Longterm Effect of Delaying Combination Therapy with Tumor Necrosis Factor Inhibitor in Patients with Aggressive Early Rheumatoid Arthritis: 10-year Efficacy and Safety of Adalimumab from the Randomized Controlled PREMIER Trial with Open-label Extension

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ABSTRACT. ***Objective.*** To evaluate the longterm safety of adalimumab administered with or without methotrexate (MTX) and compare the efficacy of combination therapy initialization to adalimumab or MTX monotherapy initialization during the open-label extension (OLE) of the PREMIER trial (ClinicalTrials.gov Identifier:NCT00195663).

Methods. Patients with early rheumatoid arthritis (RA) were randomized to receive blinded adalimumab + MTX, adalimumab alone, or MTX alone for 2 years. Following the double-blinded period, patients enrolling in the OLE were given adalimumab for up to 8 additional years, beginning as monotherapy; investigators could add MTX at their discretion. Results for clinical, functional, and radiographic progression were collected for up to 10 years of treatment.

Results. During the PREMIER OLE, 250/497 patients (50.3%) completed the trial without new safety signals arising. Similar proportions of patients discontinued the trial early, although lack of efficacy was reported less often for patients initially randomized to the adalimumab + MTX arm (9.3%; 21.2%, and 23.7% for adalimumab and MTX monotherapies, respectively). Clinical and functional disease control was maintained throughout the trial. Patients initially randomized to adalimumab + MTX displayed better outcomes, particularly in prevention of radiographic progression (modified total Sharp score change = 4.0, 8.8, 11.0 at Year 10 for the initial adalimumab + MTX, adalimumab, and MTX arms, respectively).

Conclusion. Intensive therapy with adalimumab + MTX combination in patients with early RA has longterm benefits compared to patients initiating with 2-year adalimumab or MTX monotherapy that persists up to 10 years following adalimumab OLE. No new safety findings were observed following longterm adalimumab treatment. (First Release Nov 15 2013; J Rheumatol 2014;41:5–14; doi:10.3899/jrheum.130543)

Key Indexing Terms:
ADALIMUMAB RHEUMATOID ARTHRITIS LONGTERM TREATMENT
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Rheumatoid arthritis (RA) is a chronic and debilitating inflammatory disease with a population prevalence of about 1%[1]. Progressive inflammation in the joints of patients can lead to irreversible joint damage[2,3], diminished function, and disability[4]. In many diseases, and particularly in RA, early diagnosis and intervention is advantageous for achieving comprehensive disease control (CDC), i.e., suppression of inflammation, preserving physical function, and preventing structural damage[3,5,6,7]. Longterm disease control and inhibition of radiographic progression has been demonstrated as an achievable goal for patients with early RA[8,9]. Multiple biologics are available for the treatment of RA; however, longterm data up to 10 years are limited and needed to fully understand the benefit/risk ratio[10] especially in patients diagnosed with early, aggressive RA who will require lifelong treatment.

Treatment strategies and recommendations have been carefully crafted considering many aspects of RA including, but not limited to, physical, socioeconomic, and psychological concerns. Recommendations for the management of RA based on the knowledge of treatment options, their efficacy, and safety profiles have been formulated[11,12]. Remission or low disease activity (LDA) being the target, synthetic disease-modifying antirheumatic drugs (DMARD), including methotrexate (MTX), should be the first agents prescribed, with outcomes evaluated every 1 to 3 months. If within 3 to 6 months, disease control is not achieved or other factors present themselves (e.g., high disease activity, early joint damage, etc.), addition of a second DMARD or a biologic drug, especially a tumor necrosis factor (TNF) inhibitor, should be initiated and efficacy evaluated for 3 to 6 months. These recommendations are based on numerous studies demonstrating the efficacy of TNF inhibitors in combination with MTX for the improvement in clinical symptoms of RA and inhibition of radiographic progression[13,14,15].

The PREMIER study evaluated the TNF inhibitor adalimumab in combination with MTX compared to adalimumab or MTX monotherapy, for treatment of RA patients with early aggressive disease over the course of a 2-year double-blind (DB) trial. Following the DB period, adalimumab + MTX combination therapy demonstrated substantially better clinical and functional responses, and radiographic progression was prevented[16]. This report evaluates the longterm disease control advantage, following an 8-year open-label extension (OLE), of patients randomized to adalimumab + MTX combination therapy during the PREMIER DB compared to patients who started the trial on adalimumab or MTX monotherapy. Final efficacy and safety measures for RA patients with up to 10 years of adalimumab exposure are reported.

MATERIALS AND METHODS

Study design. PREMIER (ClinicalTrials.gov. Identifier: NCT00195663) was a 2-year, randomized, DB, active comparator-controlled, multicenter, phase III study followed by an 8-year OLE. Initial patient enrollment was randomized almost equally to 1 of 3 treatment groups: subcutaneous adalimumab 40 mg every other week with weekly MTX, adalimumab 40 mg every other week + weekly placebo, or weekly MTX + placebo every other week. Oral MTX was given initially at 7.5 mg/week and escalated to 20 mg/week as tolerated by Week 8. After completion of the DB period, all patients were eligible to receive open-label (OL) adalimumab 40 mg every other week for up to 8 additional years; MTX could be added during the OLE at the investigator's discretion. The trial was conducted in accord with good clinical practice and the Declaration of Helsinki. Ethics approval was obtained for each of 133 investigational sites (11 in Australia, 85 in Europe, and 37 in North America) and all patients provided informed consent. The first adalimumab dose occurred in January 2001, with the last dose administered in June 2012.

Patients. Inclusion and exclusion criteria have been described[16]. Enrollment criteria included adults ≥ 18 years of age diagnosed with RA as defined by the 1987-revised American College of Rheumatology (ACR) criteria[17,18], and a disease duration < 3 years. Additionally, trial participants were required to have a swollen joint count (SJC) ≥ 8 of 66 assessed joints, tender joint count (TJC) ≥ 10 of 68 assessed joints, erythrocyte sedimentation rate > 28 mm/h or C-reactive protein (CRP) ≥ 1.5 mg/dl. Patients were excluded if they had received prior treatment with MTX, cyclophosphamide, cyclosporine, azathioprine, or > 2 other DMARD, or prednisone equivalent > 10 mg/day within 30 days of screening.

Clinical, functional, and radiographic assessments. Clinical and functional responses were assessed at regular intervals throughout the trial. The percentages of patients achieving ACR50/70/90 responses were summarized by visit. Physical function, measured by the Disability Index of the Health Assessment Questionnaire (HAQ-DI), was summarized by visit and as the percentages achieving normal function (HAQ-DI < 0.5). Disease Activity Score 28-joint count (DAS28) using CRP assessed the percentage of patients in LDA [DAS28 (CRP) < 3.2] or clinical remission [DAS28 (CRP) < 2.6] by visit. Radiographic progression [joint erosion and joint space narrowing (JSN), the sum yielding the modified total Sharp score (mTSS)] was assessed in 10-year completers with radiographic data available at baseline and Year 10. Radiographic scoring was performed by 2 readers blinded to patient and sequence. The proportions of patients achieving CDC (simultaneous achievement of DAS28 < 3.2, HAQ-DI < 0.5, and ΔmTSS ≤ 0.5) and comprehensive disease remission (CDR; DAS28 < 2.6 replaces DAS28 < 3.2 in CDC) at years 2, 6, and 10 were determined in 10-year completers.

Adverse events (AE) of interest were coded using the *Medical Dictionary for Drug Regulatory Affairs* version 14.1 and analyzed for presenting frequency, percentage, and events per 100 patient-years (PY) for patients who received ≥ 1 dose of adalimumab during the study. Treatment emergent adverse events (TEAE) were defined as any AE with an onset date on or after the date of the first adalimumab dose through 70 days after the last adalimumab dose in Year 10.

Statistical analyses. Efficacy measured by ACR response, HAQ-DI, and DAS28 were analyzed both as observed for all randomized patients (n = 799) and using nonresponder imputation for the population entering the OLE (n = 497) as a sensitivity analysis to account for discontinuations over the 10-year study. Additionally, last observation carried forward of all randomized patients was used to summarize final visit response. Only patients completing the trial, thus having baseline and year-10 radiographic

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data, were included in radiographic and comprehensive disease control analyses. Differences in ΔmTSS from baseline to Year 10 and from years 3 to 10 were assessed using a longitudinal ANCOVA following adjustment for baseline damage. Differences in response rates, as well as clinical and functional outcomes between the initial and delayed combination therapy groups, were assessed through generalized estimating equations analyzing yearly repeated measurement. Results are summarized by initial (randomized) treatment group. Safety measures were evaluated using all patients who received ≥ 1 dose of adalimumab (n = 697).

RESULTS

Patient disposition and patient flow. Of the 799 randomized patients, 196/268 (73.1%), 166/274 (60.6%), and 164/257 (63.8%) of patients initially treated with adalimumab + MTX, adalimumab, and MTX, respectively, completed the DB period; baseline disease characteristics for each group have been reported[16]. Following the DB period, 497 patients (62%) entered the OLE (adalimumab + MTX, n = 183; adalimumab, n = 159; MTX, n = 155; Table 1). Patients who entered the OLE possessed numerically lower baseline mean TJC (26.0 ± 16.4), SJC (18.0 ± 12.1), DAS28 (5.6 ± 1.7), HAQ-DI (1.3 ± 0.7), and physician's and patient's global assessments of disease activity (visual analog scale 55.4 ± 27.4 and 56.8 ± 29.8, respectively) compared to baseline disease characteristics for all randomized patients[16]. Among the patients who entered the OLE, 250 (50.3%) maintained OL adalimumab ± MTX through Year 10 (Table 1).

The primary reasons for study discontinuation included the following (initial treatment group adalimumab + MTX, adalimumab, and MTX, respectively): AE (25.4%, 21.5%, 16.3%), withdrawn consent (12.7%, 12.0%, 12.1%), and death (0.7%, 1.5%, 0.8%). Lack of efficacy as the primary reason for withdrawal was reported in 25/268 patients (9.3%) initiated with adalimumab + MTX compared to 58/274 (21.2%) and 61/257 (23.7%) of adalimumab and MTX monotherapy patients, respectively.

Clinical response measures. Clinical improvement in ACR responses persisted over the course of the study based on observed data at each timepoint (Figures 1A, 1B, 1C, lines with symbols). Based on the observed data, ACR50 was achieved at year 10 by 80.0%, 69.4%, and 74.0% of the original adalimumab + MTX, adalimumab, and MTX treatment groups, respectively. Similarly, ACR70 and ACR90 responses persisted for up to 10 years. Differences in ACR responses were statistically significant using the generalized estimating model for patients initially on combination therapy versus adalimumab monotherapy (ACR50/70/90, $p < 0.01$) and MTX monotherapy (ACR70/90, $p < 0.05$). Based on nonresponder imputation, the proportion of patients entering the OLE achieving ACR50/70/90 over time demonstrated an advantage to trial initialization with combination therapy during the DB (Figures 1A, 1B, 1C, dashed lines), although the differences were less striking once all patients received adalimumab ± MTX. Observed ACR50/70/90 response rates at the final visit remained high (Figures 1A, 1B, 1C, bars).

Among the 497 patients who entered the OLE, 9 never reached an ACR20 response, 2 of whom completed the 10-year trial. The reasons for remaining in the trial until completion are unclear as patient-reported scores for physical function, pain, disease activity, and TJC remained high, although radiographic progression was slowed, and improvements were observed in CRP, function, physician's global assessment, and SJC in 1 or both patients.

The cost of delaying adalimumab ± MTX in monotherapy treatment groups was also evident in the proportion of patients achieving normal physical function over time (Figure 1D). Based on observed data, 63.5% of adalimumab

Table 1. Patient enrollment and discontinuations.

Disposition	MTX → OL ADA ± MTX, n (%)	ADA → OL ADA ± MTX, n (%)	ADA + MTX → OL ADA ± MTX, n (%)
Patients randomized	257	274	268
Completed 10-year study	79 (30.7)	85 (31.0)	86 (32.1)
Completed DB phase but did not enter into OLE	9 (3.5)	7 (2.6)	13 (4.9)
Early discontinuation	169 (65.8)	182 (66.4)	169 (63.1)
Primary reason for discontinuation			
Planned selection criterion	0	1 (0.4)	0
Adverse event	42 (16.3)	59 (21.5)	68 (25.4)
Lost to followup	9 (3.5)	2 (0.7)	7 (2.6)
Recovery	1 (0.4)	2 (0.7)	3 (1.1)
Protocol violation	9 (3.5)	10 (3.6)	8 (3.0)
Death	2 (0.8)	4 (1.5)	2 (0.7)
Withdrawal of consent	31 (12.1)	33 (12.0)	34 (12.7)
Lack of efficacy/progression of disease	61 (23.7)	58 (21.2)	25 (9.3)
Administrative reasons	14 (5.4)	13 (4.7)	22 (8.2)

MTX: methotrexate; OL: open-label; ADA: adalimumab; DB: double-blind; OLE: open-label extension.

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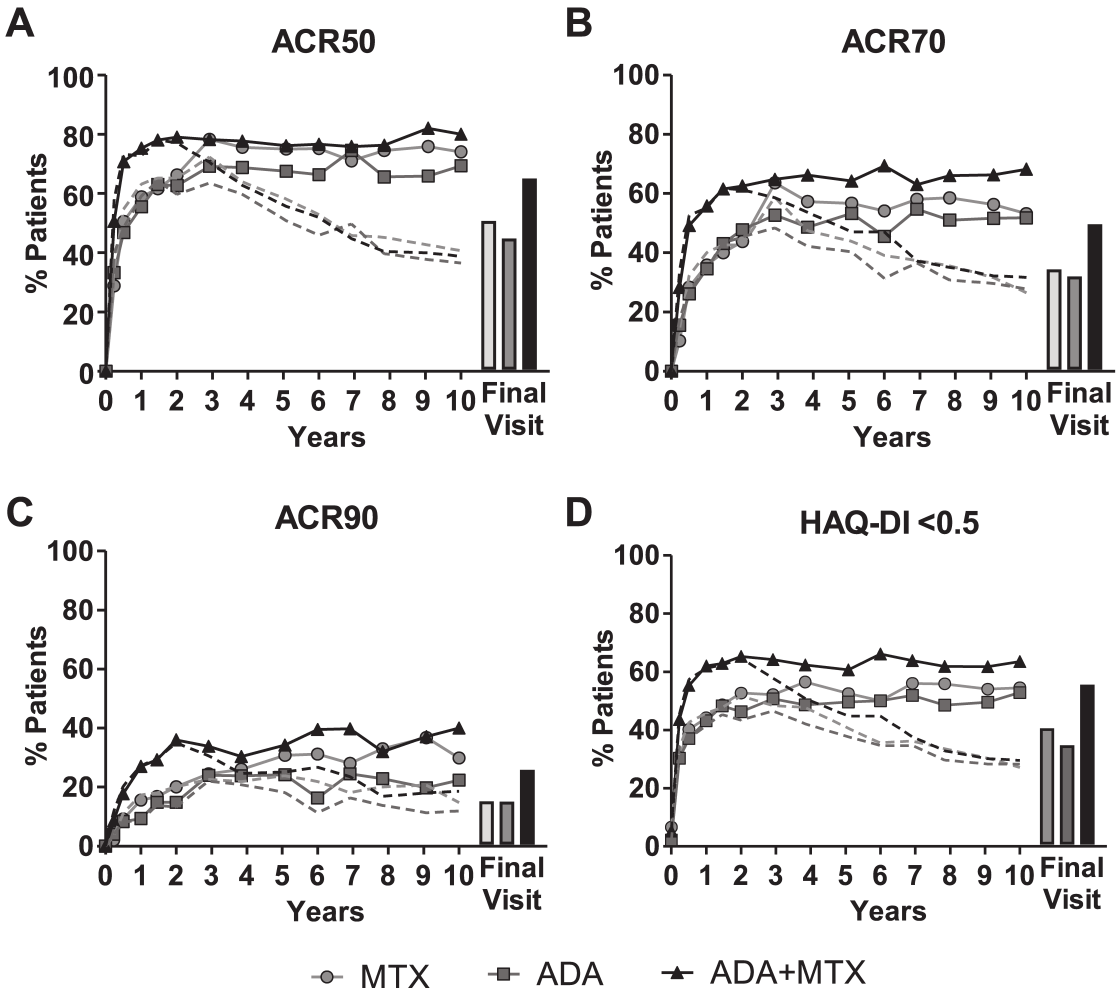

Figure 1. Response rates for patients achieving 50% (A), 70% (B), and 90% (C) improvement in ACR criteria, and normal physical function (D) over the course of 10 years of treatment. Lines with symbols represent observed response rate based on all randomized patients (n = 268, 274, and 257 for adalimumab + MTX, adalimumab, and MTX, respectively). Dashed lines represent response rate using nonresponder imputation based on all patients entering open-label extension (n = 183, 159, and 155 for adalimumab + MTX, adalimumab, and MTX, respectively). Bar graphs reflect data as observed at final visit using last observation carried forward method for all randomized patients (n = 268, 274, and 257 for adalimumab + MTX, adalimumab, and MTX, respectively). ACR: American College of Rheumatology Criteria response; ADA: adalimumab; MTX: methotrexate; HAQ-DI: Health Assessment Questionnaire–Disability Index.

+ MTX patients reported normal function at Year 10 compared to 52.9% and 54.5% of adalimumab and MTX trial initiators, respectively. Mean HAQ-DI scores at Year 10 were 0.4, 0.7, and 0.6 for adalimumab ± MTX, adalimumab, and MTX initiators, respectively. Differences in HAQ-DI scores and proportions of patients achieving normal function comparing combination therapy to either monotherapy were all statistically significant over time ($p \leq 0.05$).

Comprehensive disease control and remission. Addition of OL adalimumab ± MTX to the initial adalimumab and MTX monotherapy treatment groups led to improvements in the proportion of patients achieving CDC from the end of the DB period; however, 2-year combination therapy was superior to initial monotherapy over the course of 10 years, demonstrated by increased percentage of patients achieving DAS28 LDA, DAS28 remission, CDC, and CDR (Figure 2). For 10-year completers, patients in the adalimumab + MTX DB group achieved DAS28 LDA (92.3%) and remission (75.6%) more readily than patients who initiated treatment with adalimumab (77.8% and 61.7%, respectively) or MTX (74.0% and 56.2%, respectively) monotherapy (Figures 2A and 2B). Mean DAS28 scores were 2.1, 2.5, and 2.6 for the adalimumab + MTX, adalimumab, and MTX treatment groups, respectively. Based on observed data, differences over time in DAS28 scores and proportions of patients achieving DAS28 LDA or remission comparing combination therapy to either monotherapy were all statistically significant ($p \leq 0.001$).

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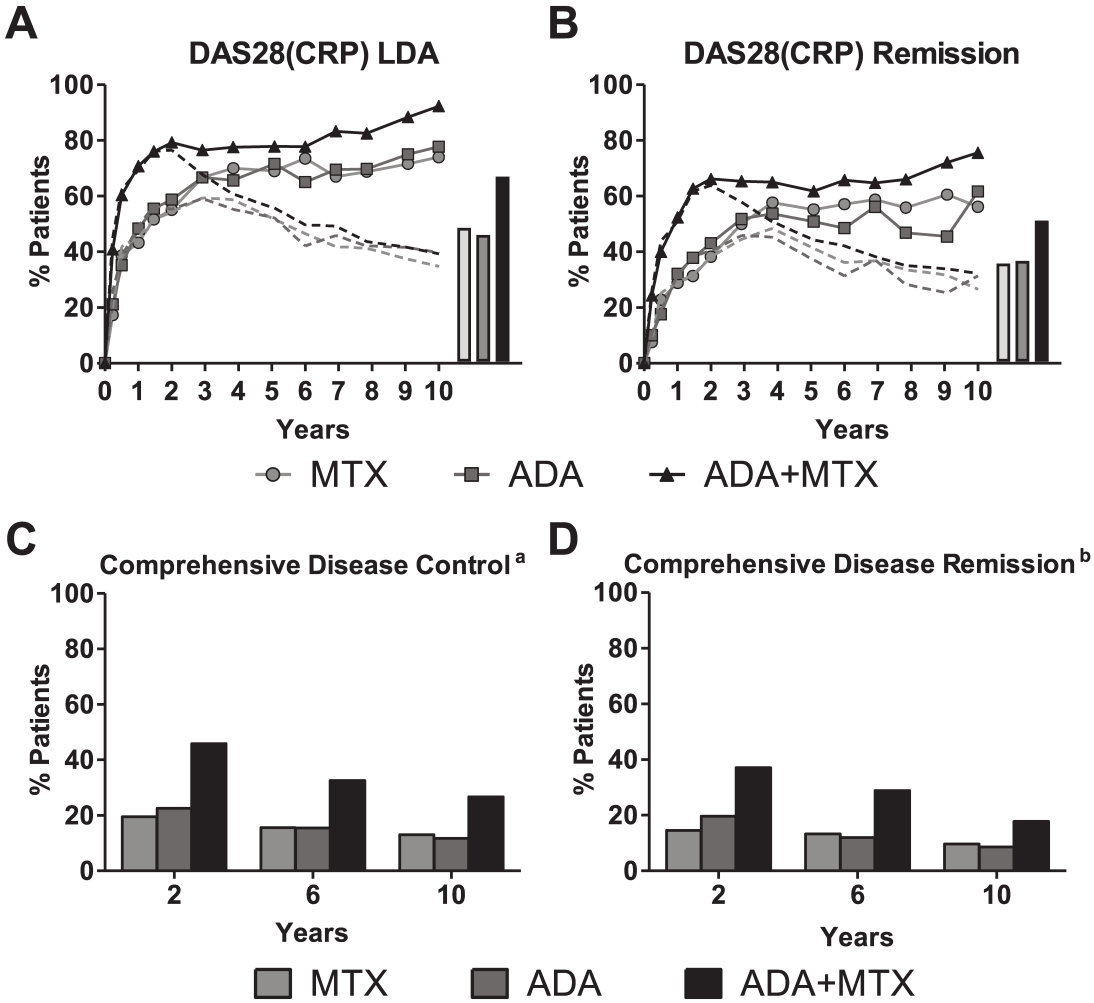

Figure 2. Percentage of patients achieving DAS28 (CRP) < 3.2 (A), DAS28 (CRP) < 2.6 (B), CDC (C), and CDR (D) during the course of 10 years of ADA ± MTX treatment. Lines with symbols represent observed response rate based on all randomized patients (n = 268, 274, and 257 for adalimumab + MTX, adalimumab, and MTX, respectively). Dashed lines represent response rate using nonresponder imputation based on all patients entering open-label extension (n = 183, 159, and 155 for adalimumab + MTX, adalimumab, and MTX, respectively). Bar graphs reflect data as observed at final visit using last observation carried forward method for all randomized patients (n = 268, 274, and 257 for adalimumab + MTX, adalimumab, and MTX, respectively). [a]Simultaneous achievement of DAS28(CRP) < 3.2 + ΔmTSS ≤ 0.5 + HAQ-DI < 0.5. [b]Simultaneous achievement of DAS28(CRP) < 2.6 + ΔmTSS ≤ 0.5 + HAQ-DI < 0.5. The CDC and CDR population are patients with radiographic data, nonresponder imputation is used if HAQ or DAS data are missing. ADA: adalimumab; MTX: methotrexate; DAS28: 28-joint Disease Activity Score; CRP: C-reactive protein; HAQ-DI: Health Assessment Questionnaire–Disability Index; ΔmTSS: change in modified total Sharp score.

Comprehensive disease control and remission further demonstrated benefits to early treatment with combination therapy. For 10-year completers, CDC was reported in 26.7%, 11.8%, and 13.0% of adalimumab + MTX, adalimumab, and MTX patients, respectively (Figure 2C); CDR was reported in 17.8%, 8.6%, and 9.6% of adalimumab + MTX, adalimumab, and MTX patients, respectively (Figure 2D). Increased proportion of combination therapy patients achieving CDC or CDR were all statistically significant compared to either monotherapy ($p \leq 0.01$).

Radiographic measures. Estimated annualized radiographic progressions from years 0 to 2 for the adalimumab + MTX, adalimumab, and MTX treatment groups were 0.95, 2.75, and 5.20, respectively. No statistical differences between groups were observed during the OLE [adalimumab + MTX mean ΔmTSS from year 3–10 = 3.68, annualized ΔmTSS = 0.46; MTX mean ΔmTSS from year 3–10 = 4.66 (vs adalimumab + MTX, $p = 0.62$), annualized ΔmTSS = 0.58; adalimumab mean ΔmTSS from year 3–10 = 3.86 (vs adalimumab + MTX, $p = 0.996$), annualized ΔmTSS = 0.48]. Over the course of the 10-year study, treatment initialization with adalimumab + MTX significantly limited radiographic progression (adalimumab + MTX vs adalimumab, $p = 0.01$; adalimumab + MTX vs MTX, $p < 0.001$), joint erosion, and

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JSN compared to initialization with either monotherapy; differences between initializing with either monotherapy were not statistically significant (Figures 3A, 3B, 3C). Among 10-year completers, 77/248 (31%) displayed no radiographic progression (ΔmTSS < 0.5) from baseline; 108/246 (43.9%) displayed no radiographic progression from the end of DB, most notably in the adalimumab + MTX treatment group (Figure 3D). Probability plots of ΔmTSS from years 0 to 10 (Figure 3E) demonstrated the superiority of initial adalimumab + MTX therapy in preventing radiographic progression compared to initializing with either monotherapy. Clinically relevant radiographic progression (ΔmTSS > 3.0) from baseline to Year 10 was reported in only one-third of patients initial-

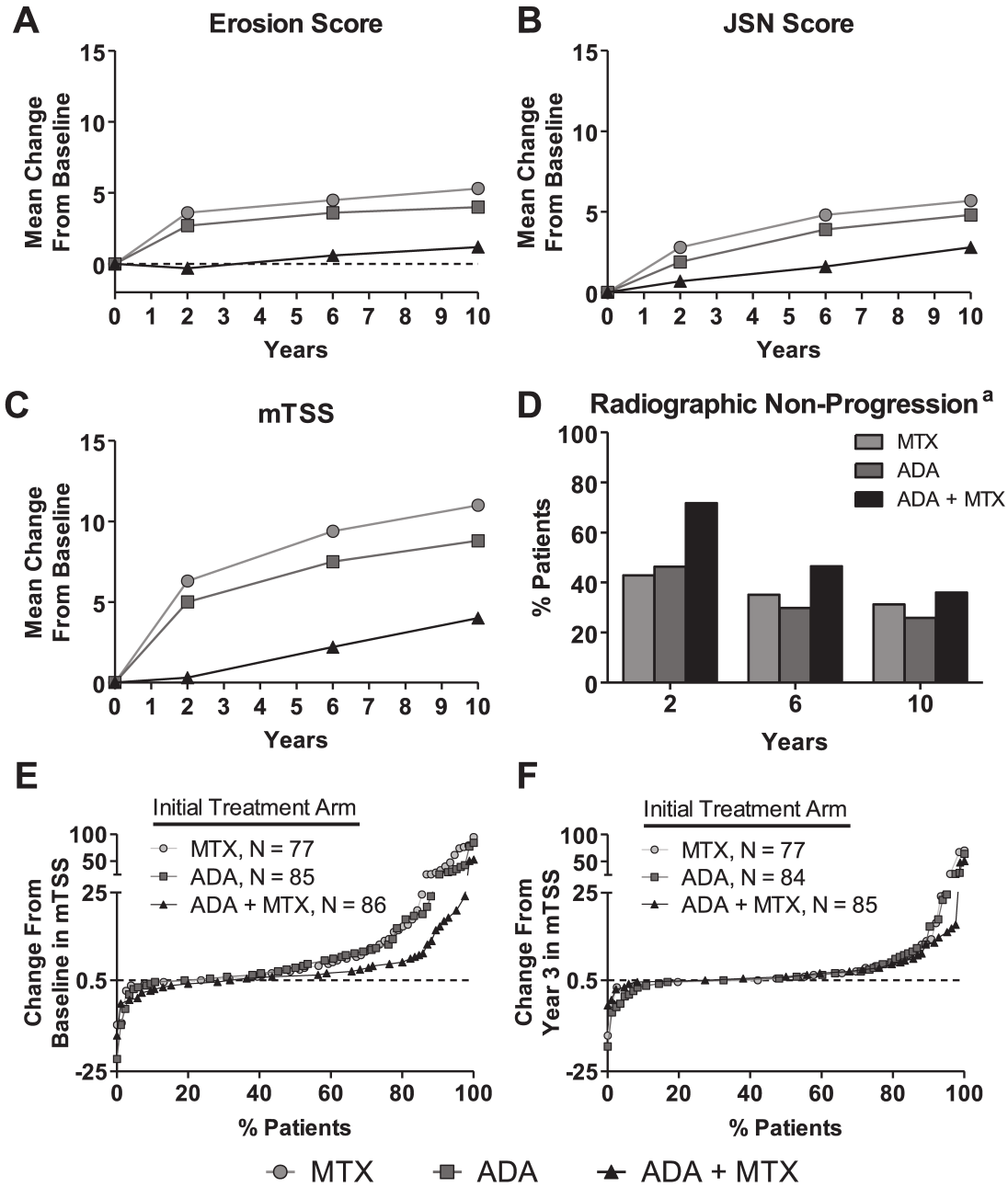

Figure 3. Changes in erosion score (A), JSN (B), and mean mTSS (C) at years 2, 6, and 10, and percentage of radiographic nonprogressors (D) over time. Radiographic change (ΔmTSS) probability plots from baseline to year 10 (E), from years 3 to 10 (F). [a]ΔmTSS ≤ 0.5. 10-year completers with radiographic data (n); ADA + MTX = 86; ADA = 85; MTX = 77. MTX: methotrexate; ADA: adalimumab; mTSS: modified total Sharp score; JSN: joint space narrowing.

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izing with combination therapy compared to over half of patients initiating with either monotherapy. During the OLE, addition of adalimumab ± MTX resulted in no significant differences between treatment groups in probability of radiographic progression (Figure 3F).

Safety data. The safety population (patients who took ≥ 1 dose of adalimumab, n = 697) totaled 3708.3 PY. Of these patients, 640 (91.8%), 483 (69.3%), and 65 (9.3%) took ≥ 1 dose of nonsteroidal antiinflammatory drugs, corticosteroids, and bisphosphonates, respectively; no significant differences in use of concomitant medications were observed for patients discontinuing the OLE. Adalimumab interruptions ≥ 70 days occurred in 43 (6.2%) patients (mean maximum length of interruption was 105.2 days). MTX use during the OLE was re-initiated in 261/497 patients (52.5%; mean dose of 13.09 mg/week, averaging 66.1% of their OLE time). Mean exposure to adalimumab was 5.32 years, averaging 146 doses.

Adverse events were reported in 97.3% of patients (Table 2); 72.2% of patients experienced a TEAE considered by the investigator to be at least possibly drug-related. Almost one-quarter (22.5%) of patients discontinued as a result of TEAE with the most frequent primary reason being RA flares (16 patients), increased alanine aminotransferase (7 patients), pneumonia, bacterial arthritis, pleural effusion, and increased aspartate aminotransferase (4 patients each). Serious infections occurred in 11.2% of patients (2.6 E/100 PY); the most frequently reported treatment-emergent serious infections were pneumonia, lobar pneumonia, cellulitis, bronchitis, sepsis, arthritis bacterial, and bronchopneumonia. In 15 patients, where serious infection was considered probably or definitely drug-related, 9 withdrew from the study. Active tuberculosis was reported in 3 patients during the study, and an additional 3 patients had a positive tuberculosis test conversion.

Malignancy standardized incidence ratio (SIR) was not elevated across all cancer sites (0.89; 95% CI 0.62–1.26); however, the SIR was elevated for all lymphomas (3.75; 95% CI 1.37–8.15), particularly Hodgkin's disease. Squamous cell nonmelanoma skin cancer SIR (2.69; 95% CI 1.23–5.11) was also elevated compared to standardized rates, although the SIR for overall nonmelanoma skin cancer (1.74; 95% CI 1.21–2.42) was closer to expected rates. Six patients had malignancies that resulted in death including colon, ovarian, and non-small cell lung cancer, malignant and hepatic neoplasm, and liver metastases. A total of 23 patients enrolled in the study died (0.6 E/100 PY). One patient taking MTX monotherapy died during the DB period and 22 patients died during the OLE [standardized mortality rate (SMR) = 0.75; 95% CI 0.51–1.07], 17 of whom experienced TEAE resulting in death (2.4%; 0.5 E/100 PY).

In general, yearly rates of TEAE from trial initiation to year 10 were stable, indicating that repeat administration of adalimumab did not increase risk for deleterious effects from extended adalimumab exposure (Table 3). The highest rates of serious infection and any malignancy were observed in adalimumab exposure Year 10, although frequencies were similar at all intervals. The SMR based on age at baseline for all randomized patients (0.72; 95% CI: 0.49–1.02) and the safety population was below 1.0, indicating that the observed number of deaths was not higher than expected in an age-matched, sex-matched, and country-matched population.

Table 2. Overview of safety-related treatment emergent adverse events (TEAE) by number (%) of patients and TEAE per 100 patient-years (PY).

Treatment Emergent Events[a]	Any Adalimumab, n = 697, n (%)	PY = 3708.3 E (E/100 PY)
Any AE	678 (97.3)	12,979 (350)
Any serious AE	320 (45.9)	729 (19.7)
Any AE leading to discontinuation	157 (22.5)	230 (6.2)
Any severe AE	300 (43.0)	669 (18.0)
Infectious AE	554 (79.5)	3077 (83)
Serious infections	78 (11.2)	98 (2.6)
Opportunistic infection (excluding oral candidiasis and TB)	1 (0.1)	1 (< 0.1)
TB	6 (0.9)	6 (0.2)
Lymphoma	6 (0.9)	6 (0.2)
NMSC	28 (4.0)	45 (1.2)
Malignancy other than lymphoma, leukemia, NMSC, or melanoma	29 (4.2)	30 (0.8)
Demyelinating disorder	2 (0.3)	2 (< 0.1)
Deaths (including non-treatment emergent events)	22 (3.2)[b]	22 (0.6)
Injection site reaction	81 (11.6)	186 (5.0)

* Events with unknown relationship to study drug are counted as drug related. Any TEAE is defined as any AE with an onset date on or after the day of the first ADA dose through 70 days after the last ADA dose in year 10.
[b] Standard mortality ratio (95% CI) = 0.75 (0.51, 1.07). E: events; AE: adverse event; TB: tuberculosis; NMSC: nonmelanoma skin cancer; ADA: adalimumab.

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Table 3. Overview of treatment emergent adverse event (TEAE) per 100 patient-years (PY) by year (intent-to-treat population).

ADA Exposure Year	N	PY	SAE	Serious Infection	Any Malignancy	AE Leading to Death
1	697	643.7	21.4	2.0	0.8	0.2
2	581	539.4	15.8	2.4	1.9	0.7
3	507	464.3	25.6	3.9	2.2	0.4
4	442	421.1	19.7	1.4	3.1	0
5	403	384.4	23.7	3.9	1.6	1.6
6	367	348.8	16.9	1.7	3.7	0.3
7	334	319.6	12.8	2.2	1.6	0.3
8	305	289.4	16.2	1.7	2.4	0
9	275	202.2	15.3	3.0	3.0	1.5
10	182	176.5	17.0	4.0	4.0	0
Overall	697	3708.3	18.0	2.6	2.2	0.6

ADA: adalimumab; SAE: severe adverse event; AE: adverse event.

DISCUSSION

Improving patient quality of life, function, and preventing joint damage are the major goals of effective treatment of RA[7]. Early diagnosis and therapeutic intervention can reduce the risk of permanent joint damage caused by chronic inflammation. Longterm studies of TNF inhibitors have demonstrated the effectiveness of achieving beneficial clinical outcomes by combination treatment with DMARD[9,19,20,21]. PREMIER was a 2-year study, longer than other trials, followed by an 8-year OLE to examine the longterm safety and effectiveness of adalimumab ± MTX therapy in patients with aggressive early RA, a population that necessitates intensive therapy to maximize benefits and will likely require lifelong therapy. PREMIER inclusion criteria mandated patients be MTX-naive, providing an opportunity to observe which treatment regimen is most beneficial for achieving disease control in patients with early RA. Longterm observations afforded by this study design permit further understanding of treatment benefit/risk profiles.

The window of opportunity for initiating combination therapy was evidenced in the disease advantage achieved by the combination therapy group in the first 2 years and maintained up to 10 years compared to patients beginning with either adalimumab or MTX monotherapy. Longterm adalimumab ± MTX treatment demonstrated effective disease control in patients with early, aggressive RA. The proportion of patients reporting normal function remained consistent over the course of the study. Similar observations were noted in regards to clinical measures as the proportion of the adalimumab + MTX treatment group achieving DAS28 LDA and remission remained stable during the OLE. Patients initiating with either monotherapy benefited from the addition of adalimumab ± MTX after Year 2, observed by increased percentages of patients attaining ACR50/70/90, DAS28 LDA, and remission, mainly between years 2 to 3 before plateauing. A possible upward trend is observed from years 6 to 10 in the percentage of patients achieving DAS28 LDA and remission. This trend may be attributed to discontinuation of patients with lack of efficacy; however, only 18.0% of all randomized patients discontinued for this reason. Additionally, patients discontinuing the trial reported high ACR, HAQ-DI, and DAS28 response at final visit, indicating that efficacy was maintained with continued adalimumab ± MTX treatment for up to 10 years.

Prevention of radiographic progression is critical for maintaining physical function in patients with aggressive RA. Annual radiographic progression (calculated by dividing the baseline mTSS by the mean baseline disease duration) for patients in the PREMIER trial was 25.9 units without significant differences between treatment groups[16], indicative of aggressive disease that may not be characteristic of all patients with early RA. Following 10 years of adalimumab ± MTX, the overall mean ΔmTSS was 7.8. This mean score was primarily influenced by radiographic progression during the first 2 years of the DB period, specifically from the monotherapy groups (Figure 3C). Annualized ΔmTSS was reduced substantially during the OLE with no statistical difference from the end of the DB. The 2-year DB period validates the superiority of adalimumab + MTX combination therapy over monotherapy in preventing joint damage, and highlights the window of opportunity for treating aggressive RA with initial combination therapy as soon as possible.

Anti-TNF modulates immune responses; thus, understanding the longterm benefit/risk profile of adalimumab is crucial to physicians and patients[22,23,24]. For the safety population, serious infection rate in the PREMIER study was numerically lower than the reported average 4.6 E/100 PY from 36 global adalimumab clinical trials treating RA through November 2010, totaling 23,942.6 PY[25], although

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the longterm nature of PREMIER has the potential to skew these data. Lymphoma SIR was elevated compared to standardized rates and to previous RA adalimumab clinical trial data[25].

In general, the majority of the most frequently reported TEAE are either consistent with the safety profile described in the currently-approved prescribing information for adalimumab, are associated with RA, or are common in a middle-aged population evaluated for up to 10 years. Therefore, no new safety findings were observed for adalimumab in this longterm study.

Longterm studies have limitations, particularly withdrawal due to persistent disease and withdrawn consent. Patients who entered the OLE generally consisted of treatment responders, because patients who were unable to tolerate the drug or did not respond discontinued treatment. Patient data lost to lack of efficacy artificially enhances the responder mean scores. However, discontinuations from PREMIER were primarily for reasons other than lack of efficacy. Because RA is a chronic condition requiring vigilance for disease control, longterm exposure studies are critical for elucidating the safety profile of anti-TNF; evidence for treatment tapering/removal once LDA or remission has been attained is still unclear[26]. Another limitation to our study is that radiographic data are presented only for Year 10 completers, which may carry bias toward the patients who did well on therapy in comparison to trial dropouts without radiographic data.

Because MTX use during OLE was allowed at the discretion of the investigator, the varying use can make interpreting data onerous as the addition of MTX may have been due to inadequate response or from increasing physician sentiment on the benefits provided by combination therapy[13,14,15,27]. However, investigator freedom to alter MTX dose accordingly was similar to actual clinical care. Regardless of the reason, patients who did not use MTX during the OLE demonstrated higher proportions achieving normal function and DAS28 LDA.

Initiated prior to the development of RA treat-to-target recommendations[7], the 10-year PREMIER study reinforces adherence to current recommendations for treatment of patients with early, aggressive RA by demonstrating the superiority of initial adalimumab + MTX combination therapy compared to either adalimumab or MTX monotherapy. Delaying combination therapy was associated with significant irreversible radiographic progression. Clinical and radiographic advantages attained within the first 2 years of the study were maintained over the 8-year OLE. The longterm benefit/risk profile of adalimumab ± MTX therapy was consistent from trial initiation to Year 10, indicating no additive harms from prolonged exposure to adalimumab ± MTX.

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