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An Oral Spleen Tyrosine Kinase (Syk) Inhibitor for Rheumatoid Arthritis

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ABSTRACT

BACKGROUND

Spleen tyrosine kinase (Syk) is an important modulator of immune signaling. The objective of this phase 2 study was to evaluate the efficacy and safety of R788, an oral inhibitor of Syk, in patients with active rheumatoid arthritis despite methotrexate therapy.

METHODS

We enrolled 457 patients who had active rheumatoid arthritis despite long-term methotrexate therapy in a 6-month, double-blind, placebo-controlled trial. The primary outcome was the American College of Rheumatology (ACR) 20 response (which indicates at least a 20% reduction in the number of both tender and swollen joints and improvement in at least three of five other criteria) at month 6.

RESULTS

R788, at a dose of 100 mg twice daily and at a dose of 150 mg once daily, was significantly superior to placebo at month 6 (ACR 20 response rates of 67% and 57%, respectively, vs. 35%; $P < 0.001$ for the comparison of both doses with placebo). It was also significantly superior with respect to ACR 50, which indicates at least a 50% improvement (43% and 32% vs. 19%; $P < 0.001$ for the comparison of the 100-mg dose with placebo, $P = 0.007$ for the comparison of the 150-mg dose with placebo) and ACR 70 (28% and 14% vs. 10%; $P < 0.001$ for the comparison of the 100-mg dose with placebo, $P = 0.34$ for the comparison of the 150-mg dose with placebo). A clinically significant effect was noted by the end of the first week of treatment. Adverse effects included diarrhea (in 19% of subjects taking the 100-mg dose of R788 vs. 3% of those taking placebo), upper respiratory infections (14% vs. 7%), and neutropenia (6% vs. 1%). R788 was associated with an increase in systolic blood pressure of approximately 3 mm Hg between baseline and month 1, as compared with a decrease of 2 mm Hg with placebo; 23% of the patients taking R788 vs. 7% of the patients receiving placebo required the initiation of or a change in antihypertensive therapy.

CONCLUSIONS

In this phase 2 study, a Syk inhibitor reduced disease activity in patients with rheumatoid arthritis; adverse events included diarrhea, hypertension, and neutropenia. Additional studies will be needed to further assess the safety and efficacy of Syk-inhibition therapy in patients with rheumatoid arthritis. (Funded by Rigel; ClinicalTrials.gov number, NCT00665925.)

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SPLEEN TYROSINE KINASE (SYK) IS AN INTRACELLULAR cytoplasmic tyrosine kinase that is an important mediator of immunoreceptor signaling in macrophages, neutrophils, mast cells, and B cells. Syk is present in the synovium of patients with rheumatoid arthritis, and activation of Syk is important for cytokine and metalloproteinase production induced by tumor necrosis factor α in fibroblast-like synoviocytes from patients with rheumatoid arthritis.¹ In rodent models of collagen-induced arthritis,² R788 (fostamatinib disodium), an oral prodrug that is rapidly converted to a potent and relatively selective inhibitor of Syk (R406),³ had potent antiinflammatory activity, suggesting a role for Syk inhibition in the treatment of rheumatoid arthritis.

In a previous 12-week, ascending-dose, randomized, placebo-controlled trial⁴ (ClinicalTrials.gov number, NCT00326339) involving 189 patients who had active rheumatoid arthritis despite methotrexate therapy, a significant reduction in arthritis activity and in serum levels of interleukin-6 and matrix metalloproteinase 3 were seen in the two groups that received the highest doses of R788 (100 mg twice daily and 150 mg twice daily), as compared with the groups that received placebo or the 50-mg dose of R788 twice daily. Notable adverse events were diarrhea, neutropenia, and an elevation of blood pressure.

On the basis of those positive results, a larger and longer phase 2 trial was designed to evaluate R788 among patients with active rheumatoid arthritis who were receiving long-term methotrexate therapy. The primary objective was to determine the efficacy and safety of R788, as compared with placebo, in this population at 6 months.

METHODS

PATIENTS AND STUDY DESIGN

We conducted this multicenter, randomized, double-blind, placebo-controlled trial at 64 sites in six countries (Bulgaria, Colombia, Mexico, Poland, Romania, and the United States). Patients were eligible if they met the American College of Rheumatology (ACR) criteria for rheumatoid arthritis,⁵ had had active rheumatoid arthritis for at least 6 months, and had been receiving a stable dose of methotrexate (between 7.5 and 25 mg per week) for a minimum of 3 months. Supplemental therapy with folic acid or folinic acid was also required. Active rheumatoid arthritis was considered to be

present if a patient had 6 or more swollen joints (assessed with the use of the 28-joint count, in which 28 specific joints are examined) and 6 or more tender joints (on the basis of the 28-joint count) and at least one of the following: an erythrocyte sedimentation rate that exceeded the upper limit of the normal range for the local laboratory or a C-reactive protein level that was higher than the upper limit of the normal range for the central reference laboratory. Previous treatment with biologic response modifiers was allowed if the patient met the criteria for a protocol-specified washout period before study treatment was initiated. Concurrent treatment with stable doses of sulfasalazine, chloroquine, hydroxychloroquine, nonsteroidal antiinflammatory drugs, or oral corticosteroids (≤ 10 mg of prednisone per day or the equivalent) was permitted.

Exclusion criteria were active or untreated latent infection, including hepatitis B or C, cancer (except for basal-cell or squamous-cell carcinoma of the skin) within the previous 5 years, uncontrolled hypertension, a serum alanine aminotransferase level that was higher than 1.2 times the upper limit of the normal range, a hemoglobin level of less than 10 g per deciliter, a platelet count of less than 125,000 per cubic millimeter, or a creatinine level that exceeded the upper limit of the normal range.

STUDY PROTOCOL

A total of 457 patients were randomly assigned, in a 2:2:1:1 ratio, to one of four study drugs: R788 at a dose of 100 mg twice daily, R788 at a dose of 150 mg once daily, placebo twice daily, or placebo once daily. Randomization to one of the four study groups was stratified according to geographic region and status with respect to previous biologic therapy (previous biologic therapy was allowed for no more than 30% of the total study population). A trained independent assessor of joints (who was unaware of the laboratory results and treatment assignments) performed the tender-joint and swollen-joint counts and a global assessment of disease activity. Patients who completed the study or withdrew early owing to a lack of efficacy were eligible to enter a long-term open-label study in which all patients received R788 according to the dosing regimen to which they had been assigned in the randomized study, so that in the case of patients in the placebo groups, those who had received placebo once daily received

the 150-mg dose of R788 once daily and those who had received placebo twice daily received the 100-mg dose twice daily.

The study was conducted in accordance with the ethical principles of the Declaration of Helsinki and was approved by the appropriate institutional review boards. All patients provided written informed consent. The study was started in May 2008 and was completed in June 2009.

The study was designed jointly by the sponsor (Rigel) and the principal investigators. The study protocol is available with the full text of this article at NEJM.org. The data were obtained by the study investigators and collected by Kendle (a contract research organization) and were analyzed by personnel at Rigel and Kendle. The authors had full access to the data, vouch for the completeness and accuracy of the data and analysis, and made the decision to submit the manuscript for publication. All drafts of the manuscript were written by the first author.

CLINICAL EFFICACY OUTCOMES

The primary outcome was the rate at 6 months of the ACR 20 response, which is defined as at least a 20% reduction from baseline in the number of both tender and swollen joints and a 20% or greater improvement in at least three of five measures: patient's assessment of pain (on the basis of a visual-analogue scale ranging from 0 to 100, with higher scores indicating more pain); levels of acute-phase reactants; physical function, as assessed with the use of the Health Assessment Questionnaire (HAQ)–Disability Index, in which scores range from 0 to 3, with higher scores indicating greater disability⁶; global assessment of the disease by the patient; and global assessment of the disease by the physician (both assessed on a scale of 0 to 100, with higher numbers indicating more severe disease).⁷ Secondary outcomes included the following: rates of ACR 50 and ACR 70 responses, defined as at least 50% and at least 70% improvement, respectively; improvements in individual components of the ACR score, including the HAQ; disease activity, as assessed with the use of the Disease Activity Score for 28-joint counts (DAS28), on a scale of 0 to 9.31, with higher scores indicating more disease activity⁸; remission of rheumatoid arthritis (DAS28 score below 2.6); the score on the Functional Assessment of Chronic Illness Therapy (FACIT)–fatigue scale, which ranges from 0 to 52, with

lower scores indicating greater fatigue⁹; and scores on the Medical Outcomes Study 36-Item Short-Form Health Survey (SF-36), which range from 0 to 100 for each of eight domains, with higher scores indicating improved health status.¹⁰

SAFETY MEASURES

Patients were evaluated at weeks 1, 2, 4, 6, and 8 and monthly thereafter. The dose of the study drug was reduced if the serum alanine aminotransferase level rose to more than 3 times the upper limit of the normal range, if the absolute neutrophil count was less than 1500 per cubic millimeter, if unacceptable gastrointestinal symptoms developed, or if there was a sustained increase in blood pressure. In cases in which doses were reduced, patients and investigators remained unaware of the study-treatment assignment. Patients in the R788 groups in whom the dose was reduced received a single dose of 100 mg of R788 daily. All vascular events or potential vascular events were adjudicated by an independent cardiologist who was unaware of the patients' treatment assignments.

STATISTICAL ANALYSIS

We estimated the sample size on the basis of a comparison of the ACR 20 response rate at month 6 between the group that received 100 mg of R788 twice daily and the group that received placebo twice daily. We estimated that with 140 patients in the R788 group and 70 patients in the placebo group, the study would have 85% power to detect a difference of at least 22% between the two groups, assuming an ACR 20 response rate in the placebo group of 38%, with the use of a two-sided test at the 0.05 level of significance.

The primary outcome was the ACR 20 response rate at month 6, and any patient who withdrew before month 6 was considered not to have had a response. The two placebo groups (those receiving placebo once daily and those receiving placebo twice daily) were pooled for all data summaries and analyses. The pooling was prespecified, since the observed difference in the ACR 20 response rate between the two placebo groups was 4% and the protocol allowed for the pooling of the placebo groups if the difference in the ACR 20 response rate between the placebo groups was less than 15%. Differences between study groups were compared with the use of Pearson's chi-square test. ACR 20, 50, and 70 response rates

were compared between each R788 group and the combined placebo group with the use of a Cochran–Mantel–Haenszel test, stratified according to geographic region and status with respect to previous biologic therapy. Among patients who had a response to treatment, the times to an ACR 20, 50, or 70 response were plotted according to study group. The primary analyses of the individual disease components were supplemented by secondary analyses in which missing values were imputed with the use of the last-observation-carried-forward method. Changes from baseline in swollen-joint counts, tender-joint counts, and C-reactive protein levels were compared between each R788 group and the placebo group with the use of a stratified Wilcoxon rank-sum test, stratified according to geographic region and status with respect to previous biologic therapy.

RESULTS

PATIENTS

A total of 457 patients were enrolled in the study; 304 patients received R788 (152 patients at a dose of 150 mg once daily and 152 at a dose of 100 mg twice daily) and 153 received placebo (77 patients once daily and 76 twice daily). The groups were well balanced with respect to demographic characteristics and disease activity (Table 1). Approximately 50% of the patients had a known history of hypertension or had hypertension (blood pressure ≥ 140 mm Hg systolic or ≥ 90 mm Hg diastolic) at the baseline or screening visit.

A total of 21% of the patients in the placebo groups, as compared with 16% in the R788 groups, did not complete the study. The predominant reason for withdrawal in the combined placebo group was lack of efficacy (in 12% of patients); in the R788 groups, the main reasons were lack of efficacy (6%) and adverse events (5%).

DOSE REDUCTIONS

The dose of the study drug was reduced in the case of 6 patients (4%) in the combined placebo group, as compared with 42 (14%) in the combined R788 group. The most common reasons for a reduction in the dose of R788 were gastrointestinal symptoms (in 5% of patients), elevations of serum alanine aminotransferase level (4%), and elevations of blood pressure (3%). Of the 42 patients in the R788 groups whose dose was reduced, 31 patients completed the study.

CLINICAL EFFICACY

Significantly more patients in the R788 groups than in the combined placebo group met the criteria for ACR 20 response (67% in the group receiving 100 mg twice daily and 57% in the group receiving 150 mg once daily vs. 35% in the placebo group, $P < 0.001$ for both comparisons with placebo). More patients in the R788 groups than in the combined placebo group met the criteria for an ACR 20 response by the end of the first week of treatment (23% in the group receiving 150 mg once daily and 36% in the group receiving 100 mg twice daily vs. 14% in the combined placebo group) ($P = 0.04$ and $P < 0.001$ for the comparison of the two R788 doses, respectively, with placebo) (Fig. 1). The percentage of patients in whom an ACR response was achieved increased over time, but the predominant effect was seen quite early.

The DAS28 was also significantly improved by month 1 (which was when the first assessment of the DAS28 was performed) in the group receiving 100 mg of R788 twice daily, and the improvement was maintained throughout the study ($P < 0.001$ for the comparison of both groups with placebo at month 1 and month 6). At month 6, the rates of remission of rheumatoid arthritis, as defined by a DAS28 below 2.6, were 21% in the group receiving R788 at a dose of 150 mg once daily and 31% in the group receiving 100 mg of R788 twice daily, as compared with 7% in the placebo group ($P = 0.003$ for the comparison of the 150-mg dose with placebo, $P < 0.001$ for the comparison of the 100-mg dose with placebo).

ACR 20 response rates in both the placebo and R788 groups were higher among patients in Latin America and in Eastern Europe than among patients in the United States (37% in the placebo group and 69% in the group receiving 100 mg of R788 twice daily in Latin America and 42% and 74%, in the two groups, respectively, in Eastern Europe vs. 22% and 56%, respectively, in the United States); however, the differences in ACR 20 response rates between the R788 groups and the combined placebo group were similar across geographic regions (32 to 34 percentage points).

A total of 15% of the patients in the trial had not had a response to previous biologic therapy. Although the response rates for the R788 and placebo groups were lower in this subgroup than in the overall population, significant differences in ACR 20 response rates were observed between the groups receiving R788 and the combined placebo

Table 1. Demographic and Clinical Characteristics of the Study Patients.*

| Variable | Placebo (N=153) | R788, 150 mg Once Daily (N=152) | R788, 100 mg Twice Daily (N=152) | P Value†‡ |
|---|--------------------|---------------------------------------|--|-----------|
| Age (yr) | | | | 0.97 |
| Mean | 52.4 | 52.6 | 52.5 | |
| Range | 24–83 | 18–81 | 21–87 | |
| Female sex (%) | 85.6 | 84.2 | 86.2 | 0.88 |
| Race or ethnic group (%):‡ | | | | |
| White | 46.4 | 49.3 | 38.2 | 0.10 |
| Hispanic | 49.0 | 48.7 | 57.9 | 0.13 |
| Duration of disease (yr) | 9.5±8.7 | 9.7±9.1 | 8.4±8.2 | 0.44 |
| Swollen joints (no.)§ | 12.2±4.9 | 12.3±5.4 | 11.8±5.0 | 0.68 |
| Score on HAQ–Disability Index¶ | 1.53±0.73 | 1.54±0.68 | 1.51±0.71 | 0.96 |
| Score on DAS28 | 6.17±0.79 | 6.13±0.86 | 6.16±0.86 | 0.89 |
| Positive for rheumatoid factor (%) | 85.0 | 81.1 | 89.1 | 0.20 |
| Treatment with prednisone, ≤10 mg/day (%) | 61.4 | 56.6 | 61.2 | 0.66 |
| Previous therapy with biologic response modifiers (%) | 14.4 | 15.8 | 14.5 | 0.20 |

* Plus–minus values are means ±SD.

† Differences between study groups in continuous end points were analyzed with the use of a general linear model, with factors for study group (three groups), region, and previous therapy with or without biologic response modifiers. Differences between study groups in categorical end points were analyzed with the use of a Cochran–Mantel–Haenszel test, stratified according to region and status with respect to previous therapy with biologic response modifiers.

‡ Race or ethnic group was determined by the investigator.

§ A total of 28 joints were assessed.

¶ The degree of disability was assessed with the use of the Health Assessment Questionnaire (HAQ)–Disability Index, in which scores range from 0 to 3, with higher scores indicating greater disability.

|| Arthritis disease activity was assessed with the use of the Disease Activity Score for 28-joint counts (DAS28); scores range from 0 to 9.31, with higher scores indicating more disease activity.

group (43% in the group receiving 100 mg of R788 twice daily and 46% in the group receiving 150 mg once daily vs. 14% in the placebo group; $P=0.04$ and $P=0.02$, respectively).

There was an improvement in individual measures of arthritis with R788 therapy as compared with placebo (Table 2). The group receiving 100 mg of R788 twice daily — but not the group receiving 150 mg once daily — had significant improvement, as compared with the placebo group, from baseline to month 6 in the FACIT–fatigue score ($P=0.04$) and in the summary score for the physical component of the SF-36 ($P=0.001$), as well as in individual scores for the SF-36 physical component, including the scores for physical function ($P=0.04$), physical role ($P=0.02$), bodily pain ($P=0.006$), and general health ($P=0.002$). No significant improvement was seen in the scores for the mental health component of the SF-36 in either the R788 groups or the placebo group.

SAFETY

A total of 21 patients (5%) withdrew from the study owing to adverse events — 6 in the placebo group and 15 in the R788 groups (10 in the group receiving 150 mg once daily and 5 in the group receiving 100 mg twice daily). Of the adverse events leading to withdrawal, nausea and diarrhea were the most common events associated with R788 therapy. A total of 24 patients (5%) had serious adverse events, including infections (4 in the placebo group, 2 in the group receiving 150 mg of R788 once daily, and 5 in the group receiving 100 mg twice daily) and gastrointestinal events (none in the placebo group, 1 in the 150-mg R788 group, and 3 in the 100-mg R788 group). The only confirmed vascular event occurred in a patient in the placebo group who had unstable angina and a hypertensive crisis.

The proportions of patients with at least one adverse event were similar in the placebo and R788

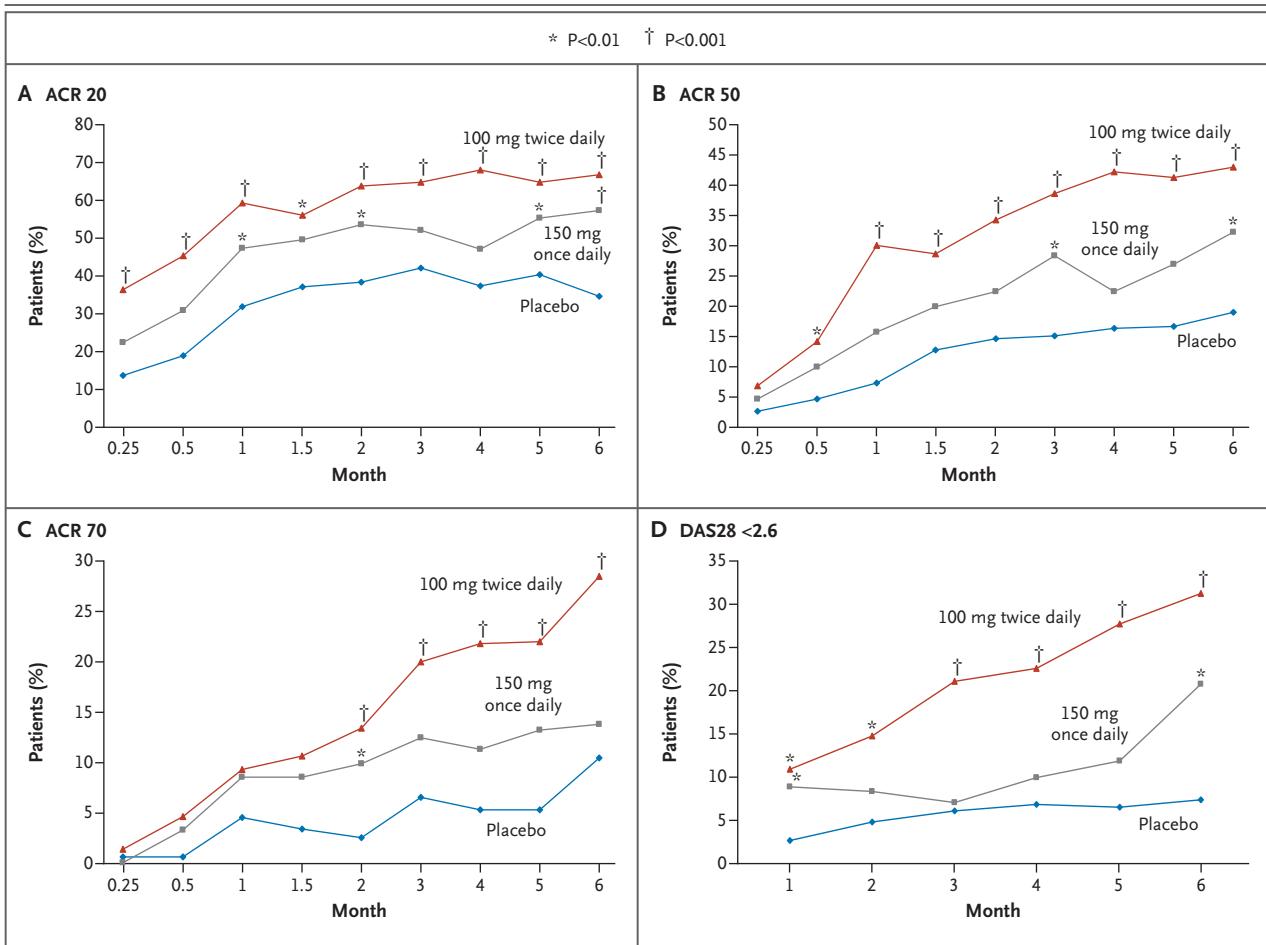


Figure 1. Clinical Responses over Time.

American College of Rheumatology (ACR) 20, ACR 50, and ACR 70 responses (Panels A, B, and C, respectively) are defined as at least a 20%, 50%, and 70% reduction, respectively, from baseline in the number of both tender and swollen joints and an equivalent or greater improvement in at least three of five measures (pain, levels of acute-phase reactants, physical function, global assessment by the patient, and global assessment by the physician). The Disease Activity Score for 28-joint counts (DAS28) ranges from 0 to 9.31, with higher scores indicating more disease activity. A DAS28 score of less than 2.6 (Panel D) indicates remission of rheumatoid arthritis.

groups, with 65% of the patients, overall, having at least one adverse event. The most common adverse events were diarrhea and headache (Table 3). Five patients receiving 150 mg of R788 once daily and nine patients receiving 100 mg of R788 twice daily — as compared with no patients receiving placebo — required a reduction in the dose of the study drug owing to gastrointestinal adverse events.

More patients in the R788 groups than in the placebo group had serum alanine aminotransferase levels that rose to more than 1.5 times the upper limit of the normal range (18% of the patients receiving 150 mg of R788 once daily and 20% of those receiving 100 mg twice daily vs. 10%

of those in the placebo group). A total of 4% of the patients in each R788 group, as compared with 2% in the placebo group, had serum alanine aminotransferase levels that rose to more than 3 times the upper limit of the normal range. Of the 12 patients in the R788 groups who had an alanine aminotransferase level that was more than 3 times the upper limit of the normal range, 1 withdrew; the other 11 patients completed the study while taking a reduced dose of R788 and did not have a recurrence of an elevated serum alanine aminotransferase level.

A larger percentage of patients in the R788 groups than in the placebo group had neutropenia, which was defined as an absolute neutrophil

Table 2. Reduction in Arthritis Activity, as Assessed According to American College of Rheumatology (ACR) Response Criteria, from Baseline to Month 6.*

| Component of ACR Response Criteria | Placebo (N=153) | R788, 150 mg Once Daily (N=152) | R788, 100 mg Twice Daily (N=152) |
|--|-----------------|---------------------------------|----------------------------------|
| Tender joints — no.† | 6.1±7.6 | 10.0±6.9‡ | 10.5±6.6‡ |
| Swollen joints — no.† | 6.0±5.0 | 7.8±5.7§ | 8.2±4.6‡ |
| Patient's assessment of pain¶ | 17.8±27.0 | 23.0±24.1 | 31.3±28.1‡ |
| Global disease assessment | | | |
| Patient's assessment | 16.7±26.6 | 20.3±25.3 | 29.1±25.9‡ |
| Physician's assessment | 24.7±24.6 | 32.1±20.7§ | 37.2±20.7‡ |
| Acute-phase reactants | | | |
| C-reactive protein — nmol/liter | 29.7±143.8 | 20.32±145.4 | 63.2 ±149.8§ |
| Erythrocyte sedimentation rate — mm/hr | 4.2±18.9 | 10.2±17.8§ | 13.6±22.2‡ |
| Score on HAQ–Disability Index** | | | |
| Mean change in score | 0.34±0.67 | 0.54±0.65§ | 0.65±0.74‡ |
| >0.22-point change from baseline — no. (%) | 76 (50) | 93 (61)§ | 107 (70)‡ |
| Score of <0.5 — no. (%) | 28 (18) | 38 (25) | 46 (30)§ |

* All values indicate a reduction from the baseline measurements. Plus–minus values are means ±SD.
 † A total of 28 joints were assessed.
 ‡ P<0.001 for the comparison with the placebo group.
 § P<0.05 for the comparison with the placebo group.
 ¶ Patients assessed their pain on the basis of a visual-analogue scale ranging from 0 to 100, with higher scores indicating more pain.
 || Global Disease Assessment was scored on the basis of a visual-analogue scale ranging from 0 to 100, with higher scores indicating greater severity of disease.
 ** Scores on the Health Assessment Questionnaire (HAQ)–Disability Index range from 0 to 3, with higher scores indicating greater disability.

count of less than 1500 per cubic millimeter (7% and 6% of the patients receiving 150 and 100 mg of R788, respectively, vs. 1% of the patients receiving placebo). No patient had an absolute neutrophil count below 1000 per cubic millimeter. In all cases, the absolute neutrophil count returned to 1500 per cubic millimeter or more within 3 to 7 days after an interruption in or reduction of the R788 dose. No infections were associated with neutropenia. There was no significant effect of R788 on serum lipid levels, the creatinine level, or other serum chemical levels.

Hypertension (defined as blood pressure ≥140 mm Hg systolic or ≥90 mm Hg diastolic) was more common at month 1 among patients treated with R788 than among those receiving placebo (29% in the combined R788 groups vs. 17% in the placebo group, P=0.006). Increases in systolic and diastolic blood pressure were more pronounced among patients who had hypertension at the screening or baseline visit than among those who did not (Table 4). Overall, the mean difference in

the change in systolic pressure from baseline to month 1 between the combined R788 group and the placebo group was an increase of approximately 5 mm Hg in the R788 group. In all cases, elevated blood pressure responded to conventional antihypertensive medications or a reduction in the dose of R788. At month 6, the mean change from baseline in systolic pressure was an increase of 0.2 mm Hg in the group receiving 150 mg of R788 once daily and an increase of 0.6 mm Hg in the group receiving 100 mg twice daily.

STUDY EXTENSION

A total of 389 patients (94% of the 412 eligible patients) enrolled in a long-term open-label extension study, in which all patients received R788. As of January 30, 2010, when 6-month data were available for 297 patients, 27% had a DAS28 of less than 2.6, and 46% a DAS28 of less than 3.2. A total of 69 patients (18%) withdrew from the extension study — 19 owing to a lack of efficacy and 21 owing to adverse events, including nausea

Table 3. Most Frequent Adverse Events.*

| Event | Placebo (N=153) | R788, 150 mg Once Daily (N=152) | R788, 100 mg Twice Daily (N=152) |
|-----------------------------|--------------------|---------------------------------------|--|
| | | percent of patients | |
| Diarrhea | 3.0 | 11.8† | 19.1† |
| Upper respiratory infection | 7.1 | 7.2 | 14.5† |
| Urinary tract infection | 4.6 | 3.3 | 5.9 |
| Nausea | 4.6 | 5.9 | 4.6 |
| Neutropenia | 0.7 | 6.6† | 5.9† |
| Headache | 5.2 | 6.6 | 5.9 |
| Abdominal pain | 2.6 | 6.6† | 5.9† |
| ALT >3× ULN | 2.0 | 3.9 | 3.9 |
| Dizziness | 2.0 | 2.6 | 4.6 |
| Hypothyroidism | 2.6 | 2.6 | 3.3 |
| Cough | 2.6 | 2.0 | 3.3 |

* Included are adverse events that occurred in more than 3% of patients. ALT denotes alanine aminotransferase, and ULN the upper limit of the normal range.

† P<0.05 for the comparison with the placebo group.

or diarrhea (in 10 patients) and recurrent elevations of the alanine aminotransferase level (in 5, with a return to normal values after discontinuation of R788 in all 5). There were three deaths: one due to septicemia (possibly pneumococcal), one due to cerebral hemorrhage in a patient with pneumonia who was receiving heparin therapy for pulmonary emboli, and one a sudden death of unknown cause in a patient with a history of myocardial infarctions. There were 27 serious adverse events, including the three deaths, one case of B-cell lymphoma, one case of cervical carcinoma, and one documented myocardial infarction. There have been no opportunistic infections reported to date. Additional serious adverse events are listed in the table in the Supplementary Appendix, available at NEJM.org.

DISCUSSION

In this randomized trial involving patients with rheumatoid arthritis who were receiving methotrexate therapy, inhibition of Syk with R788 at a dose of 100 mg twice a day was superior to placebo. A significant effect was seen with R788 therapy in the ACR 20, 50, and 70 response rates and in the rates of DAS28 remission, with a higher response observed in the group that received

R788 at a dose of 100 mg twice daily than in the group that received the drug at a dose of 150 mg once daily. The effect of R788 could be seen as early as 1 week after the initiation of treatment. Most of the patients in whom there was a response at month 6 already had a response by month 2.

There were differences in the ACR 20 response rates across geographic regions; however, there was a consistent difference (>30 percentage points) in the ACR 20 response rate between the R788 and placebo groups. The reasons for the difference in response rates across geographic regions are unknown, but this geographic difference has been noted in other clinical trials involving patients with rheumatoid arthritis.^{4,11,12} A limited number of patients (15%) in whom there had not been a response to previous treatment with biologic response modifiers were eligible to enroll in the study. Of these patients, 43% of those who were in the group that received 100 mg of R788 twice a day had an ACR 20 response, as compared with 14% in the placebo group. In a separate phase 2 study, the effects of R788 (100-mg dose twice daily) were compared with those of placebo among patients in whom there had not been a response to previous treatment with biologic response modifiers.¹³ That trial failed to achieve its primary end point; however, it did show an effect of R788 as compared with placebo on the C-reactive protein level, erythrocyte sedimentation rate, and synovitis and osteitis as observed on magnetic resonance imaging.

The adverse effects in this trial were similar to those observed in our earlier study,⁴ with diarrhea again being the most frequent adverse event, in addition to reversible neutropenia and elevated serum aminotransferase levels. In our earlier study, hypertension was seen in some patients, possibly related to an off-target inhibitory effect of R788 on vascular endothelial growth factor receptor 2.¹⁴ In the current study, an increase in blood pressure was seen by month 1 in the R788 group as compared with the placebo group and was noted primarily in patients who had a history of hypertension, were receiving concurrent antihypertensive therapy, or had received a diagnosis of hypertension at the screening or baseline visit. The elevation in blood pressure generally occurred within the first several weeks after initiation of the drug and responded to conventional antihypertensive therapy. By the end of the trial, with patients receiving antihypertensive treatment as

Table 4. Changes in Blood Pressure from Baseline to Months 1 and 6.

| Variable | Placebo (N=153) | R788, 150 mg Once Daily (N=152) | P Value for Comparison with Placebo* | R788, 100 mg Twice Daily (N=152) | P Value for Comparison with Placebo* |
|--|-----------------|---------------------------------|--------------------------------------|----------------------------------|--------------------------------------|
| Total cohort | | | | | |
| Baseline blood pressure — mm Hg | 125/76 | 125/77 | | 125/77 | |
| Change from baseline to 1 mo — mm Hg | -2.0/-0.3 | +2.5/+2.5 | <0.001 (systolic and diastolic) | +3.3/+3.1 | <0.001 (systolic and diastolic) |
| Systolic pressure >140 mm Hg or diastolic >90 mm Hg at 1 mo — no. of patients (%) | 25 (16) | 46 (30) | 0.004 | 39 (26) | 0.04 |
| Change from baseline to 6 mo — mm Hg† | -1.8/+0.4 | +0.2/+0.3 | Systolic: 0.24 Diastolic: 0.60 | +0.6/+1.4 | Systolic: 0.18 Diastolic: 0.15 |
| Antihypertensive medication initiated or changed — no. of patients (%) | 11 (7) | 27 (18) | 0.005 | 35 (23) | <0.001 |
| Patients with hypertension | | | | | |
| History of hypertension or hypertension at baseline or screening — no. of patients (%) | 73 (48) | 84 (55) | | 71 (47) | |
| Change from baseline to 1 mo — mm Hg | -4.2/-0.8 | +1.1/+3.1 | Systolic: 0.009 Diastolic: <0.001 | +5.2/+3.1 | Systolic: <0.001 Diastolic: 0.001 |
| Change from baseline to 6 mo — mm Hg† | -5.2/-1.0 | -3.6/-0.7 | Systolic: 0.57 Diastolic: 0.75 | +0.5/+1.0 | Systolic: 0.03 Diastolic: 0.10 |

* P values were calculated by means of analysis of covariance (ANCOVA), with study group and baseline value as covariates.

† Missing values were imputed with the use of the last-observation-carried-forward method.

indicated, there was no significant increase in blood pressure from the baseline measurements in the R788 group.

In conclusion, in this phase 2 study involving patients who had active rheumatoid arthritis despite treatment with methotrexate, the addition of a Syk inhibitor led to a significant clinical response. Adverse events included diarrhea, neutropenia, elevated liver enzyme levels, and hypertension. Inhibition of the Syk pathway offers a new drug target for the treatment of rheumatoid arthritis.

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