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The PREMIER Study

A Multicenter, Randomized, Double-Blind Clinical Trial of Combination Therapy With Adalimumab Plus Methotrexate Versus Methotrexate Alone or Adalimumab Alone in Patients With Early, Aggressive Rheumatoid Arthritis Who Had Not Had Previous Methotrexate Treatment

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Objective. **To compare the efficacy and safety of adalimumab plus methotrexate (MTX) versus MTX monotherapy or adalimumab monotherapy in patients with early, aggressive rheumatoid arthritis (RA) who had not previously received MTX treatment.**

Methods. **This was a 2-year, multicenter, double-blind, active comparator–controlled study of 799 RA patients with active disease of <3 years' duration who had never been treated with MTX. Treatments included adalimumab 40 mg subcutaneously every other week plus oral MTX, adalimumab 40 mg subcutaneously every other week, or weekly oral MTX. Co-primary end points at year 1 were American College of Rheumatology 50% improvement (ACR50) and mean change from baseline in the modified total Sharp score.**

Results. **Combination therapy was superior to both MTX and adalimumab monotherapy in all outcomes measured. At year 1, more patients receiving combination therapy exhibited an ACR50 response (62%) than did patients who received MTX or adalimumab monotherapy (46% and 41%, respectively; both $P < 0.001$). Similar superiority of combination therapy was seen in ACR20, ACR70, and ACR90 response rates at 1 and 2 years. There was significantly less radiographic progression ($P \leq 0.002$) among patients in the combination treatment arm at both year 1 and year 2 (1.3 and 1.9 Sharp units, respectively) than in patients in the MTX arm (5.7 and 10.4 Sharp units) or the adalimumab arm (3.0 and 5.5 Sharp units). After 2 years of treatment, 49% of patients receiving combination therapy exhibited disease remission (28-joint Disease Activity Score <2.6), and 49% exhibited a major clinical response (ACR70 response for at least 6 continuous months), rates approximately twice those found**

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among patients receiving either monotherapy. The adverse event profiles were comparable in all 3 groups.

Conclusion. **In this population of patients with early, aggressive RA, combination therapy with adalimumab plus MTX was significantly superior to either MTX alone or adalimumab alone in improving signs and symptoms of disease, inhibiting radiographic progression, and effecting clinical remission.**

Rheumatoid arthritis (RA) is a chronic inflammatory disorder characterized by progressive inflammatory synovitis and destruction of articular cartilage and marginal bone (1). Joint erosions can be seen within 6 months of disease onset in the majority of patients, and occur more rapidly in the first year compared with late disease (2,3). Although most conventional disease-modifying antirheumatic drug (DMARD) therapies have been shown to slow joint destruction, radiographic progression does not stop (3–9). Historical studies have demonstrated that moderate disability within 2 years of diagnosis is not uncommon, and after 10 years, up to 30% of patients may be unable to work (10,11). Remission rarely occurs (5,12).

There is little evidence that current therapies can reverse the sequelae of RA once they occur. Radiographic damage progresses in a linear manner after the first year, and if radiographic repair occurs, it is uncommon (13). Improvement in disability, as measured by Health Assessment Questionnaire (HAQ) disability index (DI) scores (14), can be demonstrated in the short term with DMARD therapy, but the magnitude of this improvement is substantially greater in patients with early disease compared with those whose disease is more advanced (15–20). Longitudinal studies of RA patients show that there is a progressive decline in HAQ scores with time (17,21). In patients with late disease, disability correlates with radiographic evidence of joint damage (9,11,22). Like radiographic progression, disability is also progressive, and once joint damage has occurred and patients have become disabled, there is a low likelihood of full recovery (10,23).

Early intervention that prevents irreversible damage would appear to offer the best opportunities for achievement of favorable outcomes in patients with early, aggressive RA. In early intervention studies in which radiographic progression has been measured, this therapeutic window can be as short as months (24–27). In addition to early therapy, combination treatment, rather than monotherapy, has been shown to result in more favorable short-term and long-term outcomes (24,28–30). This has been shown with traditional DMARDs as well as with biologic therapies (31,32). Although few studies have investigated outcomes with a 5–10-year horizon, extrapolation of findings in short-term (1–2-year) studies suggests that early, aggressive combination treatment has the highest likelihood of preventing the long-term sequelae of RA. No single study has compared the efficacy of anti–tumor necrosis factor (anti-TNF) therapy alone, MTX therapy alone, or the combination of MTX and anti-TNF therapy in patients with early RA who had never been treated with MTX. The present study was undertaken to compare the efficacy of early intervention with combination therapy (adalimumab plus MTX) versus either MTX monotherapy or adalimumab monotherapy in patients with early RA.

PATIENTS AND METHODS

This clinical trial, termed the PREMIER study, was sponsored by Abbott Laboratories and conducted at 133 investigational sites (11 in Australia, 85 in Europe, and 37 in North America). PREMIER study investigators are listed in Appendix A. An independent data safety monitoring board, composed of external medical expert consultants, reviewed the safety and progress of the study regularly. A central institutional review board or independent ethics committee at each participating site approved the study, and all patients provided written informed consent.

To be eligible for the study, patients had to be 18 years of age or older and had to have disease that fulfilled the American College of Rheumatology (ACR; formerly, the American Rheumatism Association) 1987 revised criteria for the classification of RA (33), with a disease duration of <3 years. In addition, they had to have had ≥ 8 swollen joints, ≥ 10 tender joints, and an erythrocyte sedimentation rate of ≥ 28 mm/hour or C-reactive protein (CRP) concentration of ≥ 1.5 mg/dl, and had to either be rheumatoid factor positive or have had at least 1 joint erosion. Patients who had received treatment with MTX, cyclophosphamide, cyclosporine, azathioprine, or >2 other DMARDs were excluded. Patients were screened for tuberculosis (TB) prior to receiving study drug (with a purified protein derivative [PPD] at North American and Australian sites and by chest radiography at European sites). Patients who were, in the investigators' opinions, at high risk for TB were allowed to enroll in the study and take concomitant isoniazid (INH; up to 300 mg/day).

The study was a multicenter, randomized, double-blind, active comparator–controlled, phase III clinical trial. Patients were randomized to 1 of 3 treatment groups: adalimumab 40 mg subcutaneously every other week plus weekly oral MTX (20 mg/week); adalimumab 40 mg subcutaneously every other week (adalimumab plus placebo); or weekly oral MTX (MTX plus placebo). Hence, all patients received an injection (adalimumab or placebo) and an oral medication (MTX or placebo). In addition, all patients received concomitant folic acid at a dosage of 5–10 mg/week. The study included a screening period, as well as a 4-week washout

period for patients taking other DMARDs. A blinded, 2-year treatment period was chosen to more completely assess anticipated treatment effects over time.

For patients in whom response according to the ACR 20% improvement criteria (ACR20) (34) was not achieved at week 16 or later, the protocol mandated that the injectable study medication (adalimumab or placebo) be increased to weekly dosing after the dosage of the oral study medication (MTX or placebo) had been optimized. Dosage escalation was permitted at week 16 or later, but "de-escalation" back to every-other-week injectable drug was not permitted. For patients randomized to receive MTX monotherapy, this decrease in the dosing interval resulted in a dosage escalation of placebo, and for those randomized to receive either combination therapy or adalimumab monotherapy, this resulted in a dosage escalation of adalimumab.

MTX was initiated at a dosage of 7.5 mg/week for the first 4 weeks of the study. If the MTX was well-tolerated and the patient continued to have any swollen or tender joints, the dosage was increased to 15 mg/week during weeks 4–8, and to 20 mg/week at week 9. In cases of typical MTX toxicities (e.g., increased aspartate transaminase or alanine transaminase, or gastrointestinal adverse effects), the MTX dosage could be reduced to as low as 7.5 mg/week. If MTX had to be reduced to <7.5 mg/week, the patient was withdrawn from the study.

The co-primary efficacy end points at year 1 were 1) the percentage of patients in whom an ACR50 response was achieved (35) and 2) the mean change from baseline in the modified total Sharp score (36), comparing the combination therapy group versus the MTX monotherapy group. An ACR50 response was chosen as a primary end point to reflect the expectations of achieving a higher magnitude of clinical improvement now seen with the use of TNF inhibitors, which were not available when the ACR definition of improvement was developed. The ACR50 was defined in a manner analogous to the ACR definition of improvement (34,35,37). Patients were considered to have achieved an ACR50 response if the following 3 criteria were met: 1) ≥50% improvement from baseline in the tender joint count; 2) ≥50% improvement from baseline in the swollen joint count; and 3) ≥50% improvement from baseline in at least 3 of the following 5 parameters: patient's assessment of pain, patient's global assessment of disease activity, physician's global assessment of disease activity, patient's assessment of physical function (HAQ DI), and acute-phase reactant value (CRP).

ACR responses were calculated using an intention-to-treat analysis, for which patients who discontinued the study prior to reaching the end point were considered to be nonresponders. The study had 80% power to detect a difference of at least 13% in ACR response rates between adalimumab plus MTX combination therapy and MTX monotherapy.

Change from baseline in the modified total Sharp score was used to evaluate inhibition of progression of joint structural damage. The maximum possible value for the total Sharp score was 398 (38). Single-emulsion radiographs of the hands (posteroanterior view) and feet (anteroposterior view) were obtained and digitized for blinded reading. Four readers with no knowledge of the treatment allocations were used for this study, with 2 of these readers reviewing the radiographs of each patient and assessing joint erosions (0–5 scale) and joint space narrowing (0–4 scale), using the modified total Sharp score. During the readings, a computer randomly displayed patient images. Images from multiple time points were displayed simultaneously to allow for comparative assessment, and the readers were blinded with regard to the time point at which the displayed images had been obtained.

Additional secondary efficacy end points included the percentage of patients in whom clinical remission was achieved (defined as a 28-joint Disease Activity Score [DAS28] [39] of <2.6), improvement in physical function (as measured by the change from baseline in the HAQ DI), percentage of patients in whom an ACR20, ACR50, ACR70, or ACR90 response was achieved at year 2, change from baseline in the modified total Sharp score at year 2, and maintained clinical response through 104 weeks, defined as an ACR70 response for ≥6 continuous months (4,17,34,35,37,40,41).

Safety assessments, including the monitoring of adverse events (AEs) and measurements of laboratory parameters, were carried out at regular intervals during the course of the study. AEs that were recorded as "serious" were those that met regulatory guidance or required prolonged hospitalization, were life-threatening or resulted in death, caused significant or permanent disability, or in the opinion of the investigator, were significant medical events.

Statistical analyses for dichotomous variables were conducted using Pearson's chi-square test for ACR response and the Mann-Whitney U test for radiographic progression. All statistical tests were 2-sided. *P* values less than 0.05 were considered significant. All patients who were randomized and received at least 1 injection of study medication were included in the efficacy and safety analyses.

RESULTS

Demographic and baseline clinical characteristics of the patients reflected a population with early RA and were comparable among the 3 treatment groups. In each treatment group, the mean duration of RA at baseline was <1 year. Moreover, 57% of the study patients had had RA for <6 months. Similar percentages of patients in each treatment group had previously received treatment with a DMARD (other than MTX). Among all patients who previously took DMARDs, 41% had received antimalarial agents, and 39% had received sulfasalazine. Approximately one-third of patients in each treatment group were taking corticosteroids at baseline. The mean corticosteroid dosage (prednisone equivalent) was 6.7 mg/day in the combination treatment arm, 6.7 mg/day in the adalimumab monotherapy arm, and 6.4 mg/day in the MTX monotherapy arm. There were small, statistically significant baseline differences among treatment groups in the HAQ DI ($P = 0.012$), patient's global assessment of disease activity ($P = 0.048$), patient's assessment of pain ($P = 0.041$), and joint erosion score ($P = 0.030$). Mean baseline total Sharp score and joint space narrowing scores were higher in the MTX monotherapy arm than in either of the adalimumab

Table 1. Baseline characteristics according to treatment group*

	Adalimumab plus MTX (n = 268)	Adalimumab monotherapy (n = 274)	MTX monotherapy (n = 257)
Demographic characteristics			
Age, years	51.9 ± 14.0	52.1 ± 13.5	52.0 ± 13.1
No. (%) female/male	193 (72.0)/75 (28.0)	212 (77.4)/62 (22.6)	190 (73.9)/67 (26.1)
Clinical characteristics			
Years of RA	0.7 ± 0.8	0.7 ± 0.8	0.8 ± 0.9
Years of RA, no. (%)			
0.0–0.5	156 (58.2)	160 (58.4)	138 (53.7)
0.5–1.0	42 (15.7)	40 (14.6)	37 (14.4)
1.0–2.0	41 (15.3)	42 (15.3)	42 (16.3)
2.0–3.0	27 (10.1)	26 (9.5)	36 (14.0)
>3.0	2 (0.7)	5 (1.8)	4 (1.6)
Previously took DMARDs, no. (%)	87 (32.5)	91 (33.2)	81 (31.5)
Taking corticosteroids, no. (%)	96 (35.8)	100 (36.5)	91 (35.4)
Tender joint count, 0–68	30.7 ± 14.2	31.8 ± 13.6	32.3 ± 14.3
Swollen joint count, 0–66	21.1 ± 11.2	21.8 ± 10.5	22.1 ± 11.7
C-reactive protein, mg/dl	3.9 ± 4.2	4.1 ± 3.9	4.0 ± 4.0
HAQ DI†	1.5 ± 0.6	1.6 ± 0.6	1.5 ± 0.6
Physician's global assessment of disease activity, 100-mm VAS†	65.1 ± 17.6	67.6 ± 18.6	65.6 ± 17.7
Patient's global assessment of disease activity, 100-mm VAS	66.8 ± 22.1	67.8 ± 23.3	63.0 ± 25.0
Patient's assessment of pain, 100-mm VAS†	62.5 ± 21.3	64.6 ± 23.6	59.6 ± 24.3
DAS28	6.3 ± 0.9	6.4 ± 0.9	6.3 ± 0.9
Radiographic findings‡			
Modified TSS	18.1 ± 20.1	18.8 ± 19.0	21.9 ± 22.2
Erosion score†	11.0 ± 12.3	11.3 ± 11.3	13.6 ± 13.6
Joint space narrowing score	7.1 ± 9.6	7.5 ± 9.4	8.2 ± 10.7
Estimated annual TSS progression, TSS duration of RA	25.6	26.7	27.4

* Except where indicated otherwise, values are the mean ± SD. RA = rheumatoid arthritis; DMARDs = disease-modifying antirheumatic drugs; HAQ = Health Assessment Questionnaire; DI = disability index; VAS = visual analog scale; DAS28 = 28-joint Disease Activity Score; TSS = total Sharp score.
† $P < 0.05$ among treatment arms.
‡ n = 267 in the adalimumab plus methotrexate (MTX) group, 271 in the adalimumab monotherapy group, and 251 in the MTX monotherapy group.

arms, but these differences did not reach statistical significance. In post hoc analyses, adjustment for these baseline imbalances had no effect on the statistical significance of the differences at end point among the 3 treatment arms. Comparably small numbers of patients had no erosions at baseline (7% of patients in the combination therapy group, 6% in the adalimumab group, and 5% in MTX group).

A total of 799 patients not previously treated with MTX were enrolled in the study, and 539 completed 2 years of treatment. Significantly more patients who received combination therapy (75.7% [203 patients]) completed the 2-year, double-blind treatment period, compared with patients who received monotherapy with either adalimumab (60.9% [167 patients]) or MTX (65.8% [169 patients]) ($P < 0.001$ across treatment arms). A total of 32 patients in the combination therapy group (11.9%), 26 patients in the adalimumab monotherapy group (9.5%), and 19 patients in the MTX monotherapy group (7.4%) withdrew because of an adverse event, but these differences were not statistically significant ($P = 0.21$). Only 13 patients in the combination therapy group (4.9%) withdrew as a result of lack of efficacy, versus 52 (19.0%) in the adalimumab monotherapy group and 46 (17.9%) in the MTX monotherapy group.

ACR response. Following 1 year of treatment, an ACR50 response (the primary end point) had been achieved in 62% of patients who had received combination therapy, compared with 41% of patients who had received adalimumab monotherapy and 46% of patients who had received MTX monotherapy ($P < 0.001$ for both comparison treatments versus combination therapy) (Figure 1). There was no statistically significant difference between the adalimumab and MTX monotherapy treatment groups. At year 2, ACR50 responses were sustained in the combination treatment group, and continued to be clinically and statistically superior to

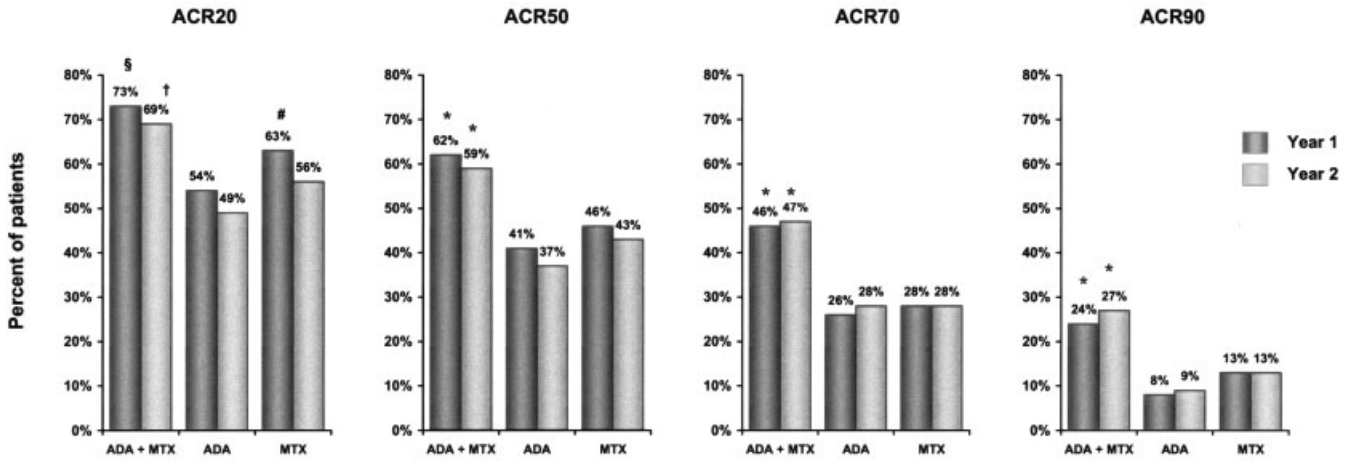

Figure 1. American College of Rheumatology 20% response (ACR20), ACR50, ACR70, and ACR90 at years 1 and 2, by treatment group. § = $P < 0.001$ versus adalimumab (ADA) alone and $P = 0.022$ versus methotrexate (MTX) alone; † = $P < 0.001$ versus ADA alone and $P = 0.002$ versus MTX alone; # = $P = 0.043$ versus ADA alone; ∗ = $P < 0.001$ versus ADA alone and versus MTX alone.

responses in both the adalimumab and MTX monotherapy treatment groups ($P < 0.001$). Similar statistically significant patterns were observed for ACR20, ACR70, and ACR90 responses.

Radiographic progression. There was significantly less radiographic disease progression at 6 months, 1 year, and 2 years among patients who had received combination therapy (Figure 2) compared with those in either monotherapy arm. At year 1, patients treated with combination therapy had a mean increase in total Sharp score (a co-primary end point) of 1.3 Sharp units, compared with 3.0 units in those receiving adalimumab monotherapy ($P = 0.002$), and 5.7 units in those receiving MTX monotherapy ($P < 0.001$). At year 2, patients treated with adalimumab plus MTX continued to have significantly less radiographic progression (mean change 1.9 Sharp units) compared with those treated with either adalimumab monotherapy (5.5 units) or MTX monotherapy (10.4 units) ($P < 0.001$ for both comparisons). Adjustment by linear regression for the higher mean baseline erosion score among patients in the MTX arm did not alter the statistical findings. Although ACR responses were comparable in the 2 monotherapy arms, there was significantly less progression in the adalimumab monotherapy arm compared with the MTX monotherapy arm at 6 months (2.1 versus 3.5), 1 year (3.0 versus 5.7), and 2 years (5.5 versus 10.4) (all $P <$ 0.001).

There was significantly less change from baseline in erosion scores among patients receiving combination therapy at 6 months, 1 year, and 2 years (0.6, 0.8, and 1.0, respectively) than in patients receiving adalimumab monotherapy (1.3, 1.7, and 3.0, respectively) or MTX monotherapy (2.4, 3.7, and 6.4, respectively) ($P < 0.001$ for all comparisons). Similarly, the combination therapy group had significantly less change in joint space narrowing scores at 6 months, 1 year, and 2 years (0.2, 0.5, and 0.9, respectively) compared with patients receiving adalimumab monotherapy (0.8, 1.3, and 2.6, respectively) or MTX monotherapy (1.0, 2.0, and 4.0, respectively) ($P < 0.001$ for all comparisons).

During year 2, radiographic progression among patients who were treated with MTX monotherapy occurred at approximately the same rate as seen during

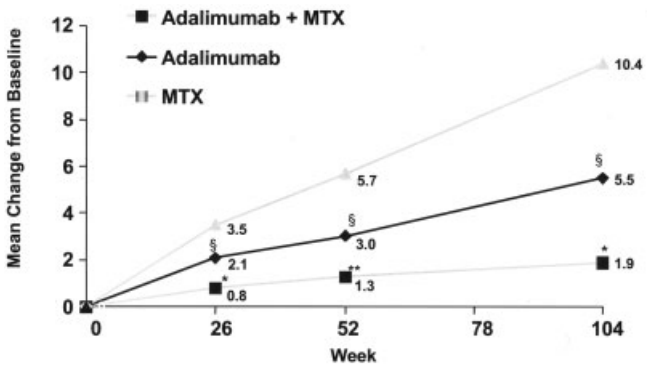

Figure 2. Mean change from baseline in total Sharp scores over time, by treatment group. ∗ = $P < 0.001$ versus adalimumab alone and versus methotrexate (MTX) alone; § = $P < 0.001$ versus MTX alone; ∗∗ = $P = 0.002$ versus adalimumab alone and $P < 0.001$ versus MTX alone.

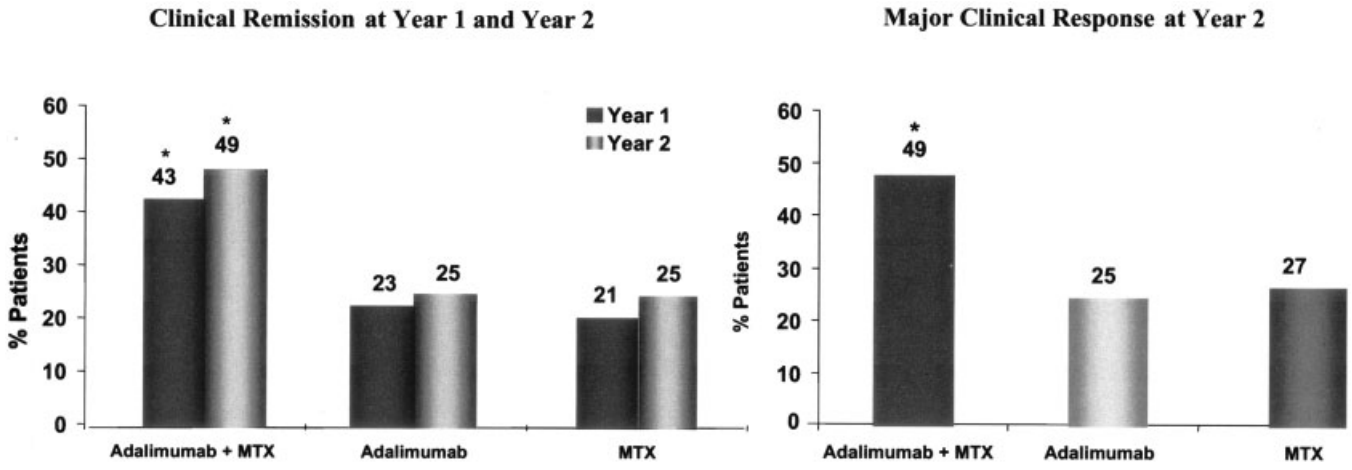

Figure 3. Clinical remission (28-joint Disease Activity Score <2.6) at year 1 and year 2 and major clinical response (ACR70 response achieved and sustained continuously for ≥6 months) at year 2, by treatment group. * = $P < 0.001$ versus adalimumab alone and versus MTX alone. See Figure 1 for definitions.

year 1 (5.7 Sharp units from baseline to year 1 and 4.7 units from year 1 to year 2), while patients who received combination therapy had less than half the progression in year 2 than they had experienced in year 1 (1.3 units from baseline to year 1 and 0.6 units from year 1 to year 2).

The percentage of patients with no radiographic progression (change in total Sharp score ≤0.5 from baseline) was higher in the combination arm (64% at year 1 and 61% at year 2) than in the adalimumab monotherapy arm (51% and 45%; $P < 0.01$) or the MTX monotherapy arm (37% and 34%; $P < 0.01$). The difference in these percentages between the adalimumab monotherapy arm and MTX monotherapy arm was also statistically significant ($P < 0.01$).

Clinical remission. *DAS28.* Following 1 year of treatment, clinical remission (defined as DAS28 <2.6) (32) was achieved in 43% of patients receiving combination therapy, compared with 23% of patients receiving adalimumab monotherapy and 21% of patients receiving MTX monotherapy (both $P < 0.001$) (Figure 3). Similarly, following 2 years of treatment, clinical remission had been attained in 49% of patients receiving combination therapy, compared with 25% of patients receiving adalimumab monotherapy and 25% of patients who had received MTX monotherapy (both $P < 0.001$).

Major clinical response. After 2 years of treatment, 49% of patients receiving combination therapy exhibited a major clinical response, compared with 25% and 27% of patients, respectively, in the adalimumab and MTX monotherapy groups ($P < 0.001$).

HAQ DI. Following 1 year of treatment, patients receiving combination therapy had significantly greater improvement in the HAQ DI (mean ± SD −1.1 ± 0.6 units) compared with patients receiving adalimumab monotherapy (−0.8 ± 0.7 units; $P = 0.002$) and MTX monotherapy (−0.8 ± 0.6 units; $P < 0.001$). Improvement in the HAQ DI at year 2 among patients in the combination treatment arm (−1.0 ± 0.7 units) was statistically superior to that among patients in the MTX monotherapy arm (−0.9 ± 0.6 units; $P < 0.05$) but not the adalimumab monotherapy arm (−0.9 ± 0.7 units; $P = 0.058$). At year 2, significantly more patients in the combination therapy arm (72%) had achieved improvement in the HAQ DI of ≥0.22 units from baseline compared with the adalimumab monotherapy arm (58%) or the MTX monotherapy arm (63%) (both $P < 0.05$).Thirty-three percent of patients in the combination therapy arm compared with 19% in each of the monotherapy arms had HAQ DI scores of 0 at year 2 ($P < 0.001$).

Dosage adjustment. As described above, the dosage of MTX could be adjusted if toxicity or intolerance developed. The mean MTX dosage was 16.9 mg/week in the MTX monotherapy group and 16.3 mg/week in the combination therapy group. At year 1, 69% of patients in the combination therapy arm and 82% of patients in the MTX monotherapy arm were taking MTX at a dosage of 20 mg weekly. At year 2, 64% of patients in the combination therapy arm and 80% of patients in the MTX monotherapy arm were taking 20 mg of MTX weekly.

Table 2. Percentage of patients who became responders at years 1 and 2 after increasing the frequency of injections to weekly*

	Adalimumab plus MTX		Adalimumab monotherapy		MTX monotherapy (placebo injection)	
	Year 1	Year 2	Year 1	Year 2	Year 1	Year 2
ACR20	1	1	2	3	4	4
ACR50	1	1	1	0	1	2
DAS28 <2.6	1	1	0	0	0	1
Major clinical response†	0		1		1	

* ACR20 = American College of Rheumatology 20% improvement (see Table 1 for other definitions).
† ACR70 improvement for ≥6 continuous months.

Increased dosing with injectable study medication (adalimumab or placebo) to weekly injections was mandated by the study protocol for those patients in whom an ACR20 response had not been achieved in 2 consecutive visits after week 16. Twenty-nine of 268 patients in the combination therapy group (11%), 69 of 274 patients in the adalimumab monotherapy group (25%), and 52 of 257 patients in the MTX monotherapy group (20%) underwent dosage escalation during year 1. Of these dosage escalators, 12 of 29 in the combination therapy arm (41%), 20 of 69 in the adalimumab alone arm (29%), and 25 of 52 in the MTX alone arm (48%) had not achieved an ACR20 response any time prior to dosage escalation. Weekly dosing had a minimal effect on improving efficacy parameters in these patients (Table 2). Similar results were seen following dosage escalation in patients who had achieved a prior ACR response (data not shown). The percentage of patients who had not achieved an ACR20 response and became ACR50 responders after dosage escalation in year 1 was similar in those receiving active injectable drug (1% of the patients in the combination therapy arm and 1% in the adalimumab monotherapy arm) and those receiving injectable placebo drug (1% in the MTX monotherapy arm). Thus, there was no impact on the primary efficacy end point. Similarly, dosage escalation had a minimal effect on the percentage of patients who achieved an ACR20 response, ACR70 response, DAS28 remission, or major clinical response.

Safety. The percentages of patients with reported AEs were comparable in the combination therapy, adalimumab monotherapy, and MTX monotherapy groups (262 of 268 patients [97.8%], 262 of 274 patients [95.6%], and 245 of 257 patients [95.3%], respectively). No statistically significant differences were observed across treatment groups in the percentages of patients who experienced serious AEs ($P = 0.192$).

The overall rate of infectious AEs did not differ significantly among the 3 treatment groups (123, 110, and 119 events per 100 patient-years in the combination therapy, adalimumab monotherapy, and MTX monotherapy groups, respectively) (Table 3). The rate of serious infections in the adalimumab monotherapy group was significantly lower than that in the combination treatment group, but not significantly different compared with the MTX monotherapy group. In the combination therapy arm, 9 serious infections were reported, including 3 pulmonary infections (including 1 case of pleural TB) and 1 case each of sinus infection, wound infection, septic arthritis, infected hygroma, cellulitis, and urinary tract infection. In the adalimumab monotherapy arm, the 3 serious infections included 1

Table 3. Patients with treatment-emergent adverse events*

Event	Adalimumab plus MTX (n = 268, patient-years = 482)	Adalimumab monotherapy (n = 274, patient-years = 435)	MTX monotherapy (n = 257, patient-years = 429)
Serious adverse events	18.5	21.1	15.9
Infectious adverse events	123	110	119
Serious infections	2.9†	0.7	1.6
Tuberculosis	0.2	0	0
Malignancies	0.4	0.9	0.9
Lymphoma	0	0	0.2
Demyelination	0	0	0

* Values are the number of events per 100 patient-years. MTX = methotrexate.
† $P < 0.05$ versus adalimumab monotherapy.

case each of pneumonia, cellulitis, and septic arthritis. In the MTX monotherapy arm, the 7 serious infections consisted of 2 cases of pneumonia and 1 each of septic arthritis, sinusitis, abscess, bacteremia, and parotitis. There was 1 death from infection in the MTX monotherapy arm, in a 58-year-old man in whom pneumonia developed 25 days after MTX treatment began.

Thirty patients in the study were identified by the investigator as being at high risk for TB and received prophylactic therapy (primarily INH) prior to the initiation of study medication. One patient in the adalimumab plus MTX treatment group developed pleural TB. She was a 78-year-old woman in Belgium who had no PPD test performed, had a negative chest radiography result at baseline, and did not receive INH prophylaxis. She recovered with treatment. No other opportunistic infections were seen.

One patient in the adalimumab monotherapy group developed a lupus-like reaction with positive antinuclear antibody and was withdrawn from the study. No demyelinating events were observed.

Ten malignancies were found among patients in the study. Two were observed in the combination treatment arm (ovarian and prostate), 4 in patients who had received adalimumab monotherapy (breast, colon, multiple myeloma, and metastatic cancer with unknown primary site), and 4 in patients who had received MTX (lymphoma, melanoma, prostate, and breast).

The standardized mortality ratio (SMR) was calculated by using the World Health Organization mortality data for the US published in 1997, categorized by age and sex. Six patients died during the study: 1 patient in the combination treatment arm died (of ovarian cancer), 4 patients in the adalimumab monotherapy arm died (1 sudden death at home in a patient with chronic obstructive pulmonary disease and pulmonary hypertension, 1 died of metastatic liver cancer [unknown primary site], 1 died of metastatic colon cancer, and 1 died of liver failure [the patient had preexisting cirrhosis]), and 1 patient in the MTX monotherapy arm died (of pneumonia). The overall SMR in the PREMIER study was 0.463 (95% confidence interval 0.169–1.007).

DISCUSSION

The findings presented here demonstrate that combination therapy with adalimumab plus MTX was superior to either adalimumab monotherapy or MTX monotherapy in the treatment of adult patients with recently diagnosed moderate-to-severe RA not previously treated with MTX. The superiority with respect to ACR responses, inhibition of radiographic progression, improvement in the HAQ, and measures of clinical remission was seen after both 1 year and 2 years of therapy. Substantially more patients receiving combination therapy had no radiographic progression compared with those receiving MTX monotherapy.

This study confirms the effectiveness of combination therapy over monotherapy, as has been shown in other published studies (31,32,42–44). However, unlike the Trial of Etanercept and Methotrexate with Radiographic Patient Outcomes study (31), it was carried out in RA patients who had early, aggressive disease and had not previously been treated with MTX. Unlike the Early Rheumatoid Arthritis (etanercept monotherapy) (ERA) (44) and Active-Controlled Study of Patients Receiving Infliximab for the Treatment of Rheumatoid Arthritis of Early Onset (32) studies, the PREMIER study included 3 treatment arms (combination therapy, anti-TNF therapy alone, and MTX alone, in patients with early, rapidly progressive RA studied for 2 years).

DAS remission, defined as a DAS28 of <2.6, represents very low disease activity (40). With the DAS28 as a measure of clinical remission, nearly half of the patients (49%) who had received combination therapy achieved a DAS28 of <2.6 at 2 years, approximately twice the number in either monotherapy arm. As another measure of the magnitude of the response in the combination therapy arm, a maintained clinical response (defined in Food and Drug Administration [FDA] guidance as achieving an ACR70 response and maintaining it for ≥ 6 consecutive months) was achieved by 49% of the patients who received combination therapy. This percentage is also approximately twice the rate seen in patients who had received either adalimumab monotherapy (25%) or MTX monotherapy (27%).

An unusual finding at baseline was the magnitude of radiographic damage present in patients who had an average disease duration of <1 year. The mean baseline radiographic scores were numerically higher in the MTX arm than in either of the adalimumab arms, although this reached statistical significance only for erosion scores. However, the estimated duration of disease prior to study entry was slightly higher in the MTX arm (0.8 years) than the adalimumab arms (0.7 years for both), which could partly explain this difference.

The projected annual progression in the total Sharp score (calculated by dividing the baseline total Sharp score by the mean duration of disease at baseline) in this early RA population was 25.9 units, and was similar across all 3 treatment arms. This is significantly greater than the rate that has been estimated to take

place in an RA population treated with traditional DMARDs (4,8,45), and reflects a population with very aggressive disease. This is likely a result of the selection criterion that required the presence of rheumatoid factor or erosive disease at baseline. As such, this population is unique in that it represents a subset of patients with particularly aggressive RA who are at high risk for radiographic progression, and may not be generalizable to all patients with early RA. Sokka and Pincus have suggested that many patients followed up by rheumatologists may have disease that is less severe than that in patients studied in clinical trials (46). However, the results from this study demonstrate that in patients with early RA who are identified by the practicing rheumatologist as having active disease with evidence of aggressive radiographic progression, early use of combination therapy with a TNF inhibitor is appropriate.

Furthermore, blinded randomized controlled trials such as this do not necessarily follow the paradigm that a clinician might follow in managing a patient with RA since, during the course of a clinical trial, all RA treatments, except as noted, cannot be changed. In routine clinical practice, flares of disease would likely be managed by adjusting medication dosages or changing medications. In a randomized trial such as this one, such changes would mandate discontinuation because of protocol violation or treatment failure. Thus, there may be an underestimate of the benefits of a specific treatment in a controlled trial, because patients in clinical practice might be able to continue treatment with modest medication adjustments. In the conservative analysis used in this study, these patients were classified as nonresponders and were not further analyzed.

While the ACR, DAS28, and HAQ responses were all statistically similar between the adalimumab and MTX monotherapy arms in this study, there was significantly less radiographic progression among patients in the adalimumab monotherapy arm at both year 1 and year 2. This suggests that there may be separate mechanistic pathways, one that mediates improvement in signs and symptoms and is similarly responsive to either TNF inhibition or MTX therapy, and another that mediates joint damage and is more responsive to TNF inhibition than to MTX therapy. This observation is similar to that seen in the ERA trial, which compared MTX monotherapy with etanercept therapy, and in which ACR responses were similar between treatment arms, but with a trend toward less radiographic progression in the etanercept arm (44). However, combination therapy was not studied in that trial.

All treatments were generally safe and well-tolerated in this study, with rates and types of AEs similar across all 3 treatment groups and comparable with reported findings in controlled trials of other TNF antagonists (31,32,38,44). The rate of serious infections, defined as infectious events that met FDA criteria for seriousness (generally requiring hospitalization), was higher in the combination therapy arm than in the adalimumab monotherapy arm, but was not statistically different from that in the MTX treatment arm. However, the study was not powered to detect differences in uncommon events such as serious infections, which occurred at a rate of $<5\%$ in this study, and the results must be interpreted in this context. The actual rate of serious infections (2.9 events per 100 patient-years) was similar to rates reported in patients with early RA treated with etanercept (2.6 per 100 patient-years) but lower than the rates reported in patients with long-standing RA treated with either adalimumab or etanercept (4.8–6.0 per 100 patient-years) (38,42–44,47). While direct comparisons among different trials cannot be made with precision, these observations suggest that RA patients with early disease may have a lower rate of serious infections than patients with long-standing disease.

Important safety considerations with the use of TNF antagonists have been identified, including serious infections, opportunistic infections (including TB), malignancies, demyelinating disease, lupus-like reactions, and congestive heart failure (48–60). Cases of TB have been reported with all TNF antagonists and are believed to represent reactivation of latent disease (56,61–63). Screening prior to initiation of anti-TNF therapy is effective in identifying patients at risk and reducing the rate of TB reactivation, and is recommended by rheumatologists and health care authorities, including the Centers for Disease Control and Prevention (61,64). In the present study, there was 1 case of TB, in a patient who recovered with treatment, but no other opportunistic infections were seen. Higher rates of lymphoma have been seen in RA patients compared with the general population (60). In this study, there was 1 case of lymphoma in the MTX monotherapy arm, and none in the other treatment arms. One case of lupus-like reaction occurred in the combination treatment arm, and symptoms resolved when the study drug was discontinued. No cases of demyelination were observed.

This study demonstrates the magnitude of response that can be achieved in treating an early, MTX-naive RA population with aggressive combination therapy and establishes the superiority of combination therapy to either MTX monotherapy or adalimumab

monotherapy. Furthermore, the results of this study demonstrate that increasing the dosage of adalimumab from 40 mg every other week to 40 mg weekly in ACR nonresponders does not provide substantial additional measurable benefit to the patient, whether the adalimumab is taken alone or in combination with MTX. For those patients who are able to tolerate MTX, combination therapy provides substantial improvement over either adalimumab monotherapy or MTX monotherapy. For the patient with early, aggressive and erosive RA, treatment with combination therapy is superior to treatment with MTX alone.

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