Adalimumab plus Methotrexate Improved SF-36 Scores and Reduced the Effect of Rheumatoid Arthritis (RA) on Work Activity for Patients with Early RA

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ABSTRACT. ***Objective.*** To compare the effect of adalimumab plus methotrexate (MTX) versus MTX monotherapy on health-related quality of life (HRQOL) and work activities in patients with early rheumatoid arthritis (RA).

Methods. Patients in this PREMIER study subanalysis (n = 525) were randomized to adalimumab 40 mg every other week plus MTX or MTX monotherapy. Medical Outcome Study Short-Form 36 Health Survey (SF-36) scores of RA patients were compared with US population norms at Weeks 12, 52, and 104.

Results. Physical Component Summary (PCS) scores at Week 12 for both groups improved from baseline and were significantly lower than US population scores (43.5 combination, 39.4 MTX, 49.4 US norm; $p < 0.001$). At Week 52, PCS score for adalimumab plus MTX was similar to that of the US population (47.5 vs 48.3; $p = 0.25$), while the PCS score for MTX was not similar to that of the US population (44.2 vs 48.3; $p < 0.001$). Criterion- and content-based interpretations for between-treatment differences in PCS scores suggest that those receiving combination therapy had fewer employment difficulties than those receiving MTX.

Conclusion. After 2 years, HRQOL for patients with early RA treated with adalimumab plus MTX improved to US norms. Combination therapy had reduced the influence of RA on work activity. (First Release Dec 15 2007; J Rheumatol 2008;35:206–15)

Key Indexing Terms:
RHEUMATOID ARTHRITIS ADALIMUMAB TUMOR NECROSIS FACTOR ANTAGONISTS
SHORT-FORM 36 HEALTH SURVEY HEALTH-RELATED QUALITY OF LIFE
RANDOMIZED CONTROLLED TRIAL

Joint damage in patients with rheumatoid arthritis (RA) is apparent in almost 50% of patients within 2 years of onset, and a decline in functional status is reported within 10 years[1]. Studies have demonstrated that patients with RA experience significant impairments in functioning and well-being, components of health-related quality of life (HRQOL)[2-4].

There is no known cure or preventive therapy for RA. Benefits from traditional disease-modifying antirheumatic drugs (DMARD) may take weeks or months to become apparent, may diminish over time, or may be limited by adverse effects such as myelosuppression and hepatotoxicity[5]. Biologic agents that work by modifying the immune response via inhibition of tumor necrosis factor (TNF) have been introduced. Used as monotherapy or in combination with methotrexate (MTX), adalimumab, a TNF antagonist, has demonstrated improvement in signs and symptoms of RA and inhibition of radiographic progression[6-11]. Clinical response with adalimumab was rapid, occurring as early as 2 weeks after treatment, and was sustained for up to 4 years[6-11].

Because there is no cure for RA and complete remission is infrequent, the goals of therapy are to control disease activity, alleviate pain, improve physical function, maintain capacity for activities of daily living and work, and maximize HRQOL[5]. Limiting disability and maintaining work ability are particularly important because loss of work accounts for the largest segment of indirect costs associated with RA[12]. Research has shown that 20% to 30% of patients with early RA become permanently work-disabled during the first 2 to 3 years of disease[13] and that the frequency of work disability increases over time, with approximately half of patients work-disabled 10 years after diagnosis[14-16]. Aggressive treatment in early RA has been shown to reduce functional disability over time[17,18] and to positively influence employment outcomes[19].

Laboratory measures and clinical markers [for example, swollen joint counts or erythrocyte sedimentation rates (ESR)] do not necessarily correlate well with patient disabili-

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ty[20-22]. Thus, the influence of RA on patients' lives is best measured through self-report of their experiences in everyday activities, functioning, and well-being. HRQOL measures are particularly useful in identifying the chronic and disabling results of RA and in quantifying its longterm effects on patient functioning and well-being[23]. The Short-Form 36 Health Survey (SF-36), in particular, is endorsed by the American College of Rheumatology (ACR) as one of the criteria for assessing response to therapy[5,24].

Although the importance of measuring the effect of disease from the patient's perspective has been established, the meaning associated with the magnitude of change in HRQOL scores is not as well established. In general, clinicians have little guidance for understanding how changes in HRQOL scores reflect changes in clinical status or functioning and how these changes may affect treatment decisions. Content-based interpretation, which uses information from the content of response choices to assign meaning to scores, and criterion-based interpretation, which uses information on the relationship of scores to external variables or to population norms to assign meaning, are approaches to relating the importance of scores in terms that are more easily understood by clinicians and patients[25].

The objectives of these analyses were to assess the effects of adalimumab combination therapy with MTX and MTX monotherapy on initial and sustained improvement in HRQOL for patients with early RA compared with the US population, to assess the effects of combination therapy and MTX monotherapy on work, and to interpret these findings in ways that are meaningful to patients and physicians, particularly using a norm-based approach.

MATERIALS AND METHODS

RA patient sample. The data for this secondary analysis came from the PREMIER trial, a 2-year, randomized, double-blind, comparator-controlled Phase III study conducted at 133 sites in North America, Europe, and Australia[6]. A total of 799 patients with RA were enrolled into one of 3 treatment groups: adalimumab 40 mg injected subcutaneously every other week plus weekly MTX (n = 268), adalimumab 40 mg subcutaneously every other week (adalimumab plus placebo; n = 274), or weekly oral MTX (MTX plus placebo; n = 257). MTX was initiated at a dosage of 7.5 mg/week for the first 4 weeks of PREMIER. As needed and tolerated, the dosage could be increased to 15 mg/week during Weeks 4 to 8 to a maximum of 20 mg/week at Week 9. In addition, all patients received concomitant folic acid 5 to 10 mg/week. To be eligible for the study, patients met the following inclusion criteria: a diagnosis of RA < 3 years, ≥ 8 swollen joints, ≥ 10 tender joints, an ESR ≥ 28 mm/h or C-reactive protein concentration ≥ 1.5 mg/dl, and a positive rheumatoid factor or at least 1 joint erosion. Patients who had received treatment with MTX, cyclophosphamide, cyclosporine, azathioprine, or more than 2 other DMARD were excluded. The study included a screening period, as well as a 4-week washout period for patients taking other DMARD[6]. Because there were no significant differences between the adalimumab monotherapy and MTX monotherapy groups on the majority of clinical or functional indicators[6], we decided to compare combination therapy with MTX monotherapy only.

Sample of the US general population. General population normative data came from 2 sources: the 1998 National Survey of Functional Health Status (NSFHS), a representative sample (n = 1982) of the noninstitutionalized adult population in the United States[26,27], and the 2001 wave of the Medical Expenditures Panel Survey (MEPS), a nationally representative sample of the noninstitutionalized US civilian population (n = 33,556)[28].

Instruments for assessment of HRQOL. The SF-36 is a 36-item general health status instrument often used in clinical trials and health services research. It consists of 8 subscales: physical function (PF), role limitations–physical (RP), vitality (VT), general health perceptions (GH), bodily pain (BP), social function (SF), role limitations–emotional (RE), and mental health (MH)[29]. Two overall summary scores can also be obtained — a Physical Component Summary score (PCS) and a Mental Component Summary score (MCS). Norm-based scoring algorithms were used for the subscales, for which scores have a mean of 50 and a standard deviation (SD) of 10. Greater scores indicate better health. Summary scores are transformed to have a mean of 50 (SD 10), greater scores indicating better health. The SF-36 has extensive evidence on reliability and validity[4,26,30]. It has demonstrated responsiveness to change in patients with RA, particularly with regard to BP, PF, VT, and MH[30,31]. SF-36 Version 1 was used in this trial.

The SF-12 contains 12 items from the SF-36, with 1 or 2 items measuring each of the 8 concepts included in the SF-36. The SF-12 summary scores, PCS and MCS, are normed with a general population mean of 50 (SD 10). Greater scores reflect better health status. The psychometric properties of the SF-12 are well established in various disease states, including RA[27,32]. Instrument developers suggest that SF-12 and SF-36 summary scores are comparable[27].

Statistical analyses. *Descriptive statistics*. Descriptive statistics were reported for demographic data and clinical characteristics such as age and years with RA. Means and standard deviations were used to describe continuous variables, whereas frequency distributions were used to describe categorical variables.

Assessing burden of RA on HRQOL. The SF-36 norms (derived from data collected in 1998[26]) for men and women 45 to 54 years of age were compared with baseline SF-36 scores for each of the PREMIER trial treatment groups (adalimumab plus MTX and placebo plus MTX) before the start of study treatment. Student t-tests for independent groups were used to assess mean score differences between groups (e.g., adalimumab plus MTX vs general US population). To limit for multiple testing, we focused on comparisons for the subscales PF, BP, and VT[33], which are most consistently influenced by treatment with TNF inhibitors[34-36]. PCS and MCS scores also were evaluated.

Assessing effect of treatment on HRQOL. SF-36 norms for men and women 45 to 54 years of age were compared with SF-36 scores by treatment group at baseline and at Weeks 12, 52, and 104[26]. Student t-tests for independent groups were used to assess mean score differences between groups (placebo plus MTX vs US norms; adalimumab plus MTX vs US norms). To limit for multiple testing, we focused on comparisons for the subscales PF, BP, and VT[33]. Similar analyses were performed using the PCS and MCS scores. To compare PCS and MCS scores of the PREMIER trial sample to the MEPS data sample, 2 analyses were performed. First, the MEPS data were adjusted to the age, gender, and race of the PREMIER trial sample using separate least-squares multiple regression models for the PCS and MCS measures using analysis of covariance. The F-test was used to test for the group factor, and the Bonferroni method was used to adjust for multiple comparisons. Second, a matched-case analysis was performed. For each patient in the PREMIER trial, 5 age, gender, and race-matched controls were randomly chosen from the MEPS data, except in cases for which fewer than 5 controls were available. Student t-tests for independent groups were used to assess mean score differences between groups. Of note, PCS and MCS scores for the PREMIER trial were calculated from the SF-36, whereas those for the MEPS were calculated from the SF-12.

Content-based interpretation was performed by assessing the percentage of patients in each treatment group with limitations in selected SF-36 items (e.g., limitations in performing vigorous activities, limitations walking one block) at baseline and Week 104. Criterion-based interpretation was performed by assessing the percentage of patients in each treatment group who

were unable to work, who lost their jobs, who were hospitalized, or who had a physician visit at baseline and Week 104.

Assessing the relationship between physical components of health and employment. The relationship between the physical components of health and employment status was assessed by examining employment categories (currently employed, has a job to return to, employed during the reference period, and not employed, with no job to return to) by PCS score categories ($0 \geq$ PCS < 30, $30 \geq$ PCS < 35, $35 \geq$ PCS < 45, $45 \geq$ PCS < 50, PCS $\geq$ 50). In addition, logistic regression models evaluated the odds of employment (currently employed vs all other categories) per 1-unit change in PCS score. The 2001 MEPS data were used for these employment analyses.

RESULTS

Demographic and clinical characteristics. A total of 525 patients from the PREMIER study were included in this analysis: 268 patients in the group received combination therapy with adalimumab plus MTX, and 257 patients in the group received MTX monotherapy. Baseline demographic and clinical characteristics were similar between the 2 treatment groups and were indicative of early, erosive RA (Table 1)[6].

Assessing the burden of early RA on HRQOL. A summary of baseline SF-36 scale scores for PREMIER trial groups and the general US population — based on men and women 45 to 54 years old in the 1998 NSFHS (N = 417) — are presented in Table 2 and Figure 1. At baseline, patients in each PREMIER trial treatment group had significantly lower SF-36 scores, on all subscales, compared with the general US population. For the PF, BP, and VT subscales, score differences between patients receiving combination therapy and the general US population were 19.2, 16.7, and 10.4 points, respectively. Similar findings were observed for differences in scores between patients receiving MTX monotherapy and the general US population.

Table 1. PREMIER baseline demographics and clinical characteristics. All mean values, except percentages.

Feature	Adalimumab plus MTX, n = 268	Placebo plus MTX, n = 257
Demographics		
Age, yrs	51.9 ± 14.0	52.0 ± 13.1
Percentage female	72.0	73.9
Clinical characteristics		
Years of RA	0.7 ± 0.8	0.8 ± 0.9
Previous DMARD, n (%)	87 (32.5)	81 (31.5)
Taking corticosteroids, n (%)	96 (35.8)	91 (35.4)
Tender joint count, 0–68	30.7 ± 14.2	32.3 ± 14.3
Swollen joint count, 0–66	21.1 ± 11.2	22.1 ± 11.7
HAQ-DI	1.5 ± 0.6	1.5 ± 0.6
Physician global assessment of disease activity, 100 mm VAS	65.1 ± 17.6	65.6 ± 17.7
Patient global asssessment of disease activity, 100 mm VAS	66.8 ± 22.1	63.0 ± 25.0
Physician assessment of pain, 100 mm VAS	62.5 ± 21.3	59.6 ± 24.3
DAS28 score, mean	6.3 ± 0.9	6.3 ± 0.9

DAS28: 28-joint Disease Activity Score, DMARD: disease modifying antirheumatic drugs, HAQ-DI: Health Assessment Questionnaire Disability Index, MTX: methotrexate, RA: rheumatoid arthritis, VAS: visual analog scale.

Baseline PCS and MCS scores also were significantly lower for patients in the PREMIER trial compared with the general US population (Table 2). Patients receiving combination therapy or MTX monotherapy had significantly lower PCS scores compared with the general US population (31.7, 32.2, and 49.4 points, respectively; $p < 0.001$ for both treatment groups). MCS scores were also significantly less for both treatment groups compared with the general US population (44.1, 43.5, and 50.3 points, respectively; $p < 0.001$ for both treatment groups). At baseline, PCS scores were strongly associated with Health Assessment Questionnaire Disability Index (HAQ-DI) and moderately associated with 28-joint Disease Activity Scores (DAS28) ($r = -0.65$ and -0.42, respectively; both $p < 0.0001$). Baseline MCS scores showed significant, but weak, associations with HAQ-DI and DAS28 ($r = -0.33$ and -0.21, respectively; both $p < 0.0001$).

Effect of treatment on HRQOL in early RA. SF-36 subscales. At Week 12, scores for the VT scale had improved and were similar between patients receiving combination therapy and the general US population (50.1 vs 50.4; $p = 0.70$; Figure 2). Scores for the PF and BP scales had improved, but were significantly lower for patients receiving combination therapy compared with the general US population. For those receiving MTX monotherapy, scores for the PF, BP, and VT scales were significantly lower compared with the general US population. MH scores were similar between the general US population and patients receiving either combination therapy or monotherapy (49.4, 48.4, and 48.4, respectively; both $p > 0.20$ compared with US general population).

At Week 52, patients receiving combination therapy or MTX monotherapy had significantly greater VT scores compared with the general US population (53.9, 52.4, and 50.4, respectively; $p < 0.001$ for combination therapy and $p = 0.03$ for MTX monotherapy). For those receiving combination therapy, scores also were significantly greater for the BP scale compared with the general US population (50.9 vs. 49.2; $p = 0.04$), whereas scores for those receiving MTX monotherapy were significantly lower than scores for the US population (47.1 vs 49.1; $p = 0.02$). In addition, scores were similar between the general US population and patients receiving either combination therapy or monotherapy for the SF and MH scales and between patients receiving combination therapy for the GH scale (Figure 3).

Similar findings were seen at Week 104, when patients receiving combination therapy or MTX monotherapy had significantly greater VT scores compared with the general US population (54.4, 53.2, and 50.4, respectively; $p < 0.0001$ for combination therapy and $p = 0.004$ for MTX monotherapy). For those receiving combination therapy, scores also were significantly greater for the BP scale compared with the general US population (51.2 vs 49.2; $p = 0.02$), whereas scores for those receiving MTX monotherapy were similar (47.7 vs

Table 2. Effect of early RA disease on health-related quality of life. Study population at baseline versus general US population.

Indicator	Adalimumab plus MTX, mean (SD)	Placebo plus MTX, mean (SD)	General US Population*, mean (SD)	Significance Testing: Adalimumab plus MTX vs General Population, p†	Significance Testing: Placebo plus MTX vs General Population, p†
SF-36 Scales					
PF	30.2 (10.0)	31.5 (10.3)	49.4 (10.0)	< 0.001	< 0.001
RP	33.1 (8.8)	32.6 (8.4)	50.1 (9.9)	< 0.001	< 0.001
BP	32.5 (7.1)	32.7 (7.7)	49.2 (10.2)	< 0.001	< 0.001
GH	40.9 (10.0)	40.5 (9.1)	49.3 (10.7)	< 0.001	< 0.001
VT	40.0 (10.0)	40.6 (9.7)	50.4 (10.5)	< 0.001	< 0.001
SF	38.3 (12.0)	38.1 (12.2)	50.1 (10.1)	< 0.001	< 0.001
RE	38.4 (14.1)	36.7 (13.8)	50.6 (9.5)	< 0.001	< 0.001
MH	42.1 (12.2)	42.6 (12.1)	49.4 (10.7)	< 0.001	< 0.001
Summary scores					
PCS	31.7 (7.8)	32.2 (7.9)	49.4 (10.4)	< 0.001	< 0.001
MCS	44.1 (12.5)	43.5 (12.4)	50.3 (10.3)	< 0.001	< 0.001

* SF-36 values for men and women ages 45 to 54 years from SF-36 manual (1998 NSFHS population; n = 417). † Student t-test for independent groups with pooled variance (2-sided). BP: bodily pain, GH: general health perceptions, MCS: Mental Component Summary score, MH: mental health, MTX: methotrexate, PCS: Physical Component Summary score, PF: physical function, RA: rheumatoid arthritis, RE: role limitations-emotional, RP: role limitations-physical, SF: social function, SF-36: Medical Outcomes Study Short-Form 36, VT: vitality.

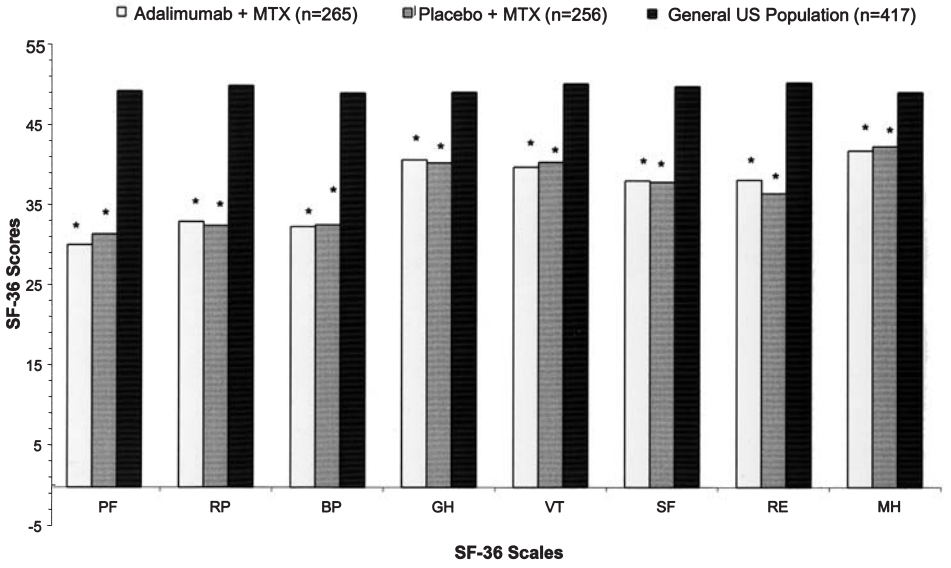

Figure 1. Mean SF-36 scores at baseline for PREMIER trial groups versus general US population (1998 National Survey of Functional Health Status). SF-36 values for men and women ages 45 to 54 years. *p < 0.001, Student t-test for independent groups with pooled variance. BP: bodily pain, GH: general health perceptions, MH: mental health, MTX: methotrexate, PF: physical function, RE: role limitations–emotional, RP: role limitations–physical, SF: social function, VT: vitality.

49.2; p = 0.11). In addition, scores were comparable between the general US population and patients receiving either combination therapy or monotherapy for the SF and MH scales and between patients receiving combination therapy for the GH scale, whereas scores for monotherapy were significantly less than for the US population (Figure 4).

Assessing SF-36 summary scores. Based on the 1998 subsample of NSFHS data (N = 417), PCS scores at Week 12 for those receiving combination therapy (43.5 points) or MTX monotherapy (39.4 points) had improved from baseline but were significantly less than those for the general US population (49.4 points; p < 0.001 for both treatment groups compared with the general US population). Similar findings were seen at Week 52 (47.5 vs 49.4; p < 0.03 for combination therapy and 44.2 vs 49.4 for MTX monotherapy; p < 0.001). At Week 104, PCS scores for those receiving combination thera-

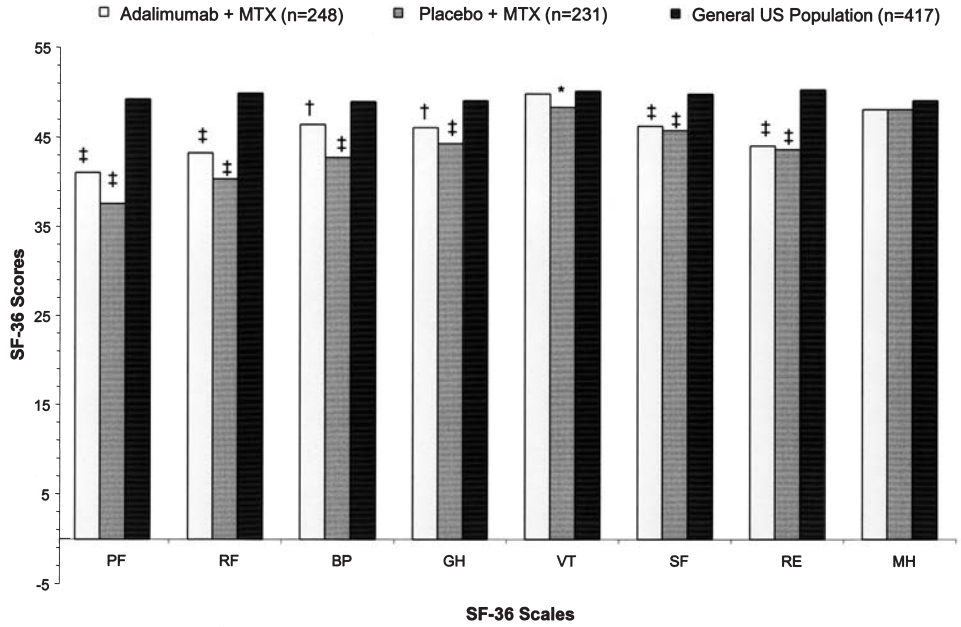

Figure 2. Mean SF-36 scores at Week 12 for PREMIER trial groups versus general US population (1998 National Survey of Functional Health Status). SF-36 values for men and women ages 45 to 54 years. *p < 0.05, †p < 0.01, ‡p < 0.001; Student t-test for independent groups with pooled variance. BP: bodily pain, GH: general health perceptions, MH: mental health, MTX: methotrexate, PF: physical function, RE: role limitations–emotional, RP: role limitations–physical, SF: social function, VT: vitality.

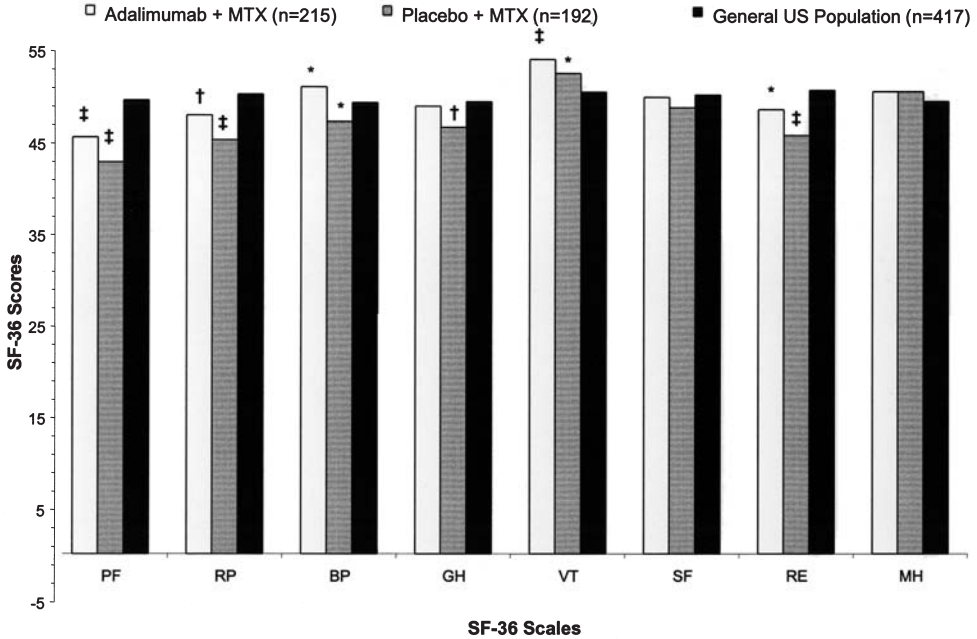

Figure 3. Mean SF-36 scale scores at Week 52 for PREMIER trial groups versus general US population (1998 National Survey of Functional Health Status). SF-36 values for men and women ages 45 to 54 years. *p < 0.05, †p < 0.01, ‡p < 0.001; Student t-test for independent groups with pooled variance. BP: bodily pain, GH: general health perceptions, MH: mental health, MTX: methotrexate, PF: physical function, RE: role limitations–emotional, RP: role limitations–physical, SF: social function, VT: vitality.

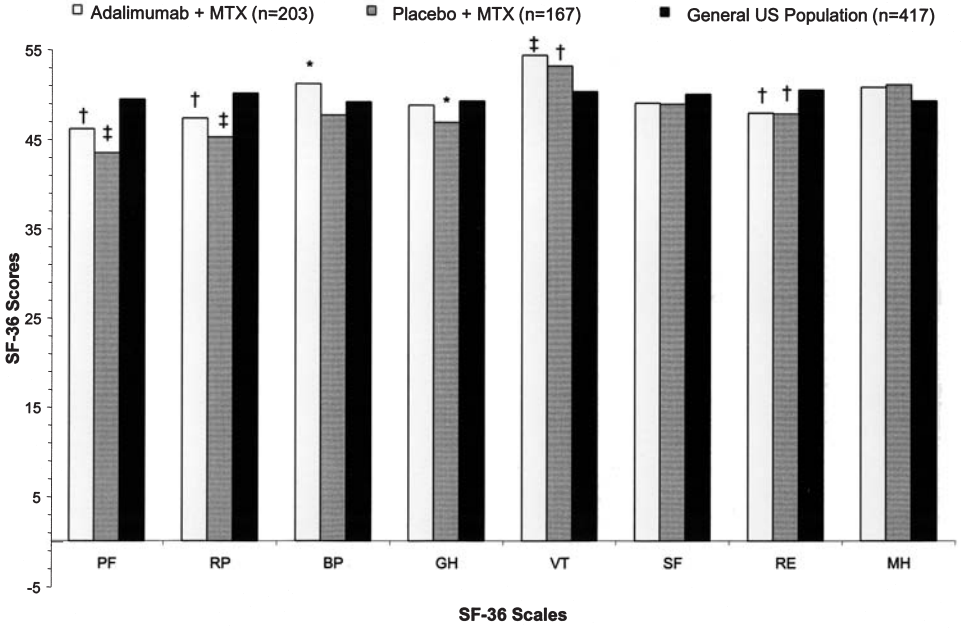

Figure 4. Mean SF-36 scale scores at Week 104 for PREMIER trial groups versus general US population (1998 National Survey of Functional Health Status). SF-36 values for men and women ages 45 to 54 years. *$p < 0.05$, †$p < 0.01$, ‡$p < 0.001$; Student t-test for independent groups with pooled variance. BP: bodily pain, GH: general health perceptions, MH: mental health, MTX: methotrexate, PF: physical function, RE: role limitations–emotional, RP: role limitations–physical, SF: social function, VT: vitality.

py were similar to those of the general population (47.8 vs 49.4; p = 0.08), whereas scores for those receiving MTX monotherapy were significantly less than for the general US population (44.4 vs 49.4, p < 0.001). Similar findings were seen for MCS scores at Weeks 12 and 52. At Week 104, scores for those receiving MTX monotherapy were significantly greater than for those of the general US population (52.6 vs 50.3 points; p = 0.01), whereas scores for those receiving combination therapy were similar to those of the general US population (51.5 vs 50.3 points; p = 0.21).

Similar findings were generally observed comparing PCS and MCS scores of the PREMIER trial groups with those of the general population based on the age, gender, and race-matched 2001 MEPS data (N = 2625; Figure 5) and the entire 2001 MEPS sample, adjusted for age, gender, and race (N = 20,643; data not shown). For the matched MEPS sample (Figure 5), however, improvements in PCS scores were similar to those of the general population by Week 52 for combination therapy (47.5 vs 48.3; p = 0.25), but not for MTX monotherapy (44.2 vs 48.3; p < 0.001).

Considering a criterion-based interpretation of PCS scores using survey questions from the NSFHS[26] and relative to patients receiving MTX monotherapy, patients receiving combination therapy were less likely to visit a physician (25.4% vs 29.9%; Table 3), lose their jobs (13.3% vs 30.3%), or be unable to work (10.7% vs 17.4%). Content-based interpretation of PCS scores showed that a smaller percentage of patients treated with combination therapy experienced limitations climbing stairs (12.0% vs 21.3%; Table 3), walking 1 block (7.5% vs 13.3%), or performing vigorous activities (82.8% vs 88.4%) compared with those treated with MTX monotherapy. In addition, fewer patients treated with combination therapy had difficulty at work or needed to cut down on work compared with those treated with MTX monotherapy (15.4% vs 34.0% and 9.0% vs 18.3%, respectively).

Assessing the relationship between the physical components of health and employment. Evaluation of the relationship between PCS scores and employment using the age, gender, and race-matched 2001 MEPS data (N = 2625) showed that employment status increases as PCS scores increase. Patients in the lowest PCS category (0 ≤ PCS < 30) had the lowest employment (21% currently employed), whereas patients in the highest category (PCS ≥ 50) had the greatest employment (73% currently employed; Figure 6). Similar findings were observed when evaluating this relationship using the entire 2001 MEPS population (N = 20,643; data not shown).

In addition, findings from logistic regression models assessing the relationship between PCS scores and employment status showed that the odds ratio for being employed per 1-point increase in PCS score is 1.076 (95% CI 1.067, 1.085; p < 0.001) for the matched 2001 MEPS population and 1.077 (95% CI 1.074, 1.080; p < 0.001) for the entire 2001 MEPS population.

DISCUSSION

This study examined the burden of early RA on patient functioning and well-being. Regardless of the data source defining the general US population, patients with early RA report sig-

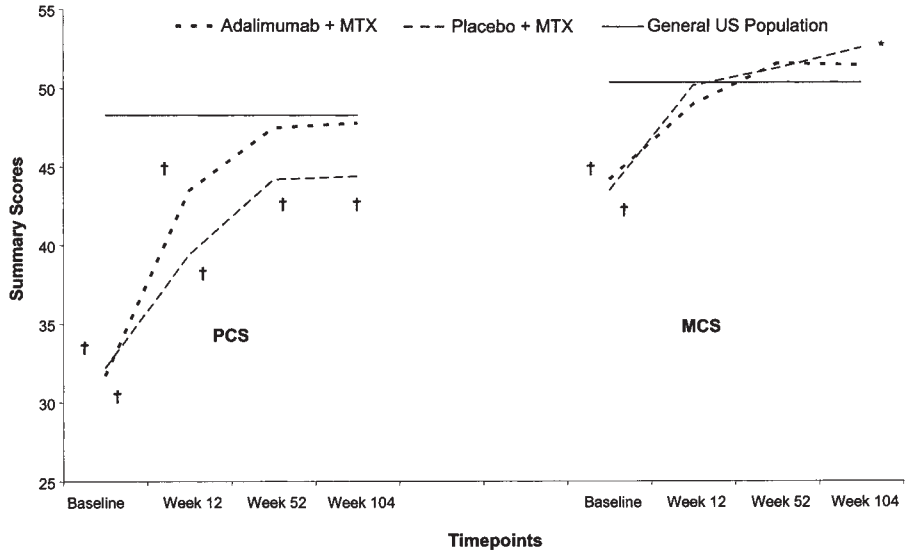

Figure 5. Mean PCS and MCS scores over 104 Weeks for PREMIER trial groups versus general US population (2001 matched Medical Expenditures Panel Survey population). SF-12 values from random sample of MEPS population matched for age, gender, and race (n = 2625). Sample size for adalimumab plus MTX group at baseline and Weeks 12, 52, and 104 = 247, 223, 188, 166, respectively. *p < 0.01, †p < 0.001; Student t-test for independent groups. MCS: Mental Component Summary score, MTX: methotrexate, PCS: Physical Component Summary score.

nificantly less functioning and well-being compared with population norms, even after adjusting for age, gender, and race. The influence of RA was primarily observed on the physical components of health status, with differences in PCS scores for treatment groups compared across the various US population samples ranging from 16.1 to 18.1 points. In addition, patients in the PREMIER trial appear to have had poorer physical functioning than patients with arthritis or rheumatism in Europe (Denmark, France, Germany, Italy, Netherlands, and Norway) and Japan, for which PCS scores are 3.5 to 9.0 points less than for the general population — defined as those who do not have any of 7 medical conditions[37].

Although treatment reduced the effects of RA over the 2-year study period, SF-36 scores for patients treated with MTX monotherapy generally remained below population norms for similar-age men and women for all physical components of

Table 3. Interpretation of SF-36 Physical Component Summary scores: percentages based on general US population norms.

	Adalimumab plus MTX		Placebo plus MTX	
	Baseline, %	Week 104, %	Baseline, %	Week 104, %
Criterion-based interpretation				
Unable to work	45.5	10.7	44.4	17.4
Job loss	30.9	13.3	30.3	17.3
Hospitalized	10.9	6.0	10.7	6.7
Physician visit	48.2	25.4	47.7	29.9
Content-based interpretation				
Limitation in vigorous activities	95.4	82.8	95.2	88.4
Limitation walking one block	46.2	7.5	44.4	13.3
Limitation climbing stairs	68.0	12.0	66.4	21.3
Difficulty at work	88.8	15.4	88.1	34.0
Reduce work time	65.9	9.0	64.8	18.3
Severe or very severe bodily pain	22.6	2.2	21.2	3.4
Have lots of energy	9.7	35.4	10.1	29.0
Feeling tired	37.8	8.4	37.2	12.1
Excellent health	0.0	5.2	0.1	4.2
Fair/poor health	61.2	12.1	60.0	18.1

MTX: methotrexate, SF-36: Medical Outcomes Study Short-Form 36.

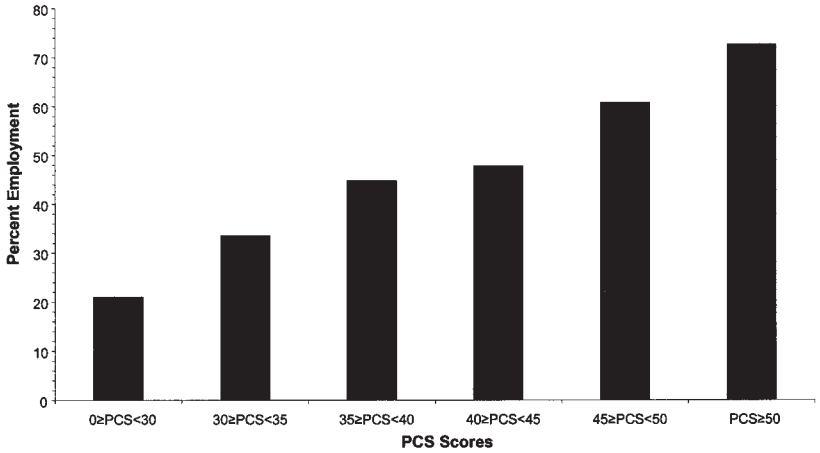

Figure 6. Relationship between employment status and PCS scores (2001 matched Medical Expenditures Panel Survey population; N = 2625). Total sample size in 2001 MEPS data is 33,556. Of 33,556 patients, 20,643 patients had PCS scores available. In the PREMIER study, 2625 patients were matched for age, gender, and race. PCS: Physical Component Summary score.

health, whereas scores for patients being treated with combination therapy improved to be equivalent to or slightly better than population norms for some components of physical health. After about 1 year of treatment, patients receiving combination therapy had significantly less bodily pain and similar general health perceptions compared to the general US population. These outcomes were maintained at 2 years, demonstrating the sustainability of HRQOL benefits with the adalimumab plus MTX treatment regimen over time.

These findings are reflected in the PCS scores across time; scores for patients receiving combination therapy were similar to those of the US general population after 2 years of treatment. The pattern of improvement in PCS scores across time and relative to the general US population was consistent among the various US population samples — scores were most similar to the age, gender, and race-matched MEPS sample after 1 and 2 years of combination therapy. In addition, the 4.2-point difference in change scores (baseline to Week 104) between those receiving combination therapy and those receiving MTX monotherapy is clinically meaningful based on a minimum important difference of 2.0 to 3.0 points for SF-36 summary scores[23,29].

Interpretation of PCS scores suggests that treatment with combination therapy positively influences the frequency of physician visits and unemployment. Criterion-based interpretation of PCS scores indicated that those receiving combination therapy were less likely to visit a physician, lose their jobs, or be unable to work relative to those receiving MTX monotherapy. Content-based interpretation of the PCS suggests that fewer patients treated with combination therapy were likely to have difficulty working or to have to cut down on their time at work compared with those treated with MTX monotherapy. These findings are consistent with those observed in evaluating the relationship between PCS scores and employment in the age, gender, and race-matched MEPS population (N = 2625), in which 61% of patients with PCS scores ≥ 45 and < 50 points (such as with combination therapy at 52 and 104 weeks) were likely to be currently employed compared with 48% of patients with PCS scores ≥ 40 and < 45 points (such as with MTX monotherapy at 52 and 104 weeks). In addition, findings from the logistic regression analysis suggest that the odds of being employed are 1.4 times greater than the odds for being unemployed for patients whose PCS scores improve by 4.2 points, the difference in PCS change scores over 104 weeks for combination therapy compared with MTX monotherapy. Similar findings for both employment evaluations were observed using the entire 2001 MEPS data (N = 20,643). Taken together, these findings suggest that treatment with adalimumab plus MTX enables patients to maintain or attain employment over time.

Treatment also improved the emotional well-being of patients with RA, particularly with regard to the VT, SF, and MH scales. Improvements were most apparent in the VT scale, for which scores at 52 and 104 weeks were greater than for the general US population and may reflect improvements in pain[38]. Improvements in emotional well-being were seen as early as 3 months after initiating treatment with adalimumab plus MTX combination therapy and were maintained or improved over 2 years. Similar improvements were also seen for patients receiving MTX monotherapy. These findings are reflected in MCS scores across time and across the 3 US population samples.

The patterns of HRQOL outcomes for patients receiving combination therapy and MTX monotherapy over a 2-year treatment period are useful in understanding the full benefit of treatment of RA. Although the effect of treatment on the mental health components of HRQOL was similar for both treatments, patients receiving combination therapy with adalimumab experienced greater HRQOL benefit in terms of the physical components of health status after 1 year of treatment.

This HRQOL benefit mirrored the clinical benefit of treatment, for which, after 1 and 2 years of treatment, a greater number of patients receiving combination therapy achieved a 50% improvement in clinical status — based on the ACR criteria — compared with those receiving MTX monotherapy[6]. In addition, patients receiving combination therapy experienced significantly less radiographic progression and joint erosion, greater clinical remission rates (defined as 28-joint DAS < 2.6), and greater improvements in function based on the HAQ-DI at 1 and 2 years compared with those receiving MTX monotherapy.

These results are directionally similar to the results observed from the ASPIRE trial of infliximab plus MTX versus MTX monotherapy in early RA (mean RA disease duration of approximately 0.9 years). In ASPIRE, improvement in the SF-36 PCS score favored the combination of infliximab plus MTX versus infliximab alone[39]. However, the differences between the infliximab plus MTX arm at the recommended infliximab dosage of 3 mg/kg every 8 weeks and the MTX monotherapy arm at Week 54 were statistically significant[39], but did not reach the level of being clinically meaningful (> 2.5-point difference)[23]. There are no trials comparable to ASPIRE or PREMIER for etanercept in early RA. However, the TEMPO study, which evaluated a different population (mean RA disease duration of roughly 6.5 years)[40], is frequently compared with both ASPIRE and PREMIER. A thorough and extensive literature search, as well as a careful review of US prescribing information for etanercept and the European Summary of Product Characteristics, indicates that there are no published SF-36 results from TEMPO for comparison.

There were several limitations associated with the normative comparisons and analyses conducted for this study. First, the study was based only on normative data on the SF-36 in the United States. However, patients with early RA participating in the PREMIER study were recruited from the United States, Europe, and Australia. There may be some differences in normative scores across different countries that may affect these findings. Second, the health status scores were based on patient self-reports and may be associated with some bias in reporting. However, this bias, if any, may be minimal given the strong associations between the clinical endpoints and the HRQOL measures and the longterm followup of patients in this study. Third, the SF-36 summary scores may sometimes yield unexpected results. At 104 weeks for the matched MEPS population, for example, MCS scores for patients receiving MTX monotherapy were significantly different than population norms, whereas MCS scores for those receiving combination therapy were not significantly better than population norms. This finding was observed even though both treatment groups had comparable scores on subscales comprising the MCS (i.e., VT, SF, RE, MH). This is partially explained by the negative weight for physical function and bodily pain in scoring the MCS. Finally, longer-term data will be beneficial in confirming the results of this study. Additional data are being collected during the third year of the trial as part of a continuing open-label extension phase; these data will be analyzed in the future and compared with the results from the initial 2-year double-blind period.

Our findings suggest that clinical and patient-reported outcomes measures are both important to fully comprehend the influence of treatment on the lives of patients with RA. Combination therapy with adalimumab and MTX for early RA was effective in improving generic measures of physical and psychological health to levels comparable to those of the general population in the United States and, more importantly, demonstrated maintenance of these effects over 2 years. In addition, combination therapy was effective in reducing the influence of RA on work activity.

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