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

Edward C. Keystone, Boulos Haraoui, Benoît Guérette, Neelufar Mozaffarian, Shufang Liu, and Arthur Kavanaugh

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. (J Rheumatol First Release Dec 1 2013; doi:10.3899/jrheum.121468)

Key Indexing Terms:
RHEUMATOID ARTHRITIS
TUMOR NECROSIS FACTOR INHIBITORS
METHOTREXATE
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

From the University of Toronto, Toronto, Ontario; the University of Montreal, Montreal, Quebec, Canada; AbbVie Inc., North Chicago, Illinois; and the University of California San Diego, La Jolla, California, USA.

Sponsored by AbbVie Inc. (NCT00195663), which contributed to the study design, and was involved in the collection, analysis, and interpretation of the data, and in the drafting, review, and approval of the manuscript. Dr. Keystone has received consulting fees or other remuneration from, and served on advisory boards on behalf of, AbbVie Inc., AstraZeneca, Biotest, BMS, Centocor, Genentech, Merck, Nycomed, Pfizer, Roche, and UCB, has received research grants from AbbVie Inc., Amgen, AstraZeneca, BMS, Centocor, Genzyme, Merck, Novartis, Pfizer, Roche, and UCB, and has speaker honoraria agreements with AbbVie Inc., Amgen, BMS, Janssen, Merck, Pfizer, Roche, and UCB. Dr. Haraoui has received consulting fees or other remuneration from AbbVie Inc., Amgen, BMS, Merck, Pfizer, Roche, and UCB. Dr. Kavanaugh has received consulting fees or other remuneration and research grants from AbbVie Inc., Amgen, Astra-Zeneca, BMS, Celgene, Centocor-Janssen, Pfizer, Roche, and UCB. Drs. Guérette and Liu are both fulltime employees of AbbVie Inc. and may hold stock or stock options. Dr. Mozaffarian is a former employee of AbbVie Inc. and is currently employed by Eli Lilly & Co.

E.C. Keystone, MD, University of Toronto; B. Haraoui, MD, University of Montreal; B. Guérette, PhD; N. Mozaffarian, MD, PhD; S. Liu, PhD, AbbVie Inc.; A. Kavanaugh, MD, University of California San Diego.

Address correspondence to Dr. E.C. Keystone, MD, Mount Sinai Hospital, University of Toronto, The Rebecca MacDonald Centre for Arthritis and Autoimmune Disease, Joseph and Wolf Lebovic Building, 2nd Floor, 60 Murray St., Toronto, Ontario M5T 3L9, Canada.
E-mail: edkeystone@mtsinai.on.ca

Full Release Article. For details see Reprints/Permissions at jrheum.org

Accepted for publication September 17, 2013.

(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

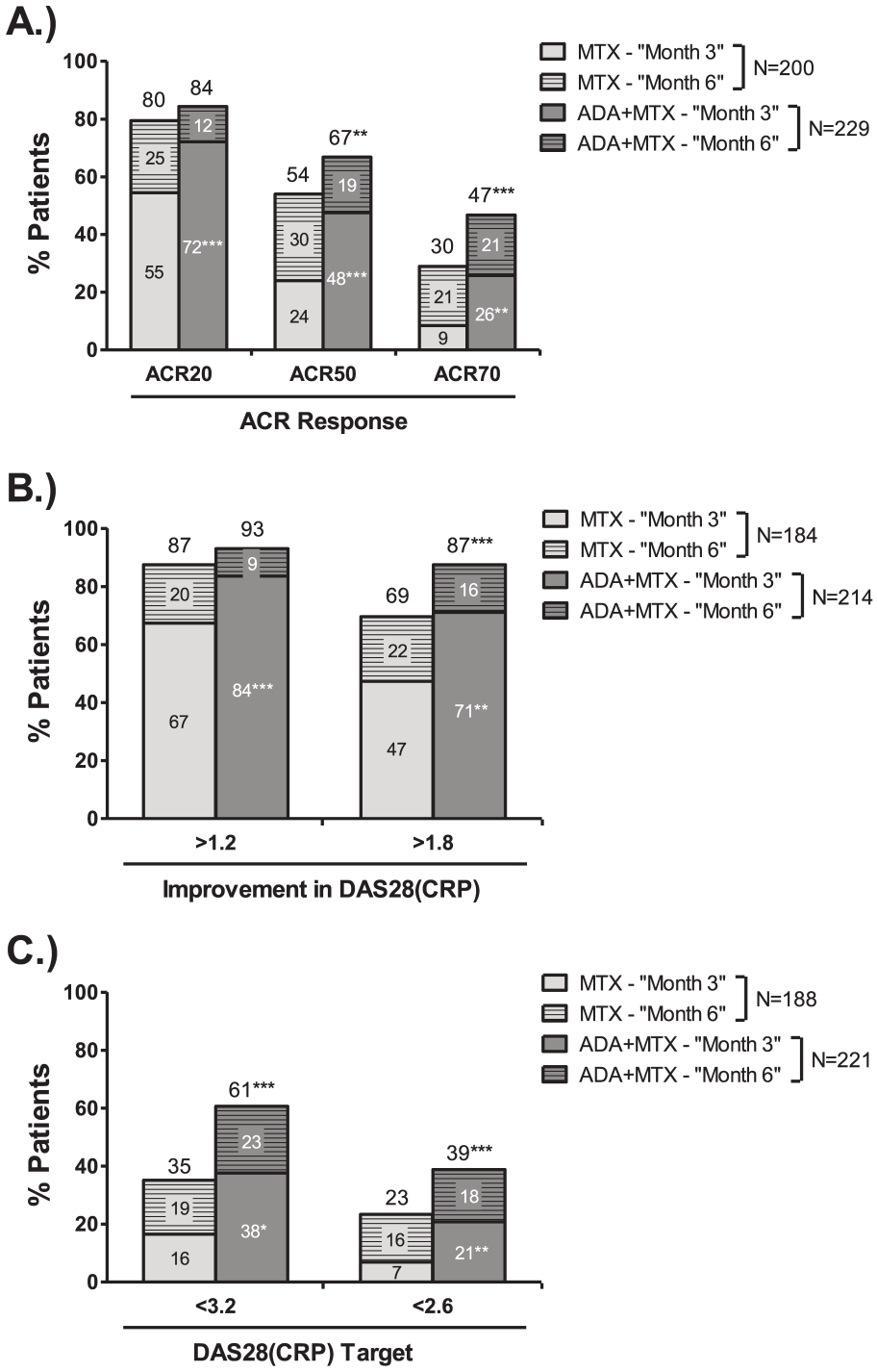

Figure 1. Proportions of MTX or ADA + MTX Month 3 and Month 6 responders. The percentages of MTX-treated or ADA + MTX-treated patients exhibiting (A) ACR responses (ACR20/50/70), (B) improvements in DAS28-CRP (improvements > 1.2/1.8), or (C) DAS28-CRP targets (LDA, DAS28-CRP < 3.2; remission, DAS28-CRP < 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 [$p \geq 0.05$ 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

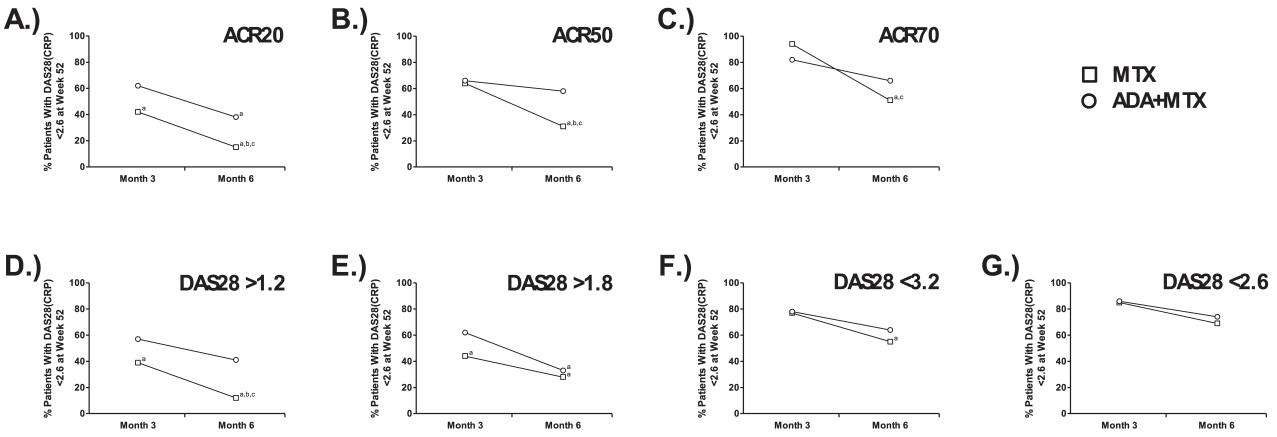

Figure 2. Clinical remission at 1 year in MTX or ADA + MTX Month 3 and Month 6 responders. The percentages of MTX or ADA + MTX-treated patients exhibiting clinical remission (DAS28-CRP < 2.6) at 1 year based on (A–C) ACR responses (ACR20/50/70), (D and E) improvements in DAS28-CRP (> 1.2/1.8), or (F 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

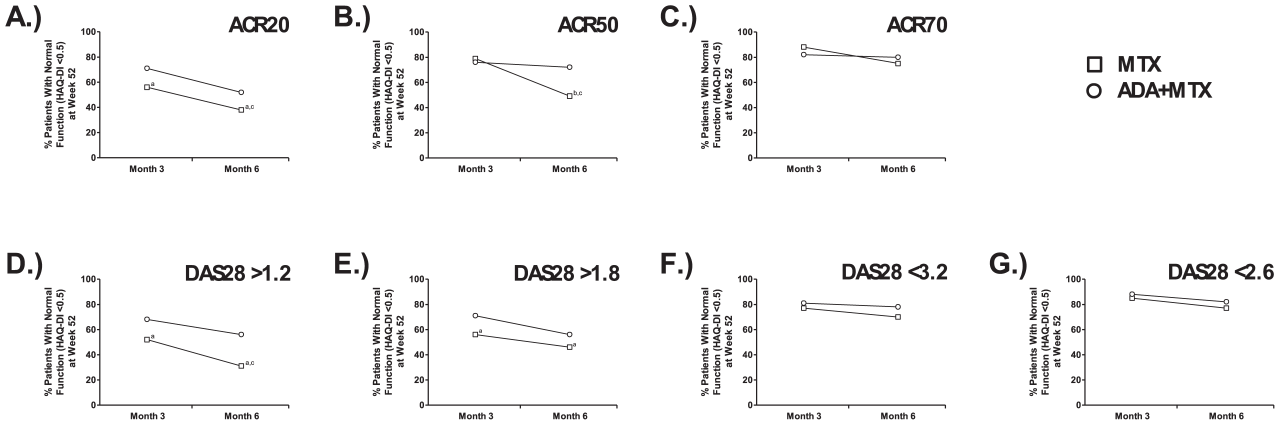

Figure 3. Normal functionality at 1 year in MTX or ADA + MTX Month 3 and Month 6 responders. The percentages of MTX or ADA + MTX–treated patients exhibiting normal function (HAQ-DI < 0.5) at 1 year based on (A–C) ACR responses (ACR20/50/70), (D–E) improvements in DAS28-CRP (improvements > 1.2/1.8), or (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..

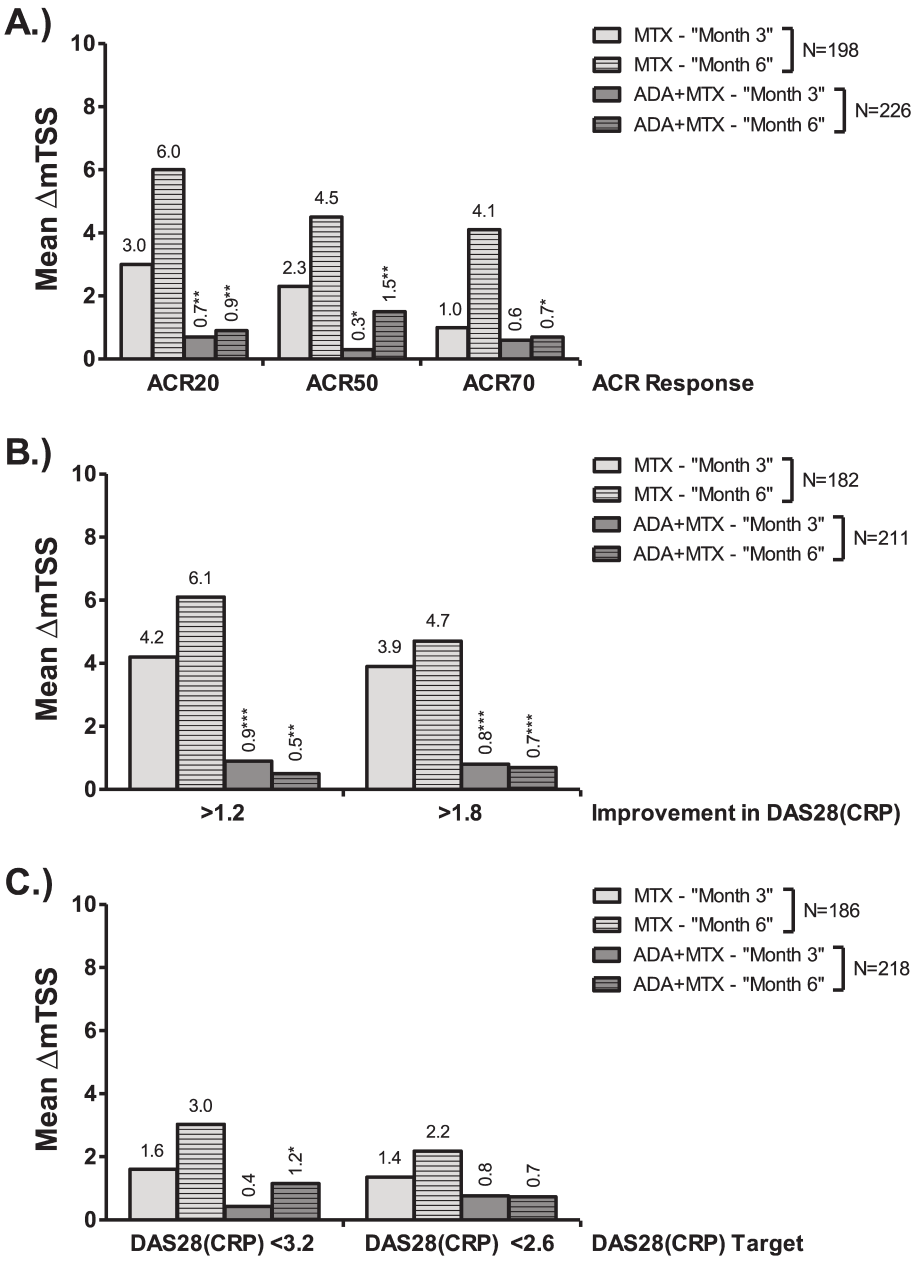

Figure 4. Radiographic progression in MTX or ADA + MTX Month 3 and Month 6 responders. Mean change in modified total Sharp score (mTSS) from baseline to 1 year in MTX-treated or ADA + MTX-treated patients exhibiting (A) ACR responses (ACR20/50/70), (B) improvements in DAS28-CRP (improvements > 1.2/1.8), 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

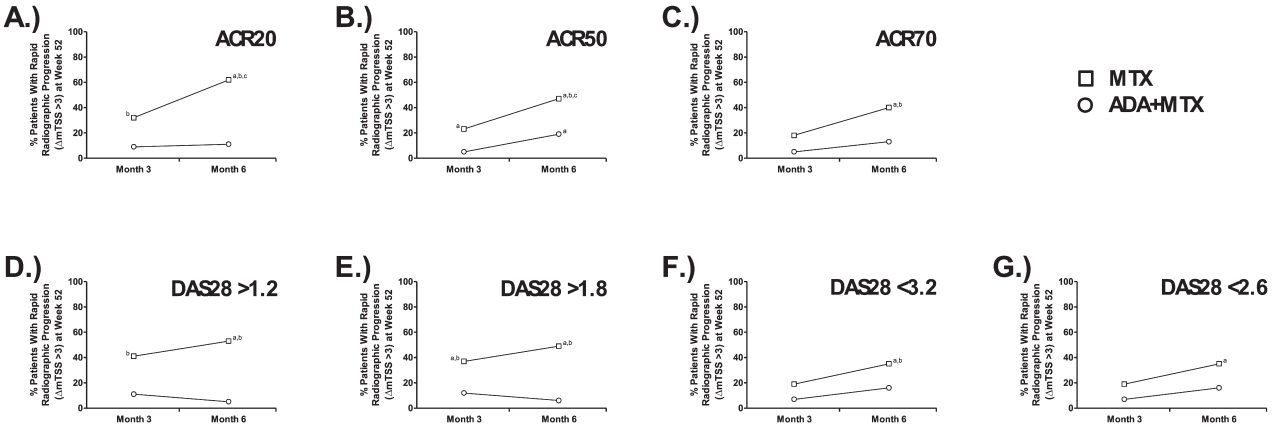

Figure 5. Rapid radiographic progression at 1 year MTX or ADA + MTX Month 3 and Month 6 responders. The percentages of MTX-treated or ADA + MTX-treated patients exhibiting rapid radiographic progression (ΔmTSS > 3) at 1 year based on (A–C) ACR responses (ACR20/50/70), (D–E) improvements in DAS28-CRP (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

The authors thank Dr. Michael Weinblatt (Boston, MA, USA) for valuable discussions during the development of this manuscript. Medical writing assistance in the development and revision of this manuscript was provided by Benjamin Wolfe, PhD, of AbbVie Inc.

REFERENCES

1. Fransen J, Moens HB, Speyer I, van Riel PL. Effectiveness of systematic monitoring of rheumatoid arthritis disease activity in daily practice: a multicentre, cluster randomised controlled trial. Ann Rheum Dis 2005;64:1294-8.
2. Goekoop-Ruiterman YP, de Vries-Bouwstra JK, Allaart CF, van Zeben D, Kerstens PJ, Hazes JM, et al. Clinical and radiographic outcomes of four different treatment strategies in patients with early rheumatoid arthritis (the BeSt study): a randomized, controlled trial. Arthritis Rheum 2005;52:3381-90.
3. Grigor C, Capell H, Stirling A, McMahon AD, Lock P, Vallance R, et al. Effect of a treatment strategy of tight control for rheumatoid arthritis (the TICORA study): a single-blind randomised controlled trial. Lancet 2004;364:263-9.
4. Smolen J, Fleischmann R, Emery P, Guerette B, Patra K, Kupper H, et al. The OPTIMA study of methotrexate and adalimumab: 78-week outcomes in early rheumatoid arthritis patients based on achieving a low DAS28 target after 26 weeks (abstract). Ann Rheum Dis 2011;70 Suppl 3:259.
5. Soubrier M, Puechal X, Sibilia J, Mariette X, Meyer O, Combe B, et al. Evaluation of two strategies (initial methotrexate monotherapy vs its combination with adalimumab) in management of early active rheumatoid arthritis: data from the GUEPARD trial. Rheumatology 2009;48:1429-34.
6. Verstappen SM, Jacobs JW, van der Veen MJ, Heurkens AH, Schenk Y, ter Borg EJ, et al. Intensive treatment with methotrexate in early rheumatoid arthritis: aiming for remission. Computer Assisted Management in Early Rheumatoid Arthritis (CAMERA, an open-label strategy trial). Ann Rheum Dis 2007;66:1443-9.
7. Smolen JS, Landewé R, Breedveld FC, Dougados M, Emery P, Gaujoux-Viala C, et al. EULAR recommendations for the management of rheumatoid arthritis with synthetic and biological disease-modifying antirheumatic drugs. Ann Rheum Dis 2010;69:964-75.
8. Smolen JS, Aletaha D, Bijlsma JW, Breedveld FC, Boumpas D, Burmester G, et al. Treating rheumatoid arthritis to target: recommendations of an international task force. Ann Rheum Dis 2010;69:631-7.
9. Singh JA, Furst DE, Bharat A, Curtis JR, Kavanaugh AF, Kremer JM, et al. 2012 update of the 2008 American College of Rheumatology recommendations for the use of disease-modifying antirheumatic drugs and biologic agents in the treatment of rheumatoid arthritis. Arthritis Care Res 2012;64:625-39.
10. Aletaha D, Funovits J, Keystone EC, Smolen JS. Disease activity early in the course of treatment predicts response to therapy after one year in rheumatoid arthritis patients. Arthritis Rheum 2007;56:3226-35.
11. Ichikawa Y, Saito T, Yamanaka H, Akizuki M, Kondo H, Kobayashi S, et al. Clinical activity after 12 weeks of treatment with nonbiologics in early rheumatoid arthritis may predict articular destruction 2 years later. J Rheumatol 2010;37:723-9.
12. Weinblatt ME, Keystone EC, Cohen MD, Freundlich B, Li J, Chon Y, et al. Factors associated with radiographic progression in patients with rheumatoid arthritis who were treated with methotrexate. J Rheumatol 2011;38:242-6.
13. Kavanaugh A, Keystone E, Feng J, Hooper M. Is a 12-week trial sufficient to evaluate clinical responses to etanercept or MTX treatment in early RA? Rheumatology 2010;49:1201-3.
14. Kavanaugh A, Klareskog L, van der Heijde D, Li J, Freundlich B, Hooper M. Improvements in clinical response between 12 and 24 weeks in patients with rheumatoid arthritis on etanercept therapy with or without methotrexate. Ann Rheum Dis 2008;67:1444-7.
15. Kremer JM, Lee JK. The safety and efficacy of the use of methotrexate in long-term therapy for rheumatoid arthritis. Arthritis Rheum 1986;29:822-31.

16. Arnett FC, Edworthy SM, Bloch DA, McShane DJ, Fries JF, Cooper NS, et al. The American Rheumatism Association 1987 revised criteria for the classification of rheumatoid arthritis. Arthritis Rheum 1988;31:315-24.
17. Breedveld FC, Weisman MH, Kavanaugh AF, Cohen SB, Pavelka K, van Vollenhoven R, et al. 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. Arthritis Rheum 2006;54:26-37.
18. Prevoo ML, van 't Hof MA, Kuper HH, van Leeuwen MA, van de Putte LB, van Riel PL. Modified disease activity scores that include twenty-eight-joint counts. Development and validation in a prospective longitudinal study of patients with rheumatoid arthritis. Arthritis Rheum 1995;38:44-8.
19. Fries JF, Spitz PW, Young DY. The dimensions of health outcomes: the health assessment questionnaire, disability and pain scales. J Rheumatol 1982;9:789-93.
20. Keystone EC, Kavanaugh AF, Sharp JT, Tannenbaum H, Hua Y, Teoh LS, et al. Radiographic, clinical, and functional outcomes of treatment with adalimumab (a human anti-tumor necrosis factor monoclonal antibody) in patients with active rheumatoid arthritis receiving concomitant methotrexate therapy: a randomized, placebo-controlled, 52-week trial. Arthritis Rheum 2004;50:1400-11.
21. Plant MJ, Saklatvala J, Borg AA, Jones PW, Dawes PT. Measurement and prediction of radiological progression in early rheumatoid arthritis. J Rheumatol 1994;21:1808-13.
22. Sharp JT, Lidsky MD, Collins LC, Moreland J. Methods of scoring the progression of radiologic changes in rheumatoid arthritis. Correlation of radiologic, clinical and laboratory abnormalities. Arthritis Rheum 1971;14:706-20.
23. Sharp JT, Young DY, Bluhm GB, Brook A, Brower AC, Corbett M, et al. How many joints in the hands and wrists should be included in a score of radiologic abnormalities used to assess rheumatoid arthritis? Arthritis Rheum 1985;28:1326-35.
24. Odegard S, Landewé R, van der Heijde D, Kvien TK, Mowinckel P, Uhlig T. Association of early radiographic damage with impaired physical function in rheumatoid arthritis: a ten-year, longitudinal observational study in 238 patients. Arthritis Rheum 2006;54:68-75.
25. van der Heijde D, Landewé R, Guerette B, Roy S, Patra K, Keystone E. Joint space narrowing has a stronger impact on physical function than joint erosion: results from 8-year longitudinal analyses (abstract). Arthritis Rheum 2010;62 Suppl 10:S466-7.
26. van der Heijde D, Landewé R, van Vollenhoven R, Fatenejad S, Klareskog L. Level of radiographic damage and radiographic progression are determinants of physical function: a longitudinal analysis of the TEMPO trial. Ann Rheum Dis 2008;67:1267-70.
27. 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.
28. Landewé R, van der Heijde D, Klareskog L, van Vollenhoven R, Fatenejad S. Disconnect between inflammation and joint destruction after treatment with etanercept plus methotrexate: results from the trial of etanercept and methotrexate with radiographic and patient outcomes. Arthritis Rheum 2006; 54:3119-25.
29. Smolen JS, Han C, Bala M, Maini RN, Kalden JR, van der Heijde D, et al. Evidence of radiographic benefit of treatment with infliximab plus methotrexate in rheumatoid arthritis patients who had no clinical improvement: a detailed subanalysis of data from the anti-tumor necrosis factor trial in rheumatoid arthritis with concomitant therapy study. Arthritis Rheum 2005;52:1020-30.
30. Smolen JS, Han C, van der Heijde DM, Emery P, Bathon JM, Keystone E, et al. Radiographic changes in rheumatoid arthritis patients attaining different disease activity states with methotrexate monotherapy and infliximab plus methotrexate: the impacts of remission and tumour necrosis factor blockade. Ann Rheum Dis 2009;68:823-7.
31. Smolen JS, Van Der Heijde DM, St Clair EW, Emery P, Bathon JM, Keystone E, et al. Predictors of joint damage in patients with early rheumatoid arthritis treated with high-dose methotrexate with or without concomitant infliximab: results from the ASPIRE trial. Arthritis Rheum 2006;54:702-10.
32. Smolen JS, van der Heijde DM, Keystone EC, van Vollenhoven RF, Goldring MB, Guerette B, et al. Association of joint space narrowing with impairment of physical function and work ability in patients with early rheumatoid arthritis: protection beyond disease control by adalimumab plus methotrexate. Ann Rheum Dis 2013;72:1156-62.
33. Keystone EC, Curtis JR, Fleischmann RM, Furst DE, Khanna D, Smolen JS, et al. Rapid improvement in the signs and symptoms of rheumatoid arthritis following certolizumab pegol treatment predicts better longterm outcomes: post-hoc analysis of a randomized controlled trial. J Rheumatol 2011;38:990-6.
34. Furst DE, Pangan AL, Harrold LR, Chang H, Reed G, Kremer JM, et al. Greater likelihood of remission in rheumatoid arthritis patients treated earlier in the disease course: results from the Consortium of Rheumatology Researchers of North America registry. Arthritis Care Res 2011;63:856-64.
35. Hetland ML, Christensen IJ, Tarp U, Dreyer L, Hansen A, Hansen IT, et al. Direct comparison of treatment responses, remission rates, and drug adherence in patients with rheumatoid arthritis treated with adalimumab, etanercept, or infliximab: results from eight years of surveillance of clinical practice in the nationwide Danish DANBIO registry. Arthritis Rheum 2010;62:22-32.
36. van Vollenhoven RF, Ernestam S, Geborek P, Petersson IF, Coster L, Waltbrand E, et al. Addition of infliximab compared with addition of sulfasalazine and hydroxychloroquine to methotrexate in patients with early rheumatoid arthritis (Swefot trial): 1-year results of a randomised trial. Lancet 2009;374:459-66.