Less Radiographic Progression with Adalimumab Plus Methotrexate Versus Methotrexate Monotherapy Across the Spectrum of Clinical Response in Early Rheumatoid Arthritis

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ABSTRACT. ***Objective.*** To determine the relationship between radiographic progression and clinical response for adalimumab plus methotrexate (MTX) versus either monotherapy in patients with early rheumatoid arthritis (RA) in the PREMIER study.

Methods. Patients with early RA who received adalimumab plus MTX (n = 240), adalimumab (n = 222), or MTX (n = 216) were grouped by American College of Rheumatology (ACR) response, 28-joint Disease Activity Score (DAS28), or remission-like state [tender joint count (TJC) = 0; DAS28 < 2.6; swollen joint count = 0; ACR100] at 26 and 104 weeks. Radiographic progression was assessed by cumulative probability plots, mean changes in total Sharp score (ΔTSS), and percentages of progressors (ΔTSS > 0.5).

Results. Across the spectrum of clinical outcomes, including ACR20 nonresponses and remission-like responses, therapy with adalimumab plus MTX permitted less radiographic progression at Weeks 26 and 104 than MTX monotherapy. Adalimumab monotherapy was generally intermediate. A strong, proportional relationship was observed between clinical response and radiographic efficacy only for MTX monotherapy. The monotherapies approximated the radiographic efficacy of adalimumab plus MTX only among remission-like responders, although progression was significantly greater with MTX monotherapy versus adalimumab plus MTX for patients with TJC = 0. Concurrent clinical (DAS28 < 2.6) and radiographic (ΔTSS ≤ 0.5) remission was significantly more frequent at Week 104 with adalimumab plus MTX (45%) than with adalimumab (25%) or MTX (18%) monotherapy.

Conclusion. In patients with early RA, adalimumab plus MTX resulted in less radiographic progression than MTX monotherapy across the spectrum of clinical response, including ACR20 nonresponses and remission-like responses. (J Rheumatol First Release April 15 2009; doi:10.3899/jrheum.081018)

Key Indexing Terms:
RHEUMATOID ARTHRITIS TUMOR NECROSIS FACTOR ANTAGONIST REMISSION
METHOTREXATE RADIOGRAPHIC PROGRESSION
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Rheumatologists often assume that if the signs and symptoms of rheumatoid arthritis (RA) are controlled, inflammatory joint damage will be controlled as well. This assumption is not entirely correct. Although the rate of joint damage in patients with RA has been found to correlate with the volume of synovitis[1,2], clinical assessments tend to underestimate the degree of synovitis, even in patients thought to be in remission[3]. Similarly, although radiographic progression is generally related to the level of clinical disease activity, degree of progression varies considerably from patient to patient[4,5]. Further, radiographic progression has been observed in patients who were in clinical remission, presumably because of undetected, residual synovitis[6]. These findings indicate that the rate of joint damage in a patient

with RA is not always accurately predicted by the clinical state.

Prevention of joint damage is a key goal in the management of patients with RA. When a patient with RA responds inadequately to methotrexate (MTX) monotherapy, a common next step is to treat with a tumor necrosis factor (TNF) antagonist, usually in combination with MTX. The initiation of combination therapy can be an important step for patients with recent-onset RA, because it has been demonstrated to provide superior clinical and radiographic efficacy compared with MTX or TNF antagonist monotherapies[7-12], and because early therapeutic efficacy can offer lasting structural and functional benefits[13-18].

In patients with early or established RA, mean radiographic progression for MTX-treated patients has been found to be greater for clinical nonresponders than for responders[7,19-21]. In contrast, treatment with infliximab plus MTX resulted in a low mean change in total Sharp score (ΔTSS), regardless of whether a clinical response had been achieved[7,10,18]. Similar findings have been reported for etanercept and MTX[22]. Thus, the radiographic efficacy of therapy with a TNF antagonist plus MTX, but not MTX monotherapy, appears to be relatively independent of the clinical response. Whether this difference between the 2 treatments (as observed for clinical nonresponders vs responders) exists across the entire spectrum of clinical response remains to be determined.

PREMIER was a 2-year, randomized, placebo-controlled trial of MTX-naive patients with early RA[11]. Patients in PREMIER were treated with MTX plus adalimumab, a fully human, anti-TNF monoclonal antibody, or with either agent alone. At baseline, patients had active inflammatory disease and aggressive joint destruction. Adalimumab plus MTX had superior clinical and radiographic efficacy from Week 26 onward. At Week 104, adalimumab plus MTX had induced a state of clinical remission [28-joint Disease Activity Score (DAS28) < 2.6] in 49% of patients, compared with 25% of those treated with either monotherapy. At Week 104, radiographic progression was least with adalimumab plus MTX, intermediate with adalimumab monotherapy, and greatest with MTX monotherapy[11].

The results of PREMIER did not indicate whether the superior radiographic efficacy of adalimumab plus MTX was entirely attributable to its superior clinical efficacy or involved an additional, independent effect. A similar question applies to adalimumab monotherapy. Of the randomized, placebo-controlled trials of TNF antagonists in patients with early RA[10-12,23], only PREMIER, with its 3 treatment arms, can fully address these questions. Therefore, radiographic outcomes in PREMIER were assessed in patients grouped according to their clinical outcomes, both early and late in the trial, using measures of clinical response and of clinical state. Results of this analysis are presented here.

MATERIALS AND METHODS

The PREMIER trial. PREMIER was a 2-year, randomized, double-blind, placebo-controlled Phase III trial of 799 MTX-naive patients with recent-onset RA (mean duration 0.7 yrs) who were treated with adalimumab 40 mg subcutaneously every other week, with weekly MTX, or with adalimumab plus MTX[11]. MTX dosages were rapidly increased to ≤ 20 mg/week. Stable dosages of nonsteroidal antiinflammatory drugs and stable low dosages of corticosteroids (≤ 10 mg of prednisone per day) were permitted during the trial. Protocol details have been reported[11].

Clinical efficacy assessments. Patients were seen regularly throughout the study for routine assessments that included the components of the American College of Rheumatology (ACR) response criteria[11,24]. Tender joint counts (TJC) and swollen joint counts (SJC) assessed 68 and 66 joints, respectively. DAS28 scores were determined using the C-reactive protein (CRP) formula[11,25].

Analysis cohorts. The present analysis included only those patients for whom ACR scores and radiographs were available at baseline and Week 26, baseline and Week 52, or baseline and Week 104. Patients without ACR scores, radiographs, or DAS28 scores at Week 26, Week 52, or Week 104 were excluded from analyses involving the missing measure for the respective timepoint. Week-52 data are presented only for the complete Week-52 cohort, and not for the individual clinical outcome groups (see below).

Clinical outcome groups. Patients who had the requisite radiographs and clinical measurements (see "Analysis cohorts") were classified post hoc according to whether they had achieved < 20%, ≥ 20%, ≥ 50%, or ≥ 70% improvements in the ACR score (< ACR20, ACR20, ACR50, or ACR70 response) from baseline to Week 26, Week 52, or Week 104; an ACR100 response (defined as no tender joints, no swollen joints, and 100% improvement in ≥ 3 of the other 5 ACR response criteria) from baseline to Week 104; TJC = 0 at Week 104; SJC = 0 at Week 104; and DAS28 ≥ 5.1, ≥ 3.2, ≥ 2.6, or < 1.6 at Week 104. Radiographic outcomes were analyzed for patient groups defined according to these clinical outcome thresholds.

Radiographic efficacy assessments. Radiographs were taken at baseline and at Weeks 26, 52, and 104. Radiographs were scored according to the modified Sharp scoring system, as described[11]. For each patient, the ΔTSS was calculated as the difference between the TSS at the followup visit and the TSS at baseline. Mean ΔTSS and percentage of patients with radiographic progression (ΔTSS > 0.5 vs baseline) were determined for patients grouped by the conventional categories of ACR response (< ACR20, ACR20, ACR50, and ACR70) at Weeks 26 and 104[11], and for patients with remission-like responses (TJC = 0, SJC = 0, DAS28 < 2.6, ACR100) at Week 104. Mean ΔTSS were also determined for patients grouped by nonoverlapping categories of ACR response (ACR20 to < 50, ACR50 to < 70, and ACR70 to < 100) and for patients grouped by nonoverlapping categories of Week-104 DAS28 score (≥ 5.1, < 5.1 to 3.2, < 3.2 to 2.6, < 2.6 to 1.6, < 1.6). Linear correlation coefficients (r) for Week-104 DAS28 scores versus ΔTSS from baseline to Week 104 were determined for the Week-104 analysis cohorts, by treatment received. Cumulative probability plots were generated to demonstrate the distribution of ΔTSS from baseline for all patients in a clinical outcome group.

Statistical analyses. Statistical significance was determined using Pearson's chi-squared test or the logistic regression method for the ACR response rates and the percentage of radiographic progressors (ΔTSS > 0.5), and the analysis of variance (ANOVA) method for mean ΔTSS. For comparison of rates of radiographic progression (TSS/disease duration since diagnosis) at baseline between treatment arms, the Kruskal-Wallis nonparametric ANOVA test was used. All statistical tests were 2-sided and considered significant at $\alpha = 0.05$. P values < 0.05 were considered statistically significant. To facilitate data interpretation, p values ≥ 0.05 and ≤ 0.10 are presented numerically but are not considered statistically significant. P values > 0.10 are not presented numerically and are indicated by NS (not significant).

RESULTS

Analysis cohorts. For our analysis of PREMIER, the Week-26, Week-52, and Week-104 analysis cohorts contained 213 (83%), 193 (75%), and 166 (65%), respectively, of the 257 patients randomized to receive MTX monotherapy; 222 (81%), 193 (70%), and 161 (59%), respectively, of the 274 patients randomized to receive adalimumab monotherapy; and 240 (90%), 217 (81%), and 199 (74%), respectively, of the 268 patients randomized to receive adalimumab plus MTX.

Baseline data. At baseline, the demographic characteristics and clinical measures of the Week-26, Week-52 (not shown), and Week-104 analysis cohorts were similar to the baseline values of the randomized cohorts from which they were derived (Table 1). The differences between treatment arms in baseline TSS were partially attributable to greater baseline disease duration in the MTX monotherapy group at randomization. The median rates of radiographic progression (ΔTSS/disease duration since diagnosis) at baseline were rapid and similar between treatment arms (Table 1). For patients receiving weekly MTX, either as monotherapy or with adalimumab, the mean MTX doses were 18.8 mg and 17.6 mg, respectively, for the Week-26 analysis cohorts on Week 26, and 17.8 mg and 16.9 mg, respectively, for the Week-104 analysis cohorts on Week 104. The corresponding median MTX doses were all 20 mg.

Arthritis outcomes overall. The Week-26 ACR20/50/70 response rates for patients who received at least 26 weeks of treatment were 79%/52%/29% for MTX monotherapy, 73%/48%/26% for adalimumab monotherapy (p = 0.097/NS/NS vs MTX monotherapy), and 82%/69%/49% for adalimumab plus MTX (p = NS/< 0.001/< 0.001 vs MTX monotherapy; p = 0.015/< 0.001/< 0.001 vs adalimumab monotherapy). For patients who received at least 52 weeks of treatment, the Week-52 ACR response rates were 83%/61%/36% for MTX monotherapy, 77%/58%/37% for adalimumab monotherapy (all p = NS vs MTX monotherapy), and 89%/75%/56% for adalimumab plus MTX (p = NS/= 0.002/< 0.001 vs MTX monotherapy; p = 0.002/< 0.001/< 0.001 vs adalimumab monotherapy). For patients who received 104 weeks of treatment, the Week-104 ACR response rates were 86%/66%/49% for MTX monotherapy, 81%/61%/47% for adalimumab monotherapy (all p = NS vs MTX monotherapy), and 92%/78%/62% for adalimumab plus MTX (p = 0.054/= 0.010/< 0.001 vs MTX monotherapy; p = 0.004/< 0.001/= 0.004 vs adalimumab monotherapy).

Overall radiographic outcomes. The mean ΔTSS values from baseline to Weeks 26, 52, or 104 for patients who received ≥ 26, ≥ 52, or 104 weeks of treatment, respectively, were 3.3, 4.4, and 6.4 for MTX monotherapy; 2.1, 3.0, and 4.8 for adalimumab monotherapy (p = 0.010, p = 0.039, and NS vs MTX monotherapy); and 0.6, 0.9, and 1.1 for

Table 1. Baseline data for intention-to-treat cohorts and Week-26 and Week-104 analysis cohorts.

	MTX monotherapy			Adalimumab plus MTX			Adalimumab monotherapy		
	ITT, n = 257	Week 26, n = 213	Week 104, n = 166	ITT, n = 268	Week 26, n = 240	Week 104, n = 199	ITT, n = 274	Week 26, n = 222	Week 104, n = 161
Age, yrs	52.0 (13.1)	52.2 (13.7)	52.6 (13.2)	51.9 (14.0)	51.7 (14.2)	51.4 (14.3)	52.1 (13.5)	51.5 (13.3)	52.3 (12.7)
Female, n (%)	190 (73.9)	159 (74.6)	123 (74.1)	193 (72.0)	172 (71.7)	144 (72.4)	212 (77.4)	170 (76.6)	123 (76.4)
Disease duration since diagnosis, yrs	0.84 (0.89)	0.82 (0.89)	0.83 (0.89)	0.72 (0.79)	0.73 (0.79)	0.73 (0.80)	0.73 (0.81)	0.70 (0.78)	0.70 (0.78)
Prior DMARD use, n (%)	81 (31.5)	64 (30.0)	51 (30.7)	87 (32.5)	74 (30.8)	62 (31.2)	91 (33.2)	75 (33.8)	56 (34.8)
Corticosteroid use, n (%)	91 (35.4)	73 (34.3)	57 (34.3)	96 (35.8)	86 (35.8)	74 (37.2)	100 (36.5)	83 (37.4)	60 (37.3)
RF-positive, n (%)	215 (84.0)	180 (84.9)	140 (84.8)	228 (85.1)	204 (85.0)	166 (83.4)	227 (83.5)	188 (84.7)	138 (85.7)
SJC (0-66)	22.1 (11.7)	22.2 (11.9)	23.2 (12.4)	21.1 (11.2)	21.2 (11.4)	21.3 (11.3)	21.8 (10.5)	21.6 (10.5)	21.2 (10.3)
TJC (0–68)	32.3 (14.3)	31.8 (14.0)	32.0 (14.1)	30.7 (14.2)	30.8 (14.3)	30.1 (14.2)	31.8 (13.6)	32.4 (13.8)	32.3 (13.7)
HAQ	1.5 (0.67)	1.5 (0.68)	1.5 (0.65)	1.5 (0.64)	1.5 (0.63)	1.4 (0.63)	1.6 (0.62)	1.6 (0.62)	1.6 (0.60)
DAS28	6.3 (0.9)	6.3 (0.9)	6.3 (0.9)	6.3 (0.9)	6.3 (0.9)	6.3 (0.9)	6.4 (0.9)	6.3 (0.9)	6.3 (0.9)
CRP, mg/dl	4.0 (4.0)	3.9 (4.0)	3.9 (4.1)	3.9 (4.2)	3.9 (4.2)	3.9 (4.1)	4.1 (3.9)	3.9 (3.7)	3.7 (3.5)
TSS	21.9 (22.2)	21.8 (22.4)	22.7 (23.0)	18.1 (20.1)	18.2 (20.3)	18.1 (20.7)	18.8 (19.0)	19.1 (18.7)	18.9 (19.4)
Erosion score	13.6 (13.5)	13.6 (13.6)	14.1 (14.0)	11.0 (12.3)	11.1 (12.7)	11.2 (13.0)	11.3 (11.3)	11.6 (11.5)	11.3 (11.6)
JSN score	8.2 (10.7)	8.1 (10.7)	8.6 (11.1)	7.1 (9.6)	7.1 (9.3)	7.0 (9.4)	7.5 (9.5)	7.5 (8.8)	7.6 (9.0)
Rate of TSS progression*	26.1	27.8	27.9	29.7	30.4	30.7	28.8	28.0	27.4

* Median of the individual values for (baseline TSS)/(disease duration since diagnosis). Values for the intention-to-treat cohorts are as reported[11]. Week 26 and Week 104 represent the cohorts of patients who completed 26 or 104 weeks of treatment, respectively. Values are mean (standard deviation) unless specified as n (%) or as median. CRP: C-reactive protein; DAS28: 28-joint Disease Activity Score; DMARD: disease modifying antirheumatic drug; HAQ: Health Assessment Questionnaire; ITT: intention-to-treat; JSN: joint space narrowing; MTX: methotrexate; RF: rheumatoid factor; SJC: swollen joint count; TJC: tender joint count; TSS: total Sharp score.

adalimumab plus MTX (all $p < 0.001$ vs MTX monotherapy; $p < 0.001$, $p = 0.002$, $p < 0.001$ vs adalimumab monotherapy). The median ΔTSS values from baseline to Weeks 26, 52, or 104 for these cohorts were 1.0, 2.0, and 2.3, respectively, for MTX monotherapy; 0.5, 0.5, and 1.0 for adalimumab monotherapy; and 0.0, 0.0, and 0.0 for adalimumab plus MTX. These clinical and radiographic outcome values were based on observed data and differ from those determined in the original intention-to-treat analysis of PREMIER[11].

Cumulative probability plots of radiographic progression by level of ACR response. For each category of ACR response (< ACR20, ACR20, ACR50, ACR70), the cumulative probability plot of the Week-26 ΔTSS was distributed further to the right for MTX monotherapy than for adalimumab plus MTX (Figure 1A). These differences were more pronounced in the Week-104 probability plots, suggesting that the ΔTSS increased more rapidly from Week 26 to 104 for MTX monotherapy than for adalimumab plus MTX (Figure 1B); analyses of the mean ΔTSS from Week 26 to 104 for the Week-104 completers were confirmatory (not shown). At Weeks 26 and 104, the curves for adalimumab monotherapy were distributed between those for the other 2 therapies, most clearly for the ACR20 nonresponders (i.e., < ACR20), and, to a lesser degree, for the ACR20 and ACR50 responders (Figures 1A and 1B). The probability plots for Week-52 completers (not shown) were intermediate and qualitatively similar to those for patients who completed 26 or 104 weeks of treatment.

Mean ΔTSS and frequency of radiographic progression by level of ACR response. The mean ΔTSS values were significantly smaller for MTX monotherapy than adalimumab plus MTX for each level of ACR response at Week 26 (except ACR70; Figure 2A) and Week 104 (Figure 2B). For adalimumab monotherapy, mean ΔTSS values were intermediate to those for the other 2 treatments, with a statistically significant difference from MTX monotherapy observed only for the < ACR20 responders (Figures 2A and 2B). Median values for the ΔTSS in the < ACR20/20/50/70 response categories were greatest for MTX monotherapy (4.3/1.0/1.0/0.5 at Week 26; 2.8/2.0/1.5/1.0 at Week 104); intermediate for adalimumab monotherapy (0.5/0.5/0.5/0.0 at Week 26; all 1.0 at Week 104); and lowest for adalimumab plus MTX (0.5/0.0/0.0/0.0 at Week 26; 0.3/0.0/0.0/0.0 at Week 104). For each category of ACR response, the percentages of patients with radiographic progression from baseline (ΔTSS > 0.5) were statistically significantly smaller — by approximately 50% at Week 104 — for patients who achieved the response with adalimumab plus MTX compared with MTX monotherapy (Table 2). The percentages of radiographic progressors were intermediate for adalimumab monotherapy, with significant differences from MTX monotherapy observed for the ACR20 and ACR50 responders at Week 26.

Mean ΔTSS by nonoverlapping categories of ACR response. For a more accurate assessment of the quantitative relationship between radiographic progression and clinical improvements in arthritis, the mean ΔTSS values at Week 104 were determined for patients grouped by 5 nonoverlapping (i.e., mutually exclusive) categories of ACR response at Week 104: < ACR20, ACR20 to < 50, ACR50 to < 70, ACR70 to < 100, and ACR100. Following 104 weeks of MTX monotherapy, a stepwise decrease was observed in mean ΔTSS for patients in the < ACR20 to ACR100 response groups, from 11.5 to 2.1 (Figure 3A). In contrast, following 104 weeks of therapy with adalimumab plus MTX, the mean ΔTSS was low for each nonoverlapping ACR response group: ~2.0 for the 3 groups < ACR70; 0.6 for the ACR70 to < 100 group; and 0.5 for ACR100 responders (Figure 3A). The ΔTSS values for adalimumab monotherapy did not demonstrate a stepwise decrease and were significantly less than the values for MTX monotherapy for the < ACR20 responders. For MTX monotherapy, but not for adalimumab plus MTX or adalimumab monotherapy, mean ΔTSS values were statistically significantly less for the ACR70 to < 100 and ACR100 groups, compared with the < ACR20 group (Figure 3A). Cumulative probability plots grouped by treatment demonstrated an ordered layering of the 5 curves for the respective nonoverlapping ACR response categories only for MTX monotherapy (not shown). Thus, these results reveal a strong proportional relationship between clinical and radiographic efficacy for MTX monotherapy but not for adalimumab plus MTX or adalimumab monotherapy.

Mean ΔTSS by nonoverlapping categories of disease activity. As a supplement to the preceding analysis, the mean ΔTSS at Week 104 were determined for patients grouped by their clinical states at Week 104, using 5 nonoverlapping categories of DAS28 score (ranging from DAS28 ≥ 5.1 to DAS28 < 1.6). The mean ΔTSS values for the DAS28 categories (Figure 3B) were distributed in patterns similar to those observed for the ACR response categories, allowing for some variation across the adalimumab groups (Figure 3A). A pronounced, statistically significant, declining-staircase configuration was observed only for MTX monotherapy. A subtle, less significant decline was observed for adalimumab plus MTX. Accordingly, linear correlation coefficients (r) for the relationships between Week-104 DAS28 scores and ΔTSS from baseline to Week 104 demonstrated a statistically significant relationship for MTX monotherapy ($r = 0.27$, slope = 2.48, $p < 0.001$) and not for adalimumab plus MTX ($r = 0.13$, slope = 0.46, $p = 0.07$) or adalimumab monotherapy ($r = 0.12$, slope = 0.90, p = NS). Thus, analyses of the mean ΔTSS yielded concordant results when patients were grouped by clinical response (ACR score) or disease activity (DAS28 score).

Radiographic progression in patients achieving remission-like responses. These findings suggested that synovitis

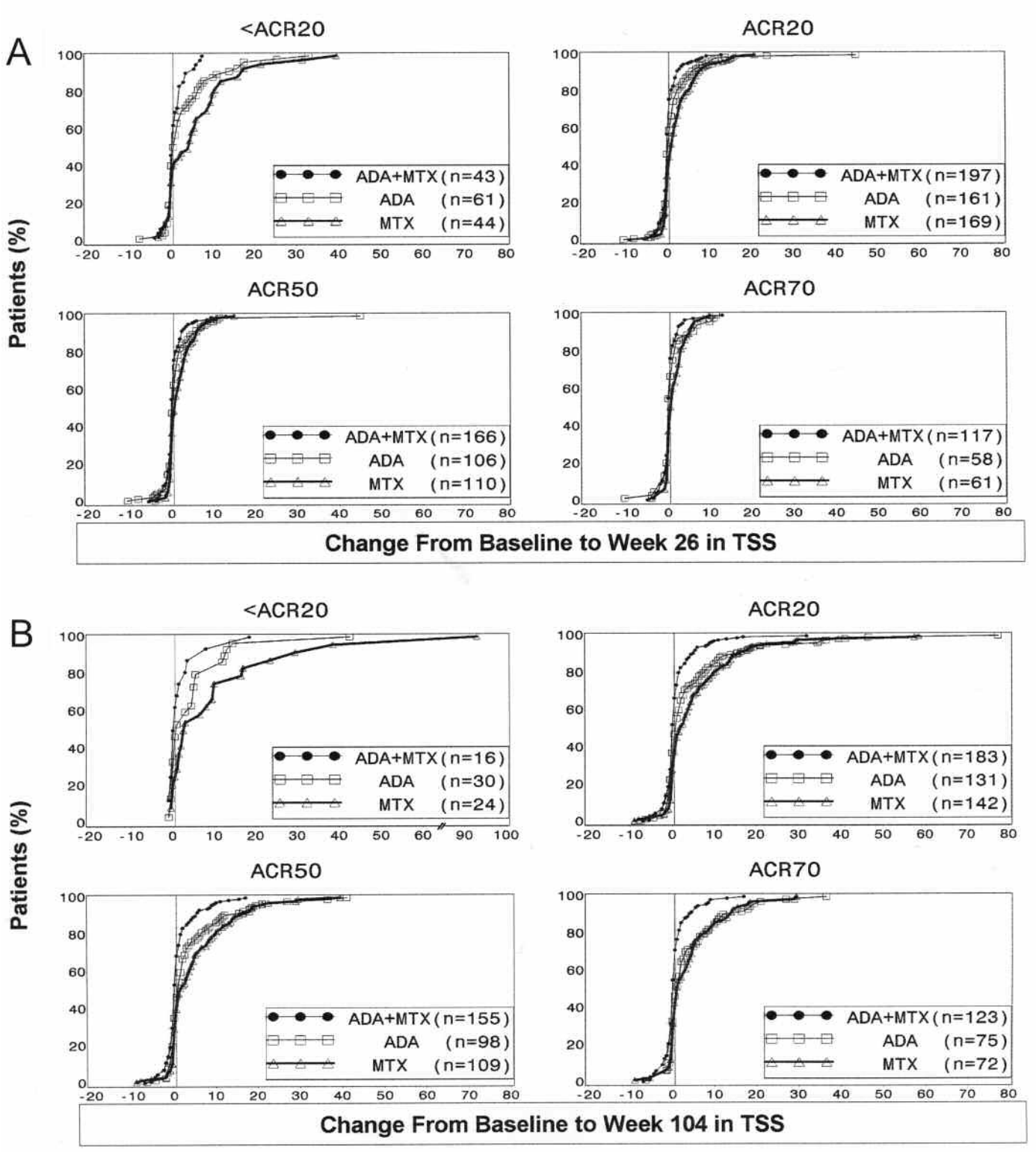

Figure 1. Radiographic progression by level of clinical response. Cumulative probability plots show changes (Δ) from baseline to Week 26 (A) or Week 104 (B) in total Sharp score (TSS) for patients in each ACR response group for each treatment. Percentage of patients with a particular ΔTSS is represented by y-axis distance between symbols for that ΔTSS and the next lowest ΔTSS. Vertical line at 0.5 on x-axis divides progressors (to the right) from nonprogressors. Patient numbers (n) are indicated in graphs for MTX monotherapy (MTX), adalimumab monotherapy (ADA), and adalimumab plus MTX (ADA plus MTX). In B, ΔTSS value for the final point in the < ACR20 curve for MTX monotherapy is 93.0.

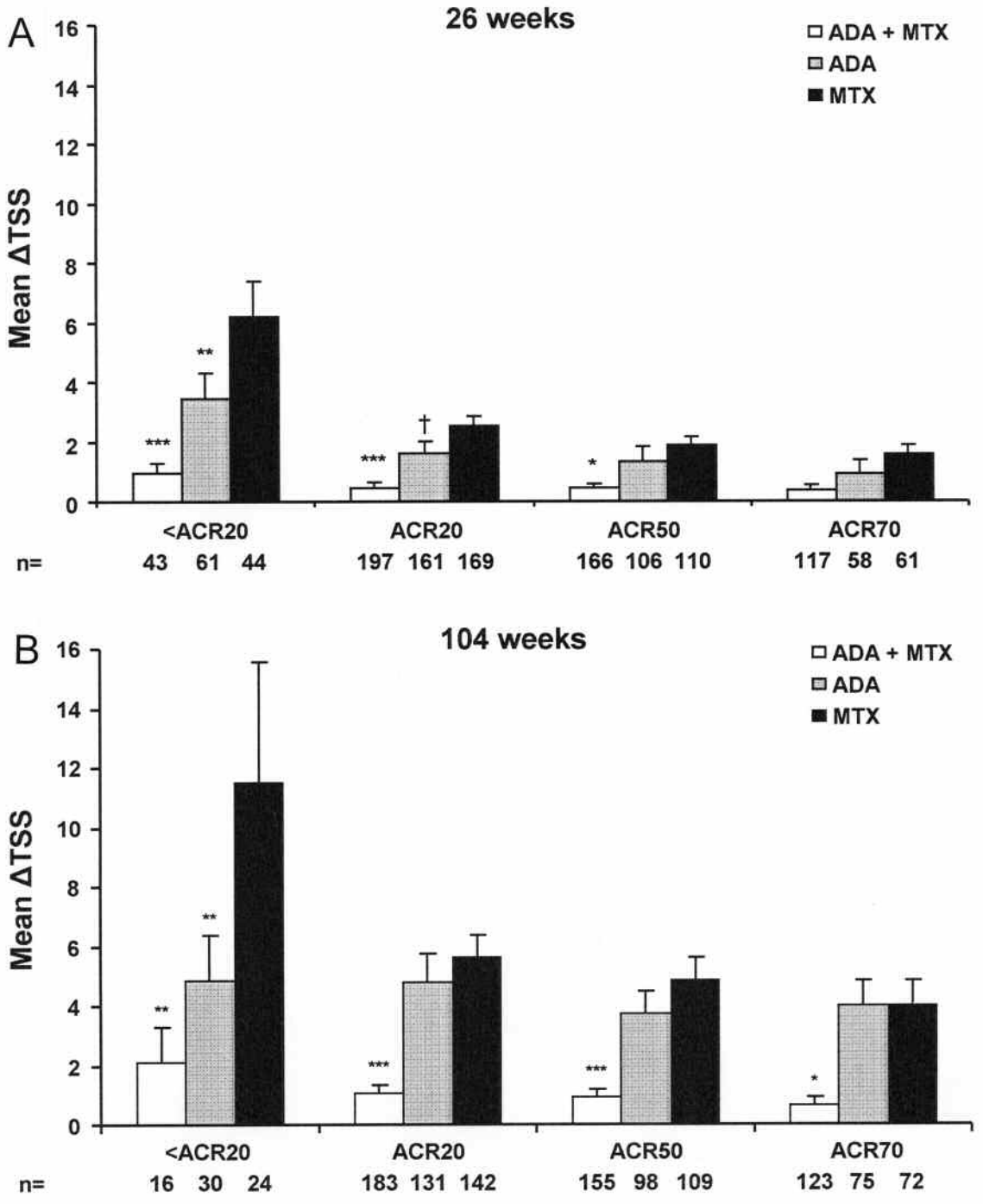

Figure 2. Mean change in total Sharp score (ΔTSS) by level of ACR response. Patients were grouped according to the level of ACR response following 26 weeks (A) or 104 weeks (B) of treatment with MTX monotherapy, adalimumab monotherapy, or adalimumab plus MTX. Mean ΔTSS and standard error are shown for each patient group, with patient numbers (n) indicated below. *$p < 0.05$, **$p < 0.01$, ***$p < 0.001$, †$p = 0.07$ vs MTX monotherapy. For comparisons of adalimumab plus MTX vs adalimumab monotherapy, $p < 0.01$, $p < 0.05$, p = NS, p = NS in A; and p = NS, $p < 0.001$, $p < 0.05$, $p < 0.05$ in B, for each ACR response level, respectively.

must be eliminated, or nearly eliminated, for the monotherapies to have similar radiographic efficacy to adalimumab plus MTX. Therefore, the therapies were compared for patients who had achieved remission-like responses at Week 104, defined by 3 indicators of very low disease activity (TJC = 0, SJC = 0, or DAS28 < 2.6) and by a measure of change indicative of complete resolution of clinical disease activity (ACR100).

Table 2. Frequency of radiographic progression by level of clinical response.

	Percentage of Progressors		
	Adalimumab plus MTX	Adalimumab	MTX
By Week-26 ACR response			
< ACR20	37*	49	59
ACR20	24***	40**	55
ACR50	23***	37*	51
ACR70	23***	33†	49
By Week-104 ACR response			
< ACR20	38*	53	75
ACR20	33***	53	62
ACR50	31***	53	60
ACR70	28***	53	57
By Week-104 remission-like response			
TJC = 0	32**	47	59
DAS28 > 2.6	33**	39	53
SJC = 0	34	37	44
ACR100	32	0	46

Radiographic progression = ΔTSS > 0.5 from baseline. Percentages of progressors are for the same timepoints as indicated for the clinical response categories. * $p < 0.05$, ** $p < 0.01$, *** $p < 0.001$, † $p = 0.07$ vs MTX monotherapy. For comparisons of adalimumab plus MTX vs adalimumab monotherapy, for < ACR20, ACR20, ACR50, ACR70 groups: p = NS, $p = 0.001$, $p < 0.05$, p = NS at Week 26 and p = NS, $p < 0.001$, $p < 0.001$, $p < 0.001$ at Week 104. For remission-like response groups, p values are all NS. Patient numbers (n) in clinical outcome subgroups are indicated in Figures 2A, 2B, and 5. ACR: American College of Rheumatology, DAS28: 28-joint Disease Activity Score, MTX: methotrexate, SJC: swollen joint count, TJC: tender joint count, TSS: total Sharp score; NS: not significant.

For each type of remission-like response, the cumulative probability plot of the ΔTSS from baseline to Week 104 was distributed further to the right for MTX monotherapy, indicating greater progression, than for adalimumab plus MTX (Figure 4). The area separating the curves was greatest for patients with TJC = 0, followed by DAS28 < 2.6, and smallest for those with SJC = 0 or an ACR100 response. In contrast, for adalimumab monotherapy, the curves for TJC = 0, DAS28 < 2.6, and SJC = 0 nearly overlapped those for adalimumab plus MTX (except for 2 adalimumab patients with ΔTSS > 30), and were distinct from the MTX monotherapy curves. The adalimumab monotherapy curve for ACR100 responders had only 3 patients, each a nonprogressor. These probability plots indicate that, for patients with remission-like responses at Week 104, radiographic progression had been prevented best with adalimumab plus MTX and nearly as well with adalimumab monotherapy. Inhibition of radiographic progression with MTX monotherapy approximated that for adalimumab plus MTX only for patients who achieved SJC = 0 or an ACR100 response. The corresponding mean ΔTSS and percentages of radiographic progressors are shown in Figure 5 and Table 2. It should be noted that the mean ΔTSS values for adalimumab monotherapy were substantially increased by outliers in the TJC = 0, DAS28 < 2.6, and SJC = 0 groups.

Clinical remission with no radiographic progression. Following 104 weeks of treatment with MTX monotherapy, adalimumab monotherapy, or adalimumab plus MTX, clinical remission (DAS28 < 2.6) was observed for 39%, 42%, and 66% of patients, respectively, and no radiographic progression from baseline (ΔTSS ≤ 0.5) was observed for 46%, 47%, and 66% of patients. A state of DAS28 < 2.6 with concurrent ΔTSS ≤ 0.5 was achieved significantly more frequently by patients treated with adalimumab plus MTX at Weeks 26, 52, and 104 (Figure 6). At Week 104, this result was observed for 18% of patients treated with MTX monotherapy, 25% treated with adalimumab monotherapy (p = NS vs MTX monotherapy), and 45% treated with adalimumab plus MTX ($p < 0.001$ vs MTX monotherapy and vs adalimumab monotherapy; Figure 6). A similar pattern of results was obtained using a simpler, but more conservative definition of clinical remission, SJC = 0 (Figure 6).

DISCUSSION

The PREMIER study of adalimumab is unique among the randomized, placebo-controlled trials of TNF antagonist therapy for early RA because it compared the combination of a TNF antagonist plus MTX to each monotherapy[10-12,23]. Further, treatment was blinded for 2 years, and the patients had particularly aggressive joint destruction at baseline. Our analysis took advantage of these features to compare the abilities of combination therapy and monotherapies to inhibit radiographic progression across the spectrum of clinical outcomes.

The 4 key findings of our study are as follows: (1) at every level of clinical response or disease activity, including

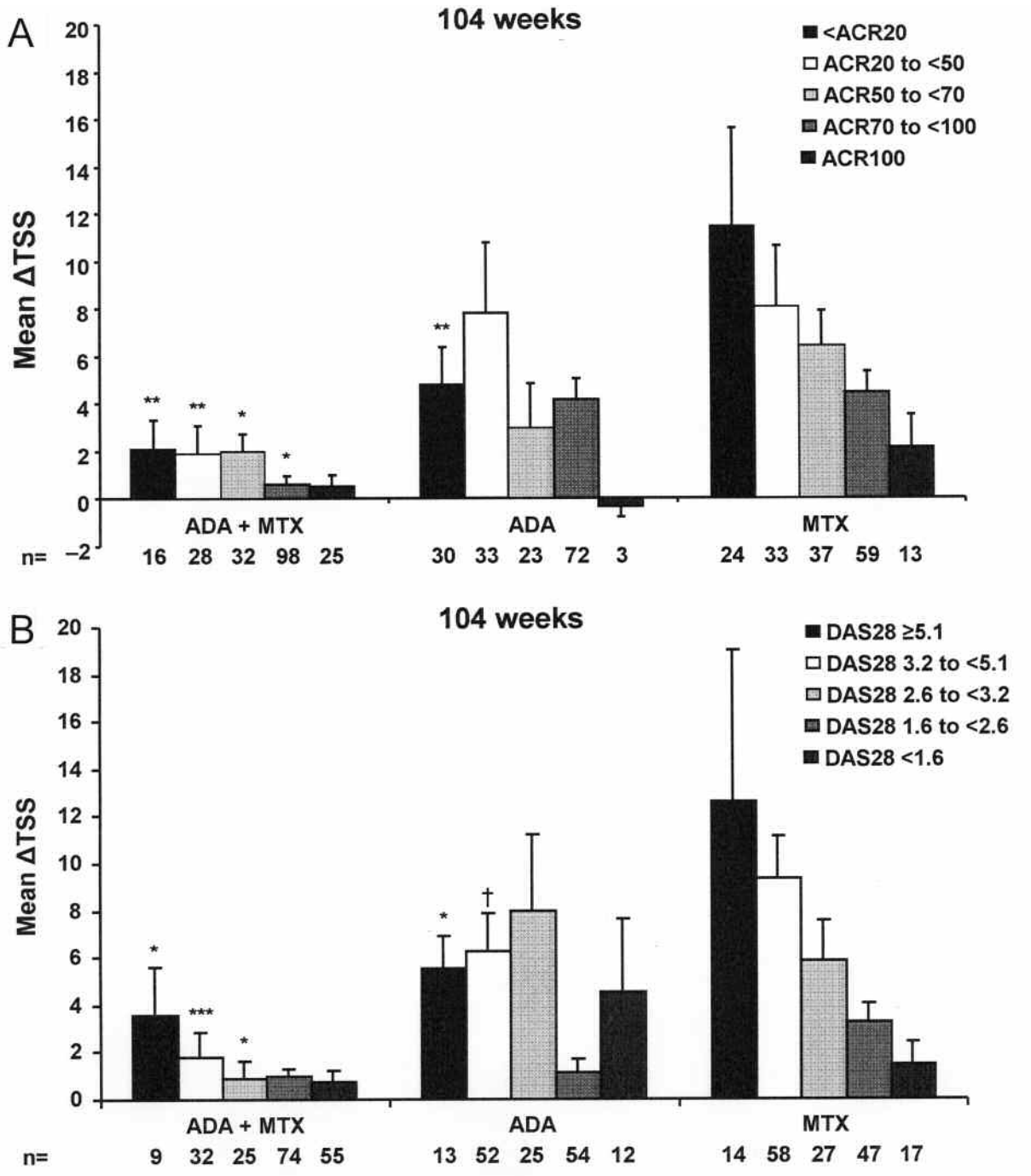

Figure 3. Mean change in total Sharp score (ΔTSS) by nonoverlapping categories of clinical outcome. Mean ΔTSS from baseline to Week 104 (with standard error) was determined for each therapy with patients grouped by nonoverlapping categories of ACR response (A) or DAS28 score (B) at Week 104. *$p < 0.05$, **$p < 0.01$, ***$p < 0.001$, †$p = 0.07$ vs MTX monotherapy. For comparisons of adalimumab plus MTX versus adalimumab monotherapy, p = NS, $p < 0.05$, p = NS, $p < 0.05$, p = NS in A; and p = NS, $p < 0.05$, $p < 0.01$, p = NS, p = NS in B. Analysis of trend: in A, for same-treatment comparisons between < ACR20 group and the other ACR response groups (ACR100 last), p = NS, NS, $p < 0.05$, $p < 0.05$ for MTX alone; and all NS for adalimumab plus MTX and for adalimumab monotherapy. In B, for same-treatment comparisons between DAS28 > 5.1 group and the other DAS28 groups (DAS28 < 1.6 last), p = NS, p = 0.082, p = 0.010, p = 0.010 for MTX alone; p = NS, NS, p = 0.073, p = 0.057 for adalimumab plus MTX; and all p = NS for adalimumab monotherapy.

both poor responses and some that can be considered remission-like, patients treated with adalimumab plus MTX had less radiographic progression from baseline than those treated with MTX alone; (2) the radiographic efficacy of adali-

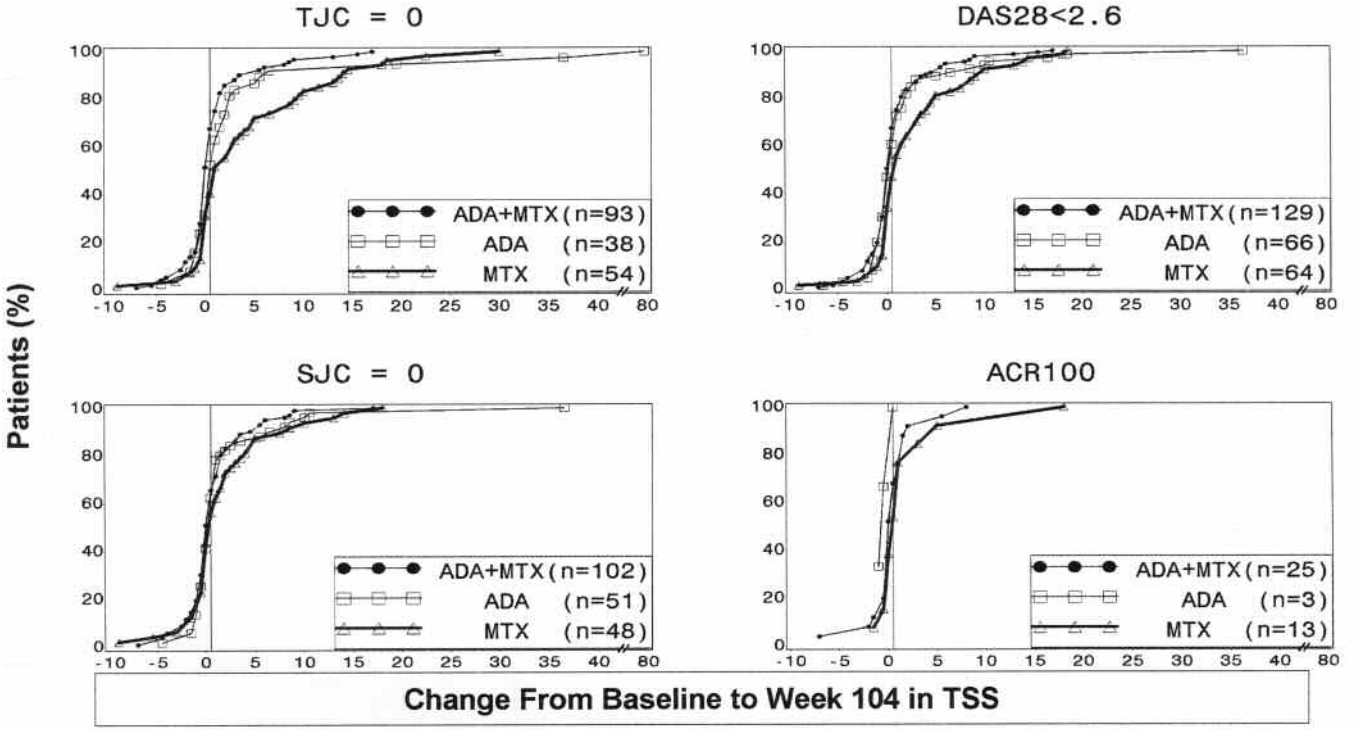

Figure 4. Radiographic progression in patients achieving remission-like responses. Patients were grouped according to 4 definitions of remission-like response [tender joint count (TJC) = 0, DAS28 < 2.6, swollen joint count (SJC) = 0, and 100% improvement by ACR100] following 104 weeks of treatment with MTX monotherapy, adalimumab monotherapy, or adalimumab plus MTX. Cumulative probability plots display the changes in total Sharp score (ΔTSS) from baseline to Week 104 for patients in each remission-like response group for each treatment. ΔTSS value for the final point in the TJC = 0 curve for adalimumab monotherapy is 77.5. For probability plot format, see Figure 1 legend.

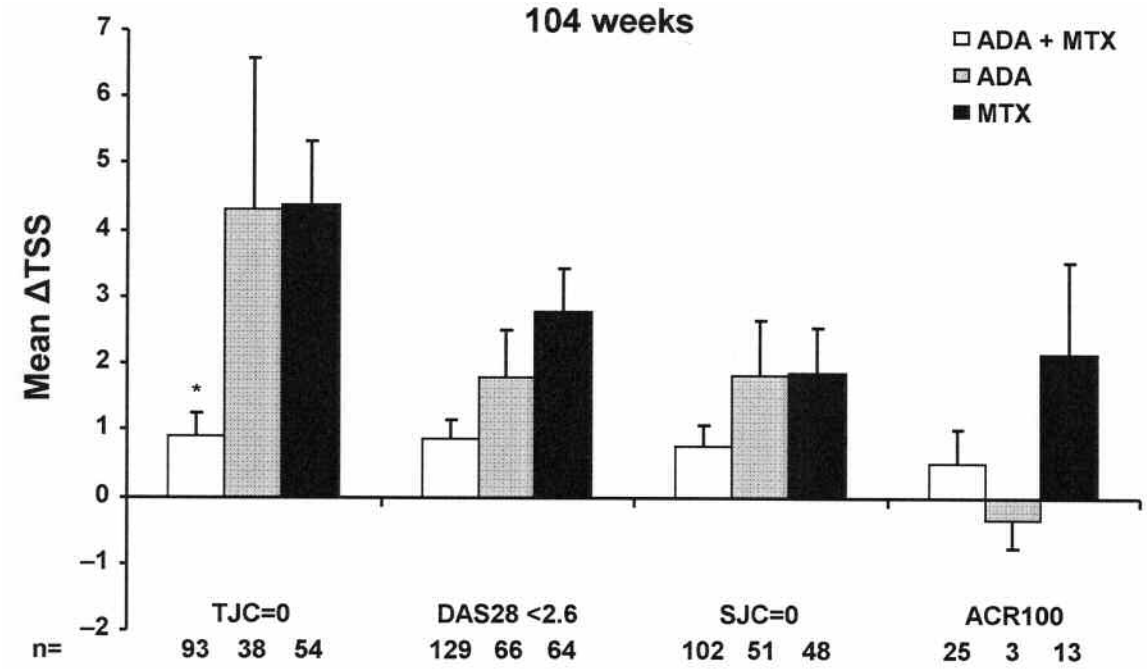

Figure 5. Mean change in total Sharp score (ΔTSS) for remission-like responders. For each type of remission-like response (see Figure 4 legend), the mean ΔTSS from baseline to Week 104 is shown with standard error. Patient numbers (n) are indicated beneath the x-axes. *p < 0.05, **p < 0.01 vs MTX monotherapy. For comparisons of adalimumab plus MTX versus adalimumab monotherapy, p = 0.054 for TJC = 0 and p = NS for all other comparisons.

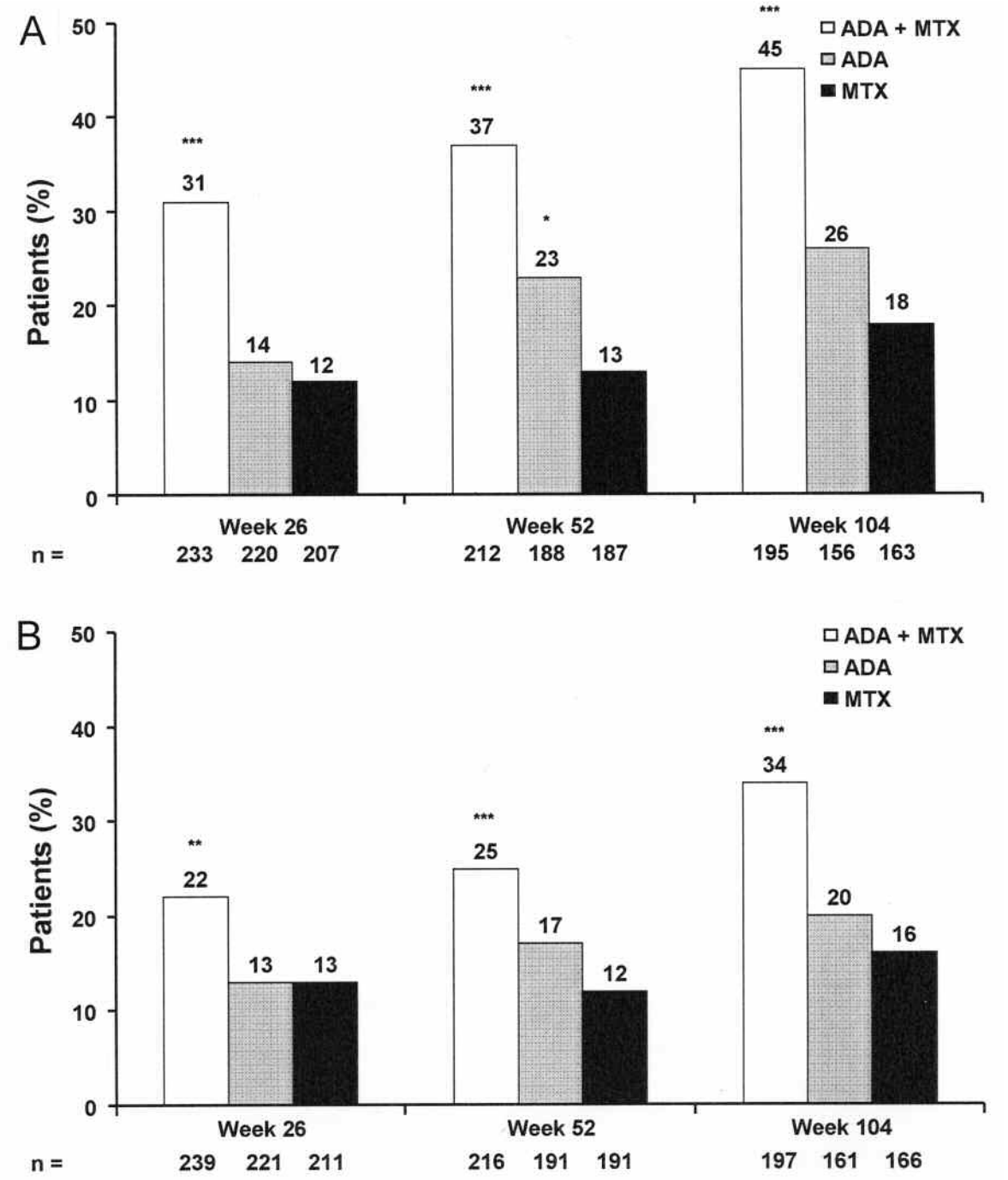

Figure 6. Concurrent clinical and radiographic remission. Percentages of patients who after 26, 52, or 104 weeks of treatment had both a remission-like response, defined as DAS28 < 2.6 (A), or swollen joint count (SJC) = 0 (B), and no radiographic progression from baseline [change in total Sharp score (ΔTSS) ≤ 0.5], are shown by treatment arm. *$p < 0.05$, **$p = 0.01$, ***$p < 0.001$ versus MTX monotherapy. For comparisons of adalimumab plus MTX with adalimumab monotherapy at 26, 52, and 104 weeks, $p < 0.001$, $p < 0.001$, $p < 0.001$, respectively, in (A), and $p < 0.001$, $p < 0.05$, and $p < 0.01$, respectively, in (B).

mumab monotherapy was generally intermediate, and its superiority to MTX monotherapy was most significant for ACR20 nonresponders; (3) radiographic and clinical efficacy had a strong proportional relationship for MTX monotherapy, but not for adalimumab plus MTX or adalimumab monotherapy; and (4) the radiographic efficacy of MTX monotherapy approximated that of adalimumab plus MTX only when clinically apparent synovitis had been eliminated (i.e., in patients with SJC = 0 or an ACR100 response).

The findings that adalimumab plus MTX had superior radiographic efficacy for patients with poor clinical responses and for patients with excellent clinical responses differ in their implications for clinical practice. The knowledge that a clinical nonresponder is relatively protected against joint destruction when treated with a TNF antagonist may not alter physician decision-making, because a poor clinical response will usually prompt a change in therapy anyhow, ideally to one offering a better clinical result and at least equivalent radiographic benefit. The Week-26 results, however, imply that a change in therapy is most urgent when a poor clinical response occurs with MTX monotherapy, rather than adalimumab plus MTX or adalimumab alone. Alternatively, the finding that radiographic progression was more frequent and often more rapid for patients with ACR70 responses or TJC = 0 after 104 weeks of MTX monotherapy, versus adalimumab plus MTX, implies that patients with excellent responses to MTX monotherapy may still require monitoring with radiographs or other imaging to identify progressors. The relevance of this concern is underscored by the fact that clinical evaluations tend to underestimate degree of synovitis[3], with the consequence that joint damage occurs in patients thought to be in remission[26].

Current evidence indicates that the overall radiographic efficacy of TNF antagonist monotherapy is greater than for MTX monotherapy, and less than for combination therapy[8,11]. Our analysis extends this finding by demonstrating that the superior radiographic efficacy of adalimumab monotherapy, compared with MTX monotherapy, was the most pronounced and statistically significant for patients with the worst clinical outcomes (i.e., < ACR20 responses or DAS28 > 5.1; Figures 1–3). This superiority was also observed for patients with remission-like responses of TJC = 0 or DAS28 < 2.6 at Week 104, which was seen most clearly in the probability plots because the corresponding mean ΔmTSS values for adalimumb monotherapy were affected by results for outliers (Figure 4). The probability plots also showed that control of radiographic progression with adalimumab monotherapy resembled that achieved with adalimumab plus MTX for patients in all 4 categories of remission-like response (TJC = 0, DAS28 < 2.6, SJC = 0, and ACR 100 response; Figure 4). These findings indicate that, overall, adalimumab protected joints better than MTX monotherapy for patients with poor clinical responses, and for patients who achieved a remission-like state but had residual synovitis. In addition, they suggest that SJC = 0, rather than TJC = 0, is a more accurate indicator that joint damage is being prevented, especially for patients receiving MTX monotherapy (Figure 5).

For more complete assessment of the relationships between radiographic and clinical efficacy, the mean ΔTSS values were also determined for patients grouped by 5 nonoverlapping categories of ACR response and 5 categories of DAS28 score. These 2 approaches complemented each other because disease activity can differ between patients with similar ACR responses, and the rates of joint damage can vary greatly between patients with similar DAS28 scores[5]. With either approach, a striking, proportional relationship was observed between clinical status and radiographic efficacy for MTX monotherapy at Week 104, but not for adalimumab monotherapy (Figures 3A and 3B). For adalimumab plus MTX, mean progression was numerically, but not statistically significantly, smaller for patients with better clinical outcomes. This trend was more evident across categories of DAS28 score than ACR response, possibly because only 9 patients had DAS28 > 5.1, and because ACR < 20 responders can have substantial reductions in TJC, SJC, or CRP. However, for all 3 therapies, radiographic progression tended to be the least when clinically detectable synovitis was absent or nearly absent.

These findings are consistent with evidence that, in the absence of a TNF antagonist, the rate of joint damage is proportional to the degree of synovitis[1,2,27,28], whereas this relationship is dampened, although not necessarily eliminated, by therapy with a TNF antagonist plus MTX and, to a lesser degree, by a TNF antagonist alone[18,20,21,27]. These results are also consistent with the mechanisms by which TNF can directly promote osteoclast activity in RA[29-34]. Our analyses suggest that adalimumab plus MTX inhibited radiographic progression both indirectly, by reducing synovitis, and directly, by blocking TNF effects on osteoclasts that occur independently or downstream of synovitis[30-32]. By contrast, MTX monotherapy appeared to prevent joint damage predominantly by reducing synovitis. The relationship of these mechanisms was less clear for adalimumab monotherapy, although the results suggest that direct effects had a significant role. These findings suggest that the "disconnect" between clinical and radiographic efficacy of TNF antagonists[22] does not require concomitant MTX, but is more pronounced when it is used.

A limitation of our study is that it was a post-hoc analysis of a trial that was not designed to predict radiographic outcomes from prior clinical status. Because all patients with data for a given timepoint were included — to optimize robustness of the analysis — patients at later timepoints were a subset of those at earlier timepoints. PREMIER lacked ultrasound or magnetic resonance imaging evaluations of joints. It is likely that patients had more synovitis than indicated by the clinical assessments, especially for patients with remission-like responses[26].

Our analysis of PREMIER has demonstrated that adalimumab plus MTX controlled radiographic progression better than MTX monotherapy across the spectrum of clinical response or disease activity. This finding is consistent with those of other studies, and probably represents a general property of TNF antagonists[19,21,22]. Results with adalimumab monotherapy tended to be intermediate. A marked, proportional relationship was observed between radiographic

and clinical outcomes only for MTX monotherapy. In contrast, for adalimumab plus MTX, radiographic progression was greatly inhibited at every level of clinical outcome. Accordingly, after 2 years of therapy, a state of true remission, defined as clinical remission without radiographic progression, was observed more than twice as frequently with adalimumab plus MTX than with MTX monotherapy. Therefore, early and sustained attention to both clinical response and joint damage is important for optimizing treatment of early RA, especially for patients receiving MTX monotherapy.

ACKNOWLEDGMENT

Drs. Emery, Genovese, van Vollenhoven, Patra, and Sasso pay tribute to coauthor John Sharp, who passed away before the publication of this report. Dr. Sharp was a pioneer in the field of radiographic progression measurement and analysis, and his contributions to this and many other investigations were invaluable. We remember and thank our colleague. He will be missed.

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Correction

Emery P, Genovese MC, van Vollenhoven R, Sharp JT, Patra K, Sasso EH. Less radiographic progression with adalimumab plus methotrexate versus methotrexate monotherapy across the spectrum of clinical response in early rheumatoid arthritis. J Rheumatol 2009;36:1429-41; doi:10.3899/jrheum.081018. In the first column of page 1432, under the heading "Mean ΔTSS and frequency of radiographic progression by level of ACR response," the first sentence of the section should read: "The mean ΔTSS values were significantly greater for MTX monotherapy than adalimumab plus MTX for each level of ACR response at Week 26 (except ACR70; Figure 2A) and Week 104 (Figure 2B)." We regret the error.

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