The Journal of Rheumatology

The Journal of Rheumatology Volume 40, no. 4

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J Rheumatol 2013;40;369-378
http://www.jrheum.org/content/40/4/369

Effects of Fostamatinib (R788), an Oral Spleen Tyrosine Kinase Inhibitor, on Health-related Quality of Life in Patients with Active Rheumatoid Arthritis: Analyses of Patient-reported Outcomes from a Randomized, Double-blind, Placebo-controlled Trial

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ABSTRACT. ***Objective.*** To assess the influence of fostamatinib on patient-reported outcomes (PRO) in patients with active rheumatoid arthritis and an inadequate response to methotrexate (MTX).

Methods. Patients taking background MTX (N = 457) were enrolled in a phase II clinical trial (NCT00665925) and randomized equally to placebo, fostamatinib 100 mg twice daily (bid), or fostamatinib 150 mg once daily (qd) for 24 weeks. Self-administered PRO measures included pain, patient's global assessment (PtGA) of disease activity, physical function, health-related quality of life (HRQOL), and fatigue. Mean change from baseline and a responder analysis of the proportion of patients achieving a minimal clinically important difference were determined.

Results. At Week 24, there were statistically significant improvements in pain, PtGA, physical function, fatigue, and the physical component summary of the Medical Outcomes Study Short Form-36 (SF-36) for fostamatinib 100 mg bid compared with placebo. Mean (standard error) changes from baseline in the fostamatinib 100 mg bid group versus the placebo group were –31.3 (2.45) versus –17.8 (2.45), $p < 0.001$ for pain; –29.1 (2.26) versus –16.7 (2.42), $p < 0.001$ for PtGA; –0.647 (0.064) versus –0.343 (0.062), $p < 0.001$ for physical function; 7.40 (1.00) versus 4.50 (0.94), $p < 0.05$ for fatigue; 8.52 (0.77) versus 4.90 (0.78), $p < 0.01$ for SF-36 physical component score; and 3.99 (0.93) versus 3.71 (0.99), $p = 0.83$ for SF-36 mental component score. Patients receiving fostamatinib 150 mg qd showed improvements in some PRO, including physical function.

Conclusion. Patients treated with fostamatinib 100 mg bid showed significant improvements in HRQOL outcomes. (First Release Feb 1 2013; J Rheumatol 2013;40:369–78; doi:10.3899/jrheum.120923)

Key Indexing Terms:
RHEUMATOID ARTHRITIS FOSTAMATINIB HEALTH-RELATED QUALITY OF LIFE
PATIENT-REPORTED OUTCOMES RANDOMIZED CLINICAL TRIAL

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Supported by Rigel Pharmaceuticals Inc. Dr. Weinblatt serves as a consultant to Rigel and AstraZeneca. Dr. Genovese serves as a consultant to Rigel and AstraZeneca and receives grant/research support from Rigel and AstraZeneca. Mr. Jones is an employee of AstraZeneca. Ms. Musser, Dr. Grossbard, and Dr. Magilavy are employees of Rigel.

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Accepted for publication December 4, 2012.

Rheumatoid arthritis (RA) is a chronic inflammatory joint disease that is characterized by pain, stiffness, and fatigue and has a substantial effect on the functioning and well-being of patients. Consequently, assessment of RA on patients' health-related quality of life (HRQOL) through the use of patient-reported outcomes (PRO) is now recommended by the American College of Rheumatology (ACR), the European League Against Rheumatism (EULAR), and experts from organizations such as the Outcome Measures in Rheumatology Clinical Trials (OMERACT) as an outcome measure in clinical trials[1,2,3]. As a result, use of PRO in the assessment of disease activity has become standard practice in randomized trials of RA treatment[4,5,6].

In clinical practice, PRO is a term that encompasses single-dimension and multidimensional measures of symptoms, HRQOL, adherence to treatment, satisfaction,

etc., as reported by the patient. HRQOL is a concept that specifically refers to the effect of an illness and its therapy upon a patient's physical, psychological, and social well-being, as perceived by the patient. In our study, a generic measure of HRQOL [the Medical Outcomes Study Short Form-36 (SF-36)] was administered alongside a number of symptom-specific and disability-specific PRO measures in a phase II clinical trial of fostamatinib to provide a broad perspective on how the patient feels and functions.

PRO serve to complement clinical assessments and capture the patient's perspective on the disability and functional impairment that result from joint inflammation and deformities associated with RA. The ACR response criteria incorporate PRO components, which include pain, patient's global assessments of disease activity (PtGA), and patient's assessment of physical function[4]. However, increasingly, it has been recognized that other PRO may also need to be considered when evaluating the influence of clinical interventions on RA[7,8]. Outcomes that have been reported to be of greatest concern to patients with RA are pain, physical health (functioning), disability, mobility, activities of daily living, fatigue, sleep, mental health (MH; emotional well-being), and social-role functioning[9,10,11]. Consequently, key RA trials have reported many of these outcomes in addition to reporting the ACR PRO criteria[4].

Fostamatinib is an oral kinase inhibitor with selectivity for spleen tyrosine kinase[12], currently in phase III clinical development for the treatment of RA. In combination with methotrexate (MTX), fostamatinib met its primary efficacy endpoint in the efficacy and safety study of R935788 to treat RA (TASKi-2) phase II clinical trial[13]. The study showed a statistically significant difference between the fostamatinib and placebo groups in ACR 20% improvement criteria (ACR20) response after 6 months of treatment. Adverse events included diarrhea, neutropenia, elevated liver enzymes, and hypertension[13]. The study population recruited in the TASKi-2 trial included patients with active RA, despite longterm MTX treatment. The primary efficacy and safety data from this trial have been reported[13]. Within the TASKi-2 trial, data from a number of PRO measures (including pain, PtGA, physical function, fatigue, and HRQOL) were collected, and the results of the PRO data are presented here.

MATERIALS AND METHODS

Patients and study design. Patients with active disease, failing treatment with MTX, were enrolled in a phase II, multicenter, randomized, double-blind, placebo-controlled study (TASKi-2; NCT00665925)[13]. Patients were randomized to receive either fostamatinib 100 mg tablets twice daily (bid) plus MTX (n = 152), fostamatinib 150 mg once daily (qd) plus MTX (n = 152), placebo bid plus MTX (n = 76), or placebo qd plus MTX (n = 77). The 2 placebo groups were pooled for the purposes of this analysis. The PRO were secondary efficacy endpoints in TASKi-2[13] and included individual assessments of each of the PRO components of the ACR response criteria for improvement in RA (pain, PtGA, physical function, fatigue, and HRQOL).

Efficacy assessments. The schedule of patients' assessments for the PRO data is presented in Table 1. Assessments of pain and PtGA were evaluated using a 100 mm visual analog scale (VAS)[14]. Physical function was evaluated using the Health Assessment Questionnaire-Disability Index (HAQ-DI)[15].

HRQOL was evaluated using SF-36[16], which includes the domains of physical functioning (PF), role physical (RP), bodily pain (BP), general health (GH), vitality (VT), social function (SF), role emotional (RE), and MH, as well as the physical and mental component summary scores (PCS and MCS). Fatigue was assessed using the Functional Assessment of Chronic Illness Therapy-Fatigue (FACIT-fatigue)[17].

Statistical analyses. The PRO analyses were based on the intent-to-treat patient population that includes all patients who received at least 1 dose of fostamatinib. The analyses were carried out for each PRO at each scheduled postbaseline assessment. The main analyses compared the mean changes from baseline between the active and placebo groups at each postbaseline assessment using a generalized linear model adjusted for geographic region and prior use of biologics. Changes from baseline were defined as the postbaseline value minus the baseline value. The changes were calculated for all endpoints and at all efficacy assessment timepoints.

A posthoc exploratory analysis was also performed. This analysis examined the change from baseline at each assessment timepoint and took into consideration the published thresholds for minimal clinically important differences (MCID) perceptible to patients for individual PRO. The MCID for pain, PtGA, HAQ-DI, and FACIT-fatigue were defined as 10, 10, 0.22, and 4, respectively[17,18,19,20]. For the SF-36 domains, the MCID were defined as the following points: PF = 3.5, RP = 3.2, BP = 4.5, GH = 5.7, VT = 5.5, SF = 5.0, RE = 3.8, MH = 5.5, PCS = 3.1, and MCS = 3.8[21].

An MCID may reflect either an improvement or worsening of symptoms. The proportion of patients reporting an improvement of symptoms based on the MCID ("the responders") were compared between the active and placebo groups at each postbaseline assessment using the Cochran Mantel-Haenszel test, stratified by geographic region and prior use of biologics. The number needed to treat (NNT) was also calculated for pain, PtGA, HAQ-DI, SF-36 PCS or MCS, or FACIT-fatigue whenever the treatment effects for these variables were statistically significant at Week 24. The NNT determines the average number of patients who need to be treated with fostamatinib for 1 more patient to achieve the MCID at Week 24 compared with the placebo group. The NNT was calculated as the reciprocal of the absolute risk reduction, where the latter was defined as the difference in the proportions of patients who had achieved the MCID in the fostamatinib and placebo groups.

In the MCID analyses, the percentage of responders in each treatment group at each postbaseline assessment was calculated based only on the observed PRO data, with no imputation for missing data. A sensitivity analysis of the MCID responder rates was also carried out for all PRO using nonresponder imputation based on the assumption that missing data indicated that the MCID had not been achieved at that timepoint. Thus, it was assumed that missing data represented nonresponse to treatment wherever missing data occurred.

An additional posthoc analysis was carried out on patients whose HAQ-DI scores were ≥ 0 at baseline and who had reverted to a HAQ-DI score of 0 at Week 24 (i.e., patients defined as having no disability at Week 24). A comparison of the proportion of patients with no disability at Week 24 between the active and placebo groups at each postbaseline assessment was carried out using the Cochran Mantel-Haenszel test, stratified by geographic region and prior use of biologics. All tests of statistical significance were 2-sided with $\alpha = 0.05$.

RESULTS

Patient disposition was as described[13]. The treatment groups were well balanced regarding baseline patient demographics, disease characteristics, and mean PRO scores (Tables 2 and 3). The study population had a mean RA

Table 1. Timing of patient-reported outcome (PRO) assessments.

PRO Assessment	Time, weeks									
	0	1	2	4	6	8	12	16	20	24
Pain, 100 mm VAS*	✓	✓	✓	✓	✓	✓	✓	✓	✓	✓
Disease activity, 100 mm VAS**	✓	✓	✓	✓	✓	✓	✓	✓	✓	✓
HAQ-DI***	✓	✓	✓	✓	✓	✓	✓	✓	✓	✓
Short Form-36 health survey†	✓									✓
FACIT-fatigue††	✓						✓			✓

* 0 = no pain, 100 = unbearable pain, for patient assessment of arthritis pain. ** 0 = very well, 100 = very poor, for patient global assessment of disease activity. *** Health Assessment Questionnaire-Disability Index to measure patient's physical function. † To measure aspects of health-related quality of life. †† To measure patient's fatigue. VAS: visual analog scale; FACIT: Functional Assessment of Chronic Illness Therapy.

Table 2. Baseline patient demographic data and disease characteristics. Data represent mean (SD) unless stated otherwise.

Characteristic	Placebo, n = 153	Fostamatinib 150 mg qd, n = 152	Fostamatinib 100 mg bid, n = 152
Age, yrs	52.4 (13.2)	52.6 (12.3)	52.5 (13.0)
Female, n (%)	131 (85.6)	128 (84.2)	131 (86.2)
Race or ethnic group, n (%)			
White	71 (46.4)	75 (49.3)	58 (38.2)
Hispanic	75 (49.0)	74 (48.7)	88 (57.9)
Disease duration, yrs	9.5 (8.7)	9.7 (9.1)	8.4 (8.2)
No. swollen joints	12.2 (4.9)	12.3 (5.4)	11.8 (5.0)
Score on DAS28	6.2 (0.8)	6.1 (0.9)	6.2 (0.9)
Positive for rheumatoid factor, %	85.0	81.1	89.1
Treatment with prednisone ≤ 10 mg/day, %	61.4	56.6	61.2
Previous therapy with biologic response modifiers, %	14.4	15.8	14.5

bid: twice daily; qd: once daily; DAS28: 28-joint Disease Activity Score.

Table 3. Baseline patient-reported outcome scores. Data represent mean (SD) unless otherwise stated.

Measure	Placebo, n = 153	Fostamatinib 150 mg qd, n = 152	Fostamatinib 100 mg bid, n = 152
Pain, 0–100 mm visual analog scale	56.3 (21.9)	57.1 (22.1)	58.3 (24.1)
Global assessment of disease activity, 0–100 mm visual analog scale	55.3 (22.0)	54.3 (23.8)	56.1 (23.9)
HAQ-DI, 0–3	1.5 (0.7)	1.5 (0.7)	1.5 (0.7)
FACIT-fatigue, 0–52	27.1 (11.2)	28.6 (11.3)	28.8 (11.5)
SF-36 physical component summary†	32.4 (8.0)	32.6 (7.8)	32.7 (8.0)
SF-36 mental component summary†	39.9 (11.1)	41.7 (11.6)	39.4 (12.2)
SF-36 domains†			
Physical functioning	30.5 (10.8)	30.9 (9.7)	30.3 (10.5)
Role physical	32.4 (9.2)	33.2 (9.0)	32.3 (9.4)
Bodily pain	33.9 (7.8)	34.4 (8.3)	34.0 (8.0)
General health	35.6 (8.5)	36.6 (8.4)	35.0 (8.6)
Vitality	41.6 (9.6)	42.0 (9.7)	42.0 (10.4)
Social function	35.8 (10.5)	38.0 (11.1)	36.3 (11.4)
Role emotional	32.8 (12.3)	34.2 (12.7)	31.6 (13.1)
Mental health	39.1 (11.2)	40.7 (10.8)	38.8 (12.4)

† Norm-based scores based on 1998 US general population. bid: twice daily; qd: once daily; HAQ-DI: Health Assessment Questionnaire-Disability Index; FACIT: Functional Assessment of Chronic Illness Therapy; SF-36: Medical Outcomes Study Short Form-36.

duration of 9.2 years and was taking a stable MTX dose for a minimum of 3 months[13]. As reported previously, a statistically significant difference was observed with fostamatinib plus MTX compared with the placebo plus MTX group; the percentage of patients who achieved the primary outcome measure — ACR20 at Week 24 — was 67% ($p < 0.001$) with fostamatinib 100 mg bid, and 57% ($p < 0.001$) with fostamatinib 150 mg qd, compared with 35% for placebo[13]. Further, the effect of fostamatinib was seen as early as 1 week after initiation of treatment[13]. The percentages of patients who completed the study in each of the fostamatinib 100 mg bid, fostamatinib 150 mg qd, and placebo treatment groups were 86.2%, 82.9%, and 79.1%, respectively. The overall completion rate was 82.7%. At Week 24, 82.7% of patients were evaluable for the analysis of pain and PtGA, 82.5% for HAQ-DI, 81.2% for SF-36 PCS, 81.4% for SF-36 MCS, and 72.9% for FACIT-fatigue.

Effects of fostamatinib on patient's assessment of pain. Patients treated with fostamatinib 100 mg bid and fostamatinib 150 mg qd showed statistically significant improvements in patient assessment of pain ($p < 0.001$ and $p < 0.05$, respectively) after 1 week of treatment compared with placebo (Figure 1A). The statistically significant improvement in pain provided by fostamatinib 100 mg bid was detected at all subsequent assessments. Patients treated with fostamatinib 150 mg qd maintained a statistically significant improvement from placebo for the first 6 weeks of treatment. At Week 24, the change from baseline in mean

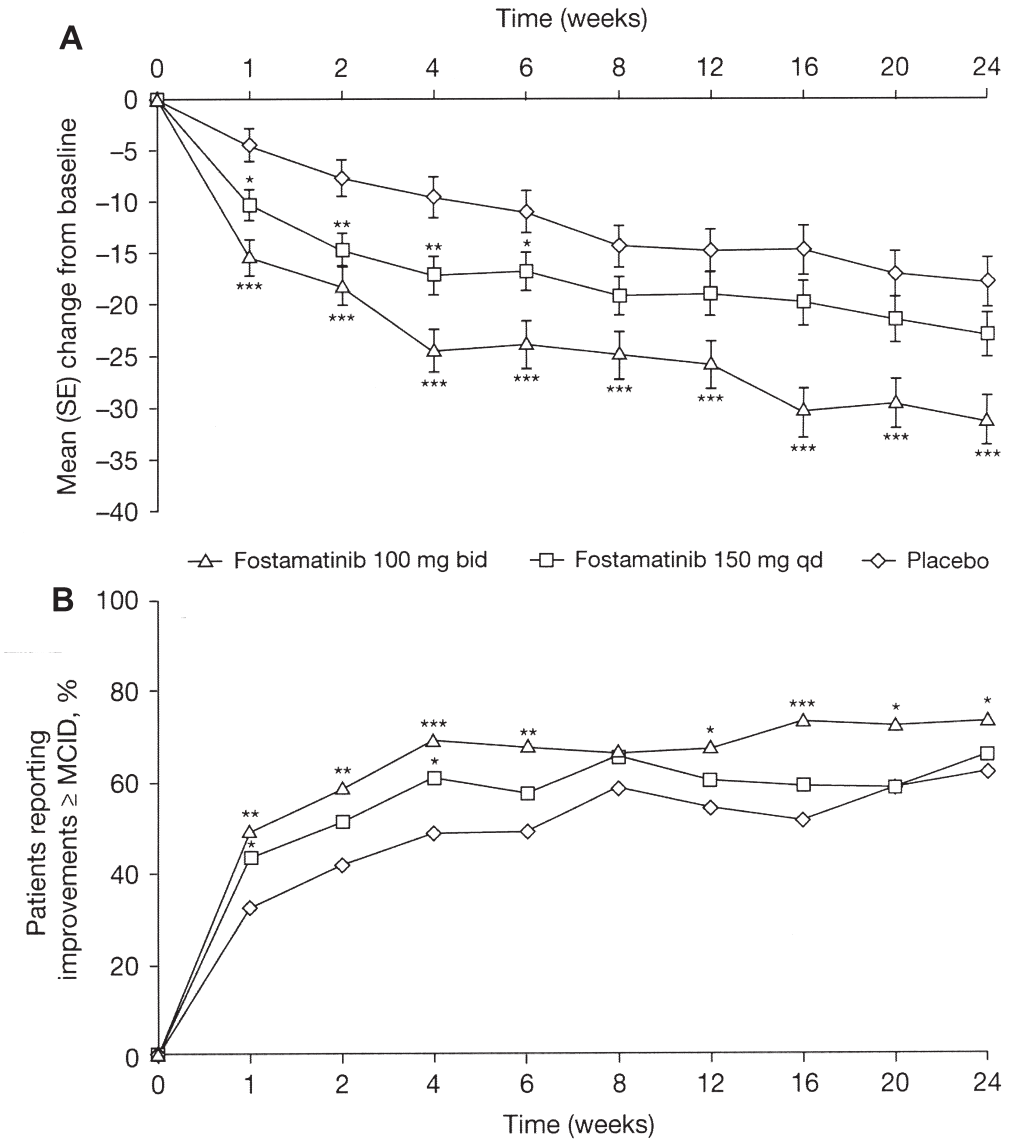

Figure 1. (A) Mean (SE) change from baseline in patient's assessment of pain (negative change reflects improvement); (B) proportion of patients reporting a minimal clinically important difference (MCID), defined as a decrease in baseline pain visual analog scale score ≥ 10. *$p < 0.05$; **$p < 0.01$; ***$p < 0.001$, versus placebo.

(standard error) VAS scores for fostamatinib 100 mg bid, fostamatinib 150 mg qd, and placebo treatment groups were –31.3 (2.45), $p < 0.001$ versus placebo; –23.0 (2.15), $p = 0.077$ versus placebo; and –17.8 (2.45), respectively (Figure 1A). The MCID analysis also showed that, compared with placebo, there was a statistically significant increase in the percentage of patients in the fostamatinib 100 mg bid treatment group who reported a clinically meaningful improvement in pain at Week 24 (73.3% vs 62.0%; $p < 0.05$; NNT = 9; Figure 1B). This effect was detected as early as Week 1 (49.3% vs 32.7%; $p < 0.01$; Figure 1B).

Effect of fostamatinib on PtGA. There was a statistically significant and sustained improvement in PtGA in patients treated with fostamatinib 100 mg bid versus placebo ($p < 0.001$ at all postbaseline visits; Figure 2A). At Week 24, the changes in mean (SE) VAS scores were –29.1 (2.26), $p < 0.001$; –20.3 (2.25), $p = 0.210$; and –16.7 (2.42) for the fostamatinib 100 mg bid, fostamatinib 150 mg qd, and placebo groups, respectively (Figure 2A). Similarly, the MCID analysis showed that, at Week 24, there was a statistically significant increase in the percentage of patients who reported a clinically meaningful improvement in PtGA in the fostamatinib 100 mg bid group compared with placebo (74.0% vs 55.4%; $p < 0.01$; NNT = 6). However, the difference in percentages was not statistically significant for fostamatinib 150 mg qd compared with placebo (66.7% vs 55.4%; $p = 0.054$; Figure 2B).

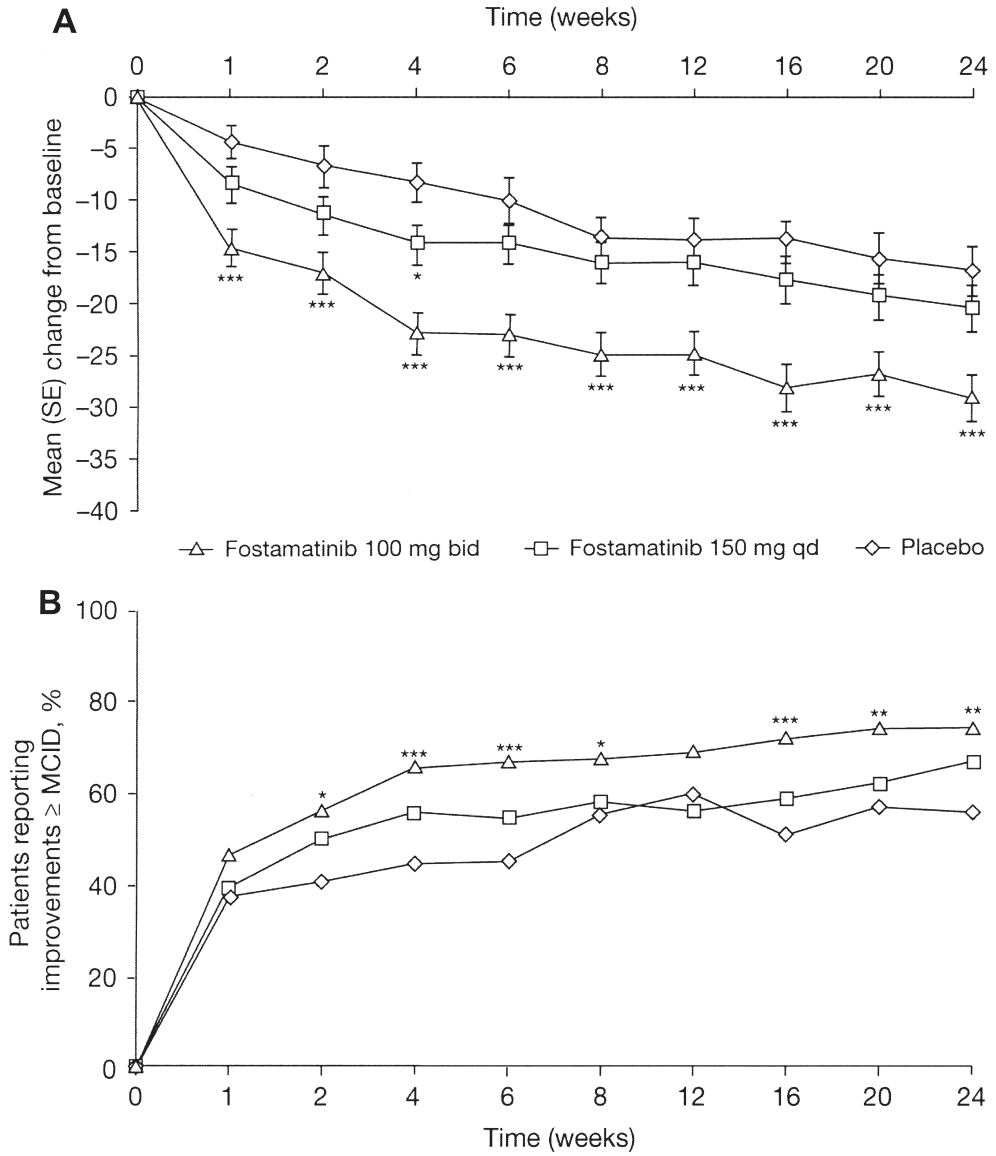

Figure 2. (A) Mean (SE) change from baseline in patient's assessment of global disease activity (negative change reflects improvement); (B) proportion of patients reporting a minimal clinically important difference (MCID), defined as a decrease in baseline patient's global assessment visual analog scale score ≥ 10. *$p < 0.05$; **$p < 0.01$; ***$p < 0.001$, versus placebo.

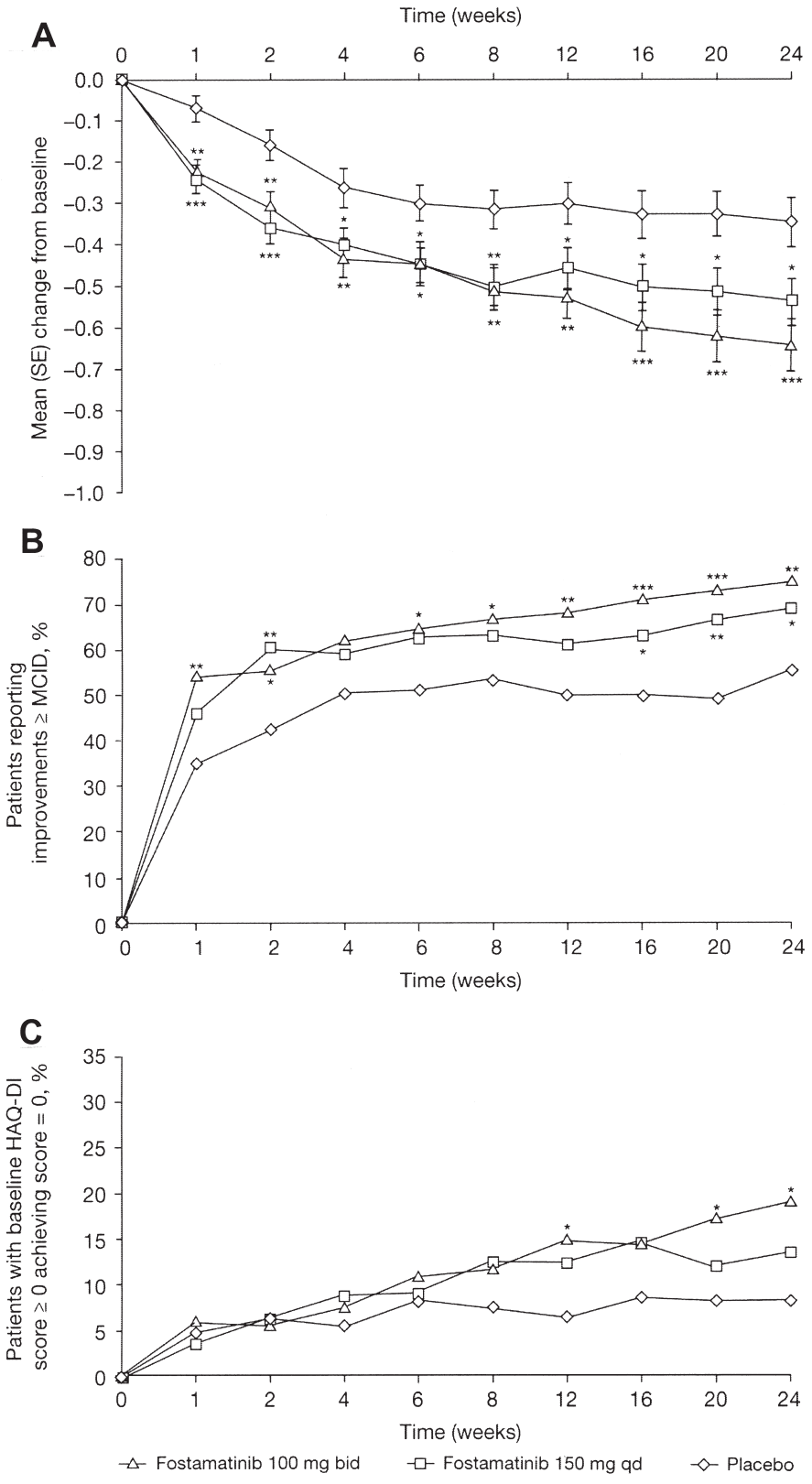

Figure 3. (A) Mean (SE) change from baseline in patient's assessment of physical function (negative change reflects improvement). (B) Percentage of patients reporting a decrease from baseline ≥ 0.22 (MCID responders). (C) Percentage of patients reporting HAQ-DI score ≥ 0 at baseline and then going on to achieve a HAQ-DI score of 0. MCID: minimal clinically important difference; HAQ-DI: Health Assessment Questionnaire-Disability Index. *p < 0.05; **p < 0.01; ***p < 0.001, versus placebo.

Effect of fostamatinib on physical function assessed using the HAQ-DI. Patients treated with fostamatinib 100 mg bid and fostamatinib 150 mg qd showed statistically significant improvement in physical function, compared with placebo, as early as 1 week after treatment ($p < 0.01$ and $p < 0.001$, respectively; Figure 3A). Statistically significant improvements were also detected for both fostamatinib dosing regimens compared with placebo at all subsequent assessments (Figure 3A). At Week 24, the changes from baseline in mean (SE) HAQ-DI scores were –0.647 (0.064), $p < 0.001$; –0.537 (0.058), $p < 0.05$; and –0.343 (0.062) in the fostamatinib 100 mg bid, fostamatinib 150 mg qd, and placebo treatment groups (Figure 3A). Significantly more patients treated with fostamatinib 100 mg bid and fostamatinib 150 mg qd achieved clinically meaningful improvements in physical function (HAQ-DI) at Week 24 compared with placebo (74.8%, $p < 0.01$; 69.0%, $p < 0.05$; and 55.8%; NNT = 6 and 8, respectively; Figure 3B). Correspondingly, 19.1%, 13.5%, and 8.3% of patients treated with fostamatinib 100 mg bid, fostamatinib 150 mg qd, and placebo achieved a HAQ-DI score of 0 at Week 24 after initially having a score ≥ 0 at baseline. This result was statistically significant for the fostamatinib 100 mg bid treatment group ($p < 0.05$; NNT = 10) compared with placebo (Figure 3C). The sensitivity analyses confirmed the findings of the main analyses.

Effect of fostamatinib on HRQOL assessed using the SF-36.

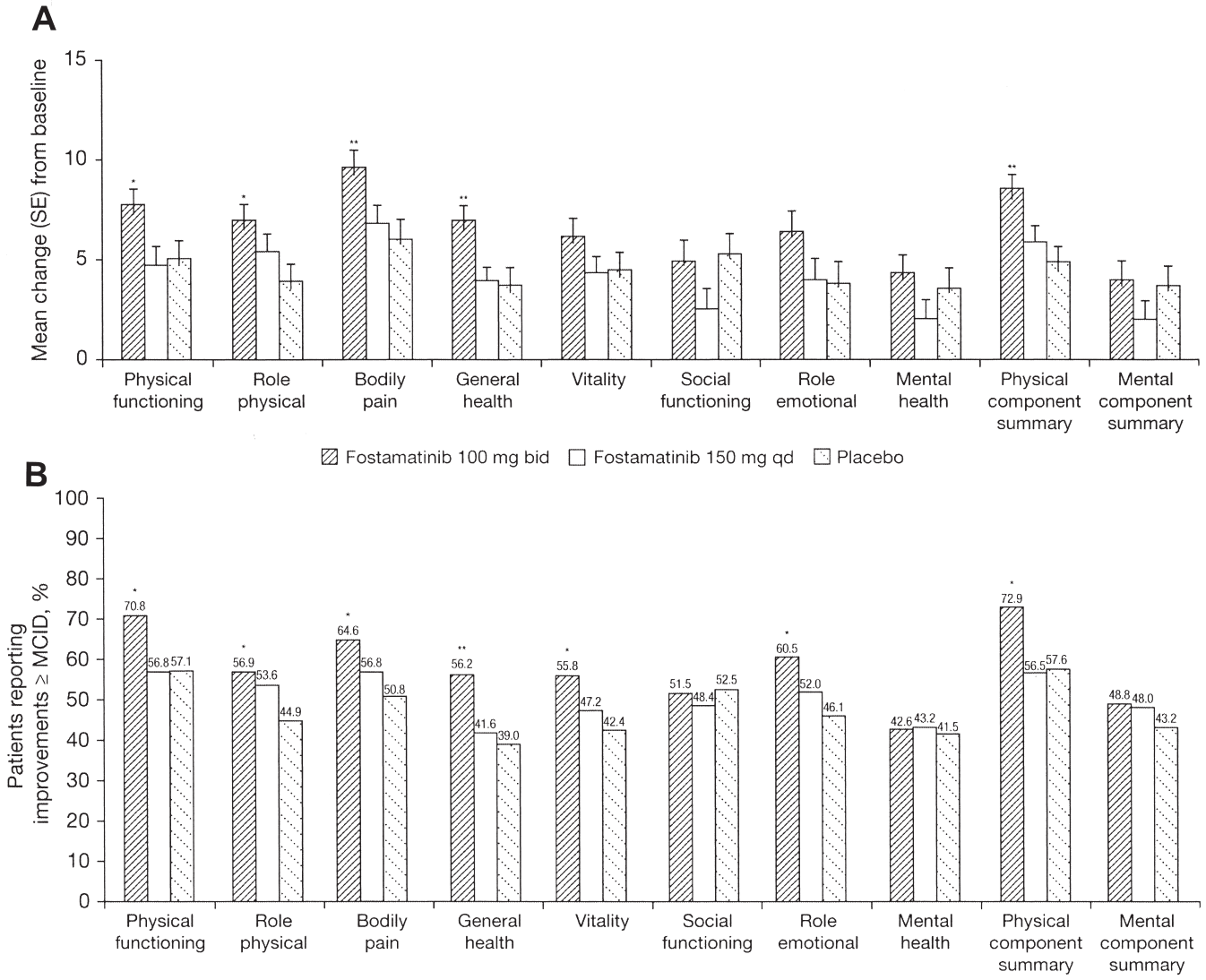

Figure 4. (A) Mean (SE) change from baseline for the domains and component scores of the Medical Outcomes Study Short Form-36 (SF-36) at Week 24 (positive change reflects improvement). (B) Percentage of patients reporting improvements greater than or equal to MCID in the domains of the SF-36 at Week 24. Clinically meaningful improvements in the domains of the SF-36 are defined as PF ≥ 3.5, RP ≥ 3.2, BP ≥ 4.5, GH ≥ 5.7, VT ≥ 5.5, SF ≥ 5.0, RE ≥ 3.8, MH ≥ 5.5, PCS score ≥ 3.1, and MCS score ≥ 3.8. BP: bodily pain; GH: general health; MCID: minimal clinically important difference; MCS: mental component summary; MH: mental health; PCS: physical component summary; PF: physical functioning; RE: role emotional; RP: role physical; SF: social functioning; VT: vitality. *$p < 0.05$; **$p < 0.01$; ***$p < 0.001$, versus placebo.

There were statistically significant improvements in the observed mean change (SE) from baseline for the fostamatinib 100 mg bid treatment group versus placebo at Week 24 for domains of the SF-36 as follows: PF, 7.73 (0.89) versus 5.05 (0.91), $p < 0.05$; RP, 6.95 (0.85) versus 3.92 (0.91), $p < 0.05$; BP, 9.61 (0.91) versus 6.11 (0.91), $p < 0.01$; and GH, 6.96 (0.75) versus 3.75 (0.85), $p < 0.01$ (Figure 4A); and also for the SF-36 PCS, 8.52 (0.77) versus 4.90 (0.78), $p < 0.01$. However, the mean change from baseline for the SF-36 MCS was not statistically significant for fostamatinib 100 mg bid compared with placebo: 3.99 (0.93) versus 3.71 (0.99), $p = 0.83$ (Figure 4A).

There was a statistically significant increase in the percentage of patients reporting clinically meaningful improvements at Week 24 for fostamatinib 100 mg bid compared with placebo for the following SF-36 domains: PF, 70.8% versus 57.1%, $p < 0.05$; RP, 56.9% versus 44.9%, $p < 0.05$; BP, 64.6% versus 50.8%, $p < 0.05$; GH, 56.2% versus 39.0%, $p < 0.01$; VT, 55.8% versus 42.4%, $p < 0.05$; and RE, 60.5% versus 46.1%, $p < 0.05$; and also for the PCS, 72.9% vs 57.6%, $p < 0.05$, NNT = 7 (Figure 4B). No statistically significant differences were detected for the SF-36 MCS for fostamatinib 100 mg bid versus placebo. No statistically significant differences were detected with fostamatinib 150 mg qd compared with placebo for any domain in the SF-36 (Figure 4B), nor for the PCS and MCS of the SF-36. The sensitivity analyses confirmed the results of the main analyses.

Effect of fostamatinib on fatigue assessed using the FACIT-fatigue. Patients treated with fostamatinib 100 mg bid showed a statistically significant improvement in fatigue at Week 24 ($p < 0.05$) versus placebo (Table 4). At Week 24, the mean changes (SE) from baseline in FACIT-fatigue scores were 7.40 (1.00), $p < 0.05$; 5.70 (0.99), $p = 0.35$; and 4.50 (0.94) for fostamatinib 100 mg bid, fostamatinib 150 mg qd, and placebo, respectively (Table 4). There were no statistically significant differences between the treatment groups with regard to the percentage of patients with clinically meaningful improvements in fatigue, although the percentages were numerically higher at all postbaseline assessments in both fostamatinib-treated groups versus placebo (Table 4). However, the results of a sensitivity analysis did show that the percentage of patients reporting clinically meaningful improvements in fatigue was significantly greater among patients receiving fostamatinib 100 mg bid at Week 24 compared with placebo ($p < 0.05$).

DISCUSSION

PRO provide a measure of how clinical interventions affect the status of a patient's health condition. Importantly, the reports come directly from the patient, without interpretation of the patient's response by a clinician or anyone else. Consequently, PRO have an important role to play in the assessment of RA where patients may face considerable physical, social, and emotional disabilities[22]. The PRO measures used in this study incorporate questions that address some of the most important concerns raised by patients with RA[9,10,11], such as pain, global disease activity, physical function, and quality of life[4]. Fatigue has also been recommended by a EULAR/ACR collaborative panel as an important outcome to measure in RA clinical studies[23].

In this study, patients treated with fostamatinib 100 mg bid showed significant improvements in pain, overall disease activity, physical function, fatigue, and the SF-36 PCS compared with placebo. Patients who received fostamatinib 150 mg qd reported improvements in some PRO, but these were less extensive than for fostamatinib 100 mg bid. The results were consistent with clinical improvements in the primary efficacy endpoint (ACR20 response) of this trial[13].

The positive effects of fostamatinib on PRO were demonstrated in the main analyses that evaluated the mean changes in baseline scores over time for individual PRO. An MCID responder analysis was also carried out to examine the effect of fostamatinib on the number of patients achieving a prespecified minimum important change from baseline. This analysis showed that patients who received fostamatinib 100 mg bid achieved significantly better

Table 4. Mean (SE) change from baseline in FACIT-fatigue scores at Weeks 12 and 24, and patients reporting improvements greater than or equal to minimal clinically important difference (≥ 4.0).

Measure	Placebo	Fostamatinib 150 mg qd	Fostamatinib 100 mg bid
Mean (SE) change from baseline, FACIT-fatigue score			
Week 12	5.60 (0.87)	5.30 (0.87)	7.40 (0.90)
Week 24	4.50 (0.94)	5.70 (0.99)	7.40 (1.00)*
Patients reporting improvements ≥ 4.0 in FACIT-fatigue score, %			
Week 12	56.2	57.4	62.6
Week 24	48.6	60.7	59.8

Versus placebo. *$p < 0.05$ (positive change reflects improvement). bid: twice daily; qd: once daily; FACIT-fatigue: Functional Assessment of Chronic Illness Therapy-Fatigue.

outcomes in the majority of individual PRO compared with placebo.

Patients treated with fostamatinib 100 mg bid showed statistically significant improvements in the physical components of the SF-36 (PCS) compared with placebo. However, no statistically significant improvements were observed in the mental component summary of the SF-36 with either dose of fostamatinib compared with placebo. In particular, no statistically significant improvements were detected in the 4 individual scales that largely comprise the MCS (i.e., VT, SF, RE, and MH), although VT and RE were significantly in favor of fostamatinib 100 mg bid compared with placebo based on the results of the responder analyses. A sensitivity analysis confirmed these results. The lack of significant improvement in the MCS, however, is in accord with the current literature; Wolfe and Michaud, and Strand, *et al*, for example, also found no significant MCS change with biological treatment[24,25,26]. Together, these findings suggest that the MCS may be less responsive to the use of disease-modifying antirheumatic drugs than other outcomes.

In our study, the following analyses of the HAQ-DI were carried out: an analysis of changes in scores from baseline, an analysis of patients achieving the MCID from baseline at each postbaseline assessment, and an analysis of patients achieving a HAQ-DI score of 0 at Week 24. The latter analyses were carried out because patients with HAQ-DI = 0 are defined as patients with no disability, and abolishing disability can be considered the ultimate goal of therapy. On the other hand, one could also consider an analysis of patients achieving a normative value for the HAQ-DI in a general population. However, choosing an appropriate normative value for the HAQ-DI can be complex because it is dependent on a number of factors such as the distribution of the age, sex, education, and social/ethnic groupings of the study population[27]. Therefore, such an analysis was considered outside the scope of our study.

Norm-based scores, which have a mean of 50 and an SD of 10, were calculated for each of the health domain scales and component summary measures of the SF-36v2 as described and recommended in the "User's Manual for the SF-36v2 Health Survey"[21]. As explained in the manual, this method of standardization facilitates interpretation of the scores in that a change of 1 point is the same as an effect size of 0.1. This also allows comparisons among the scale scores and the component summary measures, and provides the basis for comparing the scores across studies. However, the norm-based scores are derived from the 1998 US general population. This needs to be borne in mind when interpreting the scores from studies that contain a mix of US and non-US patients (such as in this particular study) because the norm-based scores are likely to be different if derived from a theoretical general population with the same mix of US and non-US people.

As expected, the NNT differed between the different HRQOL and PRO concepts, with NNT ranging from 6 for improvements in HAQ-DI at Week 24 to 9 for improvement in pain at Week 24. Therefore, on average, 1 additional patient will achieve a clinically meaningful improvement in 1 or more PRO at Week 24 for every 6 to 9 patients treated with fostamatinib.

Our study showed that patients treated with fostamatinib 100 mg bid achieved significant improvements in pain, disease activity, physical function, fatigue, and HRQOL compared with placebo. Larger studies of a longer duration in different settings will be required to fully characterize the effects of fostamatinib on PRO in patients with RA.

ACKNOWLEDGMENT

Editorial support was provided by Godfrey Lisk, PhD, and Shelley Maria Lindley, PhD, at Parexel.

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