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ORIGINAL ARTICLE

Improvement in Patient-Reported Outcomes in a Rituximab Trial in Patients With Severe Rheumatoid Arthritis Refractory to Anti–Tumor Necrosis Factor Therapy

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Objective. **To assess the effects of treatment with rituximab plus methotrexate on patient-reported outcomes in patients with active rheumatoid arthritis (RA) who experienced inadequate response to anti–tumor necrosis factor therapy.**

Methods. **Patients with active RA were randomly assigned to rituximab (1,000 mg on days 1 and 15) or placebo. The primary end point was the proportion of patients with an American College of Rheumatology 20% response at week 24. Additional goals were to assess treatment effects on pain, fatigue, functional disability, health-related quality of life, and disease activity by comparing mean changes between groups. The analysis was conducted in the intent-to-treat population. The proportion of patients who achieved the minimum clinically important difference on the Health Assessment Questionnaire (HAQ) disability index (DI), Functional Assessment of Chronic Illness Therapy–Fatigue (FACIT-F), and Short Form 36 (SF-36) was determined.**

Results. **Rituximab patients had statistically significantly greater pain relief. The FACIT-F showed significantly greater improvement in rituximab patients than placebo patients from weeks 12 through 24. Mean improvement from baseline in functional disability (measured by the HAQ DI) was significantly greater in rituximab patients from weeks 8 to 24. The mean ± SD change from baseline for the SF-36 Physical Component Score was 6.64 ± 8.74 for rituximab patients and 1.48 ± 7.32 for placebo patients ($P < 0.0001$). The mean change from baseline for the SF-36 Mental Component Score was 5.32 ± 12.41 for rituximab patients and 2.25 ± 12.23 for placebo patients ($P = 0.0269$).**

Conclusion. **Rituximab produced rapid, clinically meaningful, and statistically significant improvements in patient-reported pain, fatigue, functional disability, health-related quality of life, and disease activity. These effects were sustained throughout the study.**

INTRODUCTION

Rheumatoid arthritis (RA) is a chronic, systemic, autoimmune disease characterized by symmetrical inflammation of the affected joints (1,2). RA affects ~1% of the population (3) and despite available therapies, 55–70% of patients have progressive disease that causes joint destruction and disability (4).

The etiology of RA remains elusive, but unknown envi-

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ronmental antigenic triggers in genetically susceptible individuals may initiate a self-perpetuating cascade of autoimmune inflammatory responses in the synovial compartment (2,5,6). Recent research has focused on evidence that B lymphocytes may contribute to inflammation in RA by processing and presenting antigens to T lymphocytes, as well as by secreting proinflammatory cytokines and immunoglobulins (5,7–11).

RA is typically treated with disease-modifying antirheumatic drugs (DMARDs), and methotrexate (MTX) is the DMARD most often selected for initial RA therapy (12,13). More recently, anti–tumor necrosis factor (anti-TNF) agents such as etanercept, infliximab, and adalimumab have become available for RA treatment. These agents can limit disease progression and improve function, but 25–42% of patients given anti-TNF agents do not adequately respond to or tolerate them (14–16).

Rituximab, a therapeutic agent that works by selectively depleting anti-CD20–positive B cells, which has shown significant efficacy in modifying RA disease symptoms (17), is approved for treatment of moderately to severely active RA in patients with inadequate response to anti-TNF therapies (18). Rituximab binding to CD20 depletes peripheral B cells through cell-mediated and complement-dependent cytotoxicity and promotion of cell apoptosis (19–22).

Results have been published from the Randomized Evaluation of Long-Term Efficacy of Rituximab in RA (REFLEX) trial, which demonstrated that patients with active RA for whom anti-TNF therapies were inadequate improved significantly with rituximab plus MTX compared with MTX alone (23).

Patients' measures of success, e.g., noticeable improvement in daily function, or improvements in health-related quality of life (HRQOL), may be as important as improvement in clinical signs and symptoms such as swollen joint counts (24). Patient-reported outcome (PRO) instruments are used to measure outcomes (such as functional improvement or HRQOL) that cannot be measured otherwise by the physician. The Outcome Measures in Rheumatology Clinical Trials group (OMERACT), the European League Against Rheumatism (EULAR), and the American College of Rheumatology (ACR) recognize that PRO measures are a key method to understanding patients' experience of their disease (25–27). In the present study, we used a variety of accepted PRO measures to investigate whether the clinical improvements seen in trials of rituximab were reflected in patients' assessments.

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PATIENTS AND METHODS

Participants. The REFLEX trial was a 2-year, randomized, placebo-controlled trial that compared rituximab plus MTX with MTX alone for treatment of RA in patients who had inadequate responses to anti-TNF agents. Eligible patients between 18 and 80 years old were recruited from 114 rheumatology centers in the US, Europe, Canada, and Israel. Patients had RA, as defined by the 1987 ACR (formerly the American Rheumatism Association) criteria (28), for at least 6 months. Patients had active disease, and had failed treatment with 1 or more anti-TNF therapies (23). The study was carried out in accordance with the Declaration of Helsinki. All participating sites received approval from their governing institutional review boards (or equivalent) and all patients provided written informed consent.

Treatment and end points. Patients were randomized at a ratio of 3:2 to receive rituximab (1,000 mg on days 1 and 15) or placebo. Both groups continued receiving stable doses of MTX (10–25 mg/week orally or parenterally), and received folate (≥5 mg/week or equivalent), intravenous methylprednisolone (100 mg 30 minutes before each infusion), and oral prednisone (60 mg on days 2–7, 30 mg on days 8–14) during the 2-week treatment period (23). The primary end point was the proportion of patients with a 20% response at week 24 according to ACR criteria (ACR20) (29), defined as at least a 20% improvement from baseline in tender and swollen joint counts and in 3 of 5 remaining disease activity measures of the ACR core set (patient assessment of global status, an acute-phase reactant [erythrocyte sedimentation rate or C-reactive protein], physician assessment of global status, patient-reported physical function, and pain) (25). Specific assignment and dose details of the study were reported (23).

One of the goals of this study was to assess treatment effects of rituximab and MTX using validated and accepted PRO instruments, including 1) symptom-specific measures for pain (visual analog scale [VAS-pain]) and fatigue (Functional Assessment of Chronic Illness Therapy–Fatigue [FACIT-F]), 2) a functional disability measure (the Health Assessment Questionnaire [HAQ] disability index [DI]), 3) a generic HRQOL measure (Short Form 36 [SF-36]), and 4) Patient Global Assessment of Disease Activity (PGA) (30–35).

Pain was measured at baseline and weeks 4, 8, 12, 16, 20, and 24 using a VAS ranging from no pain to worst pain imaginable; a higher score indicated worse pain (34).

The FACIT-F is a symptom-specific scale validated for patients with RA. The 13-item subscale is self-administered using a 5-point Likert rating scale and has a range of 0–52 (31,32). This scale was administered at baseline and weeks 12, 16, 20, and 24. The scale was coded so a reduction in score indicated a reduction in fatigue.

The HAQ DI measures self-perceived disability and is one of the first instruments deliberately designed to cap-

Table 1. Baseline demographics by treatment assignment (intent-to-treat population)*

	Placebo + MTX	Rituximab + MTX	All	*P*
Patients	201 (40)	298 (60)	499	
Region				0.9988
US	116 (58)	172 (58)	288 (58)	
Non-US	85 (42)	126 (42)	211 (42)	
Sex				0.9140
Female	164 (82)	242 (81)	406 (81)	
Male	37 (18)	56 (19)	93 (19)	
Age at screening, mean ± SD years	52.89 ± 12.31	52.24 ± 12.20	52.50 ± 12.23	0.5667
RA disease duration, mean ± SD years	11.74 ± 7.68	12.15 ± 8.4	11.98 ± 8.11	0.5782
Rheumatoid factor positive at baseline	160 (80)	234 (79)	394 (79)	0.7719

* Values are the number (percentage) unless otherwise indicated. MTX = methotrexate; RA = rheumatoid arthritis.

ture the long-term influence of multiple chronic illnesses. Scores range from 0 to 3, with higher scores indicating worse disability. The HAQ DI has been validated in a variety of settings in diverse populations (30). It was administered at baseline and weeks 4, 8, 12, 16, 20, and 24.

The SF-36, a multipurpose short-form health survey, has proven useful in surveys of general and specific populations, in comparing the relative burden of diseases, and in differentiating health benefits produced by a wide range of treatments (36). The 36 items yield an 8-scale profile of functional health and well-being, as well as psychometrically based physical and mental health summary measures (Physical Component Score [PCS] and Mental Component Score [MCS]) (37). All 8 scales (bodily pain, general health, mental health, physical functioning, role emotional, role physical, social function, and vitality) as well as the 2 summary scores (PCS and MCS) were analyzed. The range of SF-36 scores and scales is 0–100, with a higher score indicating better HRQOL. The SF-36 was administered at baseline and week 24.

The PGA was measured at baseline and weeks 4, 8, 12, 16, 20, and 24 using a VAS that ranged from "no disease activity" to "maximum disease activity."

Statistical analysis. Patients in the intent-to-treat (ITT) population were eligible for inclusion in analyses. The ITT population was defined as all randomized patients who received any part of an infusion of study medication and included patients who withdrew prematurely from the study for any reason and for whom assessments were not made. The main outcomes of interest were mean changes in scores from baseline to week 24. For outcomes in which multiple repeated measures were made (VAS-pain, FACIT-F, and HAQ DI), the last observation carried forward (LOCF) method was used to replace any missing values; therefore, all patients except those with missing baseline values were included in the analysis. For SF-36 scores, only baseline and week 24 assessments were performed; therefore patients with missing scores at either point were excluded from analysis.

Based on changes from baseline to week 24, the proportion of patients who achieved the minimum clinically important difference (MCID) was determined. Patients with a reduction of at least 3.56 from baseline in FACIT-F score were classified as achieving MCID for the FACIT-F (31,38), and patients with a decrease in HAQ DI score of at least 0.22 from baseline were classified as having achieved MCID for the HAQ DI (39). For the MCS and PCS, 2 MCIDs (increases of at least 3 and 5), were used to classify patients (40). Patients with HAQ DI scores of 0, indicating no disability in their self-reported functional status, were identified at week 24, and proportions of those patients were compared between treatment groups.

Descriptive statistics were reported and stratified by treatment group. The mean ± SD was reported for continuous variables and the count and percentage were reported for categorical variables. To show the change over time for VAS-pain, FACIT-F, and HAQ DI scores, mean changes (from baseline) and 95% confidence intervals for each followup visit were reported for each treatment group. The unadjusted measures were compared between treatment groups using *t*-test and chi-square test. For FACIT-F and HAQ DI, we determined the visit at which a patient reached MCID and then sustained that improvement until study end. We performed a life table analysis to compare the time to reach and sustain MCID between the placebo and rituximab groups.

Multivariate analyses were conducted to adjust for some baseline factors. Analysis of covariance (ANCOVA) was conducted to compare the mean change from baseline in scores between treatment groups, adjusting for the relevant baseline score, baseline rheumatoid factor (positive versus negative), and region (US versus non-US). For MCID analysis, the Cochran-Mantel-Haenszel test (CMH) was used to compare the probability of achieving MCID between treatment groups, controlling for baseline rheumatoid factor and region. ANCOVA and CMH results did not differ from unadjusted results, and therefore only unadjusted results are presented. We also created 2 × 2 tables to examine the frequency of discrepant responses on ACR20 score and several PROs. All reported *P* values are 2-sided with a level of significance of 0.05. All statistical analyses were performed using SAS software, version 9.1 (SAS Institute, Cary, NC).

RESULTS

A total of 751 patients with active RA and inadequate response to at least 1 anti-TNF agent were screened and

Table 2. Baseline measures by treatment assignment (intent-to-treat population)*

	Placebo + MTX (n = 201)	Rituximab + MTX (n = 298)	All (n = 499)	*P*
Swollen joint count	22.94 ± 12.71	23.36 ± 11.85	23.19 ± 12.20	0.7094
Tender joint count	32.90 ± 15.62	33.86 ± 15.22	33.47 ± 15.37	0.4965
Disease Activity Score	6.81 ± 0.93	6.88 ± 1.00	6.85 ± 0.97	0.4650
VAS-pain	64.46 ± 21.32	64.08 ± 22.28	64.23 ± 21.88	0.8517
FACIT-F	30.24 ± 11.75	30.40 ± 10.75	30.33 ± 11.15	0.8732
HAQ DI	1.91 ± 0.54	1.86 ± 0.58	1.88 ± 0.56	0.3405
SF-36 PCS	28.87 ± 6.62	28.72 ± 6.82	28.78 ± 6.73	0.8025
Physical functioning	26.25 ± 8.65	27.02 ± 8.86	26.71 ± 8.78	
Role physical	31.16 ± 7.45	30.73 ± 6.73	30.90 ± 7.02	
Bodily pain	31.43 ± 7.60	30.86 ± 6.84	31.09 ± 7.16	
General health	34.46 ± 9.27	34.38 ± 9.26	34.41 ± 9.26	
SF-36 MCS	39.74 ± 11.56	39.95 ± 11.34	39.87 ± 11.42	0.8364
Vitality	39.96 ± 9.42	37.65 ± 8.92	37.37 ± 9.12	
Social functioning	32.94 ± 11.14	32.78 ± 11.78	32.85 ± 11.51	
Role emotional	33.17 ± 13.05	32.56 ± 12.48	32.81 ± 12.71	
Mental health	38.94 ± 12.37	40.35 ± 11.88	39.78 ± 12.09	
Total Ig RF	320.5 ± 885.7	327.6 ± 621.0	324.7 ± 738.3	0.9216
C-reactive protein, mg/dl	3.76 ± 4.07	3.75 ± 3.83	3.75 ± 3.92	0.9710
Erythrocyte sedimentation rate, mm/hour	48.37 ± 27.72	47.87 ± 25.62	48.07 ± 26.46	0.8354

* Values are the mean ± SD unless otherwise indicated. MTX = methotrexate; VAS = visual analog scale; FACIT-F = Functional Assessment of Chronic Illness Therapy–Fatigue; HAQ DI = Health Assessment Questionnaire disability index; SF-36 = Short Form 36; PCS = Physical Component Score; MCS = Mental Component Score; RF = rheumatoid factor.

520 were enrolled; 209 were randomly assigned to placebo and 311 to rituximab. A total of 21 patients were excluded from the ITT population: those for whom treatment was unblinded because of breakage of the rituximab vial, those who never received treatment, those treated before randomization, and those enrolled at a center where blinding of the efficacy assessor was potentially compromised. Thus, the ITT population consisted of 499 patients (201 in the placebo group and 298 in the rituximab group).

Baseline demographics are shown in Table 1 and baseline study measurements for the ITT population stratified by treatment group are shown in Table 2. There were no statistically significant differences between groups at baseline.

All patients were receiving MTX, and 89% had been treated with DMARDs other than MTX. Sixty percent of patients had received prior treatment with a single anti-TNF therapy; 31% and 9% had received 2 and 3 prior anti-TNF therapies, respectively. Most patients (91%) had stopped anti-TNF therapy because of inadequate efficacy (23). Patients had highly active disease at baseline (Table 2). The mean baseline HAQ DI score was quite high and SF-36 scores reflected poor HRQOL at baseline, with a mean ± SD PCS score at approximately the 10th percentile for the US population (41).

A prior publication reported the improvement in ACR20, ACR50, and ACR70 responses (23). Unadjusted mean changes in PROs are presented in Table 3. The

Table 3. Unadjusted mean changes (baseline to week 24) in patient-reported outcomes*

	Placebo/rituximab, no.	Placebo + MTX	Rituximab + MTX	*P*
SF-36 PCS	116/258	1.48 ± 7.32	6.64 ± 8.74	< 0.0001
Physical functioning		4.89 ± 21.85	13.24 ± 22.88	0.0008
Role physical		8.40 ± 37.29	22.34 ± 39.94	0.0013
Bodily pain		6.52 ± 22.50	21.96 ± 23.48	< 0.0001
General health		0.71 ± 15.14	9.04 ± 18.28	< 0.0001
SF-36 MCS	116/258	2.25 ± 12.23	5.32 ± 12.41	0.0269
Vitality		3.32 ± 21.09	13.97 ± 22.34	< 0.0001
Social functioning		7.19 ± 28.65	17.33 ± 27.15	0.0009
Role emotional		7.41 ± 45.51	21.13 ± 50.73	0.0124
Mental health		3.97 ± 20.36	6.93 ± 21.09	0.1988
VAS-pain†	201/298	−2.50 ± 23.30	−23.37 ± 29.35	< 0.0001
FACIT-F†	201/298	−0.54 ± 9.84	−9.14 ± 11.31	< 0.0001
HAQ DI†	200/298	−0.07 ± 0.45	−0.44 ± 0.60	< 0.0001

* Values are the mean ± SD unless otherwise indicated. See Table 2 for definitions.
† Last observation carried forward.

rituximab group had statistically significantly greater relief of pain as measured by the VAS-pain. The between-group difference was statistically significant at all time points after 4 weeks ($P < 0.05$ for all time points from weeks 8–24) (Figure 1A).

The FACIT-F showed a significantly greater improvement in rituximab-treated patients compared with placebo-treated patients beginning at the first posttreatment assessment (week 12) and continuing through week 24 ($P < 0.05$ for all time points from weeks 12–24) (Figure 1B). A significantly higher percentage of the rituximab group achieved an MCID on the FACIT-F scale at week 24 than patients in the placebo group ($P < 0.0001$) (Table 4).

Physical function as measured by the HAQ DI improved more in the rituximab group than in the placebo group ($P < 0.05$). The mean improvement from baseline in HAQ DI scores was significantly greater in the treatment group beginning at week 8, and remained so through week 24 ($P < 0.05$ for all time points from weeks 8–24) (Figure 1C). Life table analysis showed that patients reached and sustained an MCID for the HAQ DI and FACIT-F statistically significantly sooner in the rituximab group than in the placebo group (Figure 2). On the HAQ DI a significantly higher percentage of the rituximab group achieved an MCID on the HAQ DI at week 24 than the placebo group (Table 4). Eighteen patients (6.0%) in the rituximab group and 1 (0.5%) in the placebo group had a score of 0 on the HAQ DI at week 24.

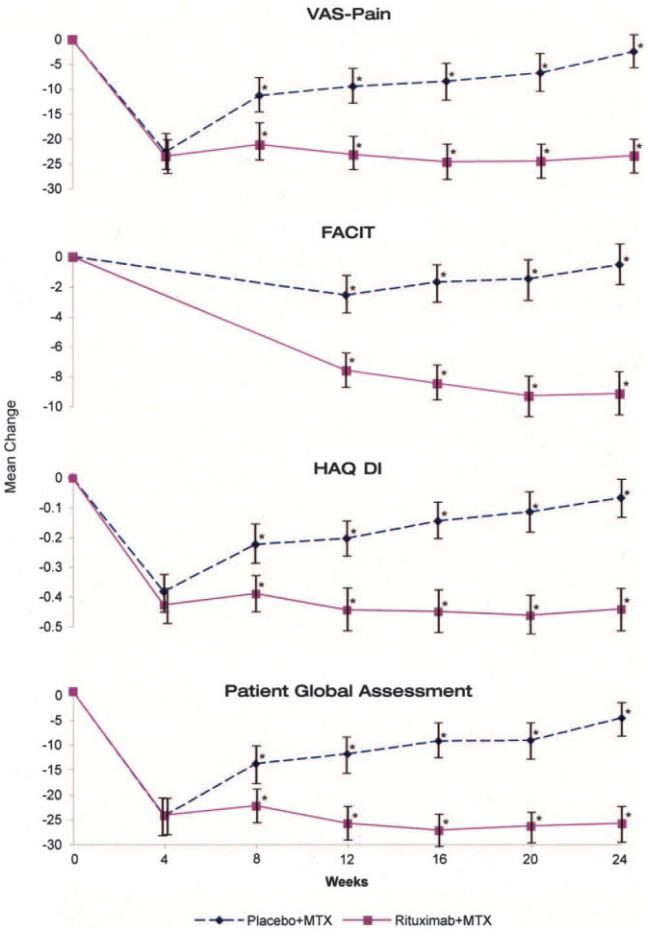


Figure 1. Mean change in outcome measures over time. * = Statistically significant. VAS-pain = visual analog scale for pain; FACIT = Functional Assessment of Chronic Illness Therapy–Fatigue; HAQ DI = Health Assessment Questionnaire disability index; MTX = methotrexate.

There were 258 patients in the rituximab group and 116 in the placebo group who completed the SF-36 at baseline and 24 weeks. The mean ± SD changes from baseline in SF-36 PCS score for the rituximab and placebo groups are presented in Table 3 and Figure 3. A higher percentage of rituximab patients achieved the more restrictive MCID threshold (improvement of at least 5 points) for the PCS compared with placebo patients (Table 4). Mean improvements in all 4 scales that contribute most to the PCS were significantly greater among rituximab patients than among placebo patients (Figure 2). The largest differences in the scale scores that contribute most to the PCS among rituximab patients were seen in role physical and bodily pain. The remaining physical health scales (physical functioning and general health) showed differences that were smaller but still significantly greater than the differences seen in the placebo group (Figure 2).

The mean ± SD changes from baseline in the SF-36 MCS for rituximab patients and placebo patients are shown in Table 3 and Figure 3. A higher percentage of the rituximab patients achieved the more restrictive definition of MCID threshold (improvement of at least 5 points) than placebo patients (Table 4).

In 3 of the 4 scales that contribute most to the MCS, the rituximab group had significantly greater improvement compared with the placebo group (vitality, social functioning, and role emotional). Only the mental health scale did not show significantly greater improvement in the rituximab group compared with the placebo group (Table 3, Figure 2).

Mean ± SD PGA scores at baseline were 68.5 ± 20.73 for the placebo group and 66.9 ± 21.06 for the rituximab group. At week 24, the mean score was 64.4 ± 25.21 for the placebo group and 42.9 ± 27.52 for the rituximab group, a 1.6% improvement for placebo patients and a 21.5% improvement for rituximab patients ($P < 0.001$). The rituximab group improved more than the placebo group at all assessments between week 8 and week 24 ($P < 0.05$) (Figure 1D).

We compared responses on PRO measures between ACR20 responders and nonresponders. Among ACR20 responders, 40 (20.6%) of 194 did not achieve MCID on the FACIT-F, 38 (20.7%) of 184 did not achieve MCID on the SF-36 PCS, and 71 (38.6%) of 184 did not achieve MCID on the MCS. Among ACR20 nonresponders, approximately one-third achieved MCID on each PRO tested: 112 (36.7%) of 305 had an improvement greater than the MCID on the FACIT-F, 68 (36.0%) of 189 on the PCS, and 75 (39.7%) of 189 on the MCS (Table 5).

DISCUSSION

Patients in this trial had severe, highly active, longstanding, intractable disease. All had persistent disease despite the use of MTX and at least 1 anti-TNF agent. Nearly 90%

Table 4. Patients who achieved minimum clinically important difference at week 24*

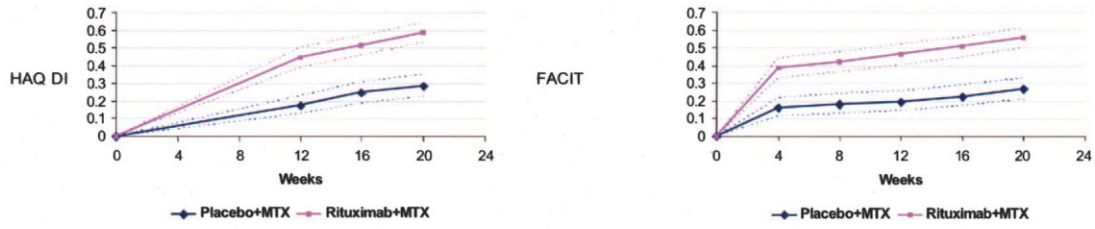
	Placebo + MTX (n = 201)	Rituximab + MTX (n = 298)	*P*
FACIT-F†	67 (33.3)	199 (66.8)	< 0.0001
HAQ DI‡	65 (32.5)	190 (63.8)	< 0.0001
PCS§	37 (31.9)	178 (69.0)	< 0.0001
PCS¶	27 (23.3)	148 (57.4)	< 0.0001
MCS§	50 (43.1)	138 (53.5)	0.0632
MCS¶	43 (37.1)	116 (45.0)	0.1533

* Values are the number (percentage) unless otherwise indicated. See Table 2 for definitions.
† Decreased at least 3.56. Last observation carried forward.
‡ Decreased at least 0.22. Last observation carried forward.
§ Increased at least 3.
¶ Increased at least 5.

had been treated with DMARDs other than MTX. Patients had few remaining options for treatment and despite prior treatments had substantially lower HRQOL than the general US population, with baseline SF-36 scores at or below the 10th percentile. Patients' SF-36 scores were below the 25th percentile even when compared with patients with congestive heart failure (41).

Improvement in PROs was seen at 4 weeks in the placebo and rituximab groups, which may have been due to background steroids. However, by week 8, rituximab patients had a significantly greater improvement than placebo patients in most outcomes. Rituximab treatment produced rapid and sustained improvements in pain, self-reported functional disability, fatigue, and PGA as seen in the primary and life table analysis. The observed changes in SF-36 summary scores and scales emphasize the degree of physical and mental impairments associated with RA as well as the improvement rituximab may bring. The magnitude of this change approaches the level seen with patients before and after heart valve replacement (7.64 points) (42).

The improvement in HRQOL was wide ranging, evidenced by improvement in almost all SF-36 scales. Rituximab-treated patients showed double-digit gains on 6 of 8 scales, with final scores on 4 scales (role physical, bodily pain, vitality, and role emotional) approaching the median score of the general US population age 45–54 (41). Role physical and bodily pain scores increased the most with rituximab treatment. Coupled with improvements in HAQ DI, this provides further evidence that rituximab improves functional ability in this population. In a study of the general US population, changes in physical functioning score of the magnitude seen here corresponded to an approximately 15% increase in the proportion of patients who could work (41). Rituximab treatment significantly improved general health scale scores. In patients with a variety of chronic illnesses, scores on this scale correlated well with health care utilization, suggesting treatment may reduce other expenditures (43). Of the 8 SF-36 scales, the only one that did not show significant improvement over placebo was mental health. This scale had the lowest correlation to physical well-being, suggesting that while improvements from rituximab were wide ranging, they affected physical HRQOL more than mental HRQOL in the 24-week period studied. Nevertheless, rituximab treatment was associated with statistically significant improvement in the MCS as well as the vitality, social functioning, and role emotional scales.



Time Interval (wks)

		[0,12)	[12, 16)	[16, 20)	[20, 24)	[0, 4)	[4, 8)	[8, 12)	[12, 16)	[16, 20)	[20, 24)
Placebo+MTX	Reach MCID and remain	35	14	8	10	32	4	3	6	8	12
	Censored	0	0	0	134	0	0	0	0	0	135
	Effective Sample Size	201	166	152	77	200	168	164	161	155	80
Rituximab+MTX	Reach MCID and remain	132	21	21	25	114	10	13	13	15	25
	Censored	0	0	0	99	0	0	0	0	0	108
	Effective Sample Size	298	166	145	75	298	184	174	161	148	79
Log-Rank *P* Value		<0.0001				<0.0001					

Figure 2. Life table analysis of time to reach minimum clinically important difference (MCID). HAQ DI = Health Assessment Questionnaire disability index; FACIT = Functional Assessment of Chronic Illness Therapy–Fatigue; MTX = methotrexate; wks = weeks.

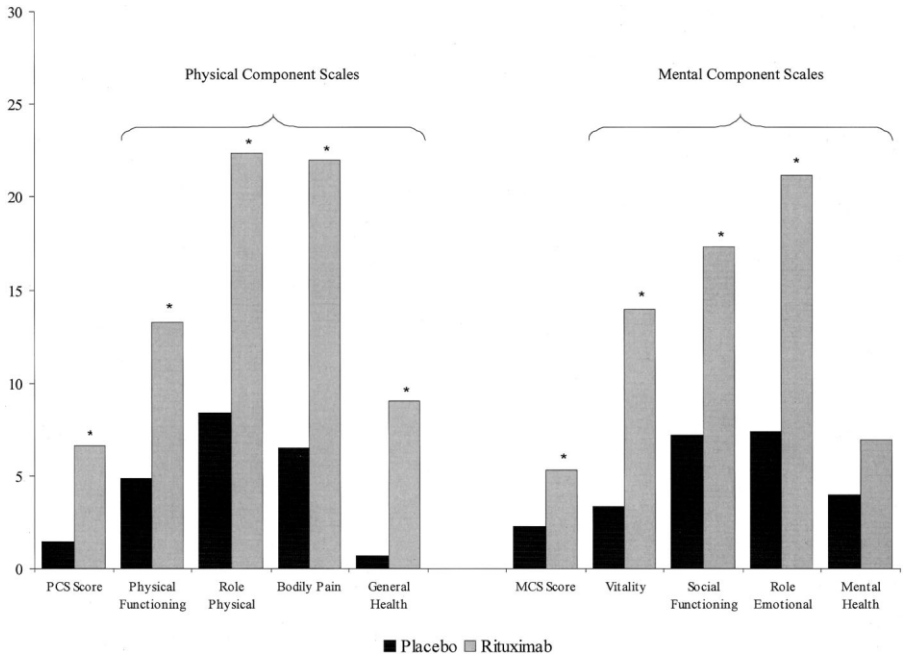


Figure 3. Mean changes in Short Form 36 summary scores and component scales from baseline to week 24. * = Statistically significant at $P < 0.05$. PCS = Physical Component Score; MCS = Mental Component Score.

Forty patients in the rituximab group and 85 in the placebo group did not complete the SF-36 at week 24 and were excluded from the SF-36 analysis. Using the LOCF method to impute these patients' end-of-study scores biased the results toward the null hypothesis (no difference between groups). As a sensitivity analysis, we used LOCF to analyze SF-36 scores and found no significant differences in the pattern or magnitude of the results.

The level of improvement in PROs is consistent with a previous study of rituximab, in which a statistically significant reduction in fatigue and improvement in physical (mainly bodily pain) and mental health scores was reported by rituximab patients compared with placebo patients (44). The results are also consistent with the improvement in the primary efficacy end point of this study (23). Even among ACR20 nonresponders, a substantial number had clinically important improvements in fatigue and overall HRQOL. Measuring outcomes with the ACR20 score alone would miss these important benefits.

Table 5. Patient-reported outcomes by ACR20 response category*

	ACR20 response†	ACR20 nonresponse†	Total
FACIT-F MCID†			
Patient count	194	305	499
Response‡	154 (79.4)	112 (36.7)	166 (53.3)
Nonresponse	40 (20.6)	193 (63.3)	233 (46.7)
SF-36 PCS MCID			
Patient count	184	189	373
Response§	146 (79.3)	68 (36.0)	214 (57.4)
Nonresponse	38 (20.7)	121 (64.0)	159 (42.6)
SF-36 MCS MCID			
Patient count	184	189	373
Response§	113 (61.4)	75 (39.7)	188 (50.4)
Nonresponse	71 (38.6)	114 (60.3)	185 (49.6)

* Values are the number (percentage) unless otherwise indicated. ACR20 = American College of Rheumatology 20% response (29); MCID = minimum clinically important difference; see Table 2 for additional definitions.
† Last observation carried forward.
‡ Decreased at least 3.56.
§ Decreased at least 3.

Studies of other biologic treatments for RA have demonstrated benefits in some of the outcomes used in this study. In a study of abatacept among patients with inadequate response to anti-TNF therapy, both SF-36 component scores improved more in the treatment group than in the control group, as did HAQ DI score and fatigue (measured using a simple VAS) (45). In a nonrandomized trial of patients who had inadequate response to anti-TNF agents, etanercept improved pain (measured using the HAQ pain VAS) (46), but the nonrandomized design makes it difficult to compare the results with ours. Other studies that reported changes in PRO measures examined patients who did not improve after DMARD treatment, unlike the current study (47–49).

The advent of anti-TNF therapy for RA brought new options for patients who did not respond to traditional DMARDS, yet a significant proportion of patients either have inadequate responses to these treatments or cannot continue them because of adverse effects (15,16,50). Previous studies and the primary results of the current trial have demonstrated that in patients with moderately to severely active RA who have inadequately responded to 1 or more TNF antagonists, rituximab significantly improves disease activity (as measured by ACR and EULAR responses as well as change in the Disease Activity Score in 28 joints). Radiographic data analyses indicated that ritux-

imab inhibited the progression of structural joint damage compared with placebo (23,44). These current analyses further demonstrate that rituximab produces rapid, clinically meaningful, and statistically significant improvements and sustained effects on nearly every tested measure of HRQOL, symptoms, and function (30,31,33,35), and therefore meaningfully improves patients' perceptions of their disease.

AUTHOR CONTRIBUTIONS

Dr. Keystone had full access to all of the data in the study and takes responsibility for the integrity of the data and the accuracy of the data analysis.

Study design. Emery, Magrini.

Acquisition of data. Keystone, Burmester, Furie, Loveless, Emery, Kremer, Tak.

Analysis and interpretation of data. Keystone, Burmester, Emery, Tak, Broder, Yu, Cravets, Magrini, Jost.

Manuscript preparation. Keystone, Burmester, Furie, Loveless, Emery, Kremer, Tak, Broder, Yu, Jost, Shaun Mason (nonauthor; Partnership for Health Analytic Research, Beverly Hills, CA).

Statistical analysis. Broder, Yu, Cravets.

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