Clinical, Functional, and Radiographic Implications of Time to Treatment Response in Patients With Early Rheumatoid Arthritis: a Posthoc Analysis of the PREMIER Study

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ABSTRACT. ***Objective.*** Rheumatoid arthritis (RA) treatment recommendations suggest target attainment within the first 3 months of therapy, yet delayed clinical responses can occur. This analysis assessed the longterm clinical, functional, and radiographic outcomes associated with delayed responses to methotrexate (MTX) monotherapy or to the combination of adalimumab (ADA) + MTX.

Methods. In this posthoc analysis, patients with early RA who received MTX monotherapy or ADA + MTX in the PREMIER study were categorized based on clinical responses at 3 and 6 months [American College of Rheumatology response, 28-joint Disease Activity Score (DAS28)-C-reactive protein (CRP) improvement and targets]. "Month 3" responders met the clinical measure at both months 3 and 6, and "Month 6" responders met the clinical measure only at Month 6. The odds of achieving longterm outcomes [remission (DAS28-CRP < 2.6), normal function (Health Assessment Questionnaire-Disability Index < 0.5), or rapid radiographic progression (Δ modified total Sharp score > 3 U/yr)] were modeled using logistic regression, including treatment, response, and interaction.

Results. A delayed or low-level response was associated with poorer longterm outcomes. Generally, MTX Month 6 responders demonstrated worse clinical, functional, and radiographic outcomes than Month 3 MTX and Month 3 or 6 ADA + MTX responders. Although similar longterm benefit was observed for ADA + MTX responders, delayed (Month 6) responders exhibited downward trends in clinical, functional, and radiographic outcomes that were comparable with those experienced by Month 3 MTX responders.

Conclusion. Response speed and magnitude predict longterm outcomes in patients with early RA treated with MTX or ADA + MTX. MTX-treated patients failing to demonstrate a Month 3 clinical response have less-favorable outcomes than other groups, while outcomes in ADA + MTX Month 3 and Month 6 responders tended to be comparable. (First Release Dec 1 2013; J Rheumatol 2014;41:235–43; doi:10.3899/jrheum.121468)

Key Indexing Terms:
RHEUMATOID ARTHRITIS   METHOTREXATE
TUMOR NECROSIS FACTOR INHIBITORS   DISEASE ACTIVITY

The goals of rheumatoid arthritis (RA) treatment are to suppress joint inflammation, preserve physical function, and prevent structural joint damage. Close, objective monitoring of disease activity, together with a rapid adjustment in therapy, if necessary, appears to be the most effective approach to RA management[1,2,3,4,5,6]. Clinical remission is the recommended goal for patients with early RA[7], and therapy is typically initiated with methotrexate

(MTX) monotherapy. Timely addition of a biologic should be considered following an inadequate response to MTX therapy[8], but may be used as an initial treatment regimen for patients with high risk factors[7,9].

The level of disease activity early in the course of treatment correlates well with longterm clinical and radiographic outcomes[10,11,12], and a 3-month treatment window has been suggested as an appropriate time at which treatment adjustment may be considered[7]. Still, clinical improvement may occur later in some patients, because some treatments require exposure beyond 3 months for maximal efficacy[13,14,15]. Some recommendations account for such a delay by suggesting that the target can instead be achieved within 6 months of therapy initiation. However, the clinical, functional, and radiographic consequences of such a delay to response remain poorly understood. Further, whether the inherent risks associated with a delayed response are the same for different RA therapies is unclear. The present analysis evaluated the longterm clinical, functional, and radiographic consequences of speed of response to either MTX monotherapy or a more aggressive biologic intervention [adalimumab (ADA) + MTX] as first-line therapy in patients with early RA.

MATERIALS AND METHODS

Patients and study design. Adults ≥ 18 years of age with a diagnosis of RA, as defined by the 1987 revised American College of Rheumatology (ACR) criteria[16], and a disease duration < 3 years were enrolled in our study. Patients were required to meet the following enrollment criteria: ≥ 8 (of 66 assessed) and ≥ 10 (of 68 assessed) swollen and tender joints, respectively; an erythrocyte sedimentation rate > 28 mm/h or a C-reactive protein (CRP) level ≥ 1.5 mg/dl; and have either a positive rheumatoid factor or at least 1 joint erosion. Patients were excluded if they had prior exposure to MTX, cyclophosphamide, cyclosporine, azathioprine, > 2 other disease-modifying antirheumatic drugs (DMARD), or had received prednisone equivalent > 10 mg/day within 30 days of screening. Patients also were excluded who had received prior treatment with any biological tumor necrosis factor (TNF) inhibitor.

PREMIER was a 2-year, phase III, randomized, placebo-controlled trial in an MTX-naive RA population fulfilling the above-mentioned criteria[17]. Patients were randomized 1:1:1 to receive weekly oral MTX monotherapy (initiated at 7.5 mg/week and rapidly escalated to 20 mg/week by Week 8, as tolerated), ADA monotherapy (40 mg subcutaneously every other week), or ADA + MTX combination therapy. All patients provided written informed consent, and the study protocol and informed consent form were approved by the local institutional review boards or independent ethics committees at participating sites. The study was conducted in accordance with the principles of the Declaration of Helsinki and good clinical practice.

Efficacy evaluations. The 28-joint Disease Activity Score with CRP (DAS28-CRP) was used to determine RA activity[18]. The Health Assessment Questionnaire Disability Index (HAQ-DI) was used to assess physical function[19]. Two readers, blinded to patient and sequence, scored radiographic images of the hands, wrist, and feet using the modified total Sharp score (mTSS). Radiographic progression was measured as the change (Δ) in mTSS from baseline[20,21,22,23]. The percentages of patients in remission (defined for this analysis as DAS28-CRP < 2.6), with normal physical function (defined as HAQ-DI < 0.5), or with rapid radiographic progression (RRP, ΔmTSS > 3 units/yr) were determined following 1 or 2 years of treatment.

Assignment of "Month 3" and "Month 6" responders. On the basis of

several clinical measures [ACR response criteria of at least 20%, 50%, and 70%, improvements in DAS28-CRP of > 1.2 and > 1.8, and DAS28-CRP targets < 3.2 (low disease activity, LDA) and < 2.6 (remission)] at Week 24 (Month 6), patients were categorized as responders or nonresponders. Responders were further categorized as Month 3 responders if they achieved the specific clinical measure at weeks 12 (Month 3) and 24 (Month 6), while Month 6 responders were those who only satisfied it at Week 24.

Statistical analyses. This posthoc analysis evaluated observed data from patients randomized to the MTX monotherapy and ADA + MTX treatment groups who had clinical data available at baseline, months 3 and 6, and clinical, functional, or radiographic data available at baseline and Year 1. Patients failing to achieve a clinical response at Month 6 (nonresponders) were not included in this analysis. A subanalysis included data from patients in the evaluable population who also had data at Year 2. ADA monotherapy data were not included in this analysis because treatment guidelines recommend initiation with MTX monotherapy, and in exceptional patients with high risk factors, the combination of a TNF inhibitor (e.g., ADA) + MTX may be initiated[7,9]. Differences between treatment groups in responder/nonresponder and Month 3 and Month 6 responder populations were assessed by chi-square test. OR with 95% CI from a logistic regression model including treatment groups (MTX, ADA + MTX), response groups (Month 3, Month 6), and their interaction were used to assess differences in clinical, functional, and radiographic outcomes. For this posthoc analysis, multiplicity adjustment was not considered for the comparisons.

RESULTS

Patients. Of the 799 patients enrolled in PREMIER, 200 of 257 randomized to MTX and 229 of 268 randomized to ADA + MTX were included in this posthoc analysis. Disease duration and activity at baseline were typical of a population with early and aggressive RA (Table 1); > 90%

Table 1. Baseline demographics and disease characteristics. All values are mean ± SD, unless otherwise indicated.

Characteristic	MTX, n = 200	ADA + MTX, n = 229
Age, yrs	52.8 ± 13.3	51.9 ± 14.1
Female, n (%)	146 (73.0)	160 (69.9)
Rheumatoid factor-positive, n (%)	170 (87.2)	186 (83.8)
Duration of RA, yrs	0.8 ± 0.9	0.7 ± 0.8
Baseline DMARD use, n (%)	59 (29.5)	73 (31.7)
Baseline corticosteroid use, n (%)	68 (34.0)	81 (35.4)
DAS28-CRP, range 0–10[a]	6.3 ± 0.8	6.3 ± 0.9
DAS28-CRP ≥ 5.1, n (%)[a]	182 (93.8)	199 (90.9)
CRP, mg/dl	4.0 ± 4.0	4.0 ± 4.2
SJC (0–66 joints)	22.4 ± 12.0	21.3 ± 11.5
TJC (0–68 joints)	32.0 ± 14.0	30.7 ± 14.6
HAQ-DI (range 0–3)	1.5 ± 0.7	1.5 ± 0.6
mTSS (range 0–398)	22.7 ± 22.7	18.6 ± 20.6
Joint erosion score (0–230)[b]	14.1 ± 13.7	11.3 ± 12.9
Joint space narrowing score (0–168)	8.6 ± 10.9	7.3 ± 9.4

[a] 195 and 220 patients from the MTX and ADA + MTX treatment groups, respectively, had DAS28-CRP values available at baseline. [b] p = 0.03 for differences between MTX and ADA + MTX. MTX: methotrexate; ADA: adalimumab; RA: rheumatoid arthritis; DMARD: (nonbiologic) disease-modifying antirheumatic drug; DAS28: 28-joint Disease Activity Score; CRP: C-reactive protein; SJC: swollen joint count; TJC: tender joint count; HAQ-DI: Health Assessment Questionnaire-Disability Index; mTSS: modified total Sharp score.

of patients demonstrated DAS28-CRP ≥ 5.1 at baseline. As was observed in the intent-to-treat population[17], only the extent of baseline erosions was significantly different between the MTX monotherapy and ADA + MTX therapy groups.

Month 3 and Month 6 responders. Following 6 months of treatment, fewer patients who had started with MTX monotherapy were ACR or DAS28-CRP responders than patients who had started on the combination of ADA + MTX at the onset of the study (Figures 1A–C). Further, MTX-treated patients required longer treatment periods to attain the higher levels of clinical response or DAS28-CRP targets. For instance, while the majority of MTX responders demonstrated an ACR20 response at months 3 and 6 (Month 3 responders), the majority of ACR50/70, LDA, or remission responses were observed only after 6 months of

Figure 1. Proportions of MTX or ADA + MTX Month 3 and Month 6 responders. The percentages of MTX-treated or ADA + MTX-treated patients exhibiting (A) ACR responses (ACR20/50/70), (B) improvements in DAS28-CRP (improvements > 1.2/1.8), or (C) DAS28-CRP targets (LDA, DAS28-CRP < 3.2; remission, DAS28-CRP < 2.6) at months 3 and 6 (Month 3 responders) or at Month 6 (Month 6 responders). *, **, and *** significantly different between treatment groups at the p < 0.05, 0.01, and 0.001 levels, respectively. Asterisks above columns reflect differences in responder and nonresponder populations across MTX and ADA + MTX groups. Asterisks within columns reflect differences in Month 3 and Month 6 responders across MTX and ADA + MTX groups. MTX: methotrexate; ADA: adalimumab; ACR: American College of Rheumatology; DAS28: 28-joint Disease Activity Score; CRP: C-reactive protein; LDA: low disease activity.

MTX therapy (Month 6 responders). In contrast, patients treated with ADA + MTX combination therapy achieved these clinical responses and targets sooner (Figures 1A–C). In fact, of the responders at Month 6, the majority of ADA + MTX-treated patients (range 54–90%) were also responders at Month 3, a pattern that was significantly different from MTX across the range of examined clinical responses and targets. Patients in both treatment groups who were responders at Month 3 were unlikely to become non-responders at Month 6 (data not shown).

Clinical outcomes. In both treatment groups, Month 3 responders had rates of longterm clinical benefit that were at least numerically higher than those in Month 6 responders (Figures 2A–G). About 40% of MTX-treated and about 60% of ADA + MTX-treated Month 3 responders were in remission at Year 1. Generally, significantly higher proportions of Month 3 MTX responders were in remission at Year 1 compared with Month 6 MTX responders across a range of clinical responses [OR (95% CI): ACR20, 4.29 (1.76, 10.46); ACR50, 4.13 (1.81, 9.41); ACR70, 15.15 (1.82, 126.34); improvement in DAS28-CRP > 1.2, 4.73 (1.56, 14.29); improvement in DAS28-CRP > 1.8, 2.08 (0.92, 4.70)]. Such a cost of delay was less apparent for MTX responders who achieved at least an LDA state at Month 3 or Month 6 [OR (95% CI): LDA, 2.82 (0.94, 8.48); remission, 2.47 (0.45, 13.54)]; achieving an LDA state at either Month 3 or Month 6 was associated with remission in 77% and 55% of patients, respectively, at Year 1.

ADA + MTX Month 3 or Month 6 responders had at least numerically higher proportions in remission at Year 1 than did their corresponding MTX responders, a finding that, with the exception of ACR70 response, was independent of the magnitude or timing of the response (Figure 2A–G). Still, delays in the achievement of the clinical response in the ADA + MTX population were associated with downward trends in longterm outcomes that were not statistically different from those experienced by MTX responders [p ≥ 0.05 for the interaction of treatment group and responder population for all clinical responses (data not shown); Figure 2A–G]. Despite such findings, ADA + MTX Month 3 and Month 6 responders generally had comparable odds of being in remission at Year 1 [OR (95% CI): ACR20, 2.67 (1.10, 6.47); ACR50, 1.42 (0.68, 2.95); ACR70, 2.32 (0.93, 5.79); improvement in DAS28-CRP > 1.2, 1.92 (0.70, 5.30); improvement in DAS28-CRP > 1.8, 3.20 (1.44, 7.11); LDA, 1.95 (0.89, 4.30); remission, 2.20 (0.72, 6.78)]. These trends continued at Year 2, although the differences between MTX Month 3 and Month 6 responders were less pronounced [OR (95% CI): ACR20, 3.19 (1.41, 7.24); ACR50, 1.97 (0.86, 4.49); ACR70, 1.67 (0.45, 6.29); improvement in DAS28-CRP > 1.2, 1.59 (0.70, 3.61); improvement in DAS28-CRP > 1.8, 1.67 (0.75, 3.71); LDA, 3.88 (1.18, 12.81); remission, 6.00 (0.67, 53.67); data not shown], possibly because of longterm selection of responders over time. Further, ADA + MTX Month 6 responders achieved remission at 1 year in proportions that were comparable with MTX Month 3 responders across the panel of examined responses [OR (95% CI): ACR20, 0.82 (0.33, 2.04); ACR50, 0.77 (0.32, 1.81); ACR70, 0.12 (0.01, 1.00); improvement in DAS28-CRP > 1.2, 1.11 (0.40, 3.12); improvement in DAS28-CRP > 1.8, 0.64 (0.27, 1.47); LDA, 0.52 (0.19, 1.44); remission, 0.51 (0.10, 2.71)]. Interestingly, achievement of at least an LDA state within the first 6 months of therapy was associated with high remission rates at Year 1 that were largely independent of the speed of

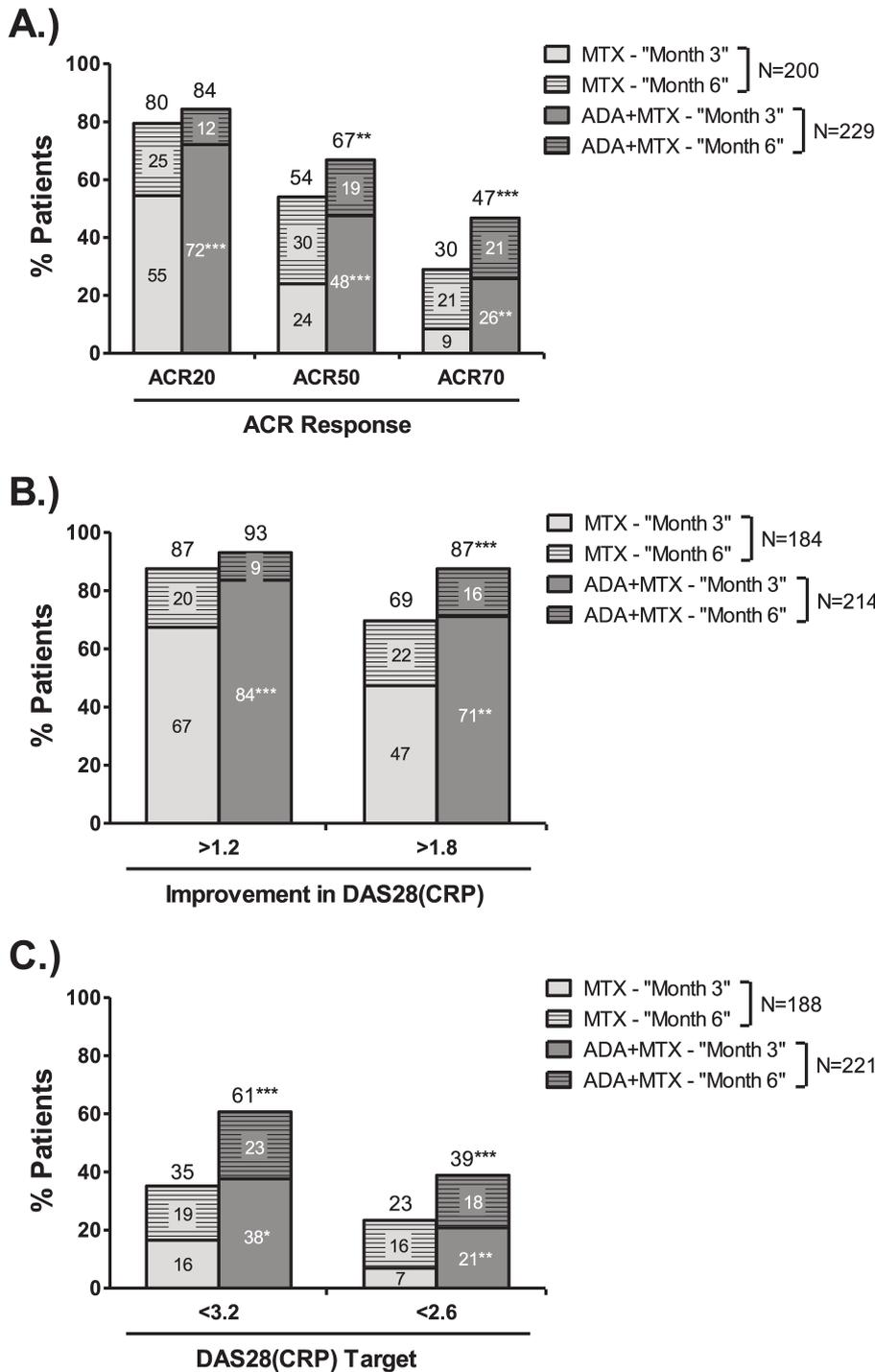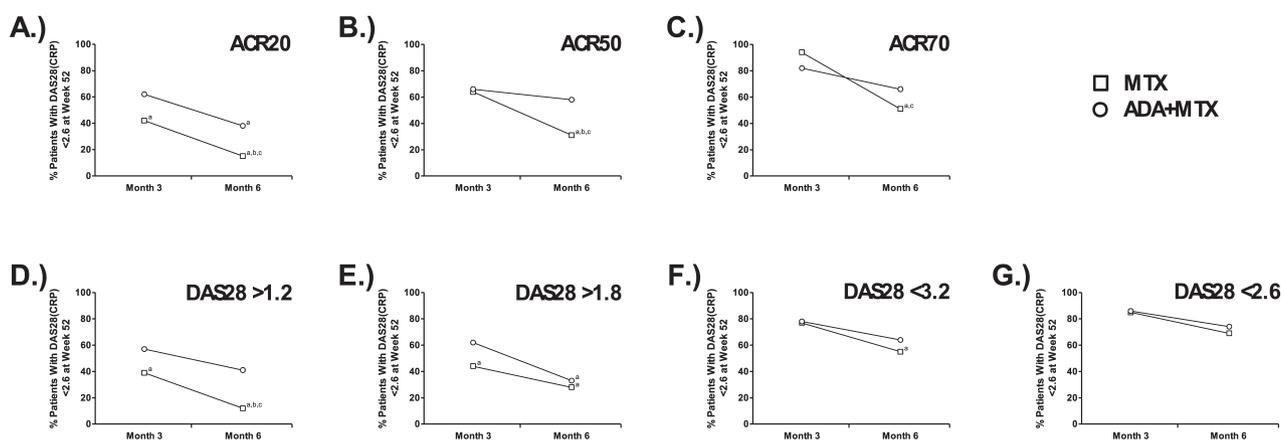*Figure 2.* Clinical remission at 1 year in MTX or ADA + MTX Month 3 and Month 6 responders. The percentages of MTX or ADA + MTX-treated patients exhibiting clinical remission (DAS28-CRP < 2.6) at 1 year based on (A–C) ACR responses (ACR20/50/70), (D and E) improvements in DAS28-CRP (> 1.2/1.8), or (F and G) DAS28-CRP targets (LDA, DAS28-CRP < 3.2; remission, DAS28-CRP < 2.6] at months 3 and 6 (Month 3 responders) or at Month 6 (Month 6 responders). A, B, and C indicate outcomes that are significantly different relative to ADA + MTX Month 3 responders, ADA + MTX Month 6 responders, and MTX Month 3 responders, respectively, by OR (95% CI). MTX: methotrexate; ADA: adalimumab; ACR: American College of Rheumatology; DAS28: 28-joint Disease Activity Score; CRP: C-reactive protein; LDA: low disease activity.

response for patients treated with either MTX or ADA + MTX.

Functional outcomes. Month 3 MTX responders generally had better functional outcomes than did Month 6 MTX responders at Year 1 [Figures 3A–G, OR (95% CI) for the presence of normal physical function (HAQ-DI < 0.5): ACR20, 2.14 (1.06, 4.30); ACR50, 3.83 (1.61, 9.09); improvement in DAS28-CRP > 1.2, 2.37 (1.07, 5.28)] and at Year 2 [OR (95% CI): ACR20, 1.70 (0.81, 3.56); ACR50, 2.41 (0.99, 5.89); improvement in DAS28-CRP > 1.2, 1.63 (0.74, 3.57); data not shown], although the differences again were less pronounced over time. In fact, only the MTX-treated patients who achieved the highest levels of clinical response or targets at months 3 or 6 demonstrated comparable odds of having normal physical function at Year 1 [OR (95% CI): ACR70, 2.50 (0.49, 12.89); improvement in DAS28-CRP > 1.8, 1.47 (0.69, 3.11); LDA, 1.49 (0.49, 4.58); remission, 1.67 (0.30, 9.42)]. In contrast, ADA + MTX-treated patients demonstrated high and comparable rates of normal physical function at Year 1 across all clinical responses or targets examined [OR (95% CI): ACR20, 2.19 (0.90, 5.32); ACR50, 1.23 (0.55, 2.75); ACR70, 1.09 (0.40, 2.98); improvement in DAS28-CRP > 1.2, 1.61 (0.57, 4.56); improvement in DAS28-CRP > 1.8, 1.87 (0.85, 4.10); LDA, 1.26 (0.52, 3.06); remission, 1.72 (0.50, 5.94)], irrespective of the timing with which the response was achieved (3 or 6 months). The relationship between responder population and treatment group appeared comparable for longterm functional outcomes [p ≥ 0.05 for the interaction of treatment group and responder population for all clinical responses (data not shown) and Figures 3A–G], as was observed for clinical outcomes. Interestingly, functional outcomes at years 1 and 2 for ADA + MTX-treated Month 6 responders were largely comparable with those from MTX-treated Month 3 responders across all clinical responses [OR (95% CI) for differences at 1 year between ADA + MTX Month 6 and MTX-Month 3 responders: ACR20, 0.85 (0.34, 2.10); ACR50, 0.70 (0.27, 1.83); ACR70, 0.55 (0.11, 2.84); improvement in DAS28-CRP > 1.2, 1.18 (0.41, 3.38); improvement in DAS28-CRP > 1.8, 1.01 (0.45, 2.30); LDA, 1.01 (0.34, 2.96); remission, 0.81 (0.14, 4.48)].

Radiographic outcomes. Month 3 MTX responders had a lower mean radiographic progression at Year 1 than did Month 6 MTX responders, regardless of clinical measure assessed (Figures 4A–C). In contrast, the extent of radiographic progression in the ADA + MTX treatment group was generally low regardless of the speed or the magnitude of the response. As with the longterm effect on disease remission and physical function, the timing and magnitude of the clinical measures were also associated with the risk of RRP following 1 year of treatment (Figures 5A–G). Patients treated with MTX required at least an ACR50 response or an LDA state by Month 3 to reduce the risk of RRP to a low level (< 30%), comparable with Month 6 ADA + MTX responders. Failure of MTX-treated patients to demonstrate a high level of clinical response by Month 3 was associated with an elevated risk of developing RRP at Year 1, even for patients who later achieved clinically important responses at Month 6 [e.g., ACR70, improvement in DAS28-CRP > 1.8, LDA]. This trend continued through Year 2: MTX-treated patients achieving a Month 6 ACR70 response or improvement in DAS28-CRP > 1.8 were associated with RRP in 31% and 41% of patients, respectively. However, the combination of ADA + MTX treatment was associated with numerically lower proportions of patients having RRP across all measures evaluated when compared with MTX, a finding that held true even for
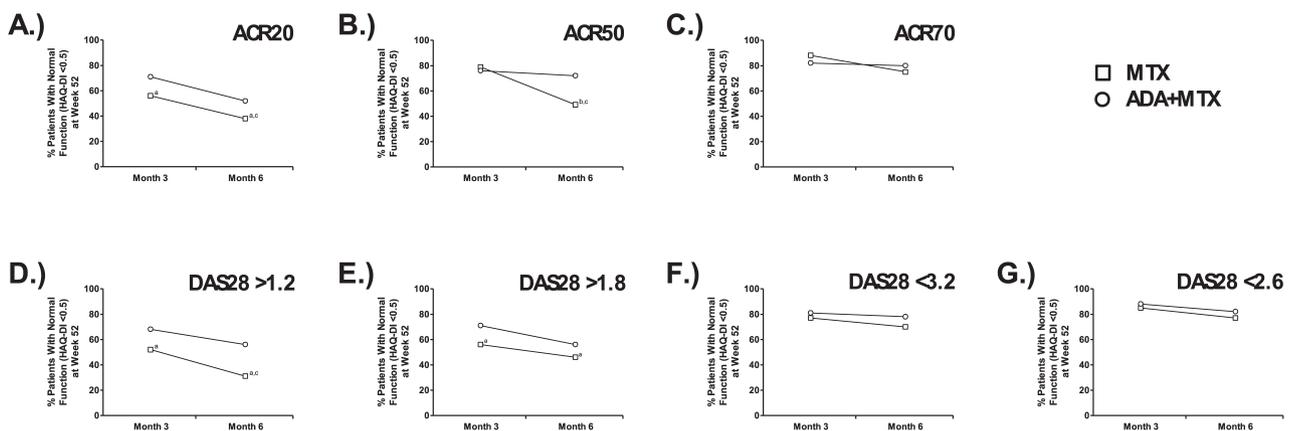

Figure 3. Normal functionality at 1 year in MTX or ADA + MTX Month 3 and Month 6 responders. The percentages of MTX or ADA + MTX–treated patients exhibiting normal function (HAQ-DI < 0.5) at 1 year based on (A–C) ACR responses (ACR20/50/70), (D–E) improvements in DAS28-CRP (improvements > 1.2/1.8), or (F–G) DAS28–CRP targets (LDA, DAS28-CRP < 3.2; remission, DAS28-CRP < 2.6) at months 3 and 6 (Month 3 responders) or at Month 6 (Month 6 responders). A, B, and C indicate outcomes that are significantly different relative to ADA + MTX Month 3 responders, ADA + MTX Month 6 responders, and MTX Month 3 responders, respectively, by OR (95% CI). MTX: methotrexate; ADA: adalimumab; ACR: American College of Rheumatology; DAS28: 28-joint Disease Activity Score; CRP: C-reactive protein; LDA: low disease activity; HAQ-DI: Health Assessment Questionnaire-Disability Index..
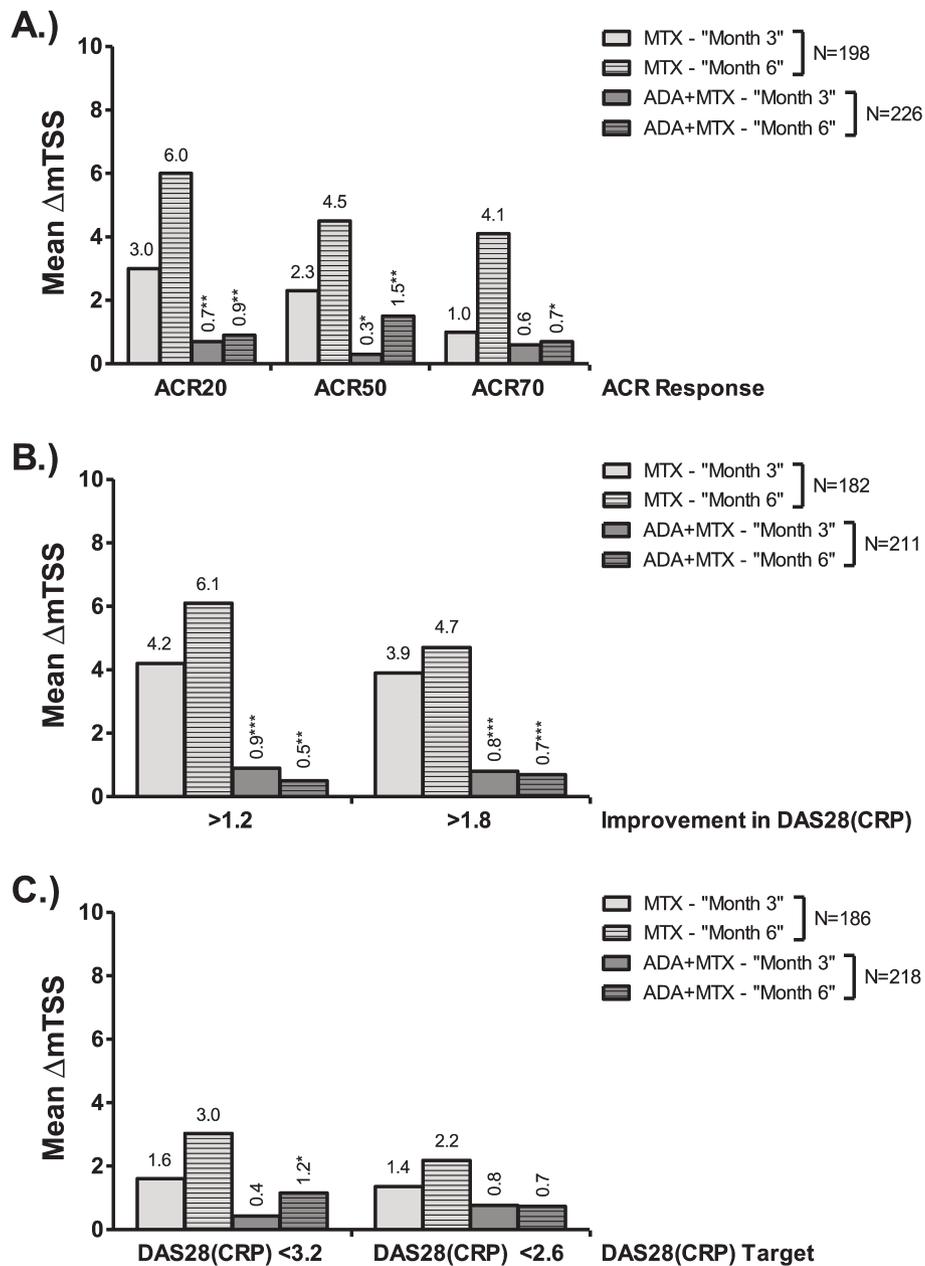
Figure 4. Radiographic progression in MTX or ADA + MTX Month 3 and Month 6 responders. Mean change in modified total Sharp score (mTSS) from baseline to 1 year in MTX-treated or ADA + MTX-treated patients exhibiting (A) ACR responses (ACR20/50/70), (B) improvements in DAS28-CRP (improvements > 1.2/1.8), or (C) DAS28-CRP targets (LDA, DAS28-CRP < 3.2; remission, DAS28-CRP < 2.6) at months 3 and 6 (Month 3 responders) or at Month 6 (Month 6 responders). MTX: methotrexate; ADA: adalimumab; ACR: American College of Rheumatology; DAS28: 28-joint Disease Activity Score; CRP: C-reactive protein.

patients who achieved an LDA target. In fact, Month 6 ADA + MTX responders maintained a persistently low risk of developing RRP (< 20%) at 1 or 2 years of treatment (Figures 5A–G and data not shown), and even had lower proportions of RRP at Year 1 than did Month 3 MTX responders.

DISCUSSION

Current treatment recommendations suggest that patients with RA should achieve a state of remission or at least LDA within the first 3 months of treatment, or an adjustment in therapy may be necessary[7]. Yet a more delayed clinical response is commonplace for many patients using various
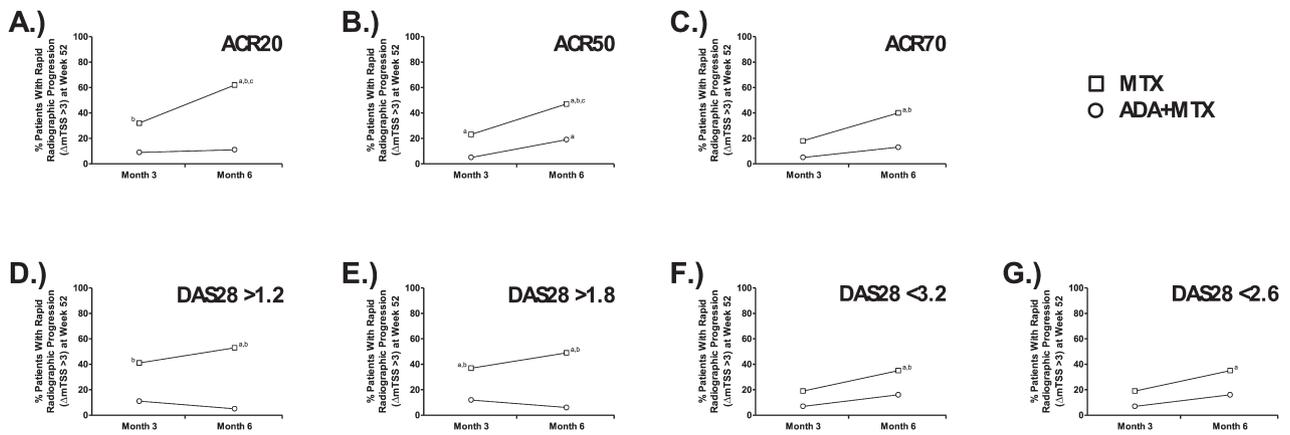
Figure 5. Rapid radiographic progression at 1 year MTX or ADA + MTX Month 3 and Month 6 responders. The percentages of MTX-treated or ADA + MTX-treated patients exhibiting rapid radiographic progression (ΔmTSS > 3) at 1 year based on (A–C) ACR responses (ACR20/50/70), (D–E) improvements in DAS28-CRP (improvements > 1.2/1.8), or (F–G) DAS28-CRP targets (LDA, DAS28-CRP < 3.2; remission, DAS28-CRP < 2.6) at months 3 and 6 (Month 3 responders) or at Month 6 (Month 6 responders). A, B, and C indicate outcomes that are significantly different relative to ADA + MTX Month 3 responders, ADA + MTX Month 6 responders, and MTX Month 3 responders, respectively, by OR (95% CI). MTX: methotrexate; ADA: adalimumab; ACR: American College of Rheumatology; DAS28: 28-joint Disease Activity Score; CRP: C-reactive protein; mTSS: modified total Sharp score; LDA: low disease activity.

disease-modifying therapies[13,14,15], and extending the treatment change decision to 6 months is still considered a reasonable approach to effective disease management[4,7]. In the present analysis, we examined the longterm clinical, functional, and radiographic outcomes associated with clinical responses observed at 3 months (12 weeks) and 6 months (24 weeks) in patients with early RA, in the context of treatment with either MTX monotherapy or the combination of ADA + MTX.

Our results suggest that both the kinetics and magnitude of the clinical response can predict longterm clinical, functional, and radiographic outcomes for patients with early RA. For patients with aggressive disease who are treated with MTX monotherapy, a high-level clinical response (e.g., ACR50 or improvement in DAS28-CRP > 1.8) should be achieved by 3 months to be associated with desirable longterm outcomes. In this analysis, MTX-treated patients who failed to meet such response criteria demonstrated poor outcomes at years 1 and 2, even if the high-level response was achieved by Month 6. In such patients, therapy may need to be adjusted after 3 months, a finding consistent with current treatment recommendations[7]. In contrast, MTX-treated patients who achieved a target of at least LDA within the first 6 months of therapy demonstrated desirable longterm outcomes that were largely independent of the timing of the response, although the risk of RRP remained elevated for Month 6 responders. Within the same responder populations, combination treatment with ADA + MTX was typically associated with numerically better clinical and functional outcomes and less radiographic progression at 1 year, irrespective of whether the clinical response was observed at Month 3 or at Month 6, although similar downward trends in outcomes were observed for Month 6 responders relative to Month 3 responders. The clinical and functional outcomes for Month 6 ADA + MTX responders were largely comparable with those from Month 3 MTX responders. These data suggest an important treatment-dependent distinction: that, in contrast to patients receiving MTX monotherapy, the decision regarding treatment adjustment may be extended to 6 months in patients receiving ADA + MTX combination therapy, without imposing significant longterm risks.

The finding that this population of patients with early and aggressive RA who are taking continuous MTX monotherapy had significant risks of rapid structural damage if a strong clinical response was not observed after 3 months of therapy is important, given the association between radiographic progression and physical disability[24,25,26]. In these cases, continuation of MTX monotherapy may leave the patient susceptible to irreversible damage and associated functional impairment. In contrast, these analyses revealed that patients initiated on ADA + MTX combination therapy had low risks for RRP, even in cases where clinical responses were not achieved until the 6-month timepoint. This finding is consistent with prior studies in which treatment with a TNF inhibitor + MTX was associated with low levels of radiographic progression even in patients with ongoing disease activity, while disease activity and radiographic damage were highly correlated in patients taking MTX monotherapy[13,14,27,28,29,30,31,32,33]. Still, the trial designs of these studies and ours did not allow for adjustments in therapy, and it is likely that the timely addition of biologic therapy following an inadequate response to MTX may have rescued longterm outcomes, as has been shown with ADA combination therapy in the OPTIMA trial[4].

Important limitations exist for this analysis. The assessment of clinical response measures at 2 specific timepoints may not be entirely reflective of when the response first occurred. Some patients classified as Month 6 responders may have transiently achieved the response prior to Month 3; however, information regarding the stability of the selected clinical responses was not integrated into this analysis. Another limitation of the present analysis is its observed nature, which could inflate the efficacy outcomes. Further, this analysis tracked patients who were considered to be responders; thus, the conclusions could be biased owing to better patient adherence to the study among responders. Still, it should be noted that this would be expected to occur similarly for both treatment groups. Lastly, patients enrolled in PREMIER had disease characteristics consistent with severely active disease, which may not be entirely reflective of patients with RA typically seen in the clinic. Patient cohort data indicate that patients seen in clinical practice often have less disease activity at the time of DMARD initiation than patients enrolled in clinical trials[34,35]. A further analysis of patients with disease activity typical of that observed in a clinical setting is warranted.

Therapy initiation for patients with early, active RA often involves MTX monotherapy. The kinetics of clinical response associated with MTX treatment may be slower than that seen with concomitant biologic therapy, but patients may respond to MTX monotherapy within a 6-month time frame[2,4,15,36]. Our analysis has demonstrated that patients who respond later to MTX therapy (at Month 6), even if achieving a clinically stringent response at that timepoint, typically have worse longterm clinical, functional, and radiographic outcomes while taking continued MTX monotherapy than those who achieve the response earlier. In fact, a high percentage of these patients developed significant amounts of structural damage within the first year of treatment. Hence, a 3-month window may be a more appropriate period in which to assess the efficacy of MTX monotherapy. In contrast, patients who initially received the combination of ADA + MTX typically demonstrated comparable longterm outcomes at 1 and 2 years of therapy, regardless of whether the desired clinical response was observed at month 3 or month 6. Therefore, in patients treated with the combination of ADA + MTX, a Month 6 clinical response was not associated with the same longterm risks seen in those with delayed responses to MTX monotherapy. Based on these and other data, important distinctions between antirheumatic therapies may need to be incorporated into RA treatment recommendations.

ACKNOWLEDGMENT

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