Health-related Quality of Life Outcomes of Adalimumab for Patients with Early Rheumatoid Arthritis: Results from a Randomized Multicenter Study

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ABSTRACT. ***Objective.*** Rheumatoid arthritis (RA) is associated with significant impairments in health-related quality of life (HRQOL). We evaluated patient-reported outcomes including HRQOL outcomes following adalimumab plus methotrexate (MTX) therapy in patients with early RA.

Methods. PREMIER was a phase III, multicenter, randomized, double-blind, active-comparator clinical trial in early RA. Patients aged ≥ 18 years were randomly assigned to receive adalimumab 40 mg every other week (eow) plus weekly MTX, weekly MTX, or adalimumab 40 mg eow for 104 weeks. American College of Rheumatology (ACR) criteria were used to evaluate clinical efficacy and response. Outcomes were assessed using the Health Assessment Questionnaire Disability Index (HAQ-DI), Short-Form 36 Health Survey (SF-36), Short-Form 6 Dimension (SF-6D), visual analog scale (VAS) assessments of global disease activity (patient's global assessment; PtGA) and pain, Functional Assessment of Chronic Illness Therapy-Fatigue (FACIT-F), and Health Utility Index Mark 3 (HUI-3).

Results. Of 799 patients enrolled, 268 received adalimumab plus MTX, 257 received MTX monotherapy, and 274 received adalimumab monotherapy. Patients treated with adalimumab plus MTX demonstrated significant baseline to Week 104 improvements in HAQ-DI ($p < 0.0001$), SF-36 Physical Component Summary ($p < 0.0001$), 4 SF-36 domains [physical function ($p < 0.0001$), bodily pain ($p < 0.0001$), vitality ($p = 0.0139$), role limitations-physical ($p = 0.0005$)], SF-6D ($p = 0.0152$), VAS-PtGA ($p < 0.0001$), VAS-pain ($p < 0.0001$), FACIT-F ($p < 0.0001$), and HUI-3 ($p = 0.0034$) scores versus patients treated with MTX monotherapy. Both SF-6D and HUI-3 were found to be sensitive preference-based measures for assessing the effects of treatment on multidimensional function. No clinically meaningful differences between adalimumab and MTX monotherapy groups were observed for most measures. For each measure, there was significant association between HRQOL improvement and ACR clinical response.

Conclusion. Adalimumab plus MTX significantly improved physical functioning and HRQOL in patients with early RA over 2 years of treatment. (ClinicalTrials.gov identifier NCT00195663). (First Release Nov 1 2011; J Rheumatol 2012;39:63–72; doi:10.3899/jrheum.101161)

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Patient-reported outcomes (PRO) provide important assessments of functioning and well-being from the patient's perspective[1,2]. Rather than simply serving as a complement to clinical (physician-reported) measures, PRO have been shown to better discriminate active treatment from placebo in randomized controlled trials in rheumatoid arthritis (RA)[3,4,5,6,7,8,9]. RA significantly affects health-related quality of life (HRQOL), including physical functioning, pain, fatigue and vitality, emotional and social well-being, and work productivity[1,3,10,11,12,13]. Preference-based HRQOL measures, such as the Short-Form 6 Dimension (SF-6D) derived from the Medical Outcomes Study Short-Form 36 Health Survey (SF-36)[14] and the Health Utilities Index Mark 3 (HUI-3)[15], contribute to our understanding of the influence of RA and

treatment-associated improvements on health outcomes and quality-adjusted life-years, thereby assisting physicians and patients in making therapeutic decisions[16].

Adalimumab is a human anti-tumor necrosis factor monoclonal antibody with demonstrated efficacy in patients with RA[17,18], psoriatic arthritis[19], ankylosing spondylitis[20], Crohn's disease[21], plaque psoriasis[22], and juvenile idiopathic arthritis[23]. The PREMIER trial demonstrated that the combination of adalimumab plus methotrexate (MTX) was well tolerated and more effective than either monotherapy in treating patients with early RA[18]. The objective of these analyses was to examine the effect of these treatments on HRQOL in this trial, comparing the relative sensitivity of SF-6D and HUI-3 measured during the trial.

MATERIALS AND METHODS

Study sample. PREMIER was a 2-year, randomized, double-blind, active comparator-controlled, phase III clinical trial conducted at 133 sites in North America, Europe, and Australia[18]. MTX-naive patients ≥ 18 years of age with active RA (≥ 8 swollen joints, ≥ 10 tender joints, and an erythrocyte sedimentation rate ≥ 28 mm/h or C-reactive protein concentration ≥ 1.5 mg/dl, in addition to rheumatoid factor positivity or ≥ 1 joint erosion) and disease duration < 3 years were randomized to receive adalimumab 40 mg subcutaneously every other week plus weekly oral MTX, adalimumab monotherapy, or MTX monotherapy. Institutional review boards at participating centers approved the protocol. All patients provided written informed consent. Results of this trial have been published[18]. (ClinicalTrials.gov identifier NCT00195663)

Baseline assessments. Demographic and clinical characteristics included age, sex, disease duration, prior use of disease-modifying antirheumatic drugs (DMARD), concomitant use of corticosteroid, all components of the American College of Rheumatology (ACR) response criteria, and 28-joint Disease Activity Score (DAS28).

Clinical and PRO measures. ACR50 response and radiographic data at Week 52 were the co-primary outcome measures; secondary outcomes included ACR 20/50/70/90 responses, radiographic data, and physical function and HRQOL data at Week 104[18]. Planned exploratory analyses of the relationship between clinical responses and HRQOL outcomes categorized patients as ACR50 responder or nonresponder status based on data from Weeks 12 to 104.

PRO included 3 components of the ACR response criteria: Health Assessment Questionnaire Disability Index (HAQ-DI[24]), visual analog scale (VAS) assessments of global disease activity (patient's global assessment; PtGA) and pain, and the Functional Assessment of Chronic Illness Therapy-Fatigue (FACIT-F). These measures are well validated in RA[25,26,27,28,29,30]. FACIT-F measures fatigue and its effect on functioning and daily activities over the previous 7 days[28]; scores range from 0 (none) to 52 (greater fatigue). A change of –0.22 in HAQ-DI and 4 points in FACIT-F are considered minimum clinically important differences (MCID)[30]. Normative values for HAQ-DI in the general population are ≤ 0.5[24,31].

HRQOL measures included SF-36 and HUI-3. Data were collected at baseline and Weeks 12, 26, 52, 76, and 104. SF-6D scores were calculated based on the SF-36. SF-36 is a generic HRQOL instrument that consists of 8 domains (physical function, bodily pain, role limitations-physical, general health, vitality, social function, role limitations-emotional, and mental health) scored from 0 to 100, with higher scores indicating better health status, and Physical (PCS) and Mental Component Summary (MCS) scores normed to the general population with a mean of 50.0 and an SD of 10.0[32]. Norm-based scores can also be calculated for the SF-36 domains, similar to the summary scores, with a mean of 50.0 and SD of 10.0 (higher scores indicating better health status). Changes of 5.0 to 10.0 points in domain scores and 2.5 to 3.0 points in PCS and MCS scores represent MCID[3,10,12,13,33,34,35]. SF-36 has demonstrated reliability and validity[3,10,32] and responsiveness to change in patients with RA[10,33]. SF-6D is a preference-based generic health measure derived from the SF-36[14]. SF-6D scores were calculated directly based on selected items from the SF-36. A change of 0.03 is considered the MCID[36,37]. SF-6D has demonstrated construct validity and responsiveness for use in RA[10,36,37,38].

The HUI-3 is a collection of preference-based HRQOL measures consisting of 8 self-administered items assessing functional capacity in 8 domains: vision, hearing, speech, ambulation, dexterity, emotion, cognition, and pain, over the previous 4 weeks[39,40]. Index scores range from 0 to 1.0, with higher scores representing better health status. A change of ≥ 0.03 points is considered the MCID[40]. The HUI-3 has good reliability and construct validity[15,39,41] and has been used in clinical studies in RA[10].

Statistical analyses. Primary HRQOL endpoints were *a priori* identified as baseline to Week 104 mean changes in HAQ-DI and SF-36 PCS and MCS scores, following the precedent set by the US Food and Drug Administration for labeling for "improvement and maintenance of physical function and HRQOL." Secondary endpoints included patient VAS (PtGA and pain), SF-36 domain, SF-6D, FACIT-F, and HUI-3 scores over 104 weeks. Analyses were conducted using the intention-to-treat population, defined as all randomized patients who received ≥ 1 treatment dose. Analyses compared adalimumab plus MTX versus MTX monotherapy and adalimumab monotherapy versus MTX monotherapy. All analyses included all observed data.

Baseline demographics, clinical characteristics, and HRQOL measures were summarized using descriptive statistics. Chi-square tests and Student t tests were performed to examine baseline differences between treatment groups.

For repeated-measurement variables, a mixed model with random intercept was applied to compare mean HRQOL scores between the treatment groups[42]. Adjusted mean scores are reported. The mixed model included terms for treatment group, week, treatment-by-week interaction, and relevant baseline score as covariates. Statistical analyses of HAQ-DI, PtGA, pain, SF-36 summary and domain scores, and FACIT-F were predefined; SF-6D and HUI-3 were considered supportive and exploratory. Spydergrams were used to compare mean SF-36 domain scores between the adalimumab plus MTX and MTX monotherapy groups[43]. For these analyses, the SF-36 domain scores for baseline, 52-week, and 104-week visits were included.

An exploratory data analysis evaluated the relationship between ACR50 response status and changes in HRQOL measures. Analysis of covariance models were used to estimate least-squares mean baseline to Week 104 change scores for HAQ-DI, SF-36 PCS and MCS, SF-6D, FACIT-F, and HUI-3 scores. The models included factors for ACR50 response status, age, sex, and relevant baseline scores.

RESULTS

A total of 799 patients participated in our study: 268 in the adalimumab plus MTX group, 257 in the MTX monotherapy group, and 274 in adalimumab monotherapy group. Baseline demographic and clinical characteristics were similar between the 3 treatment groups (Table 1). Mean duration of RA at baseline was 9 months. There were no statistically significant differences in baseline PRO scores between the combination and MTX monotherapy groups. The adalimumab and MTX monotherapy groups differed significantly in several PRO measures (HAQ-DI, SF-36 PCS, SF-36 physical function domain, SF-36 social function domain, SF-6D, FACIT-F, and HUI-3), which favored MTX monotherapy (Table 1).

Primary HRQOL endpoints

Adalimumab combination therapy vs MTX monotherapy.

Table 1. Patient demographics, disease characteristics, and patient-reported outcome scores at baseline. Data are mean (SD) unless otherwise noted.

Characteristics	Adalimumab Plus MTX, n = 268	MTX Monotherapy, n = 257	Adalimumab Monotherapy, n = 274
Age, yrs	51.9 (14.0)	52.0 (13.1)	52.1 (13.5)
Women, n (%)	193 (72.0)	190 (73.9)	212 (77.4)
Disease duration, yrs	0.7 (0.8)	0.8 (0.9)	0.7 (0.8)
Prior DMARD use, n (%)	87 (32.5)	81 (31.5)	91 (33.2)
Concomitant corticosteroid use, n (%)	96 (35.8)	91 (35.4)	100 (36.5)
Tender joint count, 0–68	30.7 (14.2)	32.3 (14.3)	31.8 (13.6)
Swollen joint count, 0–66	21.1 (11.2)	22.1 (11.7)	21.8 (10.5)
Patient's global assessment of disease activity, 100-mm VAS	66.8 (22.1)	63.0 (25.0)	67.8 (23.3)
Patient's assessment of pain, 100-mm VAS	62.5 (21.3)	59.6 (24.3)	64.6 (23.6)
DAS28	6.3 (0.9)	6.3 (0.9)	6.4 (0.9)
HAQ-DI*	1.5 (0.6) [p = 0.8719†]	1.5 (0.7)	1.6 (0.6) [p = 0.0132††]
SF-36 component summary scores*			
PCS	31.7 (7.8) [p = 0.4373†]	32.2 (7.9)	30.7 (7.4) [p = 0.0272††]
MCS	44.1 (12.5) [p = 0.5816†]	43.5 (12.4)	42.6 (12.1) [p = 0.4107††]
SF-36 domains*			
Physical function	30.2 (10.0) [p = 0.1486†]	31.5 (10.3)	29.1 (9.5) [p = 0.0061††]
Role limitations-physical	33.1 (8.8) [p = 0.4714†]	32.6 (8.4)	32.5 (8.1) [p = 0.9268††]
Social function	38.3 (12.0) [p = 08682†]	38.1 (12.2)	35.2 (12.2) [p = 0.0076††]
General health	40.9 (10.0) [p = 0.5918†]	40.5 (9.1)	39.8 (9.6) [p = 0.4400††]
Bodily pain	32.5 (7.1) [p = 0.7854†]	32.7 (7.7)	31.6 (7.8) [p = 0.0823††]
Vitality	40.0 (10.0) [p = 0.5239†]	40.6 (9.7)	39.2 (9.4) [p = 0.0954††]
Role limitations-emotional	38.4 (14.1) [p = 0.1617†]	36.7 (13.8)	37.5 (13.9) [p = 0.5280††]
Mental health	42.1 (12.2) [p = 0.6366†]	42.6 (12.1)	41.4 (11.9) [p = 0.2851††]
SF-6D*	0.55 (0.11) [p = 0.3534†]	0.56 (0.11)	0.54 (0.11) [p = 0.0362††]
FACIT-F*	28.4 (11.7) [p = 0.5770†]	29.0 (11.1)	26.2 (11.3) [p = 0.0045††]
HUI-3*	0.39 (0.27) [p = 0.9200†]	0.39 (0.29)	0.33 (0.28) [p = 0.0236††]

* Unadjusted mean (SD). † p values from Student t tests between MTX monotherapy and adalimumab plus MTX combination therapy. †† p values from Student t tests between MTX and adalimumab monotherapy groups. DAS28: 28-joint Disease Activity Score; DMARD: disease-modifying antirheumatic drug; FACIT-F: Functional Assessment of Chronic Illness Therapy-Fatigue; HAQ-DI: Health Assessment Questionnaire Disability Index; HUI-3: Health Utility Index Mark 3; MCS: mental component summary; MTX: methotrexate; PCS: physical component summary; SF-6D: Short-Form 6 Dimension; SF-36: Short-Form 36 Health Survey; VAS: visual analog scale.

Patients treated with adalimumab plus MTX reported statistically significant baseline to Week 104 improvements in HAQ-DI scores versus patients treated with MTX monotherapy. There were significant main effects of treatment ($p < 0.0001$) and significant treatment-by-week interactions for HAQ-DI scores ($p < 0.0001$; Table 2). Patients treated with adalimumab plus MTX reported early and sustained decreases (improvements) over the first 52 weeks of treatment and maintained values less than US general population norms for the remainder of the study (Figure 1). The MTX monotherapy group reported less early improvement in mean HAQ-DI scores; this difference was sustained over the study duration. Significantly more patients receiving combination therapy reported clinically meaningful improvements in physical functioning (MCID criterion of ≥ 0.22 points) at Week 104 (67.5% vs 58.7%, respectively; $p = 0.037$).

Statistically significant improvements from baseline to Week 104 in SF-36 PCS scores but not in SF-36 MCS scores were observed with adalimumab plus MTX versus MTX monotherapy. There were significant main effects of treatment ($p < 0.0001$) but no significant treatment-by-week interactions for SF-36 PCS scores (Table 2). More patients receiving combination therapy reported clinically meaningful improvements in SF-36 PCS scores (MCID criterion of ≥ 3.0 points) at Week 104 (56.4% vs 43.6%; $p = 0.0469$).

Adalimumab monotherapy vs MTX monotherapy. Patients in both monotherapy groups reported improvements in HAQ-DI scores. There was a significant treatment-by-week interaction ($p < 0.0001$) for HAQ-DI scores, but main effects of treatment were nonsignificant (Table 2). Although the adalimumab monotherapy group had more impaired physical function at baseline, the trajectory of mean HAQ-DI scores over the study duration was comparable between the monotherapy groups (Figure 1).

No significant differences were observed between the monotherapy groups in SF-36 PCS scores (Table 2). However, more patients receiving adalimumab monotherapy than those receiving MTX monotherapy reported clinically meaningful improvements in SF-PCS scores (MCID criterion of ≥ 3.0 points) at Week 104 (52.4% vs 47.6%, respectively; $p = 0.0292$). For SF-36 MCS scores, there were significant main effects of treatment ($p = 0.0148$) without significant treatment-by-week interactions (Table 2). The MTX monotherapy group reported a slightly greater mean change from baseline

Table 2. Mean patient-reported outcome scores by treatment group and study visit. Data are adjusted mean (SD).

Measure	n	Baseline	Week 12	Week 26	Week 52	Week 76	Week 104	Mixed-model Repeated-measures Analyses** Treatment Effect, p	Mixed-model Repeated-measures Analyses** Treatment-by-week Interaction, p
HAQ-DI									
Adalimumab plus MTX	266	1.5 (0.6)	0.7 (0.5)	0.6 (0.5)	0.5 (0.5)	0.4 (0.5)	0.3 (0.5)	< 0.0001†	< 0.0001†
MTX	256	1.5 (0.7)	0.9 (0.6)	0.9 (0.6)	0.7 (0.6)	0.6 (0.6)	0.5 (0.6)		
Adalimumab	272	1.6 (0.6)	1.0 (0.6)	0.9 (0.6)	0.8 (0.6)	0.7 (0.6)	0.6 (0.6)	0.0704††	< 0.0001††
SF-36 PCS*									
Adalimumab plus MTX	256	31.7 (7.8)	44.8 (8.0)	45.3 (8.2)	46.6 (8.2)	47.5 (8.8)	48.8 (8.3)	< 0.0001†	
MTX	247	32.2 (7.9)	41.0 (8.1)	42.2 (8.1)	43.5 (8.1)	44.7 (8.0)	45.9 (7.8)		
Adalimumab	264	30.7 (7.4)	39.9 (7.8)	41.1 (8.0)	42.5 (7.9)	43.9 (7.8)	44.7 (8.0)	0.3912††	
SF-36 MCS*									
Adalimumab plus MTX	256	44.1 (12.5)	49.7 (8.7)	50.3 (8.6)	50.7 (8.7)	51.4 (8.7)	51.8 (8.8)	0.7609†	
MTX	247	43.5 (12.4)	50.1 (8.8)	50.8 (8.5)	51.3 (8.5)	51.7 (8.4)	52.4 (8.4)		
Adalimumab	264	42.6 (12.1)	47.9 (8.2)	48.6 (8.0)	49.1 (8.2)	49.3 (8.1)	49.8 (8.1)	0.0148††	
VAS-PtGA									
Adalimumab plus MTX	264	66.8 (22.1)	25.0 (16.2)	22.4 (16.3)	17.8 (15.5)	13.6 (15.1)	9.4 (14.9)	< 0.0001†	< 0.0001†
MTX	256	63.0 (25.0)	35.3 (17.8)	30.7 (21.8)	24.5 (16.1)	19.1 (16.1)	12.9 (15.7)		
Adalimumab	273	67.8 (23.3)	35.9 (17.7)	32.2 (17.2)	27.7 (17.0)	23.9 (16.7)	19.8 (16.5)	0.2694††	< 0.0001††
VAS-pain assessment									
Adalimumab plus MTX	265	62.5 (21.3)	23.2 (16.5)	20.9 (16.5)	16.8 (15.7)	13.1 (15.0)	9.6 (14.9)	< 0.0001†	< 0.0001†
MTX	256	59.6 (24.3)	33.8 (17.9)	29.4 (16.5)	23.4 (16.1)	18.4 (16.1)	12.5 (15.8)		
Adalimumab	273	64.6 (23.6)	34.2 (17.9)	30.6 (17.2)	26.6 (17.1)	22.2 (16.9)	19.6 (16.6)	0.1571††	< 0.0001††
SF-36 domains*									
Physical function									
Adalimumab plus MTX	264	30.2 (10.0)	42.7 (9.0)	43.3 (9.2)	44.7 (9.2)	45.7 (9.2)	46.9 (9.2)	< 0.0001†	
MTX	256	31.5 (10.3)	39.4 (9.6)	40.6 (9.6)	41.8 (9.7)	43.3 (9.4)	44.3 (9.3)		
Adalimumab	270	29.1 (9.5)	38.0 (9.1)	39.2 (9.1)	40.5 (9.0)	41.8 (9.0)	43.0 (9.1)	0.6364††	
Bodily pain									
Adalimumab plus MTX	265	32.5 (7.1)	47.9 (7.1)	48.5 (7.4)	49.7 (7.3)	50.7 (7.3)	51.8 (7.2)	< 0.0001†	
MTX	256	32.7 (7.7)	44.3 (7.2)	45.3 (7.3)	46.5 (7.3)	47.8 (7.3)	48.8 (7.1)		
Adalimumab	271	31.6 (7.8)	42.4 (7.0)	43.6 (6.9)	44.9 (6.9)	46.0 (6.9)	47.1 (6.9)	0.0288††	
Vitality									
Adalimumab plus MTX	264	40.0 (10.0)	51.4 (8.7)	51.9 (8.9)	52.9 (8.8)	53.8 (8.9)	54.7 (9.0)	0.0139†	
MTX	255	40.6 (9.7)	49.8 (8.6)	50.8 (8.6)	51.8 (8.7)	52.7 (8.7)	53.7 (8.5)		
Adalimumab	271	39.2 (9.4)	47.5 (8.0)	48.5 (8.2)	49.6 (8.3)	50.4 (8.3)	51.4 (8.4)	0.0228††	
Role limitations-physical									
Adalimumab plus MTX	261	33.1 (8.8)	44.7 (8.2)	45.3 (8.3)	46.6 (8.2)	47.6 (8.3)	48.8 (8.2)	0.0005†	
MTX	255	32.6 (8.4)	41.7 (8.7)	42.7 (8.8)	44.1 (8.9)	45.1 (8.7)	46.5 (8.6)		
Adalimumab	268	32.5 (8.1)	41.0 (7.8)	42.0 (7.9)	43.3 (8.0)	44.6 (7.9)	45.5 (8.0)	0.2851††	
Social function									
Adalimumab plus MTX	265	38.3 (12.0)	47.8 (7.2)	48.1 (7.4)	48.7 (7.4)	49.3 (7.5)	49.9 (7.4)	0.1248†	
MTX	256	38.1 (12.2)	46.6 (7.9)	47.3 (7.8)	47.9 (7.8)	48.8 (7.7)	49.2 (7.6)		
Adalimumab	271	35.2 (12.2)	43.8 (7.7)	44.7 (7.6)	45.9 (7.4)	47.0 (7.4)	48.0 (7.6)	0.0031††	0.0250††
General health									
Adalimumab plus MTX	264	40.9 (10.0)	46.9 (8.2)	47.4 (8.3)	48.2 (8.2)	48.8 (8.2)	49.5 (8.3)	0.0870†	0.0108†
MTX	249	40.5 (9.1)	45.2 (8.2)	45.9 (8.1)	46.4 (8.2)	46.9 (8.2)	47.2 (8.2)		
Adalimumab	268	39.8 (9.6)	43.8 (7.8)	44.5 (8.0)	45.4 (7.9)	46.2 (7.9)	46.7 (8.1)	0.0235††	0.0478††
Role limitations-emotional									
Adalimumab plus MTX	260	38.4 (14.1)	45.8 (8.1)	46.5 (8.1)	47.3 (8.1)	48.3 (7.9)	49.1 (7.8)	0.2283†	
MTX	254	36.7 (13.8)	44.5 (8.6)	45.3 (8.6)	46.2 (8.6)	47.2 (8.3)	48.1 (8.0)		
Adalimumab	269	37.5 (13.9)	42.9 (7.9)	43.5 (7.9)	44.5 (7.9)	45.0 (7.9)	45.8 (7.9)	0.0281††	
Mental health									
Adalimumab plus MTX	264	42.1 (12.2)	48.8 (8.7)	49.2 (8.8)	49.9 (8.8)	50.5 (8.7)	51.1 (8.7)	0.3895†	
MTX	255	42.6 (12.1)	48.5 (9.3)	49.5 (8.9)	50.0 (9.0)	50.5 (9.2)	51.1 (9.3)		
Adalimumab	270	41.4 (11.9)	46.8 (8.6)	47.4 (8.6)	48.0 (8.7)	48.6 (8.6)	49.2 (8.7)	0.0503††	
SF-6D									
Adalimumab plus MTX	256	0.55 (0.11)	0.70 (0.13)	0.70 (0.13)	0.75 (0.13)	0.75 (0.14)	0.76 (0.14)	0.0152†	< 0.0001†
MTX	256	0.56 (0.11)	0.66 (0.12)	0.70 (0.14)	0.72 (0.14)	0.72 (0.15)	0.73 (0.14)		
Adalimumab	272	0.54 (0.11)	0.64 (0.12)	0.67 (0.13)	0.70 (0.14)	0.69 (0.13)	0.70 (0.13)	0.0480††	< 0.0001††

Table 2. Continued.

Measure	n	Baseline	Week 12	Week 26	Week 52	Week 76	Week 104	Mixed-model Repeated-measures Analyses** Treatment Effect, p	Mixed-model Repeated-measures Analyses** Treatment-by-week Interaction, p
FACIT-F									
Adalimumab plus MTX	265	28.4 (11.7)	39.2 (8.3)	40.0 (8.2)	41.1 (8.2)	42.1 (8.0)	43.0 (8.1)	< 0.0001†	0.0010†
MTX	254	29.0 (11.1)	37.5 (8.7)	38.7 (8.2)	40.0 (8.1)	41.4 (8.1)	42.5 (8.1)		
Adalimumab	272	26.2 (11.3)	35.8 (8.4)	37.0 (8.2)	38.6 (8.0)	39.7 (8.0)	40.8 (8.1)	0.8844††	
HUI-3									
Adalimumab plus MTX	239	0.39 (0.29)	0.69 (0.20)	0.72 (0.20)	0.73 (0.20)	0.76 (0.20)	0.79 (0.19)	0.0034†	
MTX	234	0.39 (0.27)	0.64 (0.20)	0.67 (0.20)	0.69 (0.20)	0.72 (0.19)	0.74 (0.19)		
Adalimumab	243	0.33 (0.28)	0.60 (0.21)	0.62 (0.21)	0.65 (0.20)	0.67 (0.20)	0.70 (0.21)	0.0975††	

* Normative scores (mean 50.0, SD 10.0), with greater scores indicating better health status. ** Two-tailed p values from repeated-measures random-intercept model, including treatment, week, treatment-by-week interaction, and baseline score as independent variables. The interaction term was retained in the model when the p value for the interaction was < 0.10. Otherwise, the interaction term was removed. † Adalimumab plus MTX monotherapy vs MTX monotherapy. †† Adalimumab monotherapy vs MTX monotherapy. FACIT-F: Functional Assessment of Chronic Illness Therapy-Fatigue; HAQ-DI: Health Assessment Questionnaire Disability Index; HUI-3: Health Utility Index Mark 3; MCS: mental component summary; MTX: methotrexate; PCS: physical component summary; SF-6D: Short-Form 6 Dimension; SF-36: Short-Form 36 Health Survey; VAS: visual analog scale.

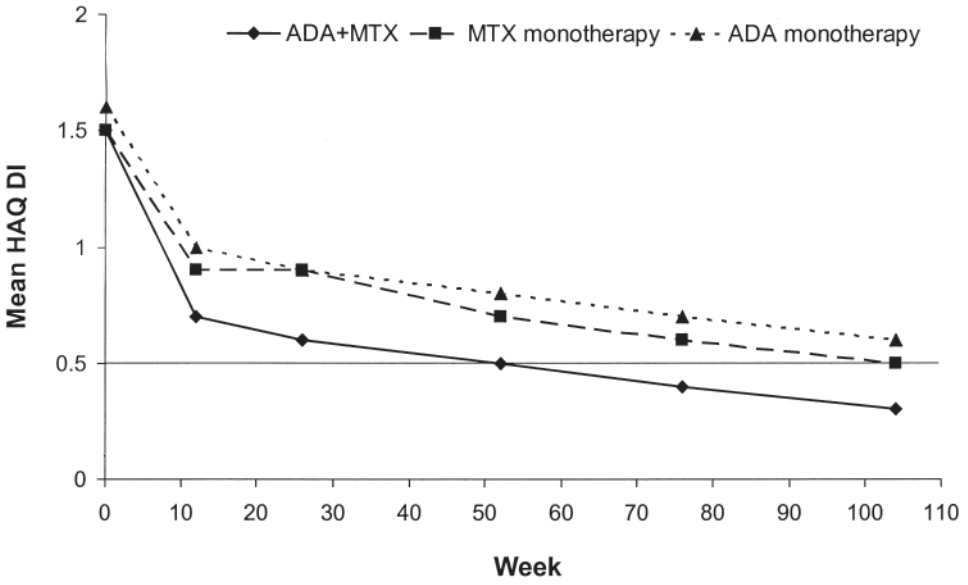

Figure 1. Mean Health Assessment Questionnaire Disability Index (HAQ-DI) scores by treatment group and study visit. Horizontal line at 0.49 is the reported mean HAQ-DI for the general population[24]. ADA: adalimumab; MTX: methotrexate.

to Week 104 in SF-36 MCS scores versus the adalimumab monotherapy group (8.8 vs 7.2 points), but this difference was not clinically meaningful.

Secondary HRQOL endpoints

Adalimumab combination therapy vs MTX monotherapy. Treatment with adalimumab plus MTX was associated with significant main treatment effects ($p < 0.0001$) and treatment-by-week interactions ($p < 0.001$) for VAS PtGA and pain assessments (Table 2). Significant main effects of treatment were also observed for 4 SF-36 domain scores (physical function, bodily pain, vitality, and role limitations-physical), and a significant treatment-by-week interaction was observed for general health (Table 2).

Figure 2 summarizes the mean SF-36 domain scores between the combination treatment and MTX monotherapy groups. The largest differences were observed between the treatment groups on physical function, bodily pain, vitality, and role limitations-physical scores, all favoring the combination therapy group.

In addition, treatment with adalimumab plus MTX was associated with significant main treatment effects for SF-6D

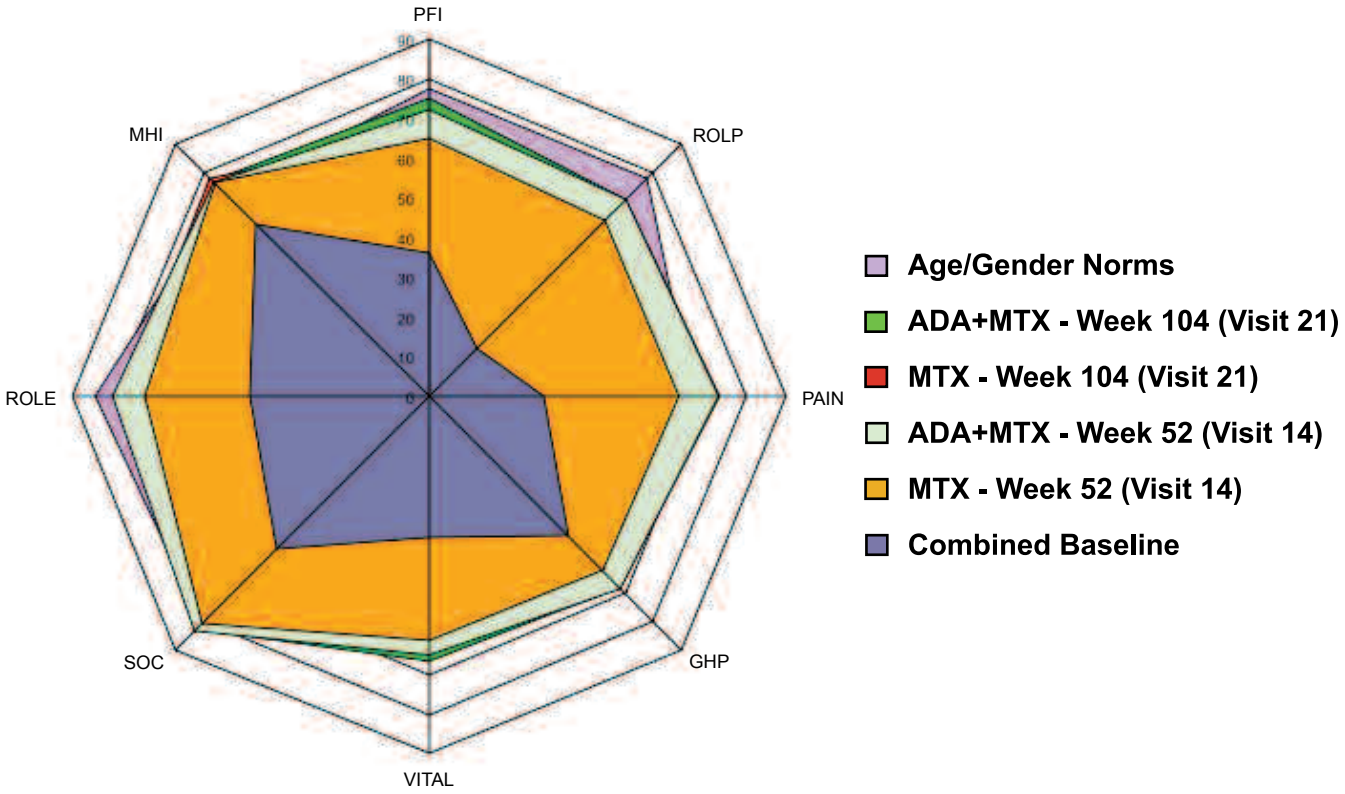

Figure 2. Spydergram summarizing mean Short-Form 36 Health Survey (SF-36) domain scores for the adalimumab (ADA) plus methotrexate (MTX) and MTX monotherapy groups at baseline, Week 52, and Week 104, compared with age-/sex-matched norms. Norm-based domain scores were converted to a scale of 0–100, consistent with other publications showing spydergrams in rheumatoid arthritis[43]. PFI: physical function, ROLP: role limitations-physical, PAIN: bodily pain, GHP: general health, VITAL: vitality, SOC: social function, ROLE: role limitations-emotional, and MHI: mental health.

($p = 0.0152$), FACIT-F ($p < 0.0001$), and HUI-3 ($p = 0.0034$) scores and treatment-by-week interactions for SF-6D ($p < 0.0001$) and FACIT-F ($p = 0.001$) scores (Table 2). Mean improvements were comparable across preference-based measures (SF-6D, HUI-3) for patients treated with adalimumab plus MTX (Figure 3A) and patients treated with MTX (Figure 3B).

Adalimumab monotherapy vs MTX monotherapy. Significant treatment-by-week interactions without main treatment effects were observed for VAS assessments (Table 2). There were significant main effects of treatment for 5 SF-36 domain scores (bodily pain, vitality, social function, general health, and role limitations-emotional) and significant treatment-by-week interactions for social function and general health (Table 2). The observed improvements in SF-36 domain scores favored the MTX monotherapy group, but differences were generally small.

There was a significant main effect of treatment for derived SF-6D ($p = 0.0480$) and a significant treatment-by-week interaction ($p < 0.0001$) for the SF-6D (Table 2). No significant differences between the monotherapy groups were observed on the FACIT-F or HUI-3 (Table 2). Mean improvements were comparable across preference-based measures for both monotherapy groups (Figures 3B, 3C).

Exploratory analysis: relationship between clinical response and PRO. Exploratory analyses examined the relationship between ACR response criteria and baseline to Week 104 changes in HAQ-DI, SF-36 PCS and MCS, SF-6D, FACIT-F, and HUI-3 scores after adjustment for age, sex, and baseline score. Mean change scores were significantly improved in ACR50 responders versus nonresponders on each measure ($p < 0.0001$; Table 3).

DISCUSSION

The PREMIER trial demonstrated the clinical efficacy and safety of adalimumab plus MTX in patients with early RA[18]. The current analyses demonstrated that these responses were associated with significant, clinically meaningful improvements in HRQOL and preference-based measures.

At study entry, patients reported significant impairments in physical function and HRQOL compared with the US general population. Baseline mean HAQ-DI scores were 1.5 to 1.6 for patients in PREMIER compared with the reported mean HAQ-DI score of 0.49 for the general population[24]. Over the 2-year study, mean HAQ-DI scores improved to 0.3 (adalimumab plus MTX group), 0.5 (MTX monotherapy group), and 0.6 (adalimumab monotherapy group). Twelve-week improvements in HAQ-DI were significantly greater in the

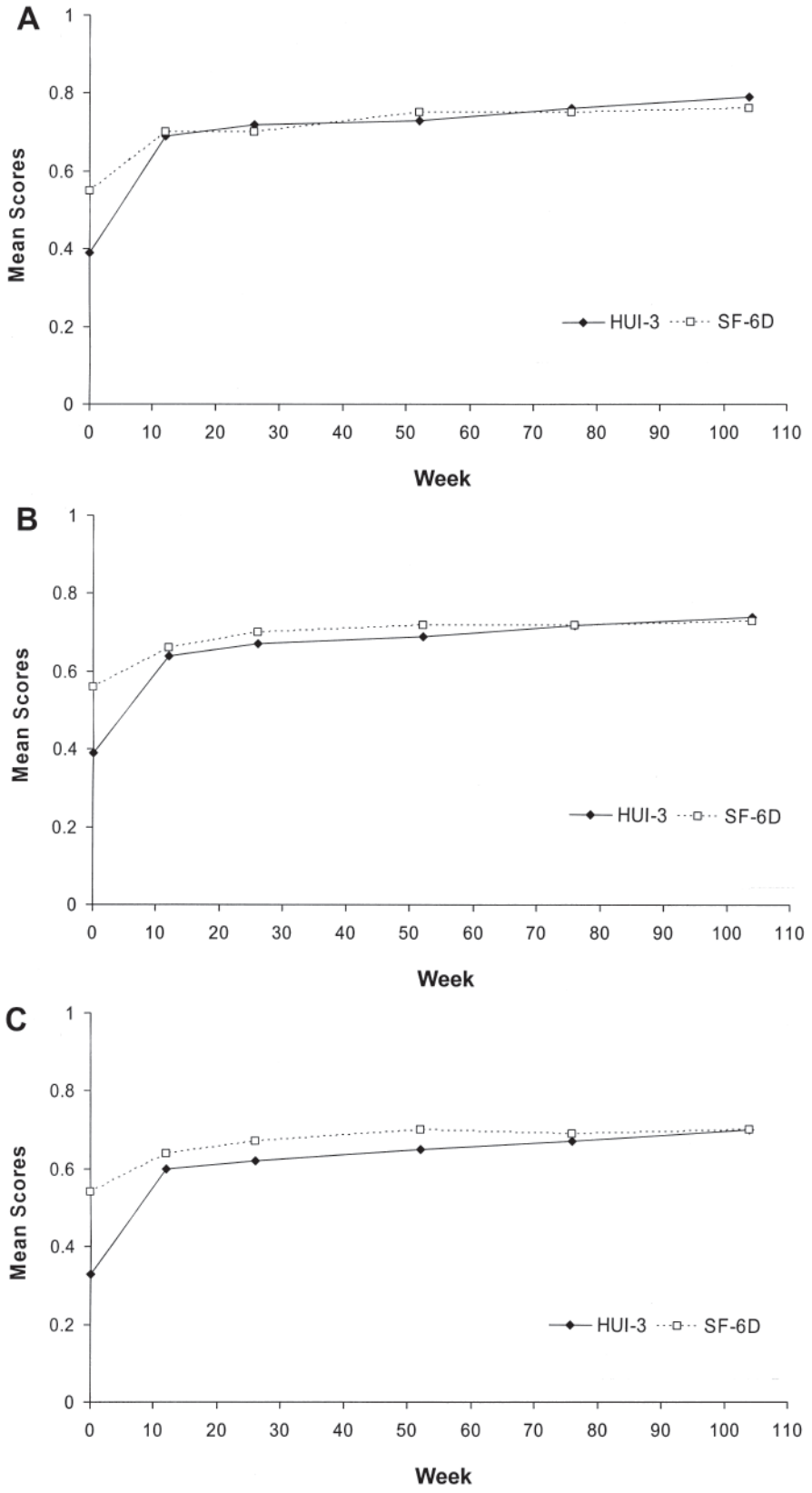

Figure 3. Mean Health Utility Index Mark 3 (HUI-3) and Short-Form 6 Dimension (SF-6D) scores by treatment group and study visit. (A) Adalimumab plus methotrexate (MTX). (B) MTX monotherapy. (C) Adalimumab monotherapy.

Table 3. Association of ACR50 response with mean changes from baseline to Week 104 in patient-reported outcome scores.

Measure	ACR50 Improvement Status, adjusted mean (SE) for change scores		
	Nonresponder, n = 169	ACR50 Responder, n = 369	Overall p†
HAQ-DI	–0.6 (0.04)	–1.2 (0.03)	< 0.0001
SF-36 PCS	7.2 (0.65)	17.4 (0.45)	< 0.0001
SF-36 MCS	4.7 (0.81)	8.8 (0.56)	< 0.0001
SF-6D	0.10 (0.01)	0.22 (0.01)	< 0.0001
FACIT-F	8.1 (0.69)	15.9 (0.47)	< 0.0001
HUI-3	0.22 (0.02)	0.41 (0.01)	< 0.0001

† p for overall test of differences between ACR50 responder groups from an analysis of covariance model that included ACR50 responder group, baseline score, age, and, sex. ACR50: American College of Rheumatology rating scale (50% or more improvement); FACIT-F: Functional Assessment of Chronic Illness Therapy-Fatigue; HAQ-DI: Health Assessment Questionnaire Disability Index; HUI-3: Health Utility Index Mark 3: MCS: mental component summary; PCS: physical component summary; SF-6D: Short-Form 6 Dimension; SF-36: Short-Form 36 Health Survey.

adalimumab plus MTX group versus the MTX monotherapy group, and improvements were maintained over the study duration. Observed differences between treatment group means of 0.26 at Week 12 and 0.29 at Week 104 exceeded the *a priori* MCID for HAQ-DI (0.22 points[24]). Moreover, mean HAQ-DI scores in the combination therapy group were comparable to or better than the mean for the general population by Week 52, suggesting improvement from moderate to severe impairment in physical function to a level of performance of daily activities similar to that of the general population.

Baseline mean SF-36 PCS scores were 30.7 to 32.2 for patients in PREMIER compared with reported mean population-based scores of 50.0[32] and 48.3 (age, sex, and race-adjusted score[12]). Over the 2-year study, mean SF-36 PCS scores improved to 48.8 (adalimumab plus MTX group), 45.9 (MTX monotherapy group), and 44.7 (adalimumab monotherapy group). Twelve-week improvements in SF-36 PCS were significantly greater in the adalimumab plus MTX group versus the MTX monotherapy group, and improvements were sustained over 2 years. Observed differences between treatment group means of 3.8 at Week 12 and 2.9 at Week 104 exceeded the *a priori* MCID criterion of 2.5 to 3.0 points[3,10,12,13,33,34,35], indicating that combination therapy improves physical functioning in patients with early RA. The effects on physical functioning observed in our study are consistent with previous clinical trials of treatments for RA[10].

These findings are further supported by improvements in SF-36 domain scores over time. Baseline scores for patients in PREMIER showed significant impairment across all domains versus age- and sex-matched norms specific to the protocol population, derived from the US population. Treatment-associated improvements over 2 years of adalimumab plus MTX treatment met the US normative values in 5 of 8 domains (pain, general health, vitality, social function, and mental health), compared with 3 of 8 domains with MTX monotherapy (vitality, social function, and mental health). In addition, there were statistically significant and clinically meaningful differences between adalimumab plus MTX and MTX monotherapy groups in SF-36 physical function, bodily pain, role limitations-physical, and vitality domain scores.

The adalimumab plus MTX group reported greater improvements on the 2 preference-based measures compared with the MTX group. SF-6D scores showed clinically meaningful improvements from baseline to Week 52 and Week 104 in both treatment groups. Differences between treatment group means at Week 104 were 0.03 for SF-6D, which met the MCID criteria of 0.03 for SF-6D[36,37]. For HUI-3 scores, the observed difference of 0.05 at Week 104 exceeded the *a priori* MCID criterion of 0.03 points[40]. Based on our study, the directly measured HUI-3 and the SF-6D were sensitive preference-based measures for assessing the effects of RA treatments.

No clinically meaningful differences between the monotherapy groups were observed for most HRQOL measures. Although significant treatment-by-week differences were observed on the HAQ-DI, the adalimumab monotherapy group was more impaired at baseline, and the significant interaction indicates that the adalimumab group demonstrated a slightly increased rate of improvement in HAQ-DI scores (baseline to Week 104 changes: adalimumab, –1.03 points; MTX, –1.01 points). Baseline to Week 104 changes on SF-36 MCS scores were nearly comparable between groups (adalimumab, 7.2 points; MTX, 8.8 points) and differences were not clinically meaningful. These results suggest that adalimumab and MTX monotherapy may provide comparable improvements in HRQOL in patients with early RA.

For each HRQOL measure, there was a significant association between HRQOL improvement and clinical response, as assessed by the ACR50 response criteria. We observed significant improvements in HAQ-DI, SF-36 PCS, SF-36 MCS, SF-6D, FACIT-F, and HUI-3 scores, with the largest effects

observed in physical health and functioning measures (HAQ-DI and SF-36 PCS scores). These findings support the clinical responsiveness of these PRO in patients with RA.

Limitations associated with HRQOL assessment in our study should be considered. First, one-third of patients in the MTX monotherapy group discontinued the study by Week 104. The use of observed data could have contributed to interaction effects because of discontinuation of a substantial number of patients from the MTX comparator group. However, because only observed data were used, the responder analyses results were not adversely affected. Moreover, the responder analyses may be conservative because 66% of the MTX monotherapy group was classified as ACR50 responders, whereas only 45% would have been considered responders if last-observation-carried-forward data had been used and only 43% would have been considered responders if data had been imputed. Second, because HRQOL endpoints are based on patient reports, it is unknown whether expectations for improvements in clinical and functional outcomes influenced the results. However, a consistent and significant relationship between clinical response levels and changes in HAQ-DI and SF-36 PCS scores was observed in our study, as reported[3]. A final consideration is that early and aggressive treatment for patients in PREMIER provided tight disease control, which may have contributed to the improvements in HRQOL observed in this patient population.

These results provide evidence supporting the statistically significant and clinically meaningful improvement in measures of physical functioning and preference-based HRQOL measures associated with adalimumab plus MTX treatment. In addition, patients treated with adalimumab plus MTX reported consistent and significant improvements across a range of HRQOL outcomes, and these improvements were maintained over a 2-year period. Together with previously reported findings on tolerability and clinical efficacy[18], these results suggest that adalimumab plus MTX improves physical and multidimensional function or HRQOL and offers a comprehensive and effective therapy for patients with RA.

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