Improved Health-Related Quality of Life for Patients with Active Rheumatoid Arthritis Receiving Rituximab — Results of the Dose-Ranging Assessment: International Clinical Evaluation of Rituximab in Rheumatoid Arthritis (DANCER) Trial

PHILIP J. MEASE, DENNIS A. REVICKI, JACEK SZECHINSKI, MARIA GREENWALD, ALAN KIVITZ, LEONOR BARILE-FABRIS, JATINDERPAL KALSI, JENNIFER EAMES, and MARJATTA LEIRISALO-REPO

ABSTRACT. ***Objective***. To evaluate the effect of rituximab treatment on health-related quality of life (HRQOL) in patients with active rheumatoid arthritis (RA), who have had an inadequate response to disease-modifying antirheumatic drugs, including biologic agents.

Methods. A randomized, multicenter, double-blind, placebo-controlled clinical trial involving 367 rheumatoid factor-positive patients was conducted. Patients received 2 infusions 2 weeks apart of placebo (n = 122), rituximab 500 mg (n = 123), or rituximab 1000 mg (n = 122), with or without glucocorticoids. All patients received stable doses of methotrexate (10–25 mg/wk). Measures included SF-36, assessed at baseline and at 24 weeks, as well as the HAQ and FACIT-Fatigue scale assessed at baseline and monthly for 24 weeks. Patients exceeding prespecified minimal clinically important differences (MCID) were examined. Clinical efficacy measurements (ACR20/50/70 and EULAR responses) were compared with HRQOL outcomes.

Results. At 24 weeks, the rituximab 500 mg and 1000 mg groups both reported statistically significantly greater improvements on the SF-36 physical component summary (4.37 and 4.89 points higher, respectively, vs placebo; $p < 0.001$). SF-36 physical function, bodily pain, vitality, social function, and role-physical subscale scores also statistically significantly improved vs placebo. At 24 weeks, 62.6% and 67.2% of the rituximab 500 mg and 1000 mg groups, respectively, exceeded the MCID of 0.22 in HAQ ($p < 0.001$). For FACIT-Fatigue, 55.3% and 65.6% of patients exceeded the MCID of 3.5 points compared with 35.2% of placebo over 24 weeks ($p < 0.001$). ACR20/50/70 and EULAR responders demonstrated greater improvements in mean baseline to 24 week changes in SF-36 and FACIT-Fatigue scores compared with nonresponders ($p < 0.05$).

Conclusion. Both rituximab doses in combination with methotrexate were effective in improving all HRQOL outcomes in patients with active RA consistent with clinical efficacy. (First Release Nov 15 2007; J Rheumatol 2008;35:20–30)

Key Indexing Terms:
RITUXIMAB METHOTREXATE PHYSICAL FUNCTION RHEUMATOID ARTHRITIS
HEALTH-RELATED QUALITY OF LIFE PATIENT-REPORTED OUTCOME

From Seattle Rheumatology Associates, Seattle, WA; United BioSource Corporation, Center for Health Outcomes Research, Bethesda, MD, USA; Medical University of Wroclaw, Wroclaw, Poland; Desert Medical Advances, Palm Desert, CA; Altoona Center for Clinical Research, Duncansville, PA, USA; Hospital Angeles, Mexico City, Mexico; Roche Products Ltd., Welwyn Garden City, UK; Genentech, Inc., South San Francisco, CA, USA; and Helsinki University Central Hospital, Helsinki, Finland.

Supported by Genentech, Inc.

P.J. Mease, MD, Seattle Rheumatology Associates; D.A. Revicki, PhD, United BioSource Corporation, Center for Health Outcomes Research; J. Szechinski, MD, Medical University of Wroclaw; M. Greenwald, MD, Desert Medical Advances; A. Kivitz, MD, Altoona Center for Clinical Research; L. Barile-Fabris, MD, Hospital Angeles; J. Kalsi, MD, Roche Products Ltd.; J. Eames, MPH, Genentech, Inc; M. Leirisalo-Repo, MD, PhD, Helsinki University Central Hospital.

Address reprint requests to Dr. P.J. Mease, Seattle Rheumatology Associates, 1101 Madison Street, Suite 1000, Seattle, WA 98104. E-mail: pmease@nwlink.com

Accepted for publication July 3, 2007.

Rheumatoid arthritis (RA) is a chronic, inflammatory disease that may gradually impair the physical function of patients, restrict the mobility and activities of daily living, and increase joint pain. Over time, the symptoms of RA affect patients' health-related quality of life (HRQOL), leading to reduction in physical function and mental health compared with the general population[1]. RA is progressive and causes significant functional disability by the first decade of onset in about 50% of patients, with an approximate life expectancy reduction of up to 18 years in 80% of the patients after the second decade of progression[2-5]. Although the etiology of RA is unknown and no cure exists, treatments have been developed to target pain reduction, improvement in physical function, and reduction in disease progression[2,6,7]. Disease modifying antirheumatic drugs (DMARD) and anti-tumor necrosis factor

(TNF) biologic therapies have generally been prescribed to slow disease progression, reduce joint and bone damage, and maintain joint function[8,9]. Randomized clinical trials have demonstrated that effective treatments for RA are associated with improvements in physical function and HRQOL[2,10-15]. However, up to 40% of patients fail to benefit from such treatment options[16].

B cells have recently been implicated in the immunopathogenesis of RA and have thus become an important new therapeutic target for RA. B cells may function as antigen-presenting cells and in the activation of T cells. Additionally, B cells secrete proinflammatory cytokines and produce rheumatoid factor (RF) autoantibodies[7].

Rituximab (Rituxan®) is the first genetically engineered chimeric anti-CD20 monoclonal antibody; this agent leads to selective CD20+ B cell depletion without targeting stem cells or existing plasma cells. Depletion of B cells by rituximab occurs via 3 putative mechanisms: antibody-dependent cell-mediated cytotoxicity, complement-dependent cytotoxicity, and promotion of CD20+ B cell apoptosis[17-23].

Randomized clinical trials of rituximab treatment using a single course of 2 intravenous infusions 2 weeks apart have supported an important role for B cells in the treatment of patients with RA[24-26]. In the phase IIb Dose-Ranging Assessment: International Clinical Evaluation of Rituximab in Rheumatoid Arthritis (DANCER) trial, both rituximab 500 mg and 1000 mg doses in combination with methotrexate (MTX) were clinically effective, well tolerated[25], and demonstrated a safety profile consistent with rituximab in earlier trials[18,25].

Increasingly, patient-reported outcomes (PRO), including the Health Assessment Questionnaire (HAQ), the Medical Outcome Study Short-Form Health Survey (SF-36), and the Functional Assessment of Chronic Illness Therapy-Fatigue (FACIT-Fatigue) scale, are used to comprehensively evaluate the effectiveness of new treatments for RA. Previous studies have demonstrated that clinical efficacy endpoints are significantly associated with HRQOL, fatigue, and functional outcomes[3,27,28]. The American College of Rheumatology (ACR) criteria[29] combine both clinical and PRO measures. HAQ, pain, and disease severity are assessed by patients as part of the ACR criteria, combined with clinician ratings of tender and swollen joints, and global disease status, and acute-phase reactants.

It is important for RA therapies with novel mechanisms of action to determine the effect on these clinically important outcomes. Consequently, PRO were assessed during the phase IIb DANCER trial[25], which evaluated the effects of the 2 doses of rituximab (500 mg and 1000 mg). We compared the effectiveness of rituximab treatment versus placebo on HRQOL outcomes, examined whether these changes exceeded prespecified minimal clinically important differences (MCID) over the 24 weeks of the study, and considered the importance of these changes in relationship to clinical efficacy. These HRQOL outcome data are presented in our present report.

MATERIALS AND METHODS

Patients. The patient eligibility criteria and study design have been described in detail[25]. Briefly, eligible patients were age 18 to 80 years and had presented at least 6 months prior to randomization with a diagnosis of RA according to the revised ACR 1987 criteria[30]. At study entry, patients had active disease defined as swollen joint count (SJC) ≥ 8 (of 66 assessed), tender joint count (TJC) ≥ 8 (of 68 assessed), and either C-reactive protein (CRP) serum levels ≥ 1.5 mg/dl or erythrocyte sedimentation rate (ESR) ≥ 28 mm/h, despite ongoing treatment with MTX (10–25 mg/wk) for at least 12 weeks before randomization; patients had to have failed to respond to treatment with at least one but not more than 5 DMARD (other than MTX) or biologic agents.

Study design. The study design was a multifactorial, randomized, multicenter, double-blind, placebo-controlled clinical trial conducted in 95 centers. Eligible patients were randomized to receive placebo, 2 × 500 mg rituximab, or 2 × 1000 mg rituximab as intravenous infusions administered on days 1 and 15. Additionally, patients were concurrently randomized to receive one of 3 doses of glucocorticoids. As study results previously showed that glucocorticoids had no significant effect on the overall treatment efficacy results[25], for this analysis the 9 treatment arms were combined into 3 groups based on rituximab dose. As reported, the 3 combined treatment arms comprised the 367 prespecified RF-positive patients of the intent-to-treat (ITT) population and reflected the population on which the HRQOL analyses were completed[25]. Concomitant MTX therapy of 10 to 25 mg/week (oral or parenteral) was required in all treatment groups.

Patients were followed for 24 weeks, and from Week 16 to Week 24, patients who demonstrated < 20% improvement from screening in SJC and TJC were eligible to enter a rescue arm to receive open-label, active treatment. Outcome measures included ACR response criteria, Disease Activity Score in 28 joints (DAS28), SF-36, FACIT-Fatigue, and HAQ. The study protocol was approved by relevant institutional review boards, and all patients provided voluntary written informed consent before participating in the clinical trial.

Patient-reported outcomes. PRO were measured by the SF-36 Health Survey[31], HAQ[32], and FACIT-Fatigue[28]. HRQOL is a multidimensional component of PRO that includes assessment of physical, psychological, and social functioning and well-being, and often includes assessment of effects of relevant symptoms by the patient.

The SF-36 has been validated and extensively used in previous clinical trials to measure HRQOL[13,15,31]. The SF-36 is a 36-item instrument with 8 subscales: physical function, role limitations-physical, vitality, general health perceptions, bodily pain, social function, role limitations-emotional, and mental health. Aggregates of the subscale scores produce the physical component summary (PCS) and mental component summary (MCS) scores[33,34]. The subscale and aggregate scores were transformed using norm-based methods that standardize the scores to a mean of 50 and standard deviation (SD) of 10 in the general US population[3]. Higher subscale and summary scores indicate better HRQOL. The SF-36 has evidence of reliability, validity, and responsiveness in the general population and in patients with RA[34,35].

The HAQ has been widely used to assess functional outcomes[32] and is closely correlated with longterm outcomes in RA, including disability and mortality[1,3]. Composites of responses to the 24-item questionnaire are evaluated according to difficulties with performing activities of daily living on a 0–3 scale relating to 8 subscales (dressing and grooming, arising, eating, walking, hygiene, reaching, gripping, and other activities). Scores over the 8 subscales are combined to produce an overall disability index. Higher scores represent more disability. The HAQ has been incorporated into the clinical development programs for RA treatments[3,11,36-38] and represents an important component to determining the ACR response criteria.

The FACIT-Fatigue is a measure of fatigue in chronic illness[28,39]. It was developed as a fatigue-specific measure consisting of 13 items. The FACIT-Fatigue has evidence supporting reliability, validity, and responsiveness to change in patients with RA[28]. Scores range from 0 to 52, with higher scores representing less fatigue.

PRO data collection procedures. PRO data were collected throughout the 24-

week clinical trial. The SF-36 scores were collected at baseline and at 24 weeks. The HAQ scores were collected at baseline and at 4, 8, 12, 16, 20, and 24 weeks, while the FACIT-Fatigue scores were collected at baseline and at 12, 16, 20, and 24 weeks. All 3 PRO were collected with a withdrawal assessment in the case of early study discontinuation. Patients who experienced < 20% ACR response in the number of tender and swollen joints after 16 weeks were eligible to be switched to rescue therapy. For these patients, the PRO endpoints were examined only during the double-blind therapy.

Clinical efficacy. The primary endpoint was the ACR20 response, with ACR50 and ACR70 responses as secondary clinical endpoints[40]. Responses were categorized using the ACR criteria based on improvement from baseline (i.e., ≥ 20% to < 50%; ≥ 50% to < 70%; and ≥ 70%). Patients with < 20% improvement were categorized as nonresponders. DAS28 and European League Against Rheumatism (EULAR) responses (i.e., good, moderate, or no response) were also measured based on a combination of significant change from baseline and current level of disease activity[41,42]. A good response is a DAS28 score ≤ 3.2 with an improvement of > 1.2, a moderate response is a DAS28 score of 3.2 to 5.1 with an improvement of 0.6 to 1.2, and no response is an improvement of ≤ 0.6.

Statistical analyses. Analyses were performed on the primary efficacy ITT population that comprised 367 RF–positive patients. As reported earlier in the DANCER trial[25], although a small number of patients were RF-negative, there were only 85 patients in this population [placebo (n = 21) and rituximab 1000 mg (n = 64)[25]]; consequently, there was no representation for the rituximab 500 mg group, and the placebo group consisting of 21 patients was significantly underpowered for meaningful comparisons. Baseline descriptive statistics by treatment group were summarized for demographic and clinical characteristics, and for the SF-36, HAQ, FACIT-Fatigue, Pain visual analog scale, patient-rated global disease activity, and physician-rated global disease activity.

Statistical analyses were performed to compare the mean change from baseline to endpoint PRO scores by the treatment groups. The rituximab 500 mg and 1000 mg groups were compared with the placebo group. Between-treatment-group differences for SF-36 summary and subscale scores were evaluated using analysis of covariance (ANCOVA). The ANCOVA models included terms for treatment group, corticosteroid group, geographic region (US vs non-US), and relevant baseline SF-36 score. The statistical analyses adjusted for geographic region to control for differences in ACR response, translated PRO scores, and healthcare systems[25]. In the DANCER study, there was no significant interaction between rituximab and region[25]. In the case of SF-36 ANCOVA, last observation carried forward (LOCF) imputation was not used, since only baseline and 24-week assessments were available. Mixed-model analysis of variance models were used to compare mean HAQ and FACIT-Fatigue scores between the rituximab and placebo-treated groups. These mixed models included fixed effects for treatment, assessment visit, treatment by assessment visit interactions, corticosteroid group, and geographic region. A random intercept was included to model between-patient variation. An overall test of the treatment effect across all assessment visits was performed. Tests of treatment differences in mean PRO scores with 95% confidence intervals (CI) and nominal p values were generated. The estimated treatment effects were based on the fixed effects of part of the mixed model ANCOVA at the mean value of the covariates.

For the PCS, MCS, HAQ, and FACIT-Fatigue, we also calculated the proportion of patients of each treatment group who reached a prespecified MCID. The MCID for the PCS and MCS have been defined as 3 to 5 points[43], 0.22 points for the HAQ[44], and 3.5 points for the FACIT-Fatigue[41]. The data for the PCS were analyzed based on an MCID of 5 points. The 5-point MCID is consistent with the one-half standard deviation rule and defines a clinically significant effect[45]. A logistic regression model was used to compare treatment effects on the proportion of patients who exceeded the MCID for the selected PRO. For the logistic regression models, the main effects were rituximab treatment, corticosteroid group, and region, with the relevant baseline PRO measure as a covariate. Missing endpoint scores were imputed using LOCF for the HAQ and FACIT-Fatigue, but no imputation was done for the PCS or MCS. Chi-square differences between the main-effect model and the treatment-by-visit interaction model were performed with 2 degrees of freedom (df = 2) to evaluate categorical variables.

We also examined the relationship between clinical efficacy measures, the ACR20/50/70 and DAS28 responses, and mean baseline to 24-week changes in selected PRO endpoints. For these analyses, ANCOVA models were used to estimate least-square mean change scores from baseline for the SF-36 subscale and summary and FACIT-Fatigue scores. The ANCOVA model included factors for ACR20/50/70 or DAS28 response groups (i.e., no response, moderate response, good response), region, duration of RA, and the relevant baseline PRO score. The Tukey-Kramer test[46] was used to determine if there were significant differences in least-square mean change scores among the ACR or DAS28 responder groups. This procedure was designed for an analysis involving all pairwise comparisons and preserved the experiment-wise (type II) error rate[47].

RESULTS

Patient characteristics. Data are presented on 367 RF-positive patients who formed the primary efficacy ITT population resulting in 122, 123, and 122 patients in the placebo, 500 mg, and 1000 mg treatment groups, respectively. Baseline demographic and clinical characteristics were comparable across the 3 treatment groups (Table 1). Of these patients, 80% were women, 79% were white, and the mean age was 51 years. Patients had RA duration of 11 years, and 32.4% (range 27.0% to 39.0%) had previously been treated with anti-TNF biologics. Baseline disease activity was high (DAS28 6.67 to 6.85; overall 6.79). No significant differences in baseline disease characteristics or PRO were observed among the 3 treatment groups.

For the SF-36 subscales, 74%, 91%, and 96% of patients in the placebo, rituximab 500 mg, and rituximab 1000 mg groups had both baseline and endpoint scores (p = 0.01). Baseline and endpoint scores were recorded for 73% to 98% of patients responding to the HAQ and 73% to 99% of patients responding to the FACIT-Fatigue.

Patient SF-36 health status outcome measures. Overall, the changes in SF-36 summary and subscale scores differed significantly between the rituximab-treated and placebo groups (Table 2). The rituximab 500 mg and 1000 mg groups both reported significantly greater improvements in PCS scores compared with placebo (p < 0.001). Improvements in PCS scores ranged from 4.37 (95% CI –6.97, –1.77) for the rituximab 500 mg group to 4.89 points (95% CI –7.50, –2.29) for the rituximab 1000 mg group compared with placebo. However, no statistically significant differences were observed between the rituximab-treated groups and the placebo group on changes from baseline in MCS scores (p > 0.05).

For the SF-36 subscale scores, significant differences were demonstrated between both rituximab 500 mg and 1000 mg groups and the placebo group on changes from baseline on the physical function, bodily pain, vitality, social function, and role-physical subscale scores. In all cases, greater improvements were seen in the rituximab-treated groups compared with placebo.

The proportion of patients achieving an MCID of 5 points

Table 1. Baseline demographic, clinical, and patient-reported outcome characteristics on 367 RF-positive patients.

Characteristic	Placebo, n = 122	Rituximab, 500 mg + MTX, n = 123	Rituximab, 1000 mg + MTX, n = 122
Mean age, yrs (SD)	50.8 (11.7)	51.4 (12.3)	52.1 (10.9)
Female, no. (%)	97 (79.5)	103 (83.7)	93 (76.2)
White, no. (%)	95 (77.9)	94 (76.4)	101 (82.8)
Mean RA disease duration, yrs (SD)	9.6 (7.7)	11.2 (8.5)	11.3 (8.5)
Swollen joint count, mean no.	21	22	22
Tender joint count, mean no.	35	33	32
Previous anti-TNF treatment, no. (%)	33 (27.0)	48 (39.0)	38 (31.1)
DAS28, mean (SE)	6.85 (0.74)	6.84 (0.79)	6.67 (0.82)
PRO at baseline, mean (SE)			
HAQ	1.71 (0.05)	1.80 (0.05)	1.69 (0.05)
FACIT-Fatigue	27.55 (0.97)	28.03 (0.96)	27.01 (0.94)
Patient rated pain, VAS	60.64 (1.65)	60.15 (2.06)	55.41 (1.88)
Patient rated global disease activity	66.70 (1.67)	66.37 (1.99)	63.84 (1.81)

PRO: patient-reported outcome; DAS28: 28-joint Disease Activity Score; HAQ: Health Assessment Questionnaire; FACIT-Fatigue: Functional Assessment of Chronic Illness Therapy-fatigue; VAS: visual analog scale.

on the PCS was significantly higher ($p < 0.05$) for both rituximab-treated groups compared with placebo (Figure 1); however, MCS scores were not significantly different (data not shown). Based on the logistic regression analysis, those patients in the rituximab 500 mg group were more than 3 times as likely to achieve the MCID of 5 points on the PCS (OR 3.21, $p = 0.01$), while those in the rituximab 1000 mg group were nearly 3 times as likely to achieve the MCID of 5 points (OR 2.96, $p = 0.01$) compared with placebo.

Physical function. Over the 24 weeks of the study, results of the mixed models indicated that only the rituximab 1000 mg had significantly different mean HAQ scores compared with placebo ($p = 0.009$). There were significant treatment-by-visit interactions for both rituximab 500 mg ($p < 0.001$) and rituximab 1000 mg groups ($p < 0.001$) compared with placebo. The rituximab 500 mg and 1000 mg groups reported decreases (improvements) in HAQ scores over 24 weeks, while the placebo group showed initial improvements and then worsening over the course of the study (Figure 2). Significant differences between the rituximab 1000 mg and placebo group were seen after 8 weeks ($p < 0.05$) and were maintained over 24 weeks. For the rituximab 500 mg versus placebo groups, significant differences were seen by 12 weeks.

The placebo and rituximab-treated groups were compared to see if those taking rituximab 500 mg and 1000 mg were more likely to exceed the MCID of 0.22 points on the HAQ. At Week 24, 62.6% and 67.2% in the rituximab 500 mg and 1000 mg groups, respectively, versus 34.4% in the placebo group achieved the prespecified MCID for the HAQ ($p < 0.05$ for both groups vs placebo).

Fatigue outcomes. Both the rituximab 500 mg and 1000 mg treatment groups had significantly different mean scores on the FACIT-Fatigue compared with the placebo group ($p = 0.009$ and $p < 0.001$, respectively). In addition, there was a significant treatment-by-visit interaction for both the rituximab 500 mg and 1000 mg groups (both, $p < 0.001$) compared with the placebo group. Both the rituximab 500 mg and 1000 mg groups reported improvements in FACIT-Fatigue scores over 12 weeks followed by maintenance of these effects over the remaining 12 weeks of the study (Figure 3). Significant differences between the rituximab groups and placebo were observed at 12 weeks, and the difference persisted over the course of the clinical trial (all $p < 0.05$). The observed change over 24 months was 7.63 points for the rituximab 500 mg group and 8.20 points for the rituximab 1000 mg group, compared with 3.91 points in the placebo group.

The placebo and rituximab-treated groups were compared to see if those receiving rituximab treatment were more likely to exceed the MCID of 3.5 points on the FACIT-Fatigue. There were significant differences between placebo (35.2%) and rituximab 500 mg (55.3%), and between placebo and rituximab 1000 mg (65.6%) on the MCID of the FACIT-Fatigue ($p < 0.05$).

Relationship between clinical outcomes and HRQOL

ACR response. Figure 4 presents results comparing ACR responders with nonresponders on the SF-36 (PCS, MCS, and subscales) and the FACIT-Fatigue. For all 3 response criteria (ACR20/50/70), those who showed greater clinical responses had significantly greater improvements in PCS, MCS, and FACIT-Fatigue scores compared with those who did not improve according to ACR response criteria.

Change in PCS scores from baseline to 24 weeks was 5.7 points higher for the ACR20 group, 7.8 points higher for the ACR50 group, and 12.4 points higher for the ACR70 group compared with the nonresponder group (all $p < 0.05$; Figure 4). The MCS scores for the change from baseline to Week 24

Table 2. Mean baseline to 24-week endpoint changes in SF-36 summary and subscale scores. Values are mean (SE).

SF-36 Characteristic	Placebo	Rituximab, 500 mg + MTX	Rituximab, 1000 mg + MTX
Physical component summary	n = 121*	n = 123	n = 115
Baseline score	30.36 (0.65)	29.52 (0.69)	30.55 (0.73)
Change from baseline	2.36 (0.78)	7.08 (0.77)	7.40 (0.78)
p vs placebo		< 0.001	< 0.001
Mental component summary	n = 121	n = 123	n = 115
Baseline score	41.11 (1.14)	40.71 (1.07)	42.51 (1.08)
Change from baseline	1.88 (1.00)	4.49 (1.22)	3.03 (1.11)
p vs placebo		0.087	0.167
Physical function	n = 122	n = 123	n = 122
Baseline score	28.27 (0.76)	27.83 (0.80)	29.29 (0.87)
Change from baseline	2.18 (0.83)	6.44 (0.90)	5.79 (0.88)
p vs placebo		0.002	0.003
Role-physical	n = 121	n = 123	n = 122
Baseline score	33.68 (0.85)	32.04 (0.70)	32.53 (0.82)
Change from baseline	0.64 (1.25)	7.19 (0.98)	5.51 (1.22)
p vs placebo		0.002	0.019
Bodily pain	n = 122	n = 123	n = 122
Baseline score	32.08 (0.67)	31.90 (0.73)	32.24 (0.64)
Change from baseline	4.16 (0.89)	8.96 (0.97)	8.51 (0.85)
p vs placebo		0.001	0.001
General health	n = 122	n = 123	n = 120
Baseline score	34.32 (0.75)	33.82 (0.78)	36.02 (0.92)
Change from baseline	2.15 (0.89)	3.94 (0.80)	4.52 (0.87)
p vs placebo		0.113	0.003
Vitality	n = 122	n = 123	n = 122
Baseline score	39.91 (0.90)	39.03 (0.87)	40.28 (0.87)
Change from baseline	2.69 (0.95)	6.71 (0.96)	6.02 (0.98)
p vs placebo		0.003	0.007
Social function	n = 122	n = 123	n = 122
Baseline score	34.27 (1.04)	33.57 (1.07)	35.87 (0.91)
Change from baseline	2.68 (1.11)	6.97 (1.22)	5.93 (0.98)
p vs placebo		0.007	0.004
Role-emotional	n = 122	n = 123	n = 117
Baseline score	36.08 (1.21)	35.30 (1.28)	36.61 (1.32)
Change from baseline	0.95 (1.39)	5.54 (1.57)	3.27 (1.57)
p vs placebo		0.065	0.203
Mental health	n = 122	n = 123	n = 122
Baseline score	39.47 (1.10)	39.21 (0.98)	40.87 (1.03)
Change from baseline	2.34 (1.03)	3.96 (1.04)	2.83 (1.01)
p vs placebo		0.205	0.313

* Baseline number (n) of patients for each subscale score.

showed a similar pattern: 3.0 points higher for the ACR20 group, 7.2 points higher for the ACR50 group, and 12.2 points higher for the ACR70 group compared with the nonresponder group (all $p < 0.05$).

ACR responders also exhibited greater improvements on the SF-36 subscales than did the nonresponders. Changes for the ACR50 group from baseline to Week 24 were largest for bodily pain, role-emotional, physical functioning, and role-physical scores ($p < 0.05$). For those meeting ACR70 responses, the greatest improvements were seen in subscales for bodily pain, role-emotional, role-physical, and vitality. These changes were significantly greater versus those of nonresponders or those meeting ACR20 or ACR50 responses ($p < 0.05$).

For the FACIT-Fatigue, we observed significant differences in mean baseline to 24-week changes between the nonresponders and ACR20, ACR50, and ACR70 responders (all $p < 0.05$). The largest changes were seen for the ACR70 responders (–17.1 points) and these changes were significantly different compared with ACR20 and ACR50 responders (both $p < 0.05$).

EULAR response. Similar results were observed for the relationship between EULAR improvement criteria and HRQOL outcomes (Figure 5). Those patients who showed a moderate or good EULAR response had significantly improved scores on the SF-36 PCS, MCS, and FACIT-Fatigue compared with nonresponders or those with a moderate response (all p <

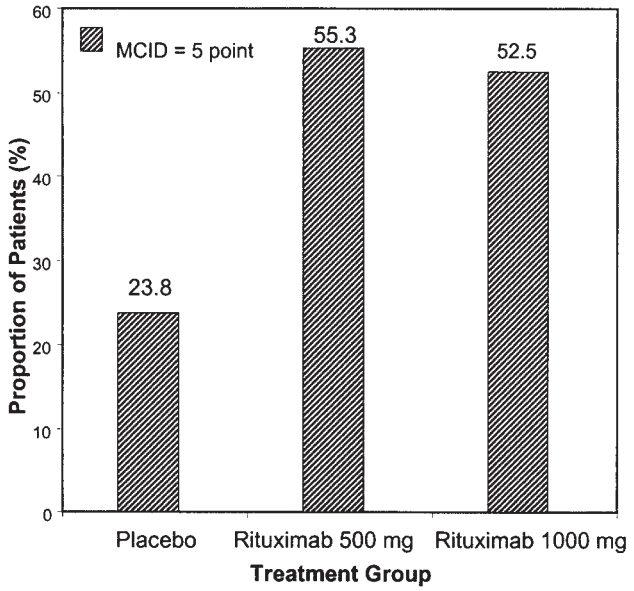

Figure 1. Proportion of patients achieving a minimal clinically important difference (MCID) of 5 points by treatment groups for the physical component summary. Both rituximab 500 mg and 1000 mg groups are significantly greater than placebo ($p < 0.05$).

0.05). The mean change in PCS scores from baseline to Week 24 was 5.5 points higher for the moderate response group and 12.3 points higher for the good response group, compared with the nonresponder group ($p < 0.05$). The mean change score for the MCS showed a similar pattern.

Responders exhibited greater improvements on the SF-36 subscales than did the nonresponders. For example, changes from baseline to Week 24 for those showing good response were largest for bodily pain, role-physical, physical functioning, role-emotional, and vitality subscale scores. In addition, these changes were significantly greater than those of the nonresponders or those who showed a moderate response (all $p < 0.05$).

For the FACIT-Fatigue, moderate and good responders reported greater improvements in fatigue scores compared with nonresponders (both $p < 0.05$). Based on the EULAR responses, there were differences between moderate and good responders on FACIT-Fatigue score changes ($p < 0.05$).

DISCUSSION

The DANCER trial demonstrated that rituximab in combination with MTX is clinically effective and well tolerated[25]. In our current analysis, we found that treatment with rituximab 2 × 500 mg and 2 × 1000 mg in combination with MTX was associated with significant improvements in patient physical functioning and well-being. At 24 weeks of followup, the rituximab-treated groups reported improvements in the PCS, as well as SF-36 physical function, bodily pain, vitality, social function, and role-physical scores. The findings further showed a significant differentiation in HAQ scores between the rituximab 1000 mg group and placebo group by 8 weeks, which was maintained over the course of the study. This study found that clinical efficacy, as measured by ACR20/50/70 and DAS28 EULAR responses, was associated with statistically significant improvements in HRQOL and functional outcomes.

The rituximab-treated groups reported greater improvements over 24 weeks in a measure of physical functioning and well-being (e.g., PCS scores) compared with the placebo-treated group. Based on a predefined MCID of 5 points, 3 times as many RA patients treated with rituximab demonstrated clinically significant improvements as compared with the

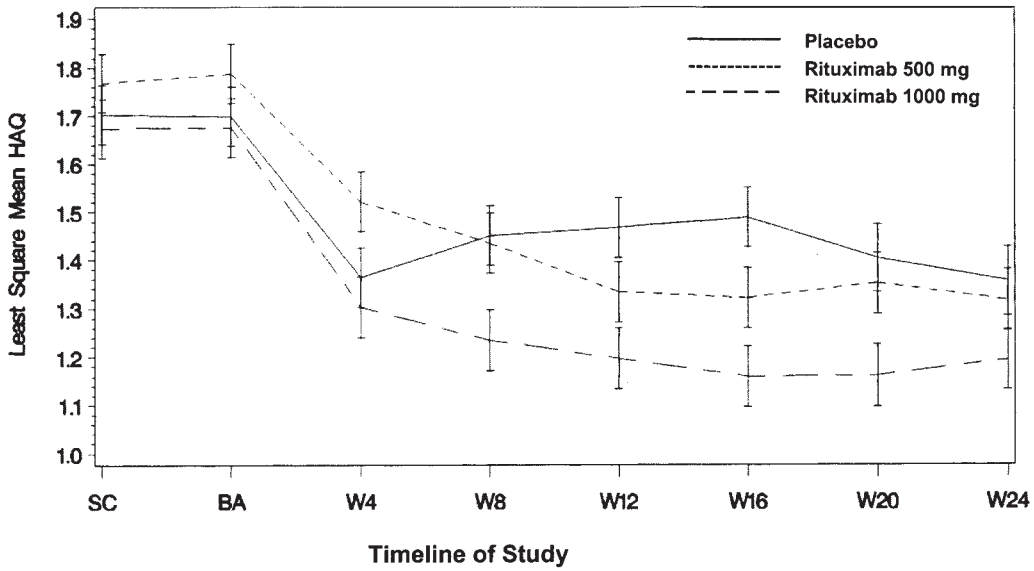

Figure 2. Mean HAQ scores (± 1 SE) by treatment group over the 24 weeks of the study. Data are presented on the primary efficacy ITT population of 367 RF-positive patients. The horizontal line is joined at the means, while the vertical line is the mean ± 1 SE. Control variables included corticosteroid use and region. SC: screening; BA: baseline; W: week. Statistically significant mean difference among the groups within visit ($p < 0.05$) occurs at Weeks 4, 8, 12, 16, and 20.

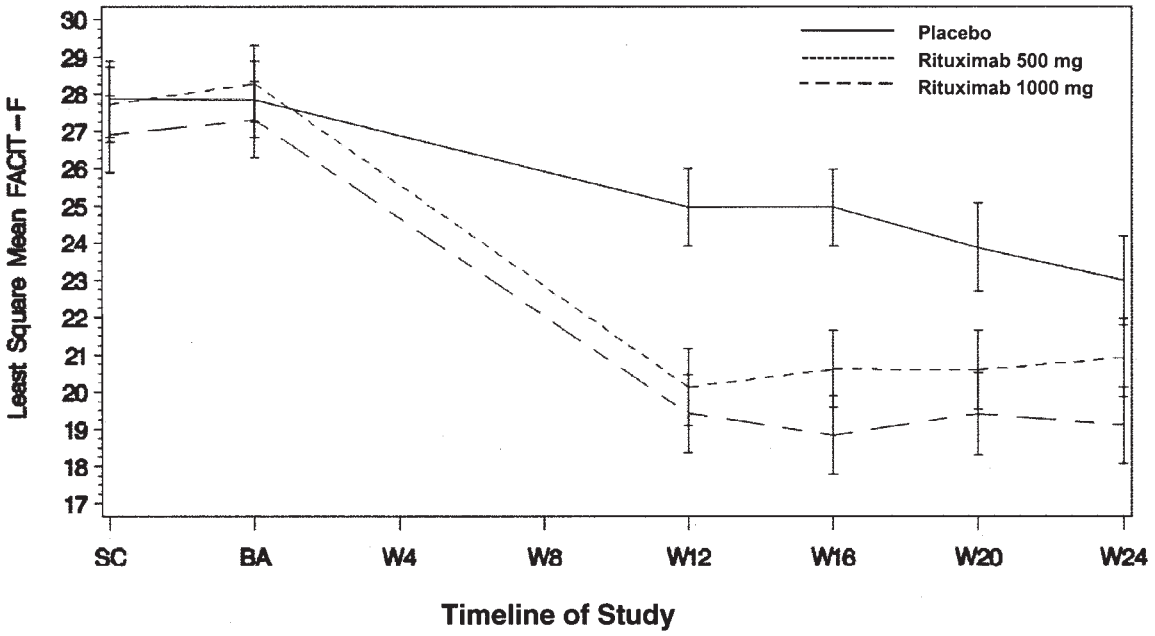

Figure 3. Mean FACIT-Fatigue scores (± 1 SE) by treatment group over the course of the study. Data are presented on the primary efficacy ITT population of 367 RF-positive patients. The horizontal line is joined at the means, while the vertical line is the mean ± 1 SE. Control variables included corticosteroid use and region. SC: screening; BA: baseline; W: week. Statistically significant mean difference among the groups within visit ($p < 0.05$) occurs at Weeks 12, 16, 20, and 24.

placebo-treated group. Consistent with the observed changes on PCS scores, the rituximab-treated patients reported significantly greater improvements compared with placebo-treated patients.

These differences were significant and consistent for the rituximab treatment groups, which have to date demonstrated significant clinical efficacy[48,49]. Not unexpectedly, no differences were observed between the rituximab and placebo-treated patients on the MCS. Since both mental health and role-emotional subscale roles are highly weighted in constructing the summary scores, statistically significant differences between placebo and rituximab-treated groups may not be observed even though numerical improvements in subscales were measured (Table 2). As observed in Table 2, the trend towards significance was observed in the rituximab 500 mg dose group versus placebo ($p = 0.087$). Moreover, the SF-36 summary scores are generated using an algorithm that, for MCS scores, positively weights the mental health-related subscales (i.e., mental health, role-emotional, social function) and negatively weights the physical health related subscales (i.e., physical function, pain, role-physical), which may distort the scores when there are differences in effects. The overall absolute MCS scores between 45 and 46 are consistent with reported values[50-55]. The effect of successful RA treatment may first affect relief of pain, mobility, physical function, and physical role activities and only later affect emotional well-being. These results are comparable to those seen in clinical trials for etanercept[50,51], adalimumab[13,52], and infliximab[51,53]. However, recent studies with abatacept treatment have suggested an improvement in MCS scores [in populations with less overall disease duration (8.5 yrs) and a lower overall DAS28 (6.4–6.5)][54,55]. The findings with rituximab treatment are significant, given that they were demonstrated in RA patients who were previously treated with at least one and up to 5 DMARD and/or TNF inhibitors before entry into this clinical trial and with disease duration of RA of 11.2 years.

Both doses of rituximab treatment regimens were associated with improvements in HAQ scores over the 24 weeks of the clinical trial. These findings indicate that rituximab positively affects the patients' activities of daily living and physical functioning. The HAQ scores demonstrated statistically and clinically meaningful improvements, compared with placebo, as soon as 8 weeks after start of rituximab treatment. The rituximab results based on the HAQ are similar to those observed for adalimumab[13] and other more recently approved treatments[2,8,53]. These observed improvements in HAQ scores are remarkable given the previous exposure to DMARD and/or TNF inhibitors among patients enrolled in the DANCER trial.

Fatigue is a symptom associated with RA[28], and there is increasing interest in understanding the effect of treatment on alleviating fatigue outcomes. In our study, rituximab was associated with significant improvements in fatigue measures, based on the FACIT-Fatigue, compared with placebo. The observed change over 24 weeks for the rituximab 500 mg and rituximab 1000 mg groups was significantly greater than for the placebo group. These mean differences exceeded the established MCID for the FACIT-Fatigue (i.e., 3.5 points)[28],

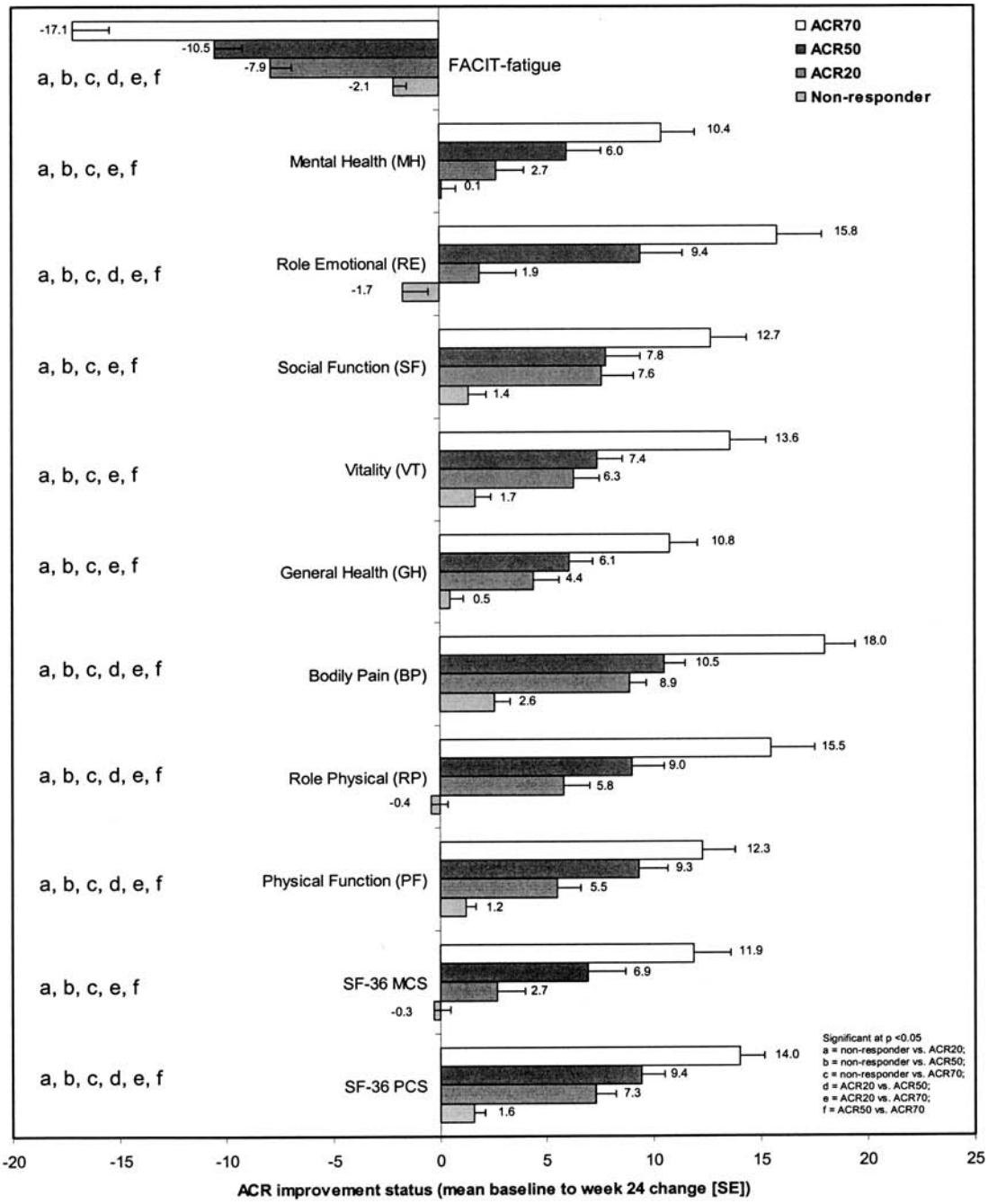

Figure 4. Mean changes in selected PRO from baseline to 24 weeks by ACR responder groups. Mean values are reported with standard errors (SE). Data on 367 RF-positive patients are presented. Responses were categorized using the ACR criteria based on improvement from baseline (i.e., ≥ 20% to < 50%; ≥ 50% to < 70%; and ≥ 70%). Patients with < 20% improvement were categorized as nonresponders. Patients with missing ACR responses are treated as nonresponders. Significant at $p < 0.05$ adjusted for baseline scores, treatment group, duration of RA, and CRP. a: nonresponder vs ACR20; b: nonresponder vs ACR50; c: nonresponder vs ACR70; d: ACR20 vs ACR50; e: ACR20 vs ACR70; f: ACR50 vs ACR70. A negative FACIT-Fatigue score indicates an improvement.

indicating that these fatigue outcomes are clinically meaningful. Few clinical trials have compared fatigue outcomes for the new RA treatments[51]; therefore, these results are important to understanding the broader influence of effective therapy on PRO.

Not surprisingly, PRO correlated well with clinical efficacy. ACR20 responders reported significantly greater improvements than nonresponders on the HAQ, FACIT-Fatigue, and the majority of the SF-36 subscale scores. Similarly, patients with ACR50 or ACR70 responses and EULAR moderate and good responses experienced even greater improvements in HRQOL. As suggested by the DANCER trial[25], trends in dif-

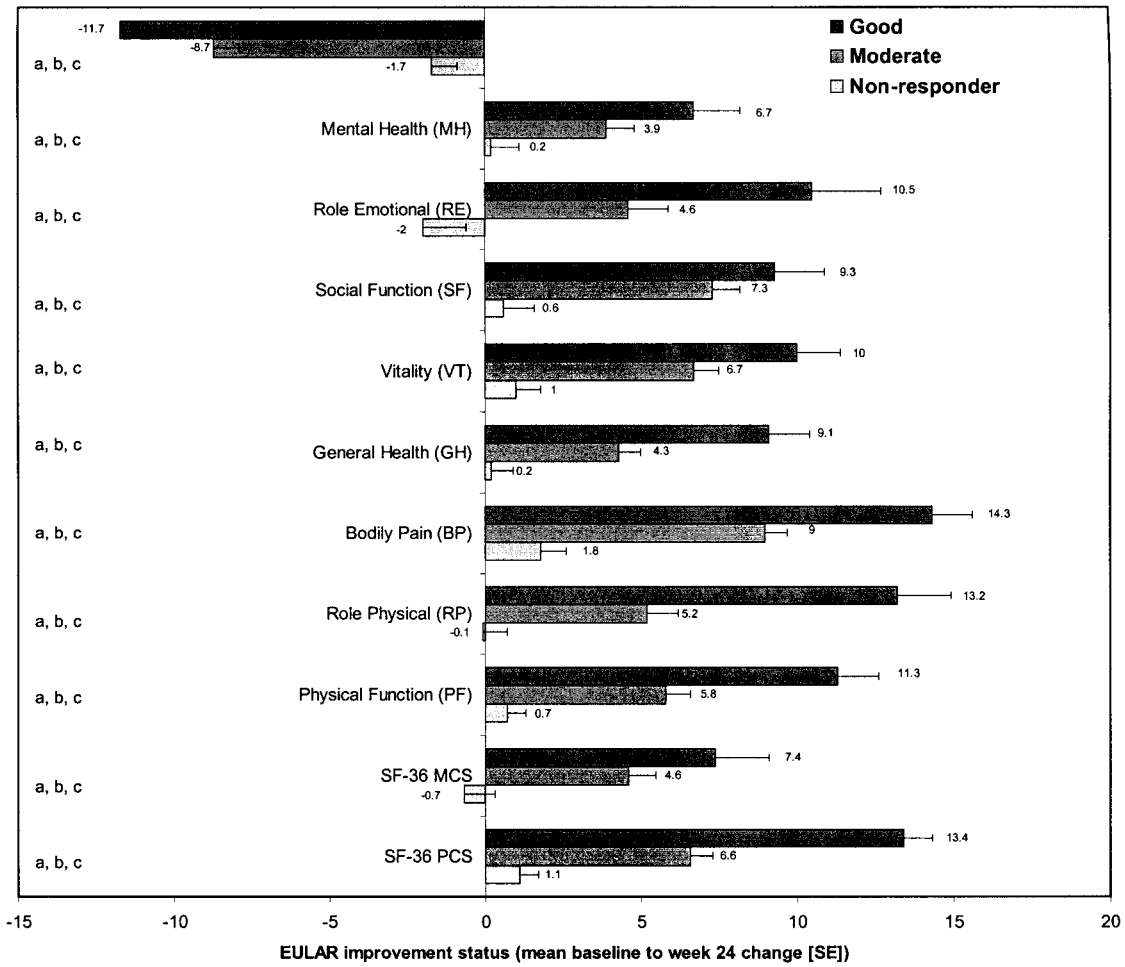

Figure 5. Mean changes in selected PRO from baseline to 24 weeks, by EULAR responder group. Mean values are reported with standard errors. Data on 367 RF-positive patients are presented. Significant at $p < 0.05$ adjusted for baseline scores, treatment group, duration of RA, and CRP. a: nonresponder versus moderate response; b: nonresponder versus good response; c: moderate response versus no response. A negative FACIT-Fatigue score indicates an improvement.

ficult-to-attain clinical efficacy responses (i.e., ACR70 and EULAR good responses) indicated that the 1000 mg dose resulted in improved HRQOL relative to the 500 mg dose. These findings further confirm previous analyses of the relationship between HRQOL and ACR response and other clinical endpoints in RA[3,27,28].

Interpretation of HRQOL outcomes for this clinical trial should acknowledge certain study limitations. First, because PRO are based on self-reports of patients with RA, measures may be biased by treatment expectations. Second, differential study treatment continuation was observed between the rituximab and placebo groups (91%–99% vs 73%–74%). Finally, RA is a lifelong chronic disease and this study reports HRQOL after only 24 weeks of followup. Although encouraging, additional clinical trials with longer followup are needed to confirm these HRQOL results.

In summary, the DANCER trial demonstrated that a single course of rituximab is associated with improvements in both clinical efficacy endpoints and HRQOL in patients with RA who had inadequate response to previous DMARD or biologic treatments. Trends in ACR70 and EULAR good responses indicated that the 1000 mg dose resulted in improved HRQOL relative to the 500 mg dose. For HAQ scores, these differences were apparent after 8 weeks and were maintained over the course of the 24-week study. The rituximab-treated groups had greater improvements in measures of fatigue and physical functioning and well-being compared with the placebo group, with the rituximab 1000 mg group demonstrating greater clinical efficacy in ACR70 and EULAR good responses. These HRQOL outcomes need to be confirmed in additional randomized clinical trials and in studies with longer followup. Based on our findings, rituximab treatment for RA has significant and clinically meaningful effects on patient functioning and health status outcomes.

ACKNOWLEDGMENT

The authors thank the principal investigators involved in the DANCER trial and participating patients, as well as Donald Stull and Jennifer Petrillo at United BioSource Corporation, Elaine Yu and Sandhya Sapra at Genentech, Inc., Fred Jost at F. Hoffman La Roche, and Keith Del Villar at Genentech, Inc. for assistance in the preparation of the manuscript.

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