The Effect of Intravenous Golimumab on Health-related Quality of Life in Rheumatoid Arthritis: 24-week Results of the Phase III GO-FURTHER Trial

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ABSTRACT. ***Objective.*** To evaluate the effects of intravenous (IV) golimumab 2 mg/kg + methotrexate (MTX) on patient-reported measures of health-related quality of life (HRQOL) in patients with active rheumatoid arthritis (RA) despite prior MTX therapy.

Methods. In this randomized, multicenter, double-blind, placebo-controlled, phase III trial, adults with RA were randomly assigned to receive IV placebo (n = 197) or golimumab 2 mg/kg (n = 395) infusions at Week 0, Week 4, and every 8 weeks thereafter. All patients continued stable oral MTX (15–25 mg/wk). HRQOL assessments included Health Assessment Questionnaire-Disability Index (HAQ-DI; physical function), Medical Outcomes Study Short Form-36 questionnaire physical/mental component summary (SF-36 PCS/MCS) scores, EQ-5D assessment of current health state, Functional Assessment of Chronic Illness Therapy-Fatigue (FACIT-Fatigue) questionnaire, and disease effect on productivity [10-cm visual analog scale (VAS)].

Results. Mean HAQ-DI improvements from baseline were significantly greater with golimumab + MTX than placebo + MTX at Week 14 and Week 24 ($p < 0.001$). Significantly greater improvements in all 8 individual SF-36 subscores and both the SF-36 PCS and MCS scores ($p < 0.001$) also accompanied golimumab + MTX therapy. Improved EQ-5D and EQ-5D VAS ($p < 0.001$) and FACIT-Fatigue ($p < 0.001$) scores were also observed for golimumab + MTX-treated patients at Week 12, Week 16, and Week 24, and greater proportions of golimumab + MTX-treated patients had clinically meaningful improvements in these measures. Greater reductions in disease effect on productivity were observed with golimumab + MTX versus placebo + MTX at Week 24 ($p < 0.001$). Improvements in physical function, HRQOL, fatigue, and productivity significantly correlated with disease activity improvement.

Conclusion. In active RA, IV golimumab + MTX significantly improved physical function, HRQOL, fatigue, and productivity using multiple measurement tools; all correlated with improvements in disease activity (NCT00973479, EudraCT 2008-006064-11). (J Rheumatol First Release May 1 2014; doi:10.3899/jrheum.130864)

Key Indexing Terms:
ANTI-TUMOR NECROSIS FACTOR RHEUMATOID ARTHRITIS
PHYSICAL FUNCTION QUALITY OF LIFE FATIGUE

The hallmark symptoms of rheumatoid arthritis (RA), i.e., joint pain, swelling, and stiffness, can have substantial detrimental effects on patients' physical function and quality of life[1,2]. Patients with RA have also identified persistent fatigue, as a cause of impaired quality of life; it has been recommended for additional evaluation[3,4,5,6]. Because of the effect of disease on multiple aspects of health-related quality of life (HRQOL), these assessments are increasingly studied in RA clinical trials, as well as in other observational studies and economic evaluations of newer therapies.

In several large, phase III clinical trials[7,8,9], patients with

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Supported by Janssen Research & Development LLC and Merck/Schering-Plough. Drs. Bingham, Weinblatt, and Westhovens have received consulting fees from Janssen. C. Han, T.A. Gathany, L. Kim, K.H. Lo, D. Baker, and A. Mendelsohn are or were employees of Janssen.

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Accepted for publication February 20, 2014.

RA who were treated with subcutaneous (SC) golimumab, a human monoclonal anti-tumor necrosis factor-α (TNF) antibody, showed significant improvement in RA-related signs and symptoms. In addition, SC golimumab plus oral methotrexate (MTX) significantly improved physical function and HRQOL and lessened fatigue through 24 weeks among patients with active RA despite treatment with MTX[10].

In the more recently conducted GO-FURTHER trial, the efficacy and safety of intravenous (IV) golimumab was assessed in patients with active RA despite MTX therapy[11]. Through Week 24, clinical response to golimumab was rapid, and significantly greater proportions of patients treated with golimumab 2 mg/kg + MTX versus placebo + MTX had improvement in disease activity [American College of Rheumatology 20% (ACR20) response rates of 59% vs 25%, respectively ($p < 0.001$)]. They also had significant improvement in physical function [median changes in Health Assessment Questionnaire Disability Index (HAQ-DI) of 0.500 vs 0.125, respectively ($p < 0.001$)]. Adverse events through Week 24 were similar between the treatment groups and consistent with previous trials of anti-TNF agents in patients with RA[11]. Here we report the effects of IV golimumab 2 mg/kg + MTX on physical function, HRQOL, fatigue, and productivity through Week 24 of the GO-FURTHER trial and explore the relationships between disease activity and these patient-reported outcomes (PRO).

MATERIALS AND METHODS

Patients and study design. The study design and patient population of this randomized, multicenter, double-blind, placebo-controlled, phase III trial (NCT00973479, EudraCT 2008-006064-11) have been described[11]. Briefly, adult patients with active RA despite MTX therapy were randomly assigned (2:1) to receive IV infusions of golimumab 2 mg/kg or placebo at weeks 0, 4, 12, and 20. All patients continued to receive a stable regimen of concomitant oral MTX (15–25 mg/wk). Randomization was stratified according to baseline C-reactive protein (CRP) level (< or ≥ 1.5 mg/dl; upper limit of normal: 1.0 mg/dl). At Week 16, patients in the placebo + MTX group who had less than 10% improvement in tender and swollen joint counts entered blinded early escape and crossed over to receive golimumab 2 mg/kg at weeks 16 and 20. Patients randomized to golimumab 2 mg/kg + MTX received placebo infusions at Week 16 to maintain the blind but did not undergo dose increase or changes in dosing frequency. Data collected through Week 24 are included in the current report.

Assessments. Physical function was evaluated with the HAQ-DI, a 20-question instrument that assesses the degree of difficulty a person has in accomplishing tasks in 8 functional areas (dressing, arising, eating, walking, hygiene, reaching, gripping, and activities of daily living)[12]. An improvement in HAQ-DI score ≥ 0.25 units was considered clinically meaningful[13,14], and normal physical function was defined as a HAQ-DI score ≤ 0.5[14]. As a major secondary endpoint, the change in HAQ-DI from baseline to Week 14 has been reported[11].

HRQOL was assessed using the Medical Outcomes Study Short Form-36 questionnaire (SF-36)[15]. Physical and mental component summary (PCS and MCS) scores as well as individual component domain scores of the SF-36 are reported, with higher scores indicating better HRQOL. In this analysis, a clinically important improvement in PCS and MCS scores was defined as a change from baseline ≥ 5 points[13].

The EQ-5D assessment of current health state was also used to assess patient function and HRQOL. The EQ-5D is a self-reported questionnaire that evaluates 5 generic areas of current health status, including mobility, self-care, usual activities, pain/discomfort, and anxiety/depression. Each dimension is scored as representing no problem, some problem, or extreme problem. The EQ-5D also contains a visual analog scale (EQ-5D VAS) to assess the current health state, which is converted into a score of 0 (worst imaginable health state) to 100 (best imaginable health state), with higher scores representing a better health state[16]. A clinically meaningful improvement was defined as a change from baseline in the VAS score of at least half of the SD[17].

The Functional Assessment of Chronic Illness Therapy-Fatigue (FACIT-Fatigue) questionnaire[18] was used to evaluate changes in patient fatigue. The FACIT-Fatigue assesses 3 scales of self-reported tiredness, weakness, and difficulty conducting usual activities because of fatigue. A change ≥ 4 points in the FACIT-Fatigue score has been determined to be a clinically meaningful improvement[19].

The effect of disease on daily productivity at work, school, or home in the previous 4 weeks was self-reported on a 10-cm VAS (0 cm = productivity not affected at all, 10 cm = productivity affected very much). Lower scores and decreases indicate less effect of disease on productivity and thus patient improvement.

Clinical response was assessed with the 28-joint Disease Activity Score using CRP (DAS28-CRP)[20]. The proportions of patients achieving a DAS28-CRP score < 2.6 were also determined[21].

Statistical analysis. Data are summarized using descriptive statistics. All endpoints were prespecified except as noted otherwise below, and all posthoc analyses were performed with the same statistical test procedures and SAS macros used for preplanned analyses, to maintain consistency. Treatment group differences were assessed with an analysis of variance on the van der Waerden normal scores for continuous variables or Cochran-Mantel-Haenszel testing for categorical variables. For patients in the placebo + MTX group who entered early escape, the last observation before dose adjustment at Week 16 was carried forward and used in the Week 24 analysis. A number-needed-to-treat (NNT) analysis was performed posthoc with regard to achievement of clinically important improvements in SF-36 PCS and MCS (change ≥ 5 points), EQ-5D VAS (change ≥ 1/2 SD), and FACIT-Fatigue (change ≥ 4 points) scores at weeks 12, 16, and 24. The NNT was determined as 1/(% golimumab minus % placebo patients achieving clinically important improvement). A Spearman correlation analysis was performed posthoc to evaluate correlations between changes in the DAS28-CRP score and changes in HRQOL assessments, fatigue, and disease effect on productivity from baseline to weeks 12, 16, and 24. The proportions of patients with normal HAQ-DI (≤ 0.5 units), FACIT-Fatigue (score ≥ 43.6), and SF-36 PCS (score ≥ 50) and MCS (score ≥ 50) scores at Week 24 were also summarized posthoc, with patients being grouped by achievement of a DAS28-CRP score < 2.6 at Week 24 (yes vs no). For patients achieving normal HAQ-DI, FACIT-Fatigue, or SF-36 summary scores, OR comparing those who achieved versus those who did not achieve the DAS28-CRP criterion were estimated posthoc using logistic regression models that adjusted for age, sex, and baseline measurement of the dependent variable.

RESULTS

Baseline demographics and disease characteristics. The baseline demographics and clinical disease characteristics of the GO-FURTHER patient population (Table 1), which were generally comparable between treatment groups, have been described[11]. Briefly, 592 patients were randomly assigned to receive placebo + MTX (n = 197) or golimumab 2 mg/kg + MTX (n = 395). Sixty-eight patients (34.5%) in the placebo + MTX group entered early escape at Week 16 and began receiving golimumab + MTX, compared with 4.6% (n = 17)

Table 1. Baseline patient and disease characteristics among randomized patients. Data presented as mean ± SD or n (%).

Characteristic	Placebo + MTX, n = 197	Golimumab, 2 mg/kg + MTX, n = 395	All Patients, n = 592
Female patients	157 (79.7)	326 (82.5)	483 (81.6)
Age, yrs	51.4 ± 11.3	51.9 ± 12.6	51.8 ± 12.1
Disease duration, yrs	7.0 ± 7.2	6.9 ± 7.0	6.9 ± 7.1
CRP, mg/dl	2.2 ± 1.9	2.8 ± 2.9	2.6 ± 2.6
Swollen joint count (0–66)	14.8 ± 8.5	15.0 ± 8.2	14.9 ± 8.3
Tender joint count (0–68)	25.9 ± 14.1	26.4 ± 13.9	26.3 ± 14.0
DAS28-CRP score	5.9 ± 0.9	6.0 ± 0.8	5.9 ± 0.9
HAQ-DI score (0–3)	1.6 ± 0.6	1.6 ± 0.7	1.6 ± 0.7
SF-36 PCS score (0–100)	30.9 ± 7.3	30.8 ± 6.8	30.8 ± 7.0
SF-36 MCS score (0–100)	38.5 ± 11.6	37.1 ± 11.1	37.6 ± 11.3
EQ-5D VAS score (0–100)	48.1 ± 21.3	45.2 ± 24.9	46.2 ± 23.8
FACIT-Fatigue score (0–52)	26.3 ± 10.8	25.4 ± 10.4	25.7 ± 10.5
Productivity VAS (0–10)	6.3 ± 2.4	6.4 ± 2.3	6.4 ± 2.3
Duration of MTX use at baseline, yrs			
< 1	48 (24.4)	102 (25.8)	150 (25.3)
≤ 1 to < 3	61 (31.0)	114 (28.9)	175 (29.6)
≥ 3	88 (44.7)	176 (44.6)	264 (44.6)
Unknown	0 (0.0)	3 (0.8)	3 (0.5)
Patient taking corticosteroids at baseline	134 (68.0)	251 (63.5)	385 (65.0)
Prednisone-equivalent dose, mg/day	7.0 ± 2.5	7.0 ± 2.5	7.0 ± 2.5

CRP: C-reactive protein; DAS28-CRP: 28-joint Disease Activity Score using CRP; FACIT-Fatigue: Functional Assessment of Chronic Illness Therapy-Fatigue; HAQ-DI: Health Assessment Questionnaire-Disability Index; MTX: methotrexate; SF-36 PCS/MCS: Medical Outcomes Study Short Form-36 questionnaire physical/mental component summary; VAS: visual analog scale.

of golimumab + MTX-treated patients who qualified for early escape.

Patient disposition through Week 24 has also been reported[11]. Briefly, 22 patients discontinued the study agent through Week 24, including 6 patients (3.0%) in the placebo + MTX group and 16 patients (4.1%) in the golimumab + MTX group. The most common reason for discontinuation of the study agent through Week 24 was adverse event (1.9% of all patients).

Physical function. Patients treated with golimumab + MTX had significantly greater improvements in the HAQ-DI score than did those who received placebo + MTX, both at Week 14[11] and Week 24 (Table 2). A clinically meaningful improvement (≥ 0.25 points) in HAQ-DI was achieved by 67.3% of patients receiving golimumab + MTX versus 45.2% of patients receiving placebo + MTX ($p < 0.001$). Compared with the placebo + MTX group, greater proportions of patients receiving golimumab + MTX also achieved improvement in HAQ-DI when responses were grouped by cutoff criteria of changes < 0 (any improvement) versus changes ranging from 0–1.25 (worsening; Figure 1A).

HRQOL. Through Week 24, mean improvements from baseline in both the PCS and MCS scores and in all 8 individual subscores of the SF-36 were significantly greater in the golimumab + MTX group than in the placebo + MTX group at weeks 12, 16, and 24 (Figure 1B, Table 2). When compared with baseline, the distributions of both the SF-36 PCS and MCS scores at Week 24 shifted toward better HRQOL in the golimumab + MTX group, while no such shift was observed in the placebo + MTX group (Figure 2).

Significant improvements in EQ-5D VAS scores were also observed among golimumab + MTX versus placebo + MTX-treated patients at weeks 12, 16, and 24 (Table 2). Additionally, greater proportions of golimumab + MTX than placebo + MTX-treated patients achieved improvement in each dimension of the EQ-5D, i.e., anxiety/depression ($p < 0.001$), mobility ($p < 0.01$), pain/discomfort ($p < 0.001$), self-care ($p < 0.01$), and usual activities ($p < 0.001$) at Week 24 (Table 3).

Fatigue. Measurements of fatigue improved through Week 24 for patients who received golimumab + MTX. At weeks 12, 16, and 24, mean improvements in FACIT-Fatigue scores were significantly greater in the golimumab + MTX group than in the placebo + MTX group (Table 2).

NNT decreased. Greater proportions of patients treated with golimumab + MTX achieved clinically meaningful improvement in SF-36 PCS and MCS, EQ-5D VAS, and FACIT-Fatigue scores at weeks 12, 16, and 24. The NNT for 1 additional treated patient to achieve clinically meaningful improvement in measures of HRQOL and fatigue decreased over time from Week 12 to Week 24. By Week 24, the NNT for clinically meaningful improvement in SF-36 PCS, SF-36

Table 2. Improvements from baseline in physical function, health-related quality of life, fatigue, and productivity through Week 24. Data shown are mean ± SD.

Scale/Visit	Placebo + MTX	Golimumab, 2 mg/kg + MTX	P Value vs Placebo + MTX
HAQ-DI score			
Week 12	0.19 ± 0.53	0.39 ± 0.59	< 0.001
Week 14	0.19 ± 0.56	0.50 ± 0.58	< 0.001
Week 16	0.21 ± 0.54	0.49 ± 0.60	< 0.001
Week 24	0.21 ± 0.55	0.53 ± 0.64	< 0.001
SF-36 PCS score			
Week 12	3.19 ± 7.42	5.92 ± 7.70	< 0.001
Week 16	3.77 ± 7.51	7.42 ± 8.11	< 0.001
Week 24	3.82 ± 7.30	8.28 ± 8.32	< 0.001
SF-36 MCS score			
Week 12	1.46 ± 9.88	4.91 ± 10.27	< 0.001
Week 16	1.33 ± 9.70	7.23 ± 10.25	< 0.001
Week 24	1.21 ± 10.07	6.94 ± 10.28	< 0.001
EQ-5D VAS score			
Week 12	2.53 ± 27.26	11.43 ± 28.87	< 0.001
Week 16	3.53 ± 25.34	17.69 ± 28.08	< 0.001
Week 24	8.25 ± 24.64	19.12 ± 29.87	< 0.001
FACIT-Fatigue score			
Week 12	2.05 ± 9.04	5.38 ± 10.32	< 0.001
Week 16	2.16 ± 9.70	7.54 ± 10.55	< 0.001
Week 24	2.54 ± 10.22	7.96 ± 10.79	< 0.001
Productivity score			
Week 12	–0.81 ± 2.44	–1.79 ± 2.71	< 0.001
Week 16	–0.66 ± 4.53	–2.36 ± 2.84	< 0.001
Week 24	–1.00 ± 2.65	–2.64 ± 2.86	< 0.001

FACIT-Fatigue: Functional Assessment of Chronic Illness Therapy-Fatigue; HAQ-DI: Health Assessment Questionnaire-Disability Index; MTX: methotrexate; SF-36 PCS/MCS: Medical Outcomes Study Short Form-36 questionnaire physical/mental component summary; VAS: visual analog scale.

MCS, EQ-5D VAS, and FACIT-Fatigue scores were 3.6, 4.5, 4.7, and 3.9, respectively (Table 4).

Effect of disease on productivity. Patients treated with golimumab + MTX had a significantly greater mean improvement in the effect of disease on productivity when compared with patients who received placebo + MTX at Week 12 (–1.79 vs –0.81; $p < 0.001$), Week 16 (–2.36 vs –0.66; $p < 0.001$), and Week 24 (–2.64 vs –1.00; $p < 0.001$; Table 2).

Improvement in disease activity and PRO. Significantly greater proportions of patients who took golimumab + MTX than patients who took placebo + MTX achieved a DAS28-CRP score < 2.6 at Week 12 (9.4% vs 3.0%; $p = 0.005$), Week 16 (12.9% vs 4.6%; $p = 0.002$), and Week 24 (17.7% vs 5.1%; $p < 0.001$). Improvement in the DAS28-CRP score significantly correlated with improvements in HRQOL (SF-36 PCS/MCS and EQ-5D scores), fatigue (FACIT-Fatigue score), and disease effect on productivity (10-cm VAS) at weeks 12, 16, and 24 (Appendix 1). In addition, greater proportions of patients who achieved DAS28-CRP score < 2.6 also achieved normalized physical function (HAQ-DI score ≤ 0.5), normalized fatigue (FACIT-Fatigue score ≥ 43.6), and clinically important improvement in HRQOL (normalization of SF-36 PCS and MCS scores to ≥ 50) at Week 24 when compared with patients who did not achieve a DAS28-CRP score < 2.6 (Appendix 2).

DISCUSSION

Rheumatoid arthritis, a chronic, systemic, inflammatory disease that affects 1.3 million adults in the United States, has a considerable effect on physical, emotional, and social health[22]. Because of the disease's associated pain, impaired physical function, and fatigue, patients with RA can experience substantially diminished HRQOL[23]. Extra-articular features and complications of RA, including rheumatoid nodules, anemia of chronic disease, and pulmonary and cardiovascular manifestations, may further affect HRQOL[3,24]. The effects of RA and its treatment on patients' daily lives are varied and far-reaching, including mental, physical, and functional impairments. We used several tools to assess HRQOL, including the SF-36, an instrument that has both composite physical and mental component scores as well as 8 different subdomain scores, and the EQ-5D, a more general assessment tool that reflects HRQOL in each of 5 dimensions, as well as the patient's overall "current health state."

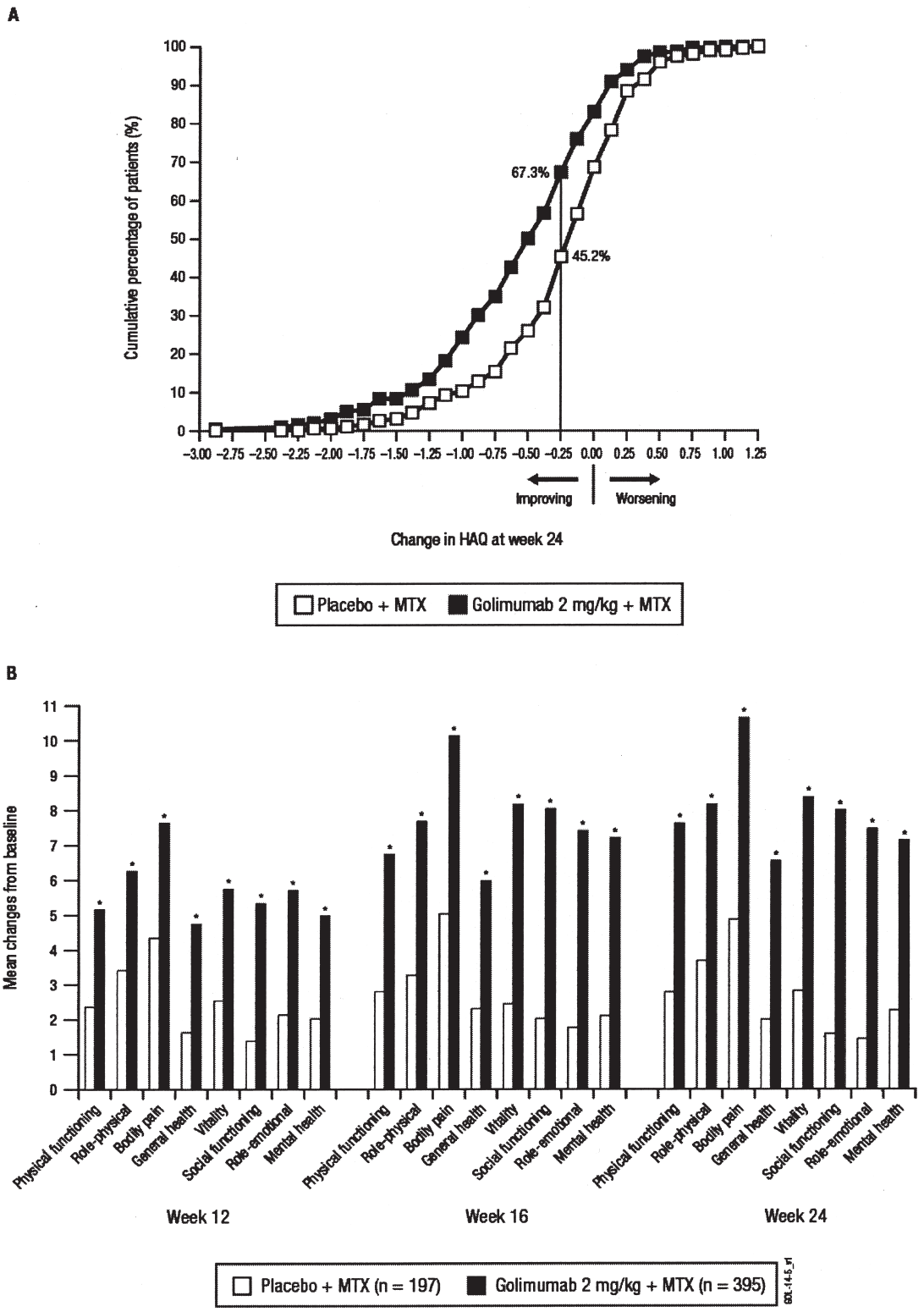

Figure 1. Changes in HAQ-DI and SF-36 through Week 24. A. Cumulative percentages of patients according to change in the HAQ-DI score from baseline to Week 24. B. Mean changes from baseline in the individual components of the SF-36 at weeks 12, 16, and 24. HAQ-DI: Health Assessment Questionnaire-Disability Index; MTX: methotrexate; SF-36: Medical Outcomes Study Short Form-36 questionnaire.

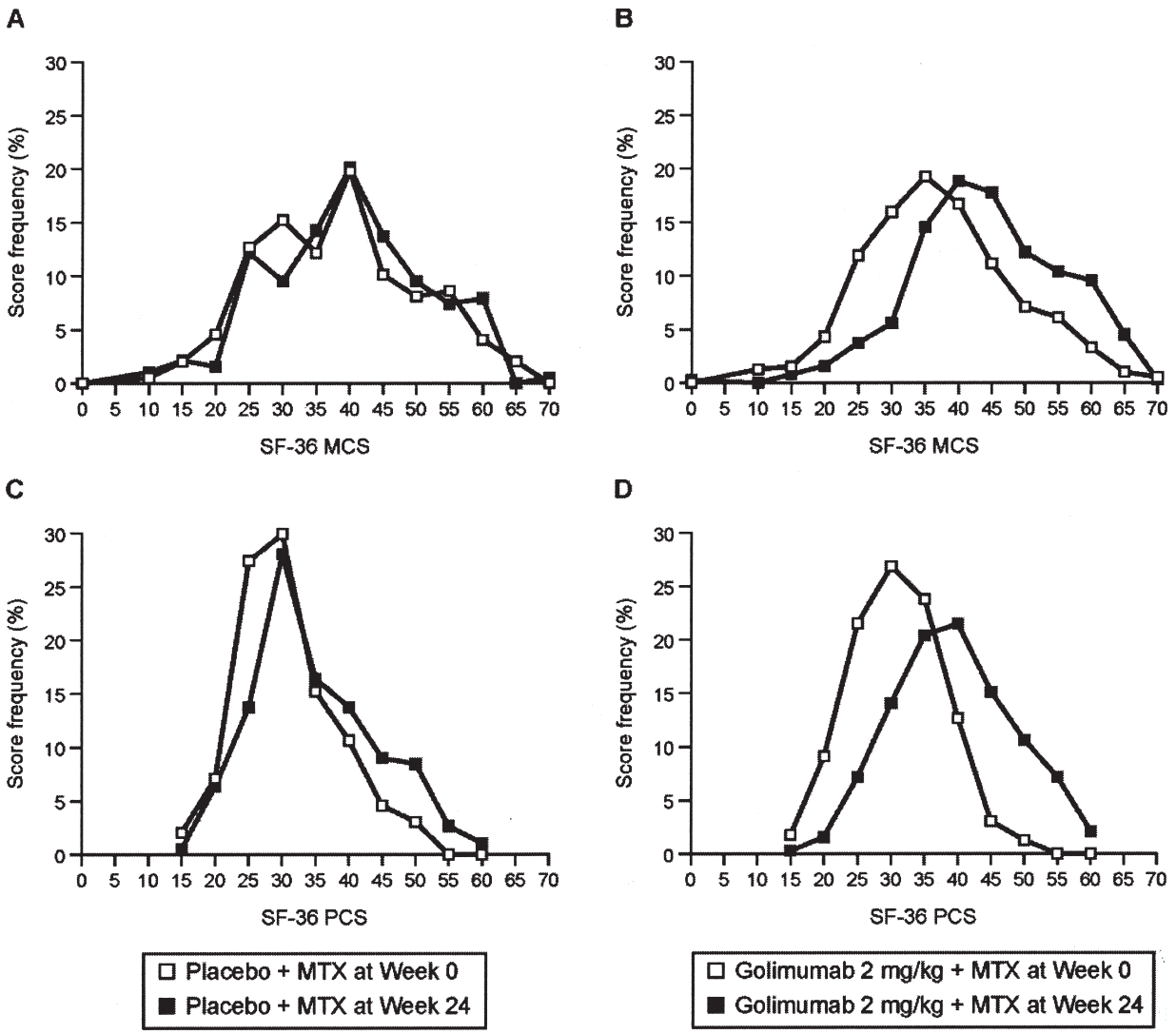

Figure 2. Distributions of SF-36 MCS (A, B) and PCS (C, D) scores at baseline and Week 24 for placebo + MTX (A, C) and golimumab + MTX (B, D). MCS: mental component summary; MTX: methotrexate; PCS: physical component summary; SF-36: Medical Outcomes Study Short Form-36 questionnaire.

Numerous clinical studies have demonstrated that treatment with the biologic disease-modifying antirheumatic drugs (DMARD) that includes anti-TNF agents can significantly improve multiple aspects of HRQOL, as reflected by improved physical and mental function and reduced fatigue. In addition to maintaining physical function, treatment goals for patients with RA have expanded to include the improvement, restoration, and preservation of HRQOL[23]. As part of these broader treatment goals, the advent of biologic DMARD has also made disease remission an achievable goal of RA therapy. Achievement of disease remission, in turn, is predictive of better radiographic and physical function outcomes[25].

The human monoclonal antibody golimumab is among the newer TNF antagonists approved for the treatment of RA. Golimumab represents the first new IV anti-TNF agent approved for treatment of RA in over a decade, an important development given that a substantial number of patients require some type of IV treatment[26]. Golimumab, which allows early disease control in concert with less frequent dosing, has been shown (in the GO-FORWARD trial[10]) to provide significant and sustained improvement in physical function, HRQOL, and fatigue when administered SC in combination with MTX to patients with active RA despite background MTX treatment. In the current GO-FURTHER trial, we evaluated the effects of IV golimumab (2 mg/kg) plus MTX on HRQOL in patients with active RA. Patients in the GO-FURTHER trial generally had similar disease characteristics at study outset as patients evaluated in the GO-FORWARD trial of subcutaneous golimumab[10].

Table 3. Proportions of patients with change from baseline in each of 5 EQ-5D dimensions at Week 24.

Dimensions	Change at Week 24	Placebo + MTX (%)	Golimumab, 2 mg/kg + MTX (%)	P Value vs Placebo + MTX
Anxiety/depression	Improved	20.6	34.6	< 0.001
	No change	61.9	57.7	
	Worsened	17.5	7.7	
Mobility	Improved	19.6	28.2	< 0.01
	No change	72.5	69.4	
	Worsened	7.9	2.4	
Pain/discomfort	Improved	25.4	39.9	< 0.001
	No change	64.0	55.9	
	Worsened	10.6	4.3	
Self-care	Improved	17.5	29.5	< 0.01
	No change	71.4	64.6	
	Worsened	11.1	5.9	
Usual activities	Improved	21.2	34.3	< 0.001
	No change	67.7	61.2	
	Worsened	11.1	4.5	

MTX: methotrexate.

Table 4. An analysis of number needed to treat to obtain clinically important improvement† in PRO with golimumab treatment.

Visit/PRO	Proportion of Patients Achieving Clinically Important Improvement†		P value vs Placebo + MTX	Number Needed to Treat
	Placebo + MTX (%)	Golimumab, 2 mg/kg + MTX (%)		
Week 12				
SF-36 PCS	32.0	52.9	< 0.001	4.8
SF-36 MCS	33.5	47.9	< 0.001	7.0
EQ-5D VAS	29.8	46.5	< 0.001	6.0
FACIT-Fatigue	42.8	57.5	< 0.001	6.8
Week 16				
SF-36 PCS	36.6	60.8	< 0.001	4.1
SF-36 MCS	35.0	58.2	< 0.001	4.3
EQ-5D VAS	31.4	54.6	< 0.001	4.3
FACIT-Fatigue	39.2	64.4	< 0.001	4.0
Week 24				
SF-36 PCS	37.6	65.6	< 0.001	3.6
SF-36 MCS	35.0	57.2	< 0.001	4.5
EQ-5D VAS	39.0	60.4	< 0.001	4.7
FACIT-Fatigue	40.3	65.8	< 0.001	3.9

†Clinically important improvements were defined as change ≥ 5 points for SF-36 PCS and MCS, change ≥ 1/2 SD for EQ-5D VAS, and change ≥ 4 points for FACIT-Fatigue. FACIT-Fatigue: Functional Assessment of Chronic Illness Therapy-Fatigue; MTX: methotrexate; SF-36 PCS/MCS: Medical Outcomes Study Short Form-36 questionnaire physical/mental component summary; PRO: patient-reported outcome: VAS: visual analog scale.

Although baseline CRP levels were higher, on average, in GO-FURTHER than GO-FORWARD, about 40% of GO-FURTHER patients started the trial at Week 0 with normal CRP levels.

IV golimumab yielded significant improvements in physical function, HRQOL, and fatigue relative to MTX alone that were similar in magnitude to those observed in the GO-FORWARD trial of SC golimumab in RA[10], even though GO-FORWARD patients exhibited lower levels of inflammation at study outset than did the GO-FURTHER population, as measured by acute-phase reactants (e.g., CRP of mean of 0.8–1.0 vs 2.2–2.8 mg/dl, respectively)[9]. In the case of the MCS score of the SF-36, IV golimumab therapy led to significant improvements through Week 24. Greater reductions in the effect of disease on productivity were also observed with IV versus SC golimumab[10]. These golimumab-related improvements observed in physical function, HRQOL, fatigue, and disease effect on produc-

tivity were significantly correlated with decline in disease activity. The NNT analysis showed that, overall, fewer than 5 treated patients would be needed for 1 additional treated patient to achieve clinically meaningful improvement in each HRQOL measure by Week 24, confirming that IV golimumab is an effective therapy for patients with RA. In addition, about half of patients who achieve low disease activity/remission can also expect to experience normalization of physical function, fatigue, and/or mental/physical components of their quality of life (Appendix 2).

Given that decreases in HRQOL are associated with reduced productivity while at work or in the home, assessment of productivity in patients with RA is a practical way to measure disability from RA. Our findings related to the effect of the disease on daily productivity at work, school, or home are consistent with data from recent trials of biological agents, demonstrating that these agents can reverse disease-related declines in productivity. We evaluated the effect of RA on daily productivity at work, school, or home in the previous 4 weeks using a self-reported 10-cm VAS. While this specific instrument has not undergone rigorous reliability testing, it has been used in clinical trials of biologic agents in ankylosing spondylitis[27] and psoriatic arthritis[28,29]. In addition, the use of a similar tool (a VAS scale of 0 to 100 in which 0 = not affected at all and 100 = completely affected) in measuring the effect of RA on work performance has demonstrated acceptable reliability and validity[30]. Future assessments of productivity can be enhanced with standardization of productivity instruments[31].

Fatigue is an important symptom of RA that can greatly affect patient HRQOL. Fatigue in RA also contributes to disability, injury, inability to participate in rehabilitative therapy, and strained interpersonal relations[19]. The FACIT-Fatigue questionnaire is a brief and validated tool for assessing fatigue in patients with RA, in which a 3-point to 4-point change has been determined to be a minimally important difference[19]. Mean/median FACIT-Fatigue scores in the general US population have been reported to be 43.6/47 and in anemic cancer patients to be 23.9/23[18]. The FACIT-Fatigue scores observed in the patients with RA who participated in the current golimumab trial indicated that their fatigue at baseline (mean FACIT-Fatigue scores of 25.4 to 26.3) was comparable to that reported by anemic cancer patients[18]. Additional analyses demonstrated that the baseline FACIT-Fatigue score was correlated with baseline physical function as measured by HAQ-DI and baseline disease activity as measured by the DAS28-CRP score (data not shown). Golimumab treatment yielded clinically important improvements in this important symptom of RA as early at Week 12 (mean change of 5.4) and continuing through Week 24 (mean change of 8.0). Improvement in FACIT-Fatigue was significantly associated with improvement in disease activity (Appendix 1), physical function, and HRQOL (data not shown). Although average FACIT-Fatigue scores cannot be "normalized" because some patients will still have active disease, improvements in average scores that are still lower than for the general population are desirable. Beyond such improvement, optimized treatment for patients with residual fatigue is needed for normalization/remission of this important RA symptom.

Although the proportions of RA patients with no change in each dimension of the EQ-5D appeared to be similar between the placebo and golimumab groups, the overall trend was that golimumab-treated patients were significantly more likely to have achieved improvement than placebo-treated patients in each EQ-5D dimension. Similarly, placebo-treated patients were more likely to have worsening or no improvement in each dimension compared with active treatment.

The data presented herein compare active treatment with placebo at the short-term 24-week timepoint. Based on this limitation of the current analyses, longer-term assessment of the effect of treatment on HRQOL, especially among patients who have achieved clinical response or remission, is warranted.

IV golimumab plus MTX significantly improved physical function, HRQOL, and productivity and lessened fatigue in patients with active RA, and these improvements correlated with improvement in disease activity.

ACKNOWLEDGMENT

The authors thank Michelle L. Perate, MS, a consultant for Janssen, and Mary H. Whitman, PhD, an employee of Janssen, for assistance with manuscript preparation and submission.

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APPENDIX 1. Associations between changes in health-related quality of life, fatigue, and productivity and changes in DAS28-CRP score from baseline to weeks 12, 16, and 24 among all randomized patients.

Change from Baseline in:	Change from Baseline in DAS28-CRP Score		
	Week 12	Week 16	Week 24
SF-36 PCS score	n = 592, ρ = –0.491	n = 592, ρ = –0.502	n = 592, ρ = –0.548
SF-36 MCS score	n = 592, ρ = –0.280	n = 592, ρ = –0.385	n = 592, ρ = –0.380
EQ-5D score	n = 575, ρ = –0.280	n = 575, ρ = –0.347	n = 564, ρ = –0.254
FACIT-Fatigue score	n = 582, ρ = –0.407	n = 582, ρ = –0.481	n = 571, ρ = –0.490
Productivity score	n = 590, ρ = 0.449	n = 590, ρ = 0.493	n = 590, ρ = 0.521

All p values calculated using Spearman correlation coefficient; $p < 0.0001$ for all associations. DAS28-CRP: 28-joint Disease Activity Score using C-reactive protein; FACIT-Fatigue: Functional Assessment of Chronic Illness Therapy-Fatigue; SF-36 PCS/MCS: Medical Outcomes Study Short Form-36 questionnaire physical/mental component summary.

APPENDIX 2. Proportions of patients achieving normal physical function, fatigue, and health-related quality of life grouped by their achievement of DAS28-CRP score < 2.6 at Week 24 among all randomized patients.

Week 24	Week 24 DAS28-CRP score < 2.6		
	No	Yes	OR[1] (p)
HAQ-DI ≤ 0.5, n = 592	101/512, 19.7%	47/80, 58.8%	5.22 (< 0.0001)
FACIT-Fatigue ≥ 43.6, n = 571	62/492, 12.6%	37/79, 46.8%	5.50 (< 0.0001)
SF-36 PCS score ≥ 50, n = 566	31/487, 6.4%	33/79, 41.8%	12.01 (< 0.0001)
SF-36 MCS score ≥ 50, n = 566	114/487, 23.4%	44/79, 55.7%	4.12 (< 0.0001)

[1]OR was estimated based on logistic regression model by adjusting for age, sex, and baseline value (HAQ-DI, FACIT-Fatigue, SF-36 PCS, or MCS) and DAS28-CRP score. DAS28-CRP: 28-joint disease activity score using C-reactive protein; FACIT-Fatigue: Functional Assessment of Chronic Illness Therapy-Fatigue; HAQ-DI: Health Assessment Questionnaire-Disability Index; MCS: mental component summary of SF-36; PCS: physical component summary of SF-36; SF-36: Medical Outcomes Study Short Form-36 questionnaire.