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Baricitinib, Methotrexate, or Combination in Patients With Rheumatoid Arthritis and No or Limited Prior Disease-Modifying Antirheumatic Drug Treatment

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Objective. **We undertook this phase III study to evaluate baricitinib, an orally administered JAK-1/JAK-2 inhibitor, as monotherapy or combined with methotrexate (MTX) compared to MTX monotherapy in patients with active rheumatoid arthritis (RA) who had received no or minimal conventional synthetic disease-modifying antirheumatic drugs (DMARDs) and who were naive to biologic DMARDs.**

Methods. **A total of 588 patients were randomized 4:3:4 to receive MTX monotherapy (once weekly), baricitinib monotherapy (4 mg once daily), or the combination of baricitinib and MTX for 52 weeks. The primary end point assessment was a noninferiority comparison of baricitinib monotherapy to MTX monotherapy based on the proportion of patients meeting the American College of Rheumatology 20% improvement criteria (achieving an ACR20 response) at week 24.**

Results. **The study met its primary objective. Moreover, baricitinib monotherapy was found to be superior to MTX monotherapy at week 24, with a higher ACR20 response rate (77% versus 62%; $P \leq 0.01$). Similar**

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results were observed for combination therapy. Compared to MTX monotherapy, significant improvements in disease activity and physical function were observed for both baricitinib groups as early as week 1. Radiographic progression was reduced in both baricitinib groups compared to MTX monotherapy; the difference was statistically significant for baricitinib plus MTX. The rates of serious adverse events (AEs) were similar across treatment groups, while rates of some treatment-emergent AEs, including infections, were increased with baricitinib plus MTX. Three deaths were reported, all occurring in the MTX monotherapy group. Malignancies, including nonmelanoma skin cancer, were reported in 1 patient receiving MTX monotherapy, 1 receiving baricitinib monotherapy, and 4 receiving baricitinib plus MTX.

Conclusion. **Baricitinib alone or in combination with MTX demonstrated superior efficacy with acceptable safety compared to MTX monotherapy as initial therapy for patients with active RA.**

Rheumatoid arthritis (RA) is a chronic systemic inflammatory disorder that primarily affects diarthrodial joints. In RA, increased circulating levels of proinflammatory cytokines contribute to the overall symptomatology of fatigue, pain, and joint stiffness. Disease severity ranges from mild limited disease to severe systemic disease associated with joint destruction, comorbid conditions (e.g., cardiovascular disease, infections, malignancies), significant disability, reduced quality of life, and shortened survival (1,2).

In patients with early RA, methotrexate (MTX) alone or in combination with other conventional synthetic disease-modifying antirheumatic drugs (csDMARDs) remains the "anchor" therapy, and early intervention improves clinical outcomes and reduces joint damage and future disability (3). However, approximately one-third of patients are intolerant of MTX treatment, with discontinuation of MTX being common in clinical practice (4,5). Therefore, determining whether new therapies in development for RA might be an alternative to MTX in patients who cannot take or tolerate MTX may be important in understanding the potential utility of any new treatment.

Furthermore, although current guidelines recommend MTX as initial DMARD therapy for patients with RA, slow onset of benefit is recognized, and use of corticosteroids to bridge to treatment response is suggested as part of initial therapy (6,7). Compared to csDMARDs with delayed onset of effect, novel therapies with rapid onset of benefit may obviate the need for bridging corticosteroid use of this kind, a potentially desirable advance in light of the recognized toxicities of corticosteroid therapy.

Multiple cytokines implicated in the pathogenesis of RA signal through a JAK-1/JAK-2 heterodimer (e.g., interleukin-6, interferons) or a JAK-2/JAK-2 homodimer (e.g., granulocyte–macrophage colony-stimulating factor). Baricitinib, an orally administered JAK-1/JAK-2 inhibitor, has shown efficacy and acceptable safety in patients with RA who had an insufficient response to csDMARDs and biologic DMARDs (bDMARDs) (8–10). This report describes the results of the RA-BEGIN trial, a phase III study of baricitinib in patients with active RA and no prior treatment with csDMARDs (no or limited exposure to MTX) or bDMARDs. The study was designed to evaluate baricitinib as monotherapy or in combination with MTX versus MTX monotherapy.

PATIENTS AND METHODS

Patients. We included patients age ≥18 years with adult-onset RA, classified by the American College of Rheumatology (ACR)/European League Against Rheumatism (EULAR) 2010 criteria (3), who had received no prior csDMARD therapy (up to 3 weekly MTX doses permitted) and no prior bDMARD therapy. Patients had active disease (≥6 of 68 tender joints and ≥6 of 66 swollen joints; serum high-sensitivity C-reactive protein [hsCRP] level ≥3.6 mg/liter [upper limit of normal 3.0 mg/liter]) and were seropositive for rheumatoid factor (RF) or anti–citrullinated protein antibodies (ACPAs) (3). Exclusion criteria included recent clinically significant infection and select laboratory abnormalities (aspartate aminotransferase or alanine aminotransferase [ALT] >1.5 times upper limit of normal, hemoglobin <10.0 gm/dl, neutropenia <1,200 cells/μl, lymphopenia <750 cells/μl, and estimated glomerular filtration rate [GFR] <40 ml/minute/1.73 m^2).

Patients with evidence of or suspected latent tuberculosis could enroll if appropriate treatment was commenced ≥4 weeks before randomization and the patient agreed to complete the remainder of treatment while in the trial.

Study protocol and oversight. RA-BEGIN was a 52-week randomized, double-blind, double-dummy, active comparator–controlled study conducted at 198 centers in 18 countries. Patients were randomized 4:3:4 to receive oral MTX monotherapy (administered once weekly), baricitinib monotherapy (4 mg administered once daily), or the combination of baricitinib and MTX. MTX was initiated at 10 mg/week and, if tolerated, increased to 20 mg/week by week 8. A lower dosage regimen was available if clinically indicated (initial dosage of 7.5 mg once weekly and maximum dosage of 12.5 mg once weekly). Randomization was stratified by geographic region and presence or absence of joint erosions on centrally read baseline radiographs. Patients with a screening estimated GFR ≥40 and <60 ml/minute/1.73 m^2 who were assigned to baricitinib monotherapy or baricitinib plus MTX received baricitinib at 2 mg. Concomitant treatment with stable doses of nonsteroidal antiinflammatory drugs (NSAIDs), analgesics, and/or oral corticosteroids (≤10 mg/day of prednisone or equivalent) was permitted. Baricitinib and placebo to match were supplied as 4-mg and 2-mg tablets. Active and placebo MTX were supplied as identical opaque capsules containing excipient with or without commercially available MTX. Folic acid was provided by the sponsor as a

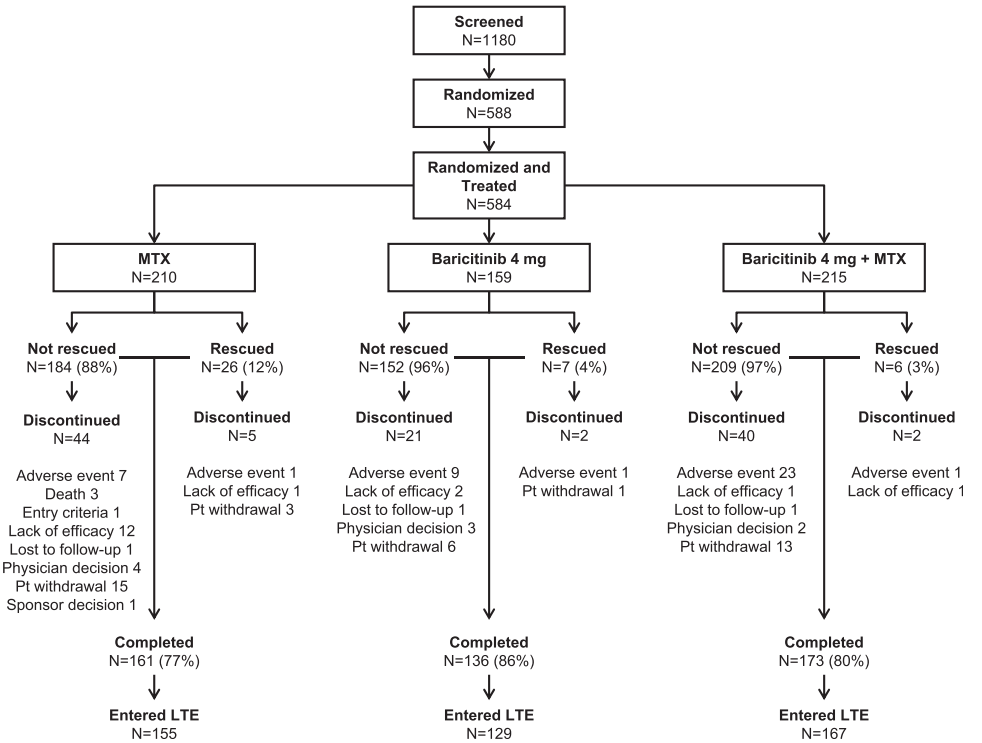

Figure 1. Patient disposition through 52 weeks. Enrollment: Central and South America 29%, US and Canada 21%, Japan 18%, Europe 14%, rest of world 19%. MTX = methotrexate; LTE = long-term extension.

noninvestigational product, and all patients were required to take at least 1 mg once daily (or per local standard of care).

Rescue treatment (baricitinib plus MTX) for those patients whose tender and swollen joint counts did not improve by ≥20% from baseline was available beginning at week 24. New or increased doses of NSAIDs, analgesics, and oral corticosteroids could also be used after rescue. Patients completing week 52 could enter a long-term extension study. Patients who did not enter the extension study or who discontinued early were followed up for ~28 days after their last dose of study drug.

The study was conducted in accordance with ethical principles of the Declaration of Helsinki and Good Clinical Practice guidelines and was approved by each center's institutional review board or ethics committee. All patients provided written informed consent. The study was initiated in November 2012 and completed in August 2015, with enrollment occurring between January 2013 and August 2014.

Efficacy. The primary end point assessment was a noninferiority comparison of baricitinib monotherapy to MTX monotherapy based on the proportion of patients meeting the American College of Rheumatology 20% improvement criteria (achieving an ACR20 response) (11) at week 24. Major secondary end points assessed at week 24 included superiority comparisons of baricitinib monotherapy or baricitinib plus MTX to MTX monotherapy based on the ACR20 response, Health Assessment Questionnaire disability index (HAQ DI) (12,13), Simplified Disease Activity Index (SDAI) remission (score of ≤3.3) (14), Disease Activity Score in 28 joints (15) based on C-reactive protein level (DAS28-CRP) (16), and modified Sharp/van der Heijde score (SHS) (17). Radiographs were scored centrally by 2 independent readers with adjudication by a third reader, if needed. Independent readers were blinded to chronological order, patient identifiers, and treatment group. The mean score obtained between the reader pair was used in the analysis. Other secondary measures included proportions of patients achieving ACR50 and ACR70 responses, DAS28 based on erythrocyte sedimentation rate (DAS28-ESR) of ≤3.2 and <2.6 (16), and Clinical Disease Activity Index (CDAI) score of ≤2.8 (14) at weeks 12, 24, and 52.

Safety. Clinical laboratory tests, recording of vital signs, and other safety assessments were performed at all scheduled visits. The incidence and severity of all adverse events (AEs) were recorded. The National Institutes of Health Common Terminology Criteria for Adverse Events (CTCAE; version 3.0) and National Cholesterol Education Program categories were used to describe selected laboratory abnormalities. During the study, an independent data safety monitoring committee periodically reviewed data from this and other ongoing phase III studies of baricitinib. An independent clinical end point committee adjudicated potential cardiovascular events.

Statistical analysis. Week 24 ACR20 response rates were anticipated to be 55% for MTX monotherapy, 60% for baricitinib monotherapy, and 68.5% for baricitinib plus MTX for the purposes of sample size and power calculations. Randomization of 200 patients per arm was estimated to provide 79% power for evaluation of baricitinib plus MTX versus MTX monotherapy, a superiority assessment. However, a smaller sample size of 150 patients was chosen for baricitinib monotherapy because this was estimated to provide 89% power for the primary evaluation of noninferiority to MTX monotherapy using a prespecified

noninferiority margin of 12%. A modified intent-to-treat (ITT) analysis was employed for efficacy analyses, which included all patients treated with ≥1 dose of study drug.

A weighted, Bonferroni-based, sequentially rejective, closed multiple-testing procedure was used to maintain strong control of Type I error for the 24-week primary and major secondary end points (see Supplementary Figure 1, available on the *Arthritis & Rheumatology* web site at http://onlinelibrary.wiley.com/doi/10.1002/art.39953/abstract) (18,19). Treatment comparisons for categorical and continuous efficacy measures were performed using logistic regression and analysis of covariance (ANCOVA), respectively, with baseline value (for continuous measures only), treatment, region, and presence of baseline joint erosions in the model. Fisher's exact test was used for categorical safety data or when sample size requirements for the logistic regression model were not met. Continuous safety data were analyzed using ANCOVA with baseline value and treatment in the model. Analyses used a significance level of 0.05 (2-sided) unless otherwise defined by the multiple-testing procedure. Prespecified sensitivity analyses included evaluation of the primary and major secondary objectives in a predetermined per-protocol population.

Patients rescued or discontinued from the study or study treatment were thereafter defined as nonresponders (nonresponder imputation) for all categorical efficacy outcomes. These patients had their last observations before rescue or discontinuation (modified last observation carried forward method) used for analyses of continuous efficacy data. For continuous secondary efficacy measures evaluated under strict Type I error control (with the exception of the SHS, see below), if the reason for discontinuation was an AE, the baseline observation was substituted at the week-24 analysis time point (modified baseline observation carried forward method). For radiographic measures, scores at weeks 24 or 52 that were missing or subsequent to rescue were imputed using linear extrapolation from baseline and the most recent postbaseline data prior to or at initiation of rescue therapy. Safety observations were analyzed by randomized treatment until the time of rescue or the end of the treatment period.

RESULTS

Patient characteristics. Of 1,180 screened patients, 588 were randomized (Figure 1). The most common

Table 1. Baseline characteristics and disease activity of the patients in the RA-BEGIN trial*

	MTX (n = 210)	Baricitinib 4 mg (n = 159)	Baricitinib 4 mg plus MTX (n = 215)
Age, years	51 ± 13	51 ± 13	49 ± 14
Women, no. (%)	148 (70)	121 (76)	156 (73)
Duration of RA, years	1.3 ± 4.0	1.9 ± 4.7	1.3 ± 2.7
Duration of RA, median years	0.2	0.2	0.2
ACPA-positive, no. (%)†	193 (92)	142 (89)	192 (89)
RF-positive, no. (%)‡	203 (97)	155 (97)	204 (95)
One or more erosions, no. (%)	138 (66)	105 (66)	137 (64)
SHS, Sharp units	11.8 ± 22.2	13.3 ± 27.0	11.4 ± 20.1
Erosion score	7.9 ± 12.5	8.7 ± 15.8	7.5 ± 11.7
Joint space narrowing score	3.9 ± 10.4	4.6 ± 11.9	4.0 ± 9.6
Concomitant corticosteroid use, no. (%)	76 (36)	47 (30)	83 (39)
Ever used DMARDs, no. (%)§	20 (10)	13 (8)	18 (8)
SJC, 66 joints	16 ± 11	16 ± 9	16 ± 10
TJC, 68 joints	27 ± 15	26 ± 14	28 ± 15
Physician's global assessment of disease activity, 0–100-mm VAS¶	67 ± 17	68 ± 17	66 ± 17
Patient's global assessment of disease activity, 0–100-mm VAS¶	66 ± 24	65 ± 22	63 ± 24
Patient's assessment of pain, 0–100-mm VAS¶	65 ± 24	64 ± 22	63 ± 23
HAQ DI score, 0–3#	1.7 ± 0.7	1.6 ± 0.7	1.6 ± 0.7
hsCRP level, mg/liter**	22 ± 22	24 ± 26	24 ± 29
ESR, mm/hour	54 ± 29	51 ± 27	49 ± 26
DAS28-hsCRP	5.9 ± 1.0	5.9 ± 1.0	5.9 ± 0.9
DAS28-ESR	6.6 ± 1.0	6.6 ± 1.1	6.6 ± 1.0
Simplified Disease Activity Index score	42 ± 14	43 ± 14	43 ± 13
Clinical Disease Activity Index score	39 ± 13	40 ± 13	40 ± 13

* Except where indicated otherwise, values are the mean ± SD. RA = rheumatoid arthritis; SHS = modified Sharp/van der Heijde score; DMARDs = disease-modifying antirheumatic drugs; SJC = swollen joint count; TJC = tender joint count; VAS = visual analog scale; HAQ DI = Health Assessment Questionnaire disability index; DAS28-hsCRP = Disease Activity Score in 28 joints based on the high-sensitivity C-reactive protein (hsCRP) level; DAS28-ESR = DAS28 based on the erythrocyte sedimentation rate (ESR).
† Anti–citrullinated protein antibody (ACPA) positivity >10 units/ml (upper limit of normal [ULN]).
‡ Rheumatoid factor (RF) positivity >14 units/ml (ULN).
§ Up to 3 weekly doses of methotrexate (MTX) permitted.
¶ Higher scores indicate greater levels of disease activity or pain.
# Higher scores indicate greater disability.
** ULN 3 mg/liter.

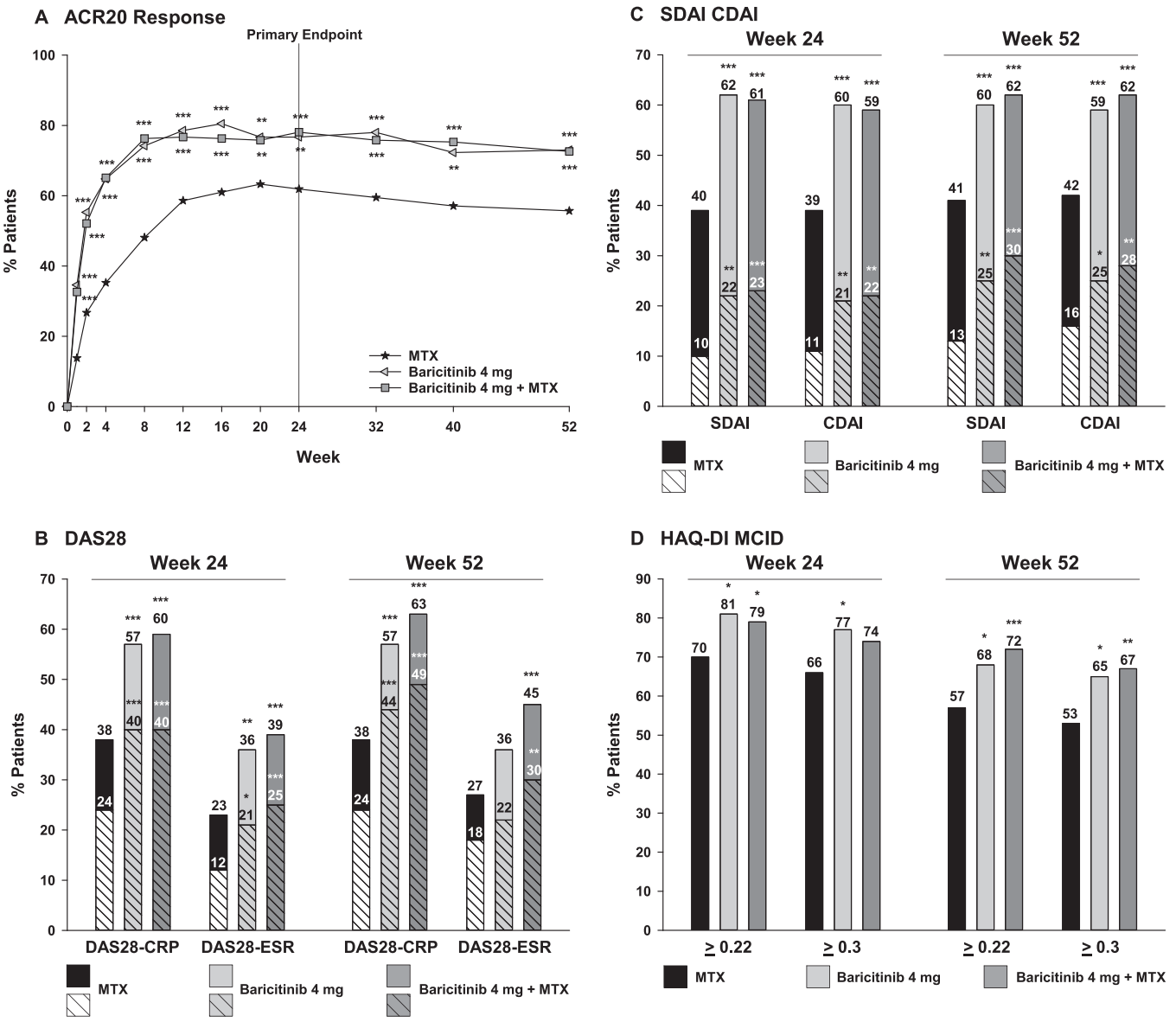

Figure 2. Primary and secondary efficacy analyses. **A,** Percentage of patients meeting the American College of Rheumatology 20% improvement criteria (ACR20) over time through week 52. The vertical line at week 24 indicates the primary efficacy time point. **B,** Percentage of patients with a Disease Activity Score in 28 joints using the C-reactive protein level (DAS28-CRP) or with a DAS28 using the erythrocyte sedimentation rate (DAS28-ESR) of <2.6 or ≤3.2 at weeks 24 and 52. Solid parts of bars represent the percentage of patients with a DAS28 of ≤3.2; patterned parts of bars represent the percentage of patients with a DAS28 of <2.6. **C,** Percentage of patients with a Clinical Disease Activity Index (CDAI) score of ≤10 or ≤2.8 at weeks 24 and 52, and percentage of patients with a Simplified Disease Activity Index (SDAI) score of ≤11 or ≤3.3 at weeks 24 and 52. For the CDAI, solid parts of bars represent the percentage of patients with a score of ≤10, and patterned parts of bars represent the percentage of patients with a score of ≤2.8. For the SDAI, solid parts of bars represent the percentage of patients with a score of ≤11, and patterned parts of bars represent the percentage of patients with a score of ≤3.3. **D,** Percentage of patients achieving improvement of ≥0.22 or ≥0.3 in the Health Assessment Questionnaire disability index (HAQ DI) score at weeks 24 and 52. * = $P \leq 0.05$; ** = $P \leq 0.01$; *** = $P \leq 0.001$ versus methotrexate (MTX) monotherapy, by logistic regression. MCID = minimum clinically important difference.

reason for screen failure was hsCRP <3.6 mg/liter, and the second reason was lack of RF and ACPA seropositivity. Baseline demographic and clinical characteristics were similar among treatment groups (Table 1). The median disease duration was 0.2 years, and >91% of patients were DMARD naive (8% of patients had received limited doses of MTX). Patients had active disease at baseline, with a mean of 27 of 68 tender joints and 16 of 66 swollen joints, a mean HAQ DI score of 1.6, and radiographic evidence of joint erosion (in 65% of patients). The mean MTX dosage

achieved was 17.7 mg/week in both the MTX monotherapy and combination treatment arms; ~23% of patients were prescribed the lower MTX dosage regimen. As anticipated, the lower dosage group was predominantly composed of Asian patients (91%), most in Japan (78%).

Baseline characteristics by MTX dosage group are shown in Supplementary Table 1, http://onlinelibrary.wiley.com/doi/10.1002/art.39953/abstract. The mean doses prescribed in the full/low-dose groups were 19.6 mg/12.1 mg in the MTX monotherapy group and 19.2 mg/12 mg in the baricitinib plus MTX group at week 24. The proportions of patients in the full-dose group who were prescribed the full intended 20-mg dose at this time point were 94.2% in the MTX monotherapy group and 87.8% in the baricitinib plus MTX group. For the MTX monotherapy, baricitinib monotherapy, and baricitinib plus MTX groups, 12%, 4%, and 3%, respectively, of patients were rescued and 23%, 14%, and 20%, respectively, were prematurely discontinued from the study (Figure 1). Eighty percent of the patients completed week 52, and most of these (96%) entered the long-term extension study.

Efficacy findings. The study met its primary noninferiority objective. The ACR20 response rate at week 24 for baricitinib monotherapy and MTX monotherapy was 77% and 62%, respectively ($P \leq 0.001$ for noninferiority). Moreover, baricitinib monotherapy was found to be superior to MTX monotherapy at week 24 ($P \leq 0.01$) (Figure 2A). Compared to MTX monotherapy, statistically significant improvements were observed for baricitinib monotherapy and baricitinib plus MTX in the 24-week major secondary measures of superiority of the ACR20 response, improvement in the DAS28-CRP, improvement in HAQ DI scores, and SDAI remission (Figure 2) (see Supplementary Figures 2F and 3A, http://onlinelibrary.wiley.com/doi/10.1002/art.39953/abstract). Less progression in the SHS was observed in both baricitinib groups compared to MTX monotherapy; however, the treatment effect was statistically significant for baricitinib plus MTX but not for baricitinib monotherapy (Figure 3). Otherwise, all major efficacy objectives were achieved, with statistical significance controlled for multiplicity (see Supplementary Table 2, http://onlinelibrary.wiley.com/doi/10.1002/art.39953/abstract).

Outside of the closed-testing procedure, statistically significant improvements were consistently observed for the baricitinib monotherapy and baricitinib plus MTX groups compared to MTX monotherapy for ACR20, ACR50, and ACR70 response rates (Figure 2A) (see Supplementary Figures 3E and F, http://onlinelibrary.wiley.com/doi/10.1002/art.39953/abstract); measures of low disease activity and remission based on the DAS28 (Figure 2B) and on the CDAI and SDAI (Figure 2C); physical function based on categorical change in HAQ DI score (Figure 2D); and changes from baseline in composite scores (see Supplementary Figures 3A–D, http://onlinelibrary.wiley.com/doi/10.1002/art.39953/abstract) and their components (see Supplementary Figure 2, http://onlinelibrary.wiley.com/doi/10.1002/art.39953/abstract). Compared to MTX monotherapy, statistically significant improvements began as early as week 1 and were sustained through 52 weeks of treatment in both baricitinib groups.

Although the study design limited statistical comparisons between baricitinib treatment groups because of insufficient power, the treatment effects observed for baricitinib monotherapy and the combination of baricitinib and MTX were similar in magnitude, including measures of how patients feel (for example, pain and patient's assessment of disease activity) and function (HAQ DI). Combination therapy was associated with apparently larger improvements in inflammation-related measures (for example, ESR). Although a relatively small proportion of patients in any group had radiographic progression, the lowest radiographic progression rates at weeks 24 and 52 were seen in the combination group (Figure 3).

In a prespecified sensitivity analysis, similar results were observed for the per-protocol population and the modified ITT population across the primary and major secondary end points (data not shown). Further sensitivity analyses exploring MTX dose and glucocorticoid use were conducted. For relevant outcome measures such as the ACR20 and ACR50 responses and a DAS28-hsCRP ≤ 3.2, significant heterogeneity was not seen based on glucocorticoid use and nonuse for treatment effects compared to MTX (see Supplementary Figures 4–6, http://onlinelibrary.wiley.com/doi/10.1002/art.39953/abstract). Importantly, treatment effects compared to MTX monotherapy were consistent irrespective of whether patients were prescribed the full-dose or the low-dose MTX regimens. Efficacy measures are summarized in Supplementary Table 3, http://onlinelibrary.wiley.com/doi/10.1002/art.39953/abstract.

Safety findings. From baseline through week 52, a total of 5%, 6%, and 11% of patients discontinued the study because of an AE in the MTX monotherapy, baricitinib monotherapy, and baricitinib plus MTX groups, respectively (Table 2). Rates of serious AEs (SAEs) through 52 weeks were similar across groups (10%, 8%, and 8%, respectively). Three deaths occurred, all in patients receiving MTX monotherapy; causes of death were interstitial lung disease, drowning, and pulmonary thromboembolism. The last event was 1 of 3 positively adjudicated major adverse cardiovascular events seen during the study; the others were a hemorrhagic stroke (in a patient receiving MTX

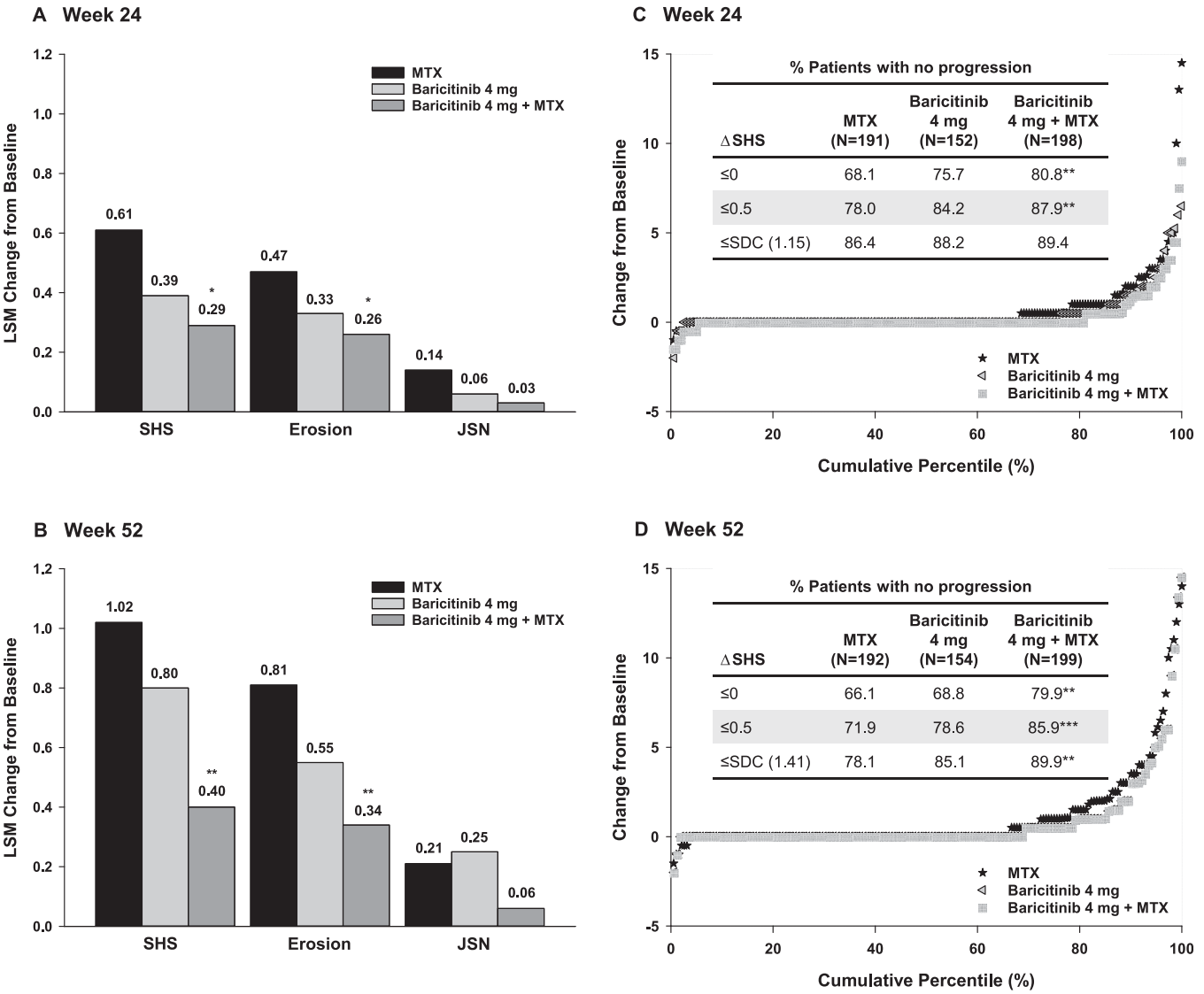

Figure 3. Radiographic progression of structural joint damage. **A** and **B,** Mean change from baseline in modified Sharp/van der Heijde score (SHS), erosion, and joint space narrowing (JSN) through week 24 (**A**) and week 52 (**B**). **C** and **D,** Cumulative probability distribution of change from baseline in SHS (using linear extrapolation) at week 24 (**C**) and week 52 (**D**). Tables within **C** and **D** show the percentage of patients with no radiographic progression as defined by change in SHS ≤0, ≤0.5, and less than or equal to smallest detectable change (SDC). * = $P \leq 0.05$; ** = $P \leq 0.01$; *** = $P \leq 0.001$ versus methotrexate (MTX) monotherapy. LSM = least squares mean.

monotherapy) and a myocardial infarction in a patient (receiving baricitinib monotherapy) with preexisting hypertension and dyslipidemia.

Serious infection rates were similar across groups (4%, 4%, and 2%, respectively, for the MTX monotherapy, baricitinib monotherapy, and baricitinib plus MTX groups) (see Supplementary Table 4, http://onlinelibrary.wiley.com/doi/10.1002/art.39953/abstract). One SAE of *Pneumocystis* pneumonia was reported in a Japanese patient (receiving baricitinib plus MTX) with fever, dyspnea, elevated blood β-D-glucan, and abnormality on computed tomography of the chest. No organism was identified, and the patient recovered following presumptive treatment for *Pneumocystis jiroveci* pneumonia. Protocol-defined SAEs through week 52 are shown in Supplementary Table 5, http://onlinelibrary.wiley.com/doi/10.1002/art.39953/abstract.

Malignancies reported during the study were as follows: for MTX monotherapy, gastrointestinal carcinoid tumor (on day 283); for baricitinib monotherapy, cervical cancer (on day 334); and for baricitinib plus MTX, basal cell carcinoma

Table 2. Safety summary through week 24 and through week 52*

	Weeks 0–24			Weeks 0–52		
	MTX (n = 210)	Baricitinib 4 mg (n = 159)	Baricitinib 4 mg plus MTX (n = 215)	MTX (n = 210)	Baricitinib 4 mg (n = 159)	Baricitinib 4 mg plus MTX (n = 215)
SAE†	9 (4)	5 (3)	8 (4)	20 (10)	12 (8)	17 (8)
Serious infection	3 (1)	2 (1)	4 (2)	8 (4)	6 (4)	5 (2)
AEs leading to study discontinuation	5 (2)	6 (4)	15 (7)	11 (5)	9 (6)	23 (11)
AEs leading to temporary interruption	20 (10)	7 (4)	24 (11)	28 (13)	13 (8)	43 (20)
TEAEs	136 (65)	103 (65)	146 (68)	151 (72)	113 (71)	167 (78)
Infections‡	58 (28)	45 (28)	74 (34)	80 (38)	69 (43)	108 (50)
Herpes zoster	1 (<1)	3 (2)	3 (1)	2 (<1)	4 (3)	5 (2)
Tuberculosis	0	0	0	0	0	0
Malignancy	0	0	2 (<1)	1 (<1)	1 (<1)	4 (2)
Nonmelanoma skin cancer	0	0	1 (<1)	0	0	1 (<1)
Adrenocortical carcinoma	0	0	1 (<1)	0	0	1 (<1)
Cervical carcinoma	0	0	0	0	1 (<1)	0
Malignant melanoma	0	0	0	0	0	1 (<1)
Gallbladder adenosquamous carcinoma	0	0	0	0	0	1 (<1)
Carcinoid tumor of the GI tract	0	0	0	1 (<1)	0	0
MACE§	0	1 (<1)	0	2 (<1)	1 (<1)	0

* Values are the number (%) of patients, to the time of rescue. TEAE = treatment-emergent adverse event; GI = gastrointestinal; MACE = major adverse cardiovascular event.
† Reported using conventional International Conference on Harmonisation definitions. Events that were serious only for the reason of protocol definition are not shown; the protocol required that any AE or laboratory value abnormality that led to permanent discontinuation of study drug be reported as a serious AE (SAE).
‡ One case of *Pneumocystis jiroveci* pneumonia and 1 case of esophageal candidiasis were reported in the group receiving baricitinib 4 mg plus methotrexate (MTX).
§ Cardiovascular death, myocardial infarction, or stroke positively adjudicated.

(on day 35 in a preexisting skin lesion), adrenocortical carcinoma (on day 49), malignant melanoma (on day 204), and gallbladder adenosquamous carcinoma (on day 346).

Rates of treatment-emergent AEs were similar across groups: 72%, 71%, and 78% for MTX monotherapy, baricitinib monotherapy, and baricitinib plus MTX groups, respectively. Infections were reported in a larger proportion of patients in the baricitinib plus MTX group (50%) than in the MTX monotherapy (38%) and baricitinib monotherapy (43%) groups (Table 2); infections of the upper respiratory tract and urinary tract were the most common types of infections reported (see Supplementary Table 6, http://onlinelibrary.wiley.com/doi/10.1002/art.39953/abstract). Herpes zoster events were reported in all treatment groups (in 2, 4, and 5 patients receiving MTX monotherapy, baricitinib monotherapy, and baricitinib plus MTX, respectively); none exhibited a complicated clinical course (dissemination, visceral or ocular involvement, nerve palsy), and the majority were reported in Japanese patients (2, 3, and 3 patients, respectively). Esophageal candidiasis (mild) was reported in 1 patient (receiving baricitinib plus MTX). The event was an incidental finding during endoscopy for gastritis; study drug was not discontinued, and the candidiasis was not treated.

Table 3 displays mean changes from baseline and increases in CTCAE grade for selected laboratory analytes through 24 and 52 weeks. No imbalance in anemia was seen among treatment groups. Neutrophil count reductions were observed in all treatment groups; low-grade neutropenia was observed more commonly in the baricitinib groups. No association between neutropenia and infection was observed. No increase in lymphopenia was seen for the baricitinib groups; transient lymphocyte count increases were seen with baricitinib in some patients (data not shown). Modest transient increases in platelet counts were seen during the initial weeks of treatment with baricitinib, followed by a return to baseline; decreases in platelet counts were seen for MTX monotherapy. No imbalance in protocol-defined thrombocytosis (>600,000 cells/mm^3) was seen among groups (see Supplementary Table 5, http://onlinelibrary.wiley.com/doi/10.1002/art.39953/abstract).

Small increases in the mean ALT level were observed across groups; the largest mean increase was seen in the baricitinib plus MTX group. The smallest proportion of patients with an increase in CTCAE grade occurred with baricitinib monotherapy. Most abnormal values were transient, and the majority of elevations

Table 3. Summary of laboratory findings through week 24 and through week 52*

	Weeks 0–24			Weeks 0–52		
	MTX (n = 210)	Baricitinib 4 mg (n = 159)	Baricitinib 4 mg plus MTX (n = 215)	MTX (n = 210)	Baricitinib 4 mg (n = 159)	Baricitinib 4 mg plus MTX (n = 215)
Hemoglobin, LSM ± SEM gm/dl†	0.04 ± 0.07	0.07 ± 0.08	−0.04 ± 0.07	0.47 ± 0.08	0.20 ± 0.09‡	0.25 ± 0.08
Neutrophil count, LSM ± SEM ×10^3 cells/mm^3†	−0.85 ± 0.14	−0.88 ± 0.15	−1.00 ± 0.13	−0.85 ± 0.15	−1.30 ± 0.16‡	−1.20 ± 0.14
Lymphocyte count, LSM ± SEM ×10^3 cells/mm^3†	−0.13 ± 0.04	−0.03 ± 0.05	−0.14 ± 0.04	−0.17 ± 0.05	−0.17 ± 0.05	−0.16 ± 0.04
Platelet count, LSM ± SEM ×10^3 cells/mm^3†	−30 ± 4	0 ± 5§	0 ± 4§	−33 ± 6	7 ± 6§	−1 ± 5§
ALT, LSM ± SEM IU/liter†	4.3 ± 1.2	3.2 ± 1.3	9.1 ± 1.1¶	6.7 ± 3.0	3.7 ± 3.1	15.4 ± 2.7‡
HDL, LSM ± SEM mg/dl†	2.8 ± 1.0	11.7 ± 1.1§	8.3 ± 1.0§	3.4 ± 1.2	9.7 ± 1.2§	9.0 ± 1.1§
LDL, LSM ± SEM mg/dl†	4 ± 2	16 ± 2§	13 ± 2§	7 ± 2	18 ± 2¶	16 ± 2¶
Creatinine, LSM ± SEM mg/dl†	0.028 ± 0.008	0.067 ± 0.009¶	0.078 ± 0.008§	0.046 ± 0.009	0.072 ± 0.010	0.090 ± 0.008§
CPK, LSM ± SEM units/liter†	5 ± 8	76 ± 9§	67 ± 8§	18 ± 7	79 ± 7§	57 ± 6§
Hemoglobin, no. (%)#						
Grade 1 (≥10 to <12 gm/dl [F] or ≥10 to <13.5 gm/dl [M])	35 (17)	35 (22)	49 (23)	40 (19)	39 (25)	51 (24)
Grade 2 (≥8.0 to <10 gm/dl)	16 (8)	10 (6)	16 (8)	16 (8)	10 (6)	17 (8)
Grade 3 (≥6.5 to <8.0 gm/dl)	0	0	1 (<1)	1 (<1)	0	1 (<1)
Neutrophils, no. (%)#						
Grade 1 (≥1,500 to <2,000 cells/μl)	11 (5)	17 (11)	15 (7)	15 (7)	20 (13)	18 (8)
Grade 2 (≥1,000 to <1,500 cells/μl)	2 (<1)	4 (3)	6 (3)	2 (<1)	4 (3)	10 (5)
Grade 3 (≥500 to <1,000 cells/μl)	0	0	0	0	0	1 (<1)
Grade 4 (<500 cells/μl)	0	0	0	0	1 (<1)	0
Lymphocytes, no. (%)#**						
Grade 1 (≥800 to <1,100 cells/mm^3)	31 (15)	11 (7)	29 (14)	35 (17)	24 (15)	38 (18)
Grade 2 (≥500 to <800 cells/mm^3)	11 (5)	3 (2)	7 (3)	13 (6)	5 (3)	11 (5)
Grade 3 (≥200 to <500 cells/mm^3)	3 (1)	1 (<1)	2 (<1)	6 (3)	1 (<1)	4 (2)
Platelets >600,000/mm^3, no. (%)#	5 (2)	4 (3)	4 (2)	6 (3)	4 (3)	4 (2)
Elevated ALT, no. (%)#††						
Grade 1 (>ULN and ≤2.5× ULN)	44 (21)	17 (11)	40 (19)	54 (26)	24 (15)	52 (25)
Grade 2 (>2.5× ULN and ≤5× ULN)	8 (4)	1 (<1)	9 (4)	12 (6)	1 (<1)	17 (8)
Grade 3 (>5× ULN and ≤20× ULN)	2 (1)	1 (<1)	2 (<1)	2 (1)	1 (<1)	3 (1)
Creatinine grade 1 (>ULN and ≤1.5× ULN), no. (%)#	3 (1)	8 (5)	6 (3)	6 (3)	9 (6)	6 (3)
CPK, no. (%)#						
Grade 1 (>ULN and ≤2.5× ULN)	17 (8)	45 (28)	52 (25)	17 (8)	65 (41)	56 (26)
Grade 2 (>2.5× ULN and ≤5× ULN)	4 (2)	10 (6)	7 (3)	6 (3)	12 (8)	12 (6)
Grade 3 (>5× ULN and ≤10× ULN)	0	1 (<1)	7 (3)	1 (<1)	1 (<1)	8 (4)
Grade 4 (>10× ULN)	0	0	2 (<1)	0	0	2 (<1)
LDL, no. (%)‡‡						
Near optimal (≥100 mg/dl and <130 mg/dl)	30 (16)	21 (14)	41 (21)	30 (16)	24 (15)	44 (22)
Borderline high (≥130 mg/dl and <160 mg/dl)	28 (15)	34 (22)	38 (19)	32 (17)	34 (22)	47 (24)
High (≥160 mg/dl and <190 mg/dl)	10 (5)	27 (17)	24 (12)	17 (9)	27 (17)	31 (16)
Very high (≥190 mg/dl)	4 (2)	8 (5)	13 (7)	6 (3)	13 (8)	13 (7)
HDL, no. (%)‡‡						
Normal (≥40 mg/dl and <60 mg/dl)	15 (8)	7 (5)	8 (4)	15 (8)	9 (6)	12 (6)
Low (<40 mg/dl)	9 (5)	2 (1)	6 (3)	15 (8)	5 (3)	7 (4)

* HDL = high-density lipoprotein; LDL = low-density lipoprotein; CPK = creatine phosphokinase; ULN = upper limit of normal.
† Least squares mean (LSM) change from baseline at week 24 or at week 52.
‡ $P \leq 0.05$ versus methotrexate (MTX) monotherapy by analysis of covariance (ANCOVA).
§ $P \leq 0.001$ versus MTX monotherapy by ANCOVA.
¶ $P \leq 0.01$ versus MTX monotherapy by ANCOVA.
# Data indicate the worst Common Terminology Criteria for Adverse Events (version 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.
** No patient discontinued study drug because of a low lymphocyte count.
†† One patient receiving baricitinib 4 mg plus MTX permanently discontinued study drug because of an alanine aminotransferase (ALT) abnormality.
‡‡ 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.

grade ≥2 occurred in patients with preexisting abnormal values. One patient receiving baricitinib plus MTX had significant (transient) concomitant elevations of ALT and bilirubin according to local laboratory data during an SAE of acute hepatitis B infection; the patient's spouse had recently tested positive for hepatitis B. Small increases in mean serum creatinine levels were seen in baricitinib groups, and most abnormal values were transient. No patient had an abnormality exceeding grade 1. Mean serum creatine phosphokinase (CPK) levels increased in both baricitinib groups; among patients who exhibited grade 3 or 4 abnormalities, most reported preceding exercise or physical activity or had elevated baseline levels. Mean low-density lipoprotein (LDL) cholesterol and high-density lipoprotein (HDL) cholesterol increased in all groups, with larger increases seen in the baricitinib groups than in the MTX monotherapy group. The ratio of LDL cholesterol to HDL cholesterol did not change over time across groups.

DISCUSSION

The RA-BEGIN trial was designed to assess the efficacy and safety of baricitinib administered as monotherapy or in combination with MTX compared to MTX monotherapy in patients with early active RA. The study enrolled a population with a median disease duration of 0.2 years and with >91% of patients being DMARD naive. Additionally, 90% of patients were ACPA positive and 96% were RF positive; the baseline mean hsCRP level was ~23 mg/liter, and approximately two-thirds of the patients had ≥1 erosion with a mean SHS of 12, suggesting aggressive RA.

In accordance with the ACR guideline and EULAR recommendations for the treatment of RA (6,20), treatment should be initiated with an MTX regimen. The effectiveness of MTX in controlling disease activity, improving patient function, and limiting radiographic progression in up to one-third of patients with early RA when used as monotherapy (21,22) underpins these recommendations. In the RA-BEGIN trial, clinical improvements in signs and symptoms, function, and patient-reported outcomes were observed with MTX monotherapy, the extents of which were consistent with prior controlled trials of MTX monotherapy (21,23,24). Baricitinib, alone or in combination with MTX, further improved outcomes compared to MTX monotherapy, as shown by significant differences in ACR20, ACR50, and ACR70 responses, the percentage of patients achieving low disease activity and remission (for the SDAI, CDAI, and DAS28), and the ≥0.22 decrease in HAQ DI score at weeks 24 and 52. Significant improvement was observed as early as week 1 in the ACR core components, including tender and swollen joints, hsCRP level, pain, and physician's and patient's global assessments. This rapidity of response is important to patients and may increase the probability of achieving better outcomes.

Radiographically, only baricitinib plus MTX was statistically superior to MTX monotherapy, as seen by the significant differences in SHS scores at 24 and 52 weeks and the proportion of patients not experiencing radiographic progression of >0 or >0.5 units. Radiographic progression through 52 weeks was observed to be less for baricitinib monotherapy than for MTX monotherapy, but the difference was not statistically significant.

With respect to safety, in this group of patients over the course of 52 weeks, there were no apparent differences in the occurrence of SAEs or serious infection events; however, there were more temporary interruptions and permanent discontinuations of medication in the baricitinib plus MTX group than in the MTX monotherapy group, with fewer temporary interruptions in the baricitinib monotherapy group. More nonserious infections were seen in the baricitinib plus MTX group than in either monotherapy group. Herpes zoster events occurred in all treatment groups. Elevations in ALT levels were more likely to occur with MTX, either as monotherapy or in combination with baricitinib. Elevations in lipids, creatinine, and CPK levels occurred more frequently with baricitinib, whether used as monotherapy or in combination with MTX.

When considering the risk and benefit of treatment of early active RA with these regimens, one could conclude that the combination of baricitinib plus MTX was more effective than MTX monotherapy clinically, functionally, and radiographically, with some increased risk. Baricitinib monotherapy was clinically and functionally superior to MTX monotherapy, with less ALT elevation than MTX monotherapy or combination therapy. In addition, progression of radiographic outcomes was less, although to a statistically nonsignificant degree, with baricitinib monotherapy than with MTX monotherapy.

The finding that baricitinib is superior to MTX monotherapy and that there is limited improvement when baricitinib is combined with MTX may be important for patients who cannot take or tolerate MTX. Treatment options for these patients frequently include bDMARD monotherapy, although when bDMARDs are used as monotherapy, they are no more effective than MTX monotherapy (21,25). Reports of well-designed clinical trials have suggested that most, if not all, bDMARDs are more effective in combination with MTX (21,25–27). Tofacitinib, another JAK inhibitor with specificity for JAK-3/JAK-1/JAK-2, has been shown to be more effective clinically, functionally, and radiographically than MTX monotherapy in MTX-naive RA patients (24). However,

that study did not compare tofacitinib monotherapy to the combination of tofacitinib and MTX.

There were some limitations to this study. The entry criterion requiring an elevated hsCRP at baseline resulted in a screen failure rate of ~50%. A high screen failure rate can reduce the external validity of a study; however, the population enrolled did have early active RA, as was the intent of the protocol. The dosage of MTX was limited to 20 mg once weekly and was not adjusted in patients having an inadequate response to treatment. However, the clinical response observed in the MTX monotherapy arm exceeded the expected response that informed the power calculation and was consistent with reported trials of MTX monotherapy in patients with early RA. Nonetheless, it cannot be assessed whether a higher dose of MTX would have been noninferior or superior to baricitinib monotherapy.

In summary, this study demonstrated that in DMARD-naive patients, baricitinib monotherapy is superior to MTX monotherapy with respect to clinical and functional end points. In this group of patients, treatment with baricitinib in combination with MTX offered modest additional benefit over baricitinib monotherapy with respect to measures of inflammation and radiographic progression of structural joint damage, but with some suggested increases in risk. Compared to MTX monotherapy, improvements in disease activity with both baricitinib monotherapy and combination therapy were observed as early as 1 week. These results may be important for patients with a contraindication to or intolerance of MTX treatment.

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AUTHOR CONTRIBUTIONS

All authors were involved in drafting the article or revising it critically for important intellectual content, and all authors approved the final version to be published. Dr. Fleischmann had full access to all of the data in the study and takes responsibility for the integrity of the data and the accuracy of the data analysis.

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Analysis and interpretation of data. Fleischmann, Schiff, van der Heijde, Ramos-Remus, Zerbini, Gurbuz, Dickson, Schlichting, Beattie, Kuo, Rooney, Macias, Takeuchi.

ROLE OF THE STUDY SPONSORS

The study was designed by Eli Lilly and Company in consultation with an academic advisory board and Incyte Corporation. Eli Lilly and Company provided data analysis, laboratory, and site-monitoring services and was involved in data interpretation. All authors and Eli Lilly and Company reviewed and approved the manuscript. The authors maintained control over the final content.

REFERENCES

1. Colmegna I, Ohata BR, Menard HA. Current understanding of rheumatoid arthritis therapy. Clin Pharmacol Ther 2012;91: 607–20.
2. Smolen JS, Steiner G. Therapeutic strategies for rheumatoid arthritis. Nat Rev Drug Discov 2003;2:473–88.
3. Aletaha D, Neogi T, Silman AJ, Funovits J, Felson DT, Bingham CO III, et al. 2010 rheumatoid arthritis classification criteria: an American College of Rheumatology/European League Against Rheumatism collaborative initiative. Arthritis Rheum 2010;62: 2569–81.
4. Fatimah N, Salim B, Nasim A, Hussain K, Gul H, Niazi S. Frequency of methotrexate intolerance in rheumatoid arthritis patients using methotrexate intolerance severity score (MISS questionnaire). Clin Rheumatol 2016;35:1341–5.
5. Nikiphorou E, Negoescu A, Fitzpatrick JD, Goudie CT, Badcock A, Östör AJ, et al. Indispensable or intolerable? Methotrexate in patients with rheumatoid and psoriatic arthritis: a retrospective review of discontinuation rates from a large UK cohort. Clin Rheumatol 2014;33:609–14.
6. Singh JA, Saag KG, Bridges SL Jr, Akl EA, Bannuru RR, Sullivan MC, et al. 2015 American College of Rheumatology guideline for the treatment of rheumatoid arthritis. Arthritis Care Res (Hoboken) 2016;68:1–25.
7. European Medicines Agency. Guideline on clinical investigation of medicinal products other than NSAIDs for treatment of rheumatoid arthritis [draft]. March 20, 2015. URL: http://www.ema.europa.eu/docs/en_GB/document_library/Scientific_guideline/2015/06/WC500187583.pdf.
8. Keystone EC, Taylor PC, Drescher E, Schlichting DE, Beattie SD, Berclaz PY, et al. Safety and efficacy of baricitinib at 24 weeks in patients with rheumatoid arthritis who have had an inadequate response to methotrexate. Ann Rheum Dis 2015;74:333–40.
9. Tanaka Y, Emoto K, Cai Z, Aoki T, Schlichting D, Rooney T, et al. Efficacy and safety of baricitinib in Japanese patients with active rheumatoid arthritis receiving background methotrexate therapy: a 12-week, double-blind, randomized placebo-controlled study. J Rheumatol 2016;43:504–11.
10. Genovese MC, Kremer J, Zamani O, Ludivico C, Krogulec M, Xie L, et al. Baricitinib in patients with refractory rheumatoid arthritis. N Engl J Med 2016;374:1243–52.
11. Felson DT, Anderson JJ, Boers M, Bombardier C, Furst D, Goldsmith C, et al. American College of Rheumatology preliminary definition of improvement in rheumatoid arthritis. Arthritis Rheum 1995;38:727–35.
12. Fries JF, Spitz P, Kraines RG, Holman HR. Measurement of patient outcome in arthritis. Arthritis Rheum 1980;23:137–45.
13. 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.
14. Aletaha D, Smolen J. The Simplified Disease Activity Index (SDAI) and the Clinical Disease Activity Index (CDAI): a review of their usefulness and validity in rheumatoid arthritis. Clin Exp Rheumatol 2005;23 Suppl 39:S100–8.
15. 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;38:44–8.
16. Disease Activity Score web site. URL: http://www.das-score.nl/das28/.
17. Van der Heijde D. How to read radiographs according to the Sharp/van der Heijde method. J Rheumatol 2000;27:261–3.

18. Alosh M, Bretz F, Huque M. Advanced multiplicity adjustment methods in clinical trials. Stat Med 2014;33:693–713.
19. Bretz F, Maurer W, Brannath W, Posch M. A graphical approach to sequentially rejective multiple test procedures. Stat Med 2009;28:586–604.
20. Smolen JS, Landewé R, Breedveld FC, Buch M, Burmester G, Dougados M, et al. EULAR recommendations for the management of rheumatoid arthritis with synthetic and biological disease-modifying antirheumatic drugs: 2013 update. Ann Rheum Dis 2014;73:492–509.
21. Breedveld FC, Weisman MH, Kavanaugh AF, Cohen SB, Pavelka K, van Vollenhoven R, et al. The PREMIER study: a multicenter, randomized, double-blind clinical trial of combination therapy with adalimumab plus methotrexate versus methotrexate alone or adalimumab alone in patients with early, aggressive rheumatoid arthritis who had not had previous methotrexate treatment. Arthritis Rheum 2006;54:26–37.
22. Van Vollenhoven RF, Ernestam S, Geborek P, Petersson IF, Cöster L, Waltbrand E, et al. Addition of infliximab compared with addition of sulfasalazine and hydroxychloroquine to methotrexate in patients with early rheumatoid arthritis (Swefot trial): 1-year results of a randomised trial. Lancet 2009; 374:459–66.
23. Jones G. The AMBITION trial: tocilizumab monotherapy for rheumatoid arthritis. Expert Rev Clin Immunol 2010;6:189–95.
24. Lee EB, Fleischmann R, Hall S, Wilkinson B, Bradley JD, Gruben D, et al. Tofacitinib versus methotrexate in rheumatoid arthritis. N Engl J Med 2014;370:2377–86.
25. Burmester GR, Rigby WF, van Vollenhoven RF, Kay J, Rubbert-Roth A, Kelman A, et al. Tocilizumab in early progressive rheumatoid arthritis: FUNCTION, a randomised controlled trial. Ann Rheum Dis 2016;75:1081–91.
26. Emery P, Burmester GR, Bykerk VP, Combe BG, Furst DE, Barré E, et al. Evaluating drug-free remission with abatacept in early rheumatoid arthritis: results from the phase 3b, multicentre, randomised, active-controlled AVERT study of 24 months, with a 12-month, double-blind treatment period. Ann Rheum Dis 2015;74:19–26.
27. Klareskog L, van der Heijde D, de Jager JP, Gough A, Kalden J, Malaise M, et al, for the TEMPO (Trial of Etanercept and Methotrexate with Radiographic Patient Outcomes) study investigators. 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.