ORIGINAL ARTICLE

Baricitinib in Patients with Refractory Rheumatoid Arthritis

Mark C. Genovese, M.D., Joel Kremer, M.D., Omid Zamani, M.D., Charles Ludivico, M.D., Marek Krogulec, M.D., Li Xie, M.S., Scott D. Beattie, Ph.D., Alisa E. Koch, M.D., Tracy E. Cardillo, M.S., Terence P. Rooney, M.D., William L. Macias, M.D., Ph.D., Stephanie de Bono, M.D., Ph.D., Douglas E. Schlichting, M.S., and Josef S. Smolen, M.D.

ABSTRACT

BACKGROUND

In phase 2 studies, baricitinib, an oral Janus kinase 1 and 2 inhibitor, reduced disease activity in patients with rheumatoid arthritis who had not previously received treatment with biologic disease-modifying antirheumatic drugs (DMARDs).

METHODS

In this phase 3 study involving 527 patients with an inadequate response to or unacceptable side effects associated with one or more tumor necrosis factor inhibitors, other biologic DMARDs, or both, we randomly assigned the patients in a 1:1:1 ratio to baricitinib at a dose of 2 or 4 mg daily or placebo for 24 weeks. End points, tested hierarchically at week 12 to control type 1 error, were the American College of Rheumatology 20% (ACR20) response (primary end point), the Health Assessment Questionnaire–Disability Index (HAQ-DI) score, the 28-joint Disease Activity Score based on C-reactive protein level (DAS28-CRP), and a Simplified Disease Activity Index (SDAI) score of 3.3 or less (on a scale of 0.1 to 86.0, with a score of 3.3 or less indicating remission). Comparisons with placebo were made first with the 4-mg dose of baricitinib and then with the 2-mg dose.

RESULTS

Significantly more patients receiving baricitinib at the 4-mg dose than those receiving placebo had an ACR20 response at week 12 (55% vs. 27%, P<0.001). Differences between the higher-dose baricitinib group and the placebo group were also significant for the HAQ-DI score and the DAS28-CRP but not for an SDAI score of 3.3 or less. Adverse-event rates through 24 weeks were higher for patients receiving the 2-mg dose of baricitinib and those receiving the 4-mg dose than for patients receiving placebo (71% and 77%, respectively, vs. 64%), including infections (44% and 40%, vs. 31%). The rates of serious adverse events were 4%, 10%, and 7% in the three groups, respectively. Two nonmelanoma skin cancers and two major adverse cardiovascular events, including a fatal stroke, occurred in the higher-dose group. Baricitinib was associated with a small reduction in neutrophil levels and increases in serum creatinine and low-density lipoprotein cholesterol levels.

CONCLUSIONS

In patients with rheumatoid arthritis and an inadequate response to biologic DMARDs, baricitinib at a daily dose of 4 mg was associated with clinical improvement at 12 weeks. (Funded by Eli Lilly and Incyte; ClinicalTrials.gov number, NCT01721044.)

From the Stanford University Medical Center, Palo Alto, CA (M.C.G.); Albany Medical College, Albany, NY (J.K.); Rheumazentrum Favoriten (O.Z.) and the Medical University of Vienna (J.S.S.) — both in Vienna; East Penn Rheumatology, Bethlehem, PA (C.L.); Rheumatology Clinic, MAK-MED, Nadarzyn, Poland (M.K.); and Eli Lilly, Indianapolis (L.X., S.D.B., A.E.K., T.E.C., T.P.R., W.L.M., S.B., D.E.S.). Address reprint requests to Dr. Genovese at the Division of Immunology and Rheumatology, Stanford University School of Medicine, 1000 Welch Rd., Suite 203, Palo Alto, CA 94304.

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The discomfort, disability, and joint damage that characterize rheumatoid arthritis result from an autoimmune inflammatory response elicited by numerous cell populations and cytokines. Biologic therapies targeting T or B cells and cytokines, such as tumor necrosis factor α (TNF-α) or interleukin-6, have improved outcomes for patients who do not have responses to treatment with conventional, synthetic disease-modifying antirheumatic drugs (DMARDs) such as methotrexate.[1] However, since many patients do not have a sufficient response to these biologic DMARDs or have unacceptable side effects, new therapies are needed.

Circulating cytokines, on binding to cell-surface receptors, signal through activation of intracellular tyrosine kinases, including Janus kinases (JAKs). Many mediators implicated in the autoimmune inflammatory response (e.g., interleukins 2, 6, 12, 15, and 23; interferons; and granulocyte–macrophage colony-stimulating factor [GM-CSF]) signal through the JAK family (JAK1, JAK2, JAK3, and tyrosine kinase 2 [Tyk2]).[2] Several small-molecule JAK inhibitors with differing degrees of specificity for the JAKs are in clinical development.[3] Baricitinib is a preferential JAK1 and JAK2 inhibitor that has shown efficacy in phase 2 studies involving patients with rheumatoid arthritis who had an insufficient response to conventional synthetic DMARDs.[4,5] This report describes the results of the RA-BEACON trial, a phase 3 study of baricitinib in patients with moderately to severely active rheumatoid arthritis who did not have a response to biologic DMARDs or had unacceptable side effects.

Methods

Patients

Patients were 18 years of age or older and had moderately to severely active rheumatoid arthritis (≥6 tender joints of 68 joints examined, ≥6 swollen joints of 66 joints examined, and a serum C-reactive protein level ≥3 mg per liter). Patients must have previously received one or more TNF inhibitors and discontinued treatment because of an insufficient response after 3 months or more or because of unacceptable side effects. Patients who had received other biologic DMARDs could also participate. Biologic DMARDs must have been discontinued at least 4 weeks before randomization (≥6 months for rituximab). At study entry, patients must have been taking one or more conventional synthetic DMARDs regularly for at least the preceding 12 weeks, with stable doses for at least the preceding 8 weeks. Patients with selected abnormal laboratory test results and those who had had a recent, clinically significant infection were excluded. Patients with evidence of latent tuberculosis could enroll if appropriate treatment had been started at least 4 weeks before randomization.

Study Protocol and Oversight

RA-BEACON was a randomized, 24-week, double-blind, placebo-controlled study conducted at 178 centers in 24 countries. The study was initiated in January 2013 and completed in September 2014, with enrollment taking place between January 2013 and March 2014. Patients were randomly assigned in a 1:1:1 ratio to receive baricitinib at a daily dose of 2 mg or 4 mg or placebo in addition to the therapies they were already receiving at enrollment. Patients with an estimated glomerular filtration rate at screening that was at least 40 but less than 60 ml per minute per 1.73 m^2 of body-surface area received baricitinib at the 2-mg dose if they were assigned to either active treatment group (with maintenance of blinding), but data for these patients were analyzed according to the assigned treatment group. Concomitant treatment with stable doses of conventional synthetic DMARDs, nonsteroidal antiinflammatory drugs, analgesic agents, glucocorticoids (≤10 mg of prednisone or the equivalent per day), or a combination of these drugs was permitted.

At week 16, patients whose tender and swollen joint counts at baseline were reduced by less than 20% at both week 14 and week 16 were given rescue treatment (baricitinib at a dose of 4 mg daily). After week 16, patients could receive rescue treatment at the investigator's discretion on the basis of joint counts. Patients completing the study could enter a long-term extension study or were seen for follow-up approximately 28 days after the end of the treatment period. Patients who entered the long-term extension study continued to receive the blinded study medication; patients taking baricitinib continued to receive it at the current dose, and those assigned to placebo received baricitinib at the 4-mg dose.

The study was designed by the sponsor, Eli Lilly; an academic advisory board that included authors who are not employees of Eli Lilly; and Incyte. The study was conducted in accordance with the 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. Eli Lilly or its representatives provided data, laboratory, and site-monitoring services. All the authors participated in the analysis and interpretation of the data. The first two authors and the last two authors wrote the first draft of the manuscript, and all the authors reviewed the draft and final manuscript and provided critical comment. The authors vouch for the veracity and completeness of the data and data analyses and for the fidelity of this report to the study protocol, available with the full text of this article at NEJM.org.

EFFICACY MEASURES

The primary end point was the proportion of patients who had an American College of Rheumatology 20% (ACR20) response at week 12. The ACR20 response is a reduction of 20% or more in the number of tender and swollen joints and an improvement of 20% or more in at least three of the following ACR core measures: a patient's assessment of pain, a physician's global assessment of disease, a patient's global assessment of disease, physical function as assessed by the Health Assessment Questionnaire–Disability Index (HAQ-DI), and the level of acute-phase reactant[6] (see Table S1 in the Supplementary Appendix, available at NEJM.org, for a detailed description of the ACR scale). The primary comparison was between the group receiving baricitinib at a dose of 4 mg and the placebo group. Secondary measures included ACR50 and ACR70 responses (i.e., improvements of at least 50% and at least 70%, respectively, according to the criteria of the ACR), physical function as assessed by the HAQ-DI (scores range from 0 to 3, with higher scores indicating greater disability),[7,8] and disease activity as assessed by the 28-joint Disease Activity Score (based on the level of high-sensitivity C-reactive protein [DAS28-CRP] or the erythrocyte sedimentation rate [DAS28-ESR]), the Clinical Disease Activity Index (CDAI), and the Simplified Disease Activity Index (SDAI) (see Table S1 in the Supplementary Appendix for descriptions of the scales).[9-13]

SAFETY ASSESSMENTS

Clinical laboratory tests, measurement of vital signs, and other safety assessments were performed at scheduled visits. The incidence and severity of all adverse events were recorded. The National Institutes of Health Common Terminology Criteria for Adverse Events (CTCAE), version 3.0, or National Cholesterol Education Program categories were used to describe abnormal results of laboratory tests after baseline. An independent data and safety monitoring committee regularly reviewed data from this and other ongoing phase 3 studies of baricitinib. A separate independent committee adjudicated potential cardiovascular events.

STATISTICAL ANALYSIS

We estimated that a sample size of approximately 175 patients per study group would provide 90% or greater power for the comparison of the ACR20 response rate between the 4-mg baricitinib group and the placebo group (with assumed rates of 45% and 25%) at week 12. Patients who underwent randomization and received at least one dose of the assigned study drug were included in the efficacy analyses on the basis of a modified intention-to-treat principle.

A stepwise hierarchical hypothesis-testing strategy was used to control type I error for the primary and key secondary end points at 12 weeks. We analyzed the ACR20 response first, then the change from baseline in the HAQ-DI score and the DAS28-CRP, and finally, an SDAI score of 3.3 or less (on a scale of 0.1 to 86.0, with higher scores indicating greater disease activity; a score of 3.3 or less indicates remission); all analyses were performed first for the 4-mg dose of baricitinib versus placebo and then for the 2-mg dose of baricitinib versus placebo (Fig. S1 in the Supplementary Appendix). Only if a test result was significant did the sequence proceed to the next test in the hierarchy; otherwise, subsequent evaluations were considered to be supportive analyses, given this method of strong control for multiple comparisons. A P value of 0.05 or less (two-sided) was considered to indicate statistical significance unless otherwise defined by the hierarchical testing scheme. Com-

parisons of categorical and continuous efficacy measures between each baricitinib group and the placebo group were performed with the use of logistic regression and analysis of covariance (ANCOVA), respectively, with the baseline score (for continuous measures only), region, and number of previous biologic DMARDs (<3 or ≥3) as explanatory factors. Fisher's exact test was used for safety and other categorical end points when sample-size requirements for logistic regression were not met. Continuous safety data were analyzed by means of ANCOVA with the baseline value included.

Patients who received rescue treatment or discontinued the study or the study treatment were thereafter considered not to have a response (nonresponse imputation) for all categorical efficacy data, including the primary end point. In addition, for analyses of continuous data, the last observations before receipt of rescue treatment or discontinuation were carried forward (modified last-observation-carried-forward method). For continuous secondary efficacy measures that were tested hierarchically (Fig. S1 in the Supplementary Appendix), the baseline observation was substituted at 12 weeks if discontinuation was due to an adverse event (modified baseline-observation-carried-forward method). Analytic methods that depended on other missing-data mechanisms (e.g., mixed models for repeated measures and tipping-point analyses) were used to ensure that the conclusions were robust. Safety observations were analyzed according to the assigned study group until the time of rescue treatment or completion of the treatment period.

RESULTS

STUDY PARTICIPANTS

Of 959 patients who were screened, 527 were randomly assigned to a study group (Fig. 1). The most common reason for exclusion after screening was a serum C-reactive protein level that was less than 3 mg per liter. Baseline demographic and clinical characteristics were similar among the three study groups (Table 1, and Table S2 in the Supplementary Appendix). The overall numbers of patients who had previously been treated with one biologic DMARD, two biologic DMARDs, or three or more biologic DMARDs were 221 (42%), 160 (30%), and 142 (27%), respectively. Approximately 38% of the patients had a history of treatment with at least one biologic DMARD that was not a TNF inhibitor (Table 1, and Table S3 in the Supplementary Appendix). In the placebo group, 32% of patients received rescue treatment, as compared with 22% and 19% of the patients in the 2-mg and 4-mg baricitinib groups, respectively (Fig. 1). Study discontinuation rates were 18% in the placebo group and 10% and 11% in the 2-mg and 4-mg baricitinib groups, respectively. Reasons for discontinuation are summarized in Figure 1. Most of the patients (97%) who completed week 24 entered the long-term extension study.

EFFICACY

At week 12, the ACR20 response rate (primary end point) was 55% among patients who received baricitinib at a dose of 4 mg, as compared with 27% among those who received placebo (P<0.001) (Fig. 2A). Patients receiving the 4-mg dose of baricitinib also had significant improvements in two of the major secondary measures (the DAS28-CRP and the HAQ-DI score) at week 12 as compared with placebo (P<0.001 for both comparisons) (Fig. 2B and Fig. 2C). For the fourth ordered end point (SDAI score ≤3.3), there was no significant difference between placebo and the 4-mg dose of baricitinib (P=0.14) (Fig. 2D); therefore, on the basis of hierarchical testing, the 2-mg dose of baricitinib was not compared with placebo under strong control for multiple comparisons (Table S4 and Fig. S2, S3, and S4 in the Supplementary Appendix). Subgroup analyses showed little evidence of a heterogeneous treatment effect according to the number of prior biologic DMARDs (<3 vs. ≥3), the number of prior TNF inhibitors among patients who had received only TNF-inhibitor biologic DMARDs (1 vs. >1), or the number of prior biologic DMARDs that were not TNF inhibitors (0 vs. ≥1) (Fig. S5 in the Supplementary Appendix).

SAFETY

From baseline through week 24, a total of 7 patients (4%) each in the placebo and lower-dose baricitinib groups and 11 patients (6%) in the higher-dose baricitinib group discontinued the study because of an adverse event (Table 2). Rates of serious adverse events through week 24 were similar among patients receiving placebo and those receiving baricitinib at a dose of 2 mg or 4 mg (7%, 4%, and 10%, respectively). One

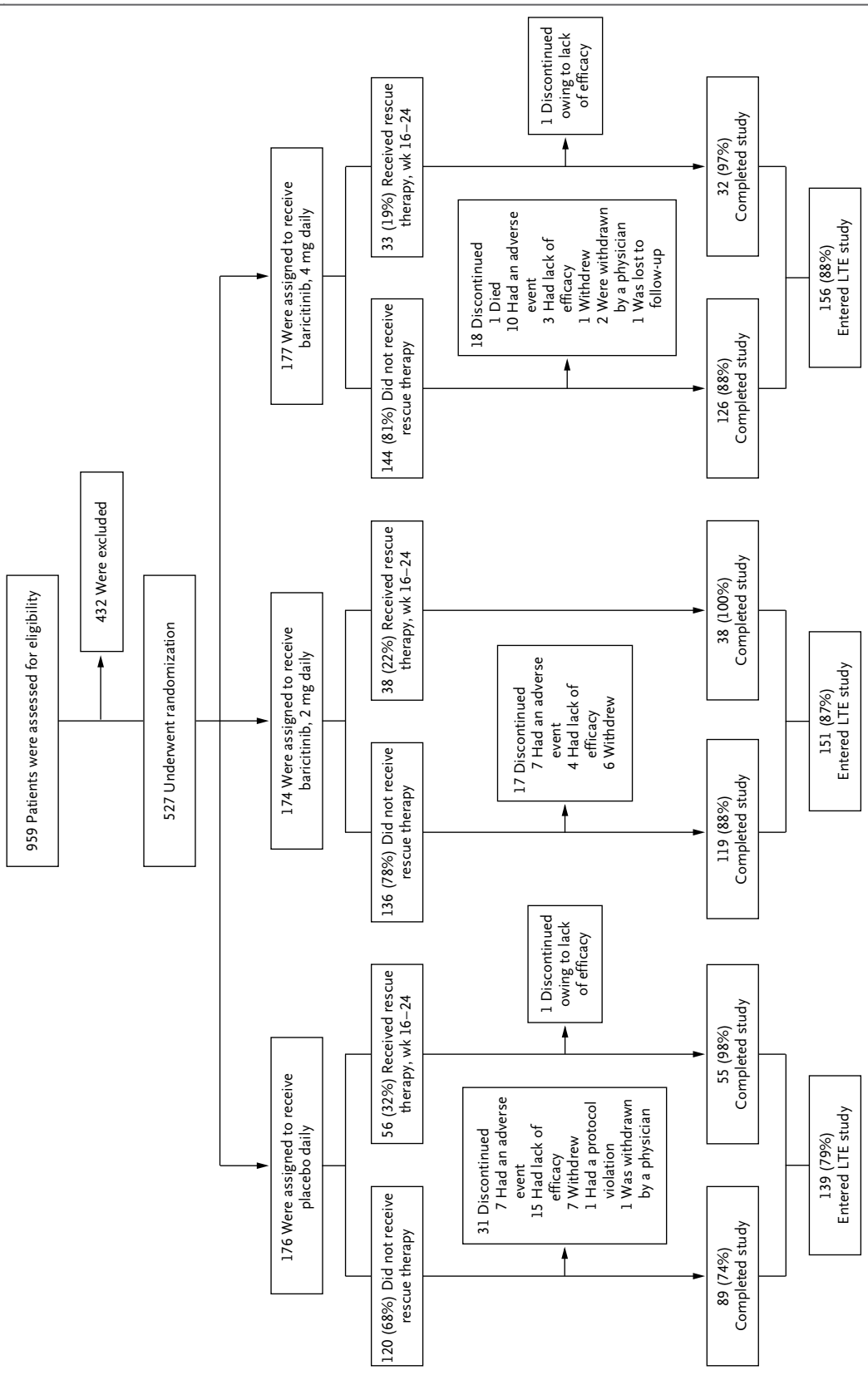

Figure 1. Numbers of Patients Who Were Randomly Assigned to a Study Group and Who Completed the Study at Week 24.

Patients who received rescue therapy (baricitinib at a daily dose of 4 mg) or discontinued the study or study treatment were classified as not having a response. For these patients, the last observations before receipt of rescue therapy or discontinuation were used in analyses of efficacy end points at subsequent time points. LTE denotes long-term extension.

Table 1. Characteristics of the Study Participants and Disease Activity at Baseline.*

Characteristic	Placebo (N=176)	Baricitinib, 2 mg Daily (N=174)	Baricitinib, 4 mg Daily (N=177)
Age — yr	56±11	55±11	56±11
Female sex — no. (%)	145 (82)	137 (79)	149 (84)
Duration of rheumatoid arthritis — yr	14±10	14±8	14±9
Positive for anti–cyclic citrullinated peptide antibody — no. (%)†	125 (71)	124 (71)	119 (67)
Positive for rheumatoid factor — no. (%)‡	130 (74)	128 (74)	128 (72)
No. of previous biologic DMARDs — no. (%)			
Total			
1	81 (46)	69 (40)	71 (40)
2	47 (27)	55 (32)	58 (33)
≥3	47 (27)	50 (29)	45 (25)
TNF inhibitors			
1	104 (59)	102 (59)	104 (59)
2	50 (28)	60 (34)	52 (29)
≥3	19 (11)	12 (7)	18 (10)
Non-TNF inhibitors			
1	37 (21)	45 (26)	43 (24)
2	15 (9)	14 (8)	14 (8)
≥3	10 (6)	11 (6)	10 (6)
Swollen-joint count, of 66 joints examined	17±11	19±12	16±9
Tender-joint count, of 68 joints examined	28±16	31±16	28±16
Scores for global and pain assessments§			
Physician's global assessment	67±19	67±17	67±18
Patient's global assessment	66±19	67±19	66±22
Patient's assessment of pain	65±19	62±22	66±23
HAQ-DI score¶	1.78±0.57	1.71±0.55	1.74±0.59
High-sensitivity CRP — mg/liter‖	21±25	20±22	20±25
ESR — mm/hr	47±24	45±24	48±26
DAS28-CRP	5.9±0.9	6.0±0.9	5.9±1.0
DAS28-ESR	6.6±0.9	6.7±1.0	6.6±1.1
Simplified Disease Activity Index score	43±14	45±14	42±14

* Plus–minus values are means ±SD. The total number of patients in each study group is the number of patients who were randomly assigned to that group and received at least one dose of the assigned study medication. There were no clinically significant between-group differences in any of the baseline characteristics. DAS28 denotes the 28-joint Disease Activity Score based on the C-reactive protein level (DAS28-CRP) or based on the erythrocyte sedimentation rate (DAS28-ESR), DMARDs disease-modifying antirheumatic drugs, and TNF tumor necrosis factor.

† Positivity for anti–cyclic citrullinated peptide antibody was defined as a value that exceeded the upper limit of the normal range (i.e., >10 U per milliliter).

‡ Positivity for rheumatoid factor was defined as a value that exceeded the upper limit of the normal range (i.e., >14 IU per milliliter).

§ Scores for the physician's global assessment, the patient's global assessment, and the patient's assessment of pain range from 0 to 100 mm on a visual-analogue scale, with higher scores indicating greater levels of reported disease activity or pain.

¶ Scores on the Health Assessment Questionnaire–Disability Index (HAQ-DI) range from 0 to 3, with higher scores indicating greater disability.

‖ The upper limit of the normal range for the high-sensitivity C-reactive protein level is 3 mg per liter.

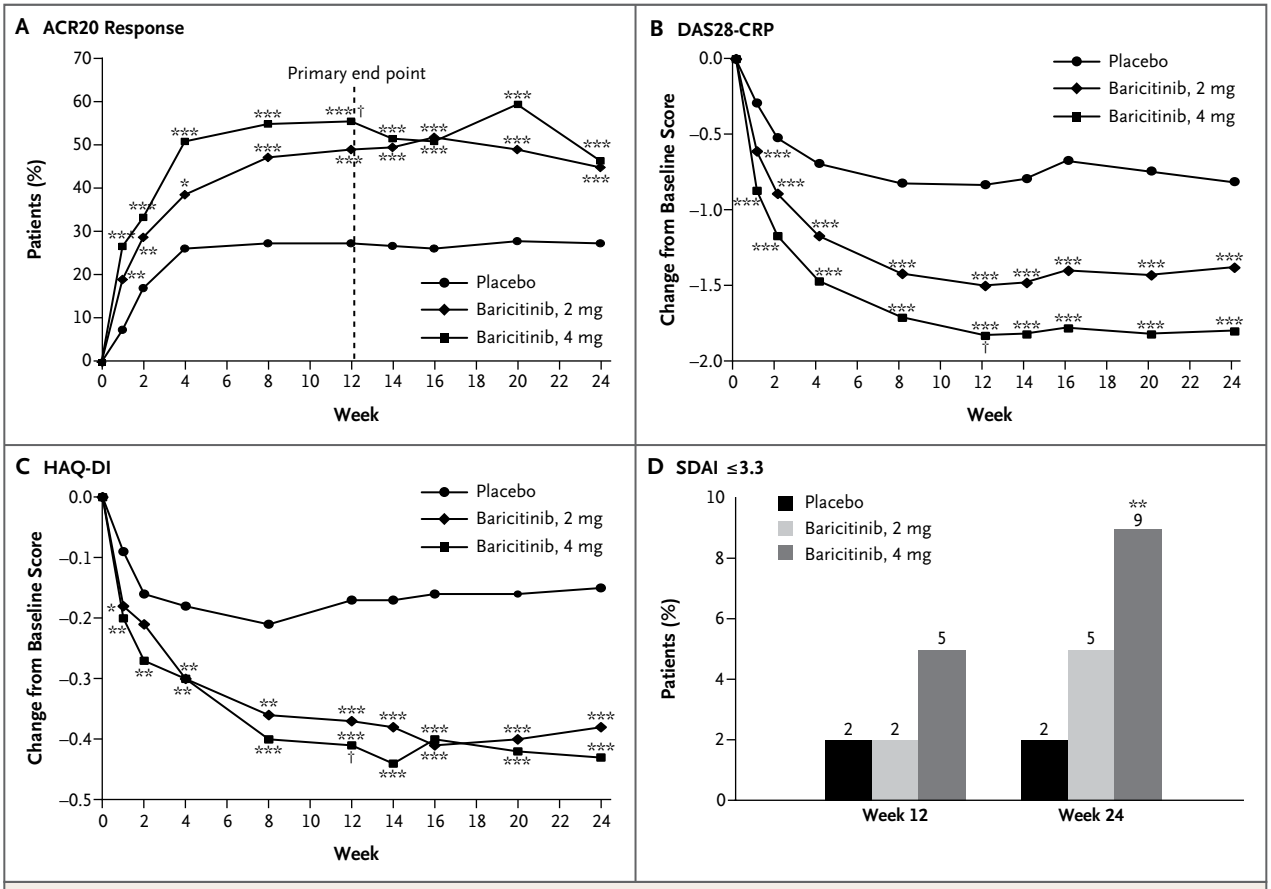

Figure 2. Primary and Secondary Efficacy End Points.

The percentage of patients who had an American College of Rheumatology 20% (ACR20) response is shown in Panel A. The vertical line at 12 weeks indicates the primary efficacy time point. Panel B shows the least-squares mean (LSM) change from baseline in the 28-joint Disease Activity Score, based on the level of high-sensitivity C-reactive protein (DAS28-CRP). A modified last-observation-carried-forward method was used for data that were missing because of receipt of rescue therapy or discontinuation of the study or study treatment. Panel C shows the LSM change from baseline in the Health Assessment Questionnaire–Disability Index (HAQ-DI) score, with the use of a modified last-observation-carried-forward method; scores range from 0 to 3, with higher scores indicating greater disability. Panel D shows the percentage of patients with a Simplified Disease Activity Index (SDAI) score of 3.3 or less (on a scale of 0.1 to 86.0, with higher scores indicating greater disease activity and a score of 3.3 or less indicating remission) at weeks 12 and 24. The DAS28-CRP and the HAQ-DI score were analyzed at week 12 by means of a modified baseline-observation-carried-forward method, which substituted the baseline observation for the last observation in the case of patients who discontinued the study or the study drug because of an adverse event. For the fourth ordered outcome (an SDAI score of ≤3.3 at week 12), the difference between baricitinib at the 4-mg dose and placebo was not significant (P=0.14). One asterisk denotes P≤0.05, two asterisks denote P≤0.01, and three asterisks denote P≤0.001 for supportive analyses comparing baricitinib with placebo, without adjustment for multiple comparisons. The dagger denotes P≤0.001 for comparisons between baricitinib at the 4-mg dose and placebo for the end points of the ACR20 response at week 12 and the changes from baseline in the DAS28-CRP and the HAQ-DI score at week 12, in an analysis that was strongly controlled for multiple comparisons, meaning that the analysis was included in a multiple hypothesis testing framework that controlled for the type I error rate.

death occurred; a 76-year-old patient with preexisting diabetes mellitus who was receiving baricitinib at the 4-mg dose died on day 47 as a result of basilar-artery thrombosis. This was one of two adjudicated major adverse cardiovascular events that occurred during the study; the second was a non–ST-segment elevation myocardial infarction on day 92 in a 46-year-old patient with preexisting diabetes mellitus and hypertension who was receiving baricitinib at the 4-mg dose. Two nonmelanoma skin cancers were reported in the group receiving baricitinib at a dose of 4 mg.

During the treatment period, there were more adverse events, including infections, with barici-

Table 2. Safety and Laboratory Data, Week 0 to Week 12 and Week 0 to Week 24.*

Variable	Week 0 to Week 12			Week 0 to Week 24		
	Placebo (N=176)	Baricitinib, 2 mg Daily (N=174)	Baricitinib, 4 mg Daily (N=177)	Placebo (N=176)	Baricitinib, 2 mg Daily (N=174)	Baricitinib, 4 mg Daily (N=177)
Treatment exposure — no. of patient-yr	38.4	38.6	40.0	65.8	69.9	73.3
Safety data						
Serious adverse events — no. (%)†	7 (4)	3 (2)	11 (6)	13 (7)	7 (4)	18 (10)
Any adverse event after the start of therapy — no. (%)	96 (55)	107 (61)	119 (67)	112 (64)	123 (71)	137 (77)
Withdrawal from study because of adverse event — no. (%)	4 (2)	7 (4)	9 (5)	7 (4)	7 (4)	11 (6)
Infections — no. (%)	35 (20)	61 (35)	48 (27)	55 (31)	76 (44)	70 (40)
Herpes zoster — no. (%)	1 (<1)	2 (1)	4 (2)	2 (1)	2 (1)	7 (4)
Serious infections — no. (%)	3 (2)	3 (2)	3 (2)	5 (3)	4 (2)	6 (3)
Cancers — no. (%)	0	0	0	0	0	2 (1)
Nonmelanoma skin cancer — no. (%)	0	0	0	0	0	2 (1)
Major adverse cardiovascular event — no. (%)‡	0	0	1 (<1)	0	0	2 (1)
GI perforation — no. (%)	0	0	0	0	0	0
Laboratory data§						
Hemoglobin — g/dl	−0.19±0.06	−0.23±0.06	−0.32±0.06	−0.15±0.08	−0.28±0.07	−0.20±0.07
Neutrophil count — per mm^3	190±160	−250±160	−720±160¶	130±190	−560±170‖	−630±160‖
Lymphocyte count — per mm^3	−70±50	20±50	0±50	−60±60	−90±50	−20±50
Platelet count — per mm^3	6,000±5,000	20,000±4,000**	29,000±4,000¶	10,000±6,000	18,000±6,000	31,000±5,000**
Alanine aminotransferase — U/liter	−1.1±0.8	1.6±0.8**	3.0±0.8¶	1.9±1.1	2.6±1.0	2.2±0.9
Creatinine — mg/dl	0.01±0.01	0.03±0.01**	0.05±0.01¶	0.03±0.01	0.03±0.01	0.06±0.01
Creatine kinase — U/liter	1±6	32±6¶	60±6¶	57±26	38±23	61±22
Cholesterol — mg/dl						
LDL	0±2	8±2‖	16±2¶	−2±3	9±3‖	20±3¶
HDL	0.0±0.8	7.2±0.8¶	8.4±0.8¶	0.6±1.3	5.1±1.1‖	8.8±1.1¶

* Plus–minus values are means ±SE. GI denotes gastrointestinal, HDL high-density lipoprotein, and LDL low-density lipoprotein. To convert the values for creatinine to micromoles per liter, multiply by 88.4. To convert the values for cholesterol to millimoles per liter, multiply by 0.02586.

† Serious adverse events are reported on the basis of conventional International Conference on Harmonization definitions and not on the basis of the study protocol; the protocol required that adverse events or laboratory abnormalities leading to permanent discontinuation of the study drug be designated as serious adverse events. The data shown are numbers and percentages of patients with serious adverse events up to the time of receipt of rescue therapy.

‡ A major adverse cardiovascular event was defined as death from cardiovascular causes, myocardial infarction, or stroke, as adjudicated by an independent cardiovascular evaluation committee.

§ Laboratory values are reported as the least-squares mean change from baseline at week 12 and week 24.

¶ P≤0.001 for the comparison with the placebo group on the basis of analysis of covariance (ANCOVA).

‖ P≤0.01 for the comparison with the placebo group on the basis of ANCOVA.

** P≤0.05 for the comparison with the placebo group on the basis of ANCOVA.

tinib than with placebo (Table 2, and Table S5 in the Supplementary Appendix). Serious adverse events are listed in Table S6 in the Supplementary Appendix. Serious infections occurred in 3%, 2%, and 3% of patients in the placebo group, the lower-dose baricitinib group, and the higher-dose baricitinib group, respectively. Infection rates were similar in the two baricitinib groups; respiratory infections, bronchitis, and urinary tract infections were the most common types reported. Herpes zoster infections were seen in all three groups; the largest number was seen with baricitinib at the 4-mg dose. Among baricitinib-treated patients who had herpes zoster infection, the majority had received three or more previous biologic DMARDs. There were no cases of visceral or disseminated herpes zoster.

Table 2 shows mean changes from baseline, and Table S7 in the Supplementary Appendix shows CTCAE grade increases for selected laboratory analytes through 24 weeks. Reductions in hemoglobin levels were observed in all study groups; no imbalance in the number of cases of anemia was seen between the baricitinib and placebo groups. Reductions in neutrophil levels were observed with baricitinib. There were transient increases in lymphocyte counts with baricitinib in some patients (data not shown); no imbalance in the numbers of patients with lymphopenia was seen between the baricitinib and placebo groups. Moderate increases in platelet counts were seen with baricitinib; there was no imbalance in the number of patients with protocol-defined thrombocytosis (>600,000 cells per cubic millimeter) between the baricitinib and placebo groups. Small increases in alanine aminotransferase levels were observed in both baricitinib groups; most of the abnormal values were transient, the majority of grade 2 elevations occurred in patients with preexisting abnormal values, none coincided with increased bilirubin levels, and no grade 3 elevations occurred. Small increases in serum creatinine levels were seen with baricitinib, and most of the abnormal values were transient. Only one patient had an increase in the creatinine level that was higher than grade 1, and the value was normal on repeat testing. Serum creatine kinase levels increased in both baricitinib groups; all the patients who had grade 3 or 4 abnormalities reported having engaged in exercise or other physical activity before being tested or had elevated baseline levels. Low-density lipoprotein and high-density lipoprotein cholesterol levels were higher with both baricitinib doses than with placebo.

DISCUSSION

The field of rheumatology has seen major changes in the therapeutic approach to rheumatoid arthritis since the mid-1990s. Treatment paradigms have evolved with more intensive use of conventional synthetic DMARDs, the introduction of biologic agents, and most recently, new small molecules targeting the JAK pathway. Baricitinib is a potent and selective inhibitor of JAK1 and JAK2. It has been hypothesized that agents with different JAK inhibition profiles may have distinct clinical effects.[14]

This study was designed to assess the safety and efficacy of baricitinib in patients with active rheumatoid arthritis who were taking conventional synthetic DMARDs and had had an inadequate response to previous treatment with biologic DMARDs. In this patient population, once-daily oral baricitinib resulted in significant clinical improvements, as compared with placebo, at 12 weeks. The treatment benefits were larger with the 4-mg dose than with the 2-mg dose. Adverse events, including nonserious infections, were more frequent in the baricitinib groups than in the placebo group. Baricitinib was associated with reductions in neutrophil counts, an increase in creatinine levels, and an increase in low-density lipoprotein cholesterol levels. These changes were predominantly minor and did not lead to withdrawal from the study.

In comparison with previous phase 3 trials of treatments for rheumatoid arthritis,[15-20] this study enrolled a high proportion of patients (more than one third) with an inadequate response to or unacceptable side effects associated with both TNF-inhibitor and non–TNF-inhibitor biologic DMARDs. Thus, our study population had particularly refractory disease, having received multiple previous biologic therapies. A beneficial treatment effect was observed in all analyzed subgroups, irrespective of the number or type of prior biologic DMARDs received. The observed clinical responses appeared to be favorable in the context of studies of currently approved therapies in patients with inadequate responses to previous TNF-inhibitors.[15-20] Our findings have

particular relevance because of the unmet need for effective treatment of rheumatoid arthritis in patients receiving a conventional synthetic DMARD with inadequate disease control despite previous treatment with multiple biologic agents; the number of such patients has been consistently increasing since biologic DMARDs first became available more than 15 years ago.

There are some limitations to the conclusions that can be drawn from this trial. The time frame for interpretation of safety data and durability of treatment effectiveness is limited to 24 weeks. The lack of radiographic end points limits the ability to draw conclusions regarding the capacity of baricitinib to slow the rate of structural joint damage in this patient population. Evaluation of progressive radiographic joint damage is an objective of other phase 3 studies in the baricitinib development program (ClinicalTrials.gov numbers, NCT01721057, NCT01885078, NCT01710358, NCT01711359, NCT02265705).

In conclusion, these results provide evidence that selective inhibition of JAK1 and JAK2 with once-daily baricitinib has clinical efficacy in patients with active rheumatoid arthritis that is refractory to aggressive standard-of-care treatment with both conventional synthetic DMARDs and biologic DMARDs. Adverse events with baricitinib included infections, and abnormal laboratory test results included increases in low-density lipoprotein cholesterol and creatinine levels. Additional studies are needed to assess long-term safety and durability of response.

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