LDL and HDL cholesterol. Importantly, there were no differences in serious infections between baricitinib and placebo; and although herpes zoster infections were more common with baricitinib, the numbers of cases were small in both groups. Patients with RA are at greater risk of cardiovascular disease, including myocardial infarction, stroke, and venous thromboembolism (32, 33). However, findings from pooled analyses suggest no association between exposure to baricitinib and risk of major cardiovascular events, arterial thrombotic events, or congestive heart failure (34, 35). In a pooled analysis of phase 3 studies, 6 venous thromboembolism events were reported for baricitinib 4-mg (n=997 patients) but not placebo (n=1070 patients) during placebo-controlled studies up to 24 weeks; during longer-term evaluation, incidence rates of deep vein thrombosis/pulmonary embolism were similar between baricitinib 2-mg and 4-mg doses, consistent over time, and within the range for patients with RA (34).

The limitations of this study include the relatively short time frame for the placebo-controlled phase (24 weeks) and the relatively small sample size compared to previous global studies. In particular, the potential long-term effect of baricitinib on increases in laboratory parameters could not be assessed because of the relatively short duration of the study. To reflect current ethical standards and consistent with current clinical trials of RA, the placebo-controlled phase of the study was relatively short and patients on placebo with active disease who did not meet the criteria for treatment response could be rescued at 16 weeks.

In conclusion, findings from this study of patients with moderately to severely active RA and an inadequate response to MTX showed once-daily oral baricitinib 4-mg to be associated with rapid and durable improvements compared to placebo in signs and symptoms, physical function, and patient-reported outcomes. Baricitinib was well tolerated with an acceptable safety profile through 52 weeks of treatment. Overall, the efficacy and safety of baricitinib in this phase 3 study, conducted mainly in patients from China, was consistent with the findings for baricitinib in previous clinical trials of baricitinib in global populations.

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