

ORIGINAL ARTICLE

Sustained Remission with Etanercept Tapering in Early Rheumatoid Arthritis

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ABSTRACT

BACKGROUND

We assessed the effects of reduction and withdrawal of treatment in patients with rheumatoid arthritis who had a remission while receiving etanercept-plus-methotrexate therapy.

METHODS

Patients with early active disease who had not previously received methotrexate or biologic therapy received 50 mg of etanercept plus methotrexate weekly for 52 weeks (open-label phase). We then randomly assigned patients who had qualifying responses at weeks 39 and 52 to receive 25 mg of etanercept plus methotrexate (combination-therapy group), methotrexate alone, or placebo for 39 weeks (double-blind phase). Patients who had qualifying responses at week 39 of the double-blind phase had all treatment withdrawn at that time and were followed to week 65 (treatment-withdrawal phase). The primary end point was the proportion of patients with sustained remission in the double-blind phase.

RESULTS

Of 306 patients enrolled, 193 underwent randomization in the double-blind phase; 131 qualified for the treatment-withdrawal phase. More patients in the combination-therapy group than in the methotrexate-alone group or the placebo group met the criterion for the primary end point (40 of 63 [63%] vs. 26 of 65 [40%] and 15 of 65 [23%], respectively; $P=0.009$ for combination therapy vs. methotrexate alone; $P<0.001$ for combination therapy vs. placebo). At 65 weeks, 28 patients (44%) who had received combination therapy, 19 (29%) who had received methotrexate alone, and 15 (23%) who had received placebo were in remission ($P=0.10$ for combination therapy vs. methotrexate alone; $P=0.02$ for combination therapy vs. placebo; $P=0.55$ for methotrexate alone vs. placebo). No significant between-group differences were observed in radiographic progression of disease. Serious adverse events were reported in 3 patients (5%) in the combination-therapy group, 2 (3%) in the methotrexate-alone group, and 2 (3%) in the placebo group.

CONCLUSIONS

In patients with early rheumatoid arthritis who had a remission while receiving full-dose etanercept-plus-methotrexate therapy, continuing combination therapy at a reduced dose resulted in better disease control than switching to methotrexate alone or placebo, but no significant difference was observed in radiographic progression. (Funded by Pfizer; ClinicalTrials.gov number, NCT00913458.)

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THE DURATION OF DISEASE ACTIVITY IN persons with rheumatoid arthritis is an important factor influencing joint destruction and functional disability.^{1,2} Joint damage frequently begins within weeks or months after the onset of symptoms and is detectable on radiographs within 2 years.^{3,4} Evidence indicates that early aggressive treatment results in greater improvement than therapy initiated later in the disease course.⁵⁻⁸ Clinical remission, or at least low disease activity, is a critical treatment target in early rheumatoid arthritis, since control of inflammatory processes may limit structural damage and functional impairment.⁹

High rates of clinical remission, as well as significant improvements in radiographic and functional outcomes, have been observed in patients with early rheumatoid arthritis who were treated with the combination of an anti-tumor necrosis factor (TNF) agent and the conventional disease-modifying antirheumatic drug methotrexate.¹⁰⁻¹⁶ Remission is achieved most rapidly with biologic agents, and remission early in the course of disease is associated with a long-term benefit.¹⁷⁻¹⁹ However, relatively few studies have investigated whether remission achieved with such therapy can be maintained after the dose is reduced or the drug is discontinued, and the patients who may be the best candidates for reduction or withdrawal of therapy have not been identified.^{10,11,20-25} Reduced-dose regimens, step-down therapy, and treatment-free periods are often desirable to address patient preferences, long-term safety concerns, and the cost burden of biologic therapy. The three-phase Productivity and Remission in a Randomized Controlled Trial of Etanercept vs. Standard of Care in Early Rheumatoid Arthritis (PRIZE) was designed to evaluate the efficacy of etanercept (Enbrel, Pfizer), a fully human, soluble TNF receptor, plus methotrexate, in inducing and maintaining clinical remission in patients with early, moderate-to-severe rheumatoid arthritis and to determine the effect of treatment reduction or withdrawal on outcomes.

METHODS

PATIENTS

Adults with rheumatoid arthritis²⁶ were eligible for enrollment in the initial, open-label phase if they had moderate-to-severe disease activity (Disease Activity Score for 28-joint counts [DAS28]

of more than 3.2 [on a scale from 0 to 9.4, with higher scores indicating more severe disease]), an onset of symptoms within 12 months before enrollment, no prior exposure to methotrexate or biologic agents, and paid employment or unpaid but measurable work (e.g., caring for a family and home). Other disease-modifying antirheumatic drugs were allowed after specified washout periods, and oral glucocorticoids were permitted in stable doses (≤ 10 mg of prednisone or prednisone equivalent per day) for 4 weeks before screening and until week 26 of the open-label phase. Tapering of the latter agents was initiated by week 26, with complete withdrawal by week 39. All patients provided written informed consent before participation in the study.

STUDY DESIGN

This three-phase study was conducted at 57 centers in Europe and Asia between October 20, 2009, and December 17, 2012 (Fig. 1). Patients who were enrolled in the initial, open-label induction phase received subcutaneous injections of 50 mg of etanercept plus oral methotrexate weekly for 52 weeks. Methotrexate was initiated at a dose of 10 mg per week (minimum required dose); the dose was adjusted at the investigator's discretion during the first 8 weeks to a maximum dose of 25 mg per week (see Table S1 in the Supplementary Appendix, available with the full text of this article at NEJM.org). Patients who did not meet the criterion for low disease activity (DAS28 ≤ 3.2) at week 13 or week 26 of the open-label phase were required to receive glucocorticoids as rescue medication unless those drugs were contraindicated or the patients had unacceptable side effects (Table S1 in the Supplementary Appendix). Patients who did not meet the criterion for low disease activity at week 39 and remission (DAS28 < 2.6) at week 52 of the open-label phase were considered not to have had a response and were withdrawn from the study.

Patients who met the criteria for response in the open-label phase (i.e., patients who had a DAS28 ≤ 3.2 at week 39 and a DAS28 < 2.6 at week 52) were eligible for enrollment in the 39-week, randomized, double-blind phase. At week 0 of the double-blind phase, patients who had had a response in the open-label phase were randomly assigned through a centralized system, in a 1:1:1 ratio, to one of three treatment groups: a group that received etanercept at a dose of 25 mg, admin-

istered as a subcutaneous injection, plus oral methotrexate (combination-therapy group); a group that received a placebo subcutaneous injection plus oral methotrexate (methotrexate-alone group); or a group that received a placebo subcutaneous injection plus oral placebo capsules (placebo group). Glucocorticoid rescue therapy was required in patients who did not meet the criterion for low disease activity at week 4 or week 12 of the double-blind phase. At the first visit after each of those visits (i.e., at week 12 or week 24, respectively) or at the final visit of the double-blind phase (at week 39), patients who did not meet the criterion for a response (i.e., those who had a DAS28 >3.2) were withdrawn from the study (and were classified at subsequent visits as not having had a response). Patients who did have a response (i.e., patients with a DAS28 ≤ 3.2) at week 39 had the study drugs withdrawn and were observed through week 65. Etanercept and placebo injections were stopped at week 39; methotrexate and placebo capsules were tapered over the course of 2 to 4 weeks. Patients and investigators remained unaware of the study-group assignments until the end of the study (week 65).

STUDY OVERSIGHT

The institutional review board or ethics committee at each participating center approved the study protocol (which is available at NEJM.org). The study was conducted in accordance with the ethical principles of the Declaration of Helsinki and the Good Clinical Practice guidelines of the International Conference on Harmonisation.

The study was funded by Pfizer, and representatives of Pfizer designed the study, collected the data from the study centers, and performed the data analyses. All the authors had full access to all the study data, interpreted the data, and collaborated on the writing of the manuscript. Editorial and medical writing support was provided by Engage Scientific Solutions and was funded by Pfizer. All the authors made the decision to submit the manuscript for publication, approved the final submitted version, and vouch for the completeness and accuracy of the data and analyses and for the fidelity of the study to the protocol.

EVALUATIONS

The primary efficacy end point was the percentage of patients with sustained remission, defined as a DAS28 of less than 2.6 at weeks 24 and 39

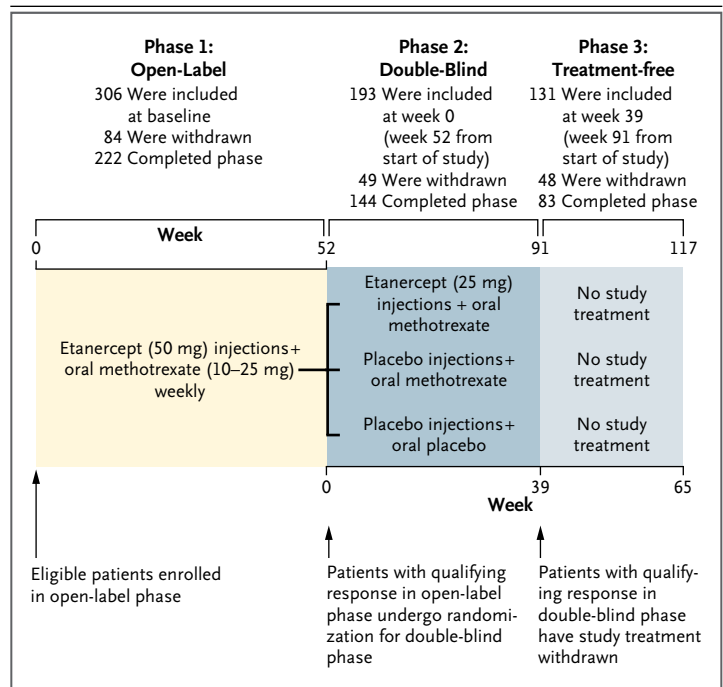


Figure 1. Study Design and Patient Disposition.

Patients with rheumatoid arthritis were eligible for enrollment in the initial 52-week open-label phase if they had moderate-to-severe disease activity (Disease Activity Score for 28-joint counts [DAS28] of more than 3.2 [range, 0 to 9.4, with higher scores indicating more severe disease]), an onset of symptoms within 12 months before enrollment, no prior exposure to methotrexate or biologic agents, and paid employment or unpaid but measurable work. Patients who met the criteria for a response in the open-label phase (i.e., patients who had a DAS28 ≤ 3.2 at week 39 and a DAS28 <2.6 at week 52) were eligible for enrollment in the 39-week, randomized, double-blind phase. Patients who had a response (i.e., DAS28 ≤ 3.2) at week 39 of the double-blind phase had the study drugs withdrawn and were observed through week 65.

of the double-blind phase, with no glucocorticoids administered between weeks 0 and 12. Secondary end points included remission according to the DAS28 criterion (DAS28 <2.6); remission according to the American College of Rheumatology (ACR) and European League against Rheumatism (EULAR) Boolean-based definition (i.e., tender-joint count, based on 28 joints, of 0 or 1; a swollen-joint count, based on 28 joints, of 0 or 1; a C-reactive protein level of 1 mg per deciliter or less; and a patient global assessment score of 1 or less, on a scale from 0 to 10, with higher scores indicating greater disease activity); low disease activity (DAS28 ≤ 3.2); ACR20, ACR50, ACR70, and ACR90 responses (20%, 50%, 70%, and 90% reduction, respectively, in the number of tender and swollen joints and improvement in

three other ACR core set variables); and a normal score (≤ 0.5) on the Health Assessment Questionnaire–Disability Index (HAQ-DI, on which scores range from 0, indicating no disability, to 3, indicating complete disability). Changes from baseline in DAS28 through the double-blind and treatment-withdrawal phases were also assessed (Table S1 in the Supplementary Appendix).

Radiographs of the hands, wrists, and feet were obtained at baseline in the open-label phase and at weeks 0 and 39 of the double-blind phase (or at the time of early withdrawal if withdrawal occurred 4 months or more after the baseline or week 0 assessment). A central reader, who was unaware of the study-group assignments, assessed the radiographs and assigned them a score according to the van der Heijde modification of the total Sharp score (modified total Sharp score). This score, which ranges from 0 to 448 (with higher scores indicating greater joint damage), quantifies erosions on a scale from 0 to 280 and joint-space narrowing on a scale from 0 to 168. A rate of progression of 0.5 units or less per year on the modified total Sharp score was considered to indicate nonprogression) and was evaluated as a secondary end point.

STATISTICAL ANALYSIS

We estimated that with a sample of 55 patients in each group in the randomized, double-blind phase, the study would have at least 90% power to detect a 30% difference in sustained remission rates between the combination-therapy group and the placebo group, at a 5% level of significance (two-sided test). Given a 1:1:1 randomization ratio, 165 patients had to undergo randomization in this phase. With the assumption that 55% of the patients would meet the criterion for a response at week 52, an initial enrollment of 300 patients was planned.

Analyses for the double-blind and treatment-withdrawal phases were performed in the modified intention-to-treat population, which included all patients who underwent at least one efficacy evaluation after randomization. Missing values for visits after discontinuation of the study drug were imputed with the use of the last-observation-carried-forward approach, with the last value before discontinuation carried through both phases. For the analysis of the proportion of patients who met the criterion for the primary end point, we used a logistic-regression model with treat-

ment as the only factor and with all patients who dropped out considered not to have had a response (i.e., with nonresponse imputation). A complete description of the study populations that were evaluated and the statistical analyses that were performed is provided in Table S1 in the Supplementary Appendix.

RESULTS

CHARACTERISTICS OF THE PATIENTS

The disposition of the patients through the course of the study is shown in Figure 1, and in Figure S1 in the Supplementary Appendix. Of the 306 enrolled patients, 222 completed the 52-week open-label phase. A total of 198 patients were eligible to enter the double-blind phase, and 193 patients were randomly assigned to receive a double-blind study regimen; 63 patients were assigned to the combination-therapy group, 65 to the methotrexate-alone group, and 65 to the placebo group. A total of 131 patients were followed in the treatment-withdrawal phase. Demographic and baseline disease characteristics were similar among the study groups at the start of the double-blind and treatment-withdrawal phases, except for prior glucocorticoid use and positivity for rheumatoid factor (Table 1). Summaries of the glucocorticoid rescue therapy administered and the weekly etanercept and methotrexate doses administered are provided in Tables S2 and S3, respectively, in the Supplementary Appendix.

EFFICACY

Response in Open-Label Phase

In the open-label phase, in which patients received 50 mg of etanercept plus methotrexate, 215 patients (70% of the 305 patients included in the analysis of this end point) had a remission according to the DAS28 criterion, 157 patients (51% of the 305 patients included in the analysis of this end point) had a remission according to ACR–EULAR Boolean-based criteria, and 201 patients (67% of the 302 patients included in the analysis of this end point) had a normal HAQ-DI score.

Response in Double-Blind Phase

Among patients who met the criteria for a response at the end of the open-label phase and who were randomly assigned to one of the three study groups for the double-blind phase, a significantly

Table 1. Baseline Characteristics of the Patients.*

Characteristic	Double-Blind Phase		Treatment-Withdrawal Phase		
	Combination Therapy (N = 63)	Methotrexate Alone (N = 65)	Combination Therapy (N = 53)	Methotrexate Alone (N = 46)	Placebo (N = 32)
Age — yr	49.6±15.0	47.7±14.1	48.9±15.3	46.8±15.3	51.4±17.0
Female sex — no. (%)	47 (75)	36 (55)	40 (75)	27 (59)	22 (69)
White race — no. (%)†	60 (95)	62 (95)	52 (98)	44 (96)	30 (94)
Body-mass index‡	25.8±4.6	25.5±4.1	25.9±4.7	25.6±4.1	25.7±3.9
Duration of symptomatic disease — mo	6.5±3.1	6.9±2.7	6.6±3.0	6.9±2.8	6.7±2.5
Time since diagnosis — mo	2.9±2.2	3.4±2.9	3.0±2.3	3.6±2.9	2.8±2.5
Positive for rheumatoid factor — no. (%)	35 (56)	41 (63)	31 (58)	30 (65)	12 (38)
Positive for anticyclic citrullinated peptide antibody — no. (%)	38 (60)	45 (69)	33 (62)	32 (70)	16 (50)
Prior use of DMARDs — no. (%)	8 (13)	8 (12)	8 (15)	7 (15)	9 (28)
Prior use of glucocorticoids — no. (%)	26 (41)	19 (29)	21 (40)	13 (28)	15 (47)
DAS28§	5.9±1.1	5.7±1.0	5.9±1.0	5.9±0.9	5.7±1.1
Simplified Disease Activity Index¶	1.7±1.5	1.7±1.6	2.2±2.5	2.8±3.4	4.8±6.5
Tender-joint count	13.5±6.0	13.4±6.5	13.8±6.0	13.9±6.5	12.6±7.2
Swollen-joint count	10.3±5.5	9.4±5.3	10.2±5.3	9.7±5.6	10.8±6.5
C-reactive protein — mg/liter**	16.4±25.3	11.3±12.6	16.4±25.6	10.7±10.2	15.7±16.3
HAQ-DI score††	1.2±0.7	1.1±0.6	1.2±0.6	1.2±0.5	1.1±0.6
Work productivity activity impairment (%)‡‡	8.6±11.0	10.0±15.9	7.9±12.9	9.8±13.1	16.8±19.2
Modified total Sharp score§§	8.1±13.4	8.5±16.0	—	—	—

* Plus-minus values are means ±SD. In the double-blind phase, patients in the combination-therapy group received 25 mg of etanercept weekly (a reduced dose from the 50 mg received in the preceding open-label phase) administered as a subcutaneous injection, plus oral methotrexate (with doses ranging from 10 mg to 25 mg weekly). Patients who had a qualifying response at week 39 in the double-blind period had the study drugs withdrawn (treatment-withdrawal phase) and were observed through week 65. There were no significant differences among the groups (at P<0.05) in the double-blind and treatment-withdrawal phases except for differences between the placebo group and the active-treatment groups with respect to positivity for rheumatoid factor during the treatment-withdrawal phase (P=0.046) and with respect to prior use of glucocorticoids during the double-blind phase (P=0.03). DMARD denotes disease-modifying antirheumatic drug.

† Race was self-reported.

‡ The body-mass index is the weight in kilograms divided by the square of the height in meters.

§ The Disease Activity Score for 28-joint counts (DAS28) ranges from 0 to 9.4, with higher scores indicating more severe disease.

¶ The Simplified Disease Activity Index ranges from 0.1 to 86.0, with higher scores indicating more active disease.

|| This assessment is based on an examination of 28 joints, with a larger number of affected joints indicating more severe disease.

** Normal values range from 0.1 to 10.0 mg per liter, with higher levels indicating a higher risk of disease.

†† Scores on the Health Assessment Questionnaire-Disability Index (HAQ-DI) range from 0, indicating no disability, to 3, indicating complete disability.

‡‡ Impairment in work productivity activity owing to rheumatoid arthritis was rated on a scale of 0 to 100%, with higher percentages indicating more impairment.

§§ The van der Heijde modification of the total Sharp score (modified total Sharp score), which ranges from 0 to 448 (with higher scores indicating greater joint damage), quantifies erosions on a scale from 0 to 280 and joint-space narrowing on a scale from 0 to 168. In the double-blind phase, this assessment was performed in 58 patients in the group receiving combination therapy, 56 patients in the group receiving methotrexate alone, and 49 patients in the group receiving placebo.

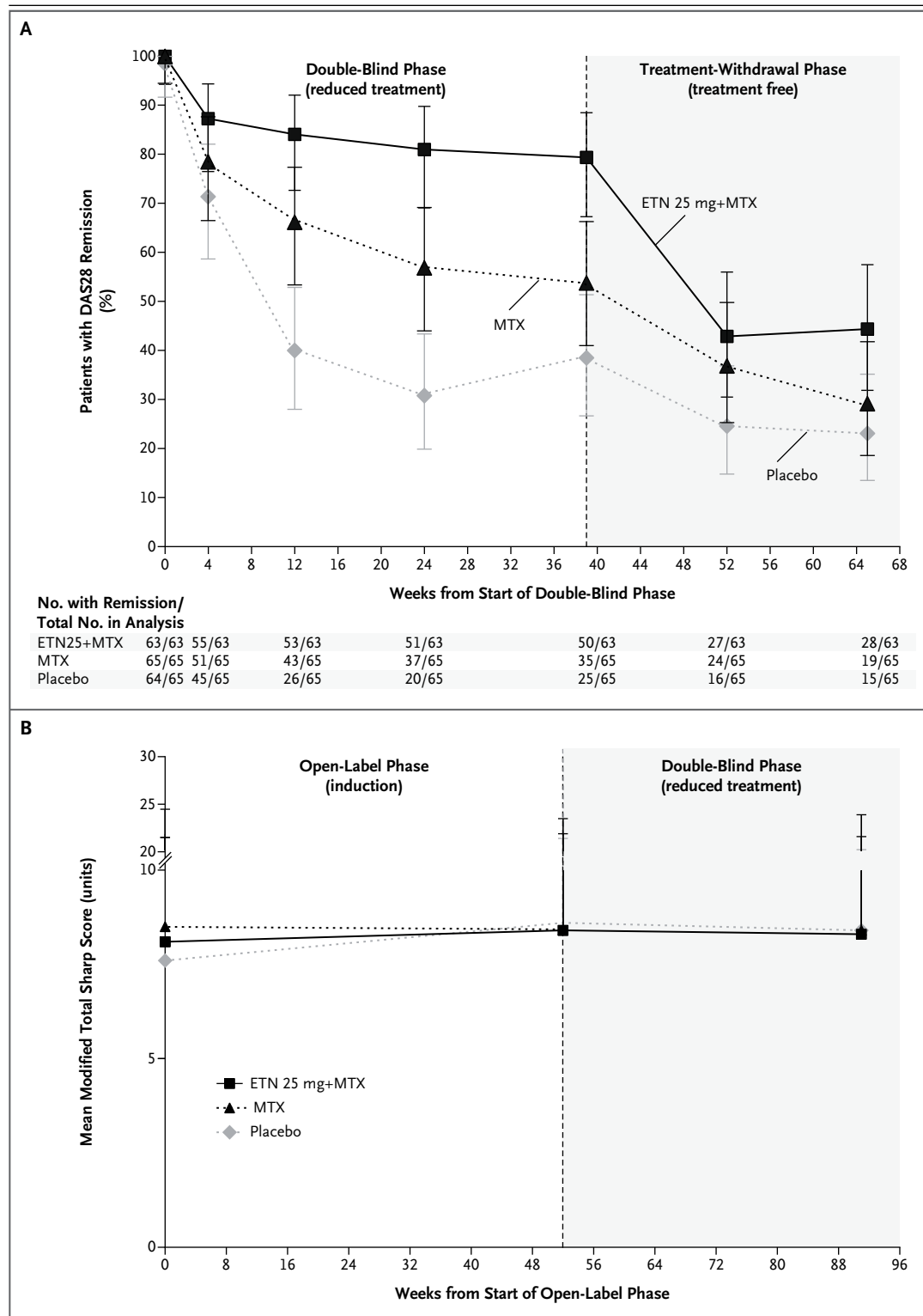
higher proportion of patients in the combination-therapy group than in the methotrexate-alone group or the placebo group met the criteria for the primary study end point of sustained remission (i.e., DAS28 <2.6 at weeks 24 and 39 of the double-blind phase, with no glucocorticoids administered between weeks 0 and 12): 63% versus 40% and 23%, respectively ($P=0.009$ for the comparison of combination therapy with methotrexate alone and $P<0.001$ for the comparison of combination therapy with placebo). Between weeks 0 and 39 of the double-blind phase, the proportion of patients who had a remission according to the DAS28 criterion, who had a remission according to ACR–EULAR Boolean-based criteria, and who had low disease activity (DAS28 ≤ 3.2) declined more slowly in the combination-therapy group than in the methotrexate-alone group or the placebo group (Fig. 2A, and Fig. S2A and S2B in the Supplementary Appendix). The differences between the combination-therapy group and the methotrexate-only and placebo groups in the proportions of patients who had a sustained DAS28 remission and low disease activity were significant from weeks 12 to 39 (Fig. 2A, and Fig. S2B in the Supplementary Appendix). Significant differences were also observed between the combination-therapy group and the placebo group in the proportion of patients who had a remission according to ACR–EULAR Boolean-based criteria and who had a normal HAQ-DI score (Fig. S2A and S2C in the Supplementary Appendix) from weeks 12 to 39. In addition, similar results were seen for patients meeting the criteria for ACR20, ACR50, ACR70, and ACR90 end points (Fig. S3 in the Supplementary Appendix). At week 39, a total of 79% of the patients in the combination-therapy group, 54% in the methotrexate-alone group, and 38% in the placebo group had a remission according to DAS28 criteria; 68%, 46%, and 23%, respectively, had a remission according to ACR–EULAR Boolean-based criteria; and 89%, 69%, and 46%, respectively met the criteria for low disease activity (Fig. 2A, and Fig. S2A and S2B in the Supplementary Appendix). At this time point, 78% of patients in the combination-therapy group had a normal HAQ-DI score, as compared with 72% in the methotrexate-alone group and 45% in the placebo group ($P<0.001$ for the comparison of combination therapy with placebo) (Fig. S2C in the Supplementary Appendix).

Figure 2 (facing page). DAS28 Remission and Radiographic Results.

Panel A shows the percentage of patients in each study group who met the criteria for remission according to DAS28 criteria (i.e., DAS28 <2.6) in the double-blind and treatment-withdrawal phases. $P=0.02$ at week 12 and $P<0.01$ at weeks 24 and 39 for combination therapy (etanercept [ETN] 25 mg + methotrexate [MTX]) versus MTX alone; $P<0.05$ at weeks 4, 52, and 65 and $P<0.001$ at weeks 12, 24, and 39 for combination therapy versus placebo; and $P<0.01$ at weeks 12 and 24 for MTX versus placebo. Panel B shows the mean scores on the van der Heijde modification of the total Sharp score (modified total Sharp score) over the course of the open-label and double-blind phases. This score, which ranges from 0 to 448 (with higher scores indicating greater joint damage) quantifies erosions on a scale from 0 to 280 and joint-space narrowing on a scale from 0 to 168. Percentages and continuous data in the double-blind and treatment-withdrawal phases are based on the modified intention-to-treat population, which included all patients who underwent at least one efficacy evaluation after randomization in the double-blind phase (with the last-observation-carried-forward approach used for missing values). I bars indicate 95% confidence intervals in Panel A and standard deviations in Panel B.

Response in Treatment-Withdrawal Phase

At week 65, in an analysis of the 193 patients in the modified intention-to-treat population who had participated in the double-blind phase (which included 132 patients who had a response [DAS28 ≤ 3.2] at week 39 and had treatment withdrawn and 61 patients who did not have a response or withdrew from the study for other reasons by week 39 and whose last observations were carried forward), a significantly higher proportion of patients in the combination-therapy group than in the placebo group were in remission according to DAS28 and ACR–EULAR Boolean-based criteria and had a normal HAQ-DI score (Fig. 2A, and Fig. S2A and S2C in the Supplementary Appendix). At week 65, the difference between the combination-therapy group and the methotrexate-alone group was no longer significant with respect to remission according to DAS28 criteria or with respect to a normal HAQ-DI score but remained significant with respect to remission according to ACR–EULAR Boolean-based criteria. Patients in the combination-therapy group maintained remission significantly longer after remission induction than did the patients in the methotrexate-alone group or the placebo group ($P=0.04$ for the comparison of combination therapy with metho-



trexate alone and $P < 0.001$ for the comparison of combination therapy with placebo) (Fig. S4 in the Supplementary Appendix).

Other Efficacy Outcomes

In the double-blind phase, the mean DAS28 score was significantly lower among patients receiving

Table 2. Clinical, Patient-Reported, and Radiographic Changes.*

Change and Outcome	Combination Therapy (N=63)	Methotrexate Alone (N=65)	Placebo (N=65)	P Value		
				Combination Therapy vs. Methotrexate Alone	Combination Therapy vs. Placebo	Methotrexate Alone vs. Placebo
Change from Baseline of Double-Blind Phase to End of Double-Blind Phase						
DAS28	0.3±0.2	1.0±0.2	2.0±0.2	0.008	<0.001	<0.001
Simplified Disease Activity Index	1.4±1.5	6.3±1.5	14.2±1.5	0.02	<0.001	<0.001
Tender-joint count	0.3±0.6	1.9±0.5	4.3±0.5	0.04	<0.001	0.003
Swollen-joint count	0.3±0.4	1.2±0.4	3.4±0.4	0.13	<0.001	<0.001
C-reactive protein — mg/liter	0.8±1.5	4.4±1.5	9.7±1.5	0.11	<0.001	0.01
HAQ-DI score	0.1±0.1	0.2±0.1	0.5±0.1	0.36	<0.001	0.001
Work productivity activity impairment (%)	−0.6±3.3	12.4±3.1	23.8±3.2	0.004	<0.001	0.01
Modified total Sharp score	0.1±0.1	−0.0±0.2	0.4±0.2	0.79	0.48	0.34
Change from Baseline of Double-Blind Phase to End of Treatment-Withdrawal Phase						
DAS28	1.4±0.2	1.8±0.2	2.3±0.2	0.21	0.003	0.07
Simplified Disease Activity Index	9.4±1.8	10.4±1.8	15.8±1.8	0.68	0.01	0.03
Tender-joint count	3.5±0.7	3.7±0.7	4.7±0.7	0.80	0.22	0.32
Swollen-joint count	2.3±0.5	2.3±0.5	3.7±0.5	0.99	0.07	0.07
C-reactive protein — mg/liter	5.2±1.8	5.2±1.8	10.2±1.8	0.99	0.0497	0.046
HAQ-DI score	0.2±0.1	0.3±0.1	0.5±0.1	0.64	0.01	0.04
Work productivity activity impairment (%)	11.2±3.6	19.0±3.5	28.5±3.5	0.12	<0.001	0.06
Modified total Sharp score	—	—	—			

* Values are mean adjusted changes ±SE. For clinical and patient-reported outcomes, the changes were assessed from the beginning of the double-blind phase to week 39 (end of double-blind phase) and week 65 (end of treatment-withdrawal phase) in the modified intention-to-treat population, which included all patients who underwent at least one efficacy evaluation after randomization in the double-blind phase (with the last-observation-carried-forward approach used for missing values). For the radiographic outcome (modified total Sharp score), the values are mean adjusted changes from baseline to the final on-therapy visit in the radiographic intention-to-treat population, which included all patients in the double-blind phase who received at least one dose of study drug and had at least one radiograph, at baseline and post-baseline of the double-blind phase, that could be evaluated.

combination therapy than among those receiving methotrexate alone or placebo at weeks 12, 24, and 39 ($P=0.003$, $P=0.01$, and $P=0.008$, respectively, for combination therapy vs. methotrexate alone and $P<0.001$ at all three time points for combination therapy vs. placebo) (Fig. S2D in the Supplementary Appendix). In an analysis of the patients in the modified intention-to-treat population who had participated in the double-blind phase, the mean DAS28 scores after all treatment was withdrawn in the final phase remained significantly lower in the combination-therapy group than in the placebo group at week 52 ($P=0.002$)

and week 65 ($P=0.003$) in the treatment-withdrawal phase (Table 2). The results of analyses of the patients in the modified intention-to-treat population who had participated in the double-blind phase and the patients who had a qualifying response at week 39 (i.e., DAS28 ≤ 3.2) and were followed during the treatment-withdrawal phase are shown in Figures S5, S6, and S7 and Table S4 in the Supplementary Appendix.

At study baseline, patients with early disease had minimal joint damage on radiography, with a mean (\pm SD) modified total Sharp score of 7.9 ± 12.7 (Table 1). No significant radiographic progression

Table 3. Safety Findings.*

Event	Double-Blind Phase			Treatment-Withdrawal Phase		
	Combination Therapy (N=63)	Methotrexate Alone (N=65)	Placebo (N=65)	Combination Therapy (N=53)	Methotrexate Alone (N=46)	Placebo (N=32)
	<i>number of patients (percent)</i>					
Any adverse event	38 (60)	34 (52)	32 (49)	15 (28)	6 (13)	5 (16)
Serious adverse event†	3 (5)	2 (3)	2 (3)	0	0	2 (6)
Adverse event leading to discontinuation	4 (6)	1 (2)	1 (2)	4 (8)	0	1 (3)
Adverse events of special interest						
Infection	17 (27)	13 (20)	19 (29)	3 (6)	2 (4)	2 (6)
Serious infection	1 (2)‡	0	0	0	0	1 (3)§
Cancer	0	0	0	0	1 (2)¶	0
Grade 3 elevation in liver enzymes						
Alanine aminotransferase	1 (2)	0	0	0	0	0
Total bilirubin	1 (2)	0	0	0	0	0

* The double-blind phase lasted for 39 weeks, and the treatment-withdrawal phase for an additional 26 weeks. There were no deaths, nor did any of the following adverse events of special interest occur: opportunistic infections, tuberculosis, or demyelinating disorders.

† In the double-blind phase, the serious adverse events were pericarditis, ear-canal stenosis (postoperative), bacterial pyelonephritis, and cystocele in the combination-therapy group; femoral neck fracture and headache in the methotrexate-alone group; and anal fissure and rheumatoid arthritis in the placebo group. In the treatment-withdrawal phase, the serious adverse events were oral infection and vasculitis in the placebo group. Table S6 in the Supplementary Appendix shows all the serious adverse events observed in the study.

‡ This involved a case of bacterial pyelonephritis, which resulted in the patient's withdrawal from the study.

§ This involved a case of oral infection, for which the patient was hospitalized; the infection subsequently resolved.

¶ This patient had basal-cell carcinoma.

of disease was seen in any study group at the end of the double-blind phase, and no significant between-group differences were found (Table 2 and Fig. 2B, and Table S5 in the Supplementary Appendix).

SAFETY

A summary of safety findings across the three study phases is provided in Table 3. Serious adverse events were reported in 9% of patients in the open-label phase; in 5%, 3%, and 3% of the patients in the combination-therapy group, methotrexate-alone group, and placebo group, respectively, in the double-blind phase; and in 0%, 0%, and 6% of the patients in the three groups, respectively, in the treatment-withdrawal phase (Table 3, and Table S6 in the Supplementary Appendix).

DISCUSSION

PRIZE had a three-phase design (treatment induction, dose reduction, and treatment withdrawal) to address the following clinical question: does

biologic therapy remain effective after reduction or withdrawal in patients with early, moderate-to-severe rheumatoid arthritis who have had a response to initial therapy? In the double-blind phase of the study, remissions according to DAS28 criteria and according to the more stringent ACR-EULAR Boolean-based criteria were more effectively maintained with a reduced dose of etanercept plus methotrexate than with withdrawal of the biologic agent. However, continuing methotrexate with or without etanercept, as compared with switching to placebo, did not affect radiographic progression. After withdrawal of all treatment, steep declines were observed in the rates of remission maintenance. In analyses that included all the patients who underwent randomization for the 39-week double-blind phase, at the end of 65 weeks (which included 26 weeks off treatment for the subgroup of patients who had a qualifying response at week 39), significantly more patients who had received the reduced-dose regimen were in remission according to the DAS28 criteria or the more stringent

ACR–EULAR Boolean-based criteria than patients who had received no therapy throughout the final two study phases. After treatment withdrawal, the difference between the two groups that had previously received active treatment (the combination-therapy group and the methotrexate-alone group) was no longer significant with respect to DAS28 remission but remained significant with respect to ACR–EULAR remission.

Several studies have explored whether clinical remission can be maintained after disease activity has been controlled if anti-TNF agents are reduced or discontinued in patients with early rheumatoid arthritis who have not previously received methotrexate^{10,11,20–24,27,28} or in patients with active rheumatoid arthritis despite methotrexate therapy.^{24,29–38} Results from the PRIZE double-blind phase are similar to those from the randomized, double-blind OPTIMA (Study of the Optimal Protocol for Methotrexate and Adalimumab Combination Therapy in Early Rheumatoid Arthritis) trial, in which adalimumab was withdrawn after a 26-week induction period in patients with early rheumatoid arthritis (mean disease duration, 3.9 months) who had not previously received methotrexate.²⁵ As in PRIZE, improvements in clinical and patient-reported outcomes significantly favored combination therapy with the anti-TNF agent plus methotrexate over methotrexate monotherapy at week 78, and between-group differences in radiographic progression were not significant. Some similarities are also apparent between our findings in PRIZE and those in PRESERVE (A Prospective, Randomized Etanercept Combined with MTX versus Full Dose Etanercept Combined with MTX versus MTX Alone for Effectiveness and Radiographic Endpoints in a Moderate Rheumatoid Arthritis Population),³⁷ which included patients with less severe but more long-standing disease (mean disease duration, 6.9 years) who had an inadequate response to methotrexate therapy. In the PRESERVE study, combination therapy with reduced-dose etanercept plus methotrexate was superior to methotrexate-alone in maintaining remission. However, combination

therapy in the PRESERVE study was also superior to methotrexate alone in preventing radiographic progression — a finding that contrasts with the results of the PRIZE and OPTIMA studies. This contrast may be due to the methotrexate-resistant, longer-standing, more moderate disease in the PRESERVE study. In PRIZE, little radiographic damage was seen at baseline, and no evidence of progression was observed after treatment reduction or withdrawal.

Our study has several limitations. First, the initial 52-week phase had an open-label, remission-induction design. However, remission rates in the open-label phase of this trial were similar to those observed among patients with early disease in two randomized, controlled studies.^{18,39} Second, our study involved primarily patients who had received no previous treatment, and the findings from this study population may not be generalizable to patients with later, treated disease. Finally, given that the induction, maintenance, and withdrawal phases of PRIZE were limited to 52, 39, and 26 weeks, respectively, results should not be extrapolated beyond this temporal context.

In conclusion, findings from our study suggest that after induction of remission or low disease activity with early, aggressive treatment, a reduction in or withdrawal of biologic therapy may be reasonable in some patients, particularly those who have sustained remission according to ACR–EULAR Boolean-based criteria. Such an approach would address possible concerns about the safety of long-term drug exposure and the economic burden of therapy but would require vigilant monitoring for increases in disease activity, functional impairment, or radiographic progression, which would signal the need for prompt retreatment.

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