Treatment of Psoriatic Arthritis with Tumor Necrosis Factor Inhibitors: Longer-term Outcomes Including Enthesitis and Dactylitis with Golimumab Treatment in the Longterm Extension of a Randomized, Placebo-controlled Study (GO-REVEAL)

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ABSTRACT. ***Objective.*** To assess longer-term outcomes, including enthesitis and dactylitis, in patients with active psoriatic arthritis (PsA), in a study of golimumab treatment.

Methods. Adult patients with active PsA were randomized to receive subcutaneous injections of placebo (n = 113), golimumab 50 mg (n = 146), or golimumab 100 mg (n = 146) every 4 weeks through Week 20. All patients received golimumab 50 mg or 100 mg from Week 24 onward. Entheses tenderness was scored in 15 body sites using the PsA-modified Maastricht Ankylosing Spondylitis Enthesitis Score (MASES). Dactylitis was assessed in 20 digits of the hands and feet.

Results. Among the 405 randomized patients, 77% presented with enthesitis and 34% dactylitis at baseline. At Week 24 of the placebo-controlled study phase, significant differences were observed between golimumab 50 mg and/or 100 mg and placebo for mean percent improvement in the PsA-modified MASES [46% ($p < 0.001$) and 52% ($p < 0.001$) vs 13%, respectively] and the dactylitis score [66% ($p = 0.09$) and 82% ($p < 0.001$) vs 28%, respectively]. By Week 52, improvements were maintained among patients randomized to receive golimumab (mean improvements of 54% for PsA-modified MASES and 77% for the dactylitis score). Those given placebo who had enthesitis or dactylitis at baseline and who crossed over to golimumab at Week 16 or 24 had somewhat less improvement at Week 52 (i.e., 39% for the PsA-modified MASES, 57% for dactylitis score).

Conclusion. Treatment of PsA patients with the TNF inhibitor golimumab was effective across all components of disease, including enthesitis and dactylitis, and efficacy was maintained over longer-term followup. (J Rheumatol 2012;39 Suppl 89:90–3; doi:10.3899/jrheum.120254)

Key Indexing Terms:
PSORIATIC ARTHRITIS ENTHESITIS DACTYLITIS TNF INHIBITORS GOLIMUMAB

In recent years there has been a tremendous increase in interest in psoriatic arthritis (PsA)[1,2]. To a large extent, this has been driven by developments in the therapeutic approach to patients, such that greater improvements in all aspects of this heterogeneous disease can be achieved. In particular, inhibitors of the proinflammatory cytokine tumor necrosis factor (TNF) have proven effective in improving peripheral arthritis, skin and nail psoriasis, enthesitis, and dactylitis. Therapeutic progress has in turn fueled research into defining the optimal methods to measure disease involvement and activity in these domains. More recent clinical trials have included assessments of these discrete aspects of disease. In addition, because PsA tends to be a chronic inflammatory disease, clinicians have great interest in the efficacy of therapies not only in the shorter term but also over longer periods of time. We investigated longer-term outcomes in patients with PsA in a study of golimumab treatment.

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Supported by Janssen Biotech Inc., Malvern, Pennsylvania, USA.

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MATERIALS AND METHODS

Patients. Details of and some results from the GO-REVEAL trial have been published[3]. In brief, to be eligible for enrollment, patients were required to have active PsA, defined by having at least 3 swollen and 3 tender joints, and also having active plaque psoriasis with at least 1 qualifying lesion at least 2 cm in diameter, despite therapy with disease-modifying antirheumatic drugs or nonsteroidal antiinflammatory drugs (NSAID). Previous use of anti-TNF agents was prohibited. Stable doses of methotrexate (MTX; ≤ 25 mg/week), NSAID, and corticosteroids (prednisone ≤ 10 mg/day) were allowed. Institutional review board or ethics committee approval and patient written informed consent were obtained.

Study design. In the multicenter, randomized, double-blind, placebo-controlled trial[3], 405 patients were randomized (1:1.3:1.3) by a centralized interactive voice response system (ClinPhone Inc., Princeton, NJ, USA) to receive blinded subcutaneous injections of placebo, golimumab 50 mg, or golimum-

ab 100 mg at weeks 0, 4, 8, 12, 16, and 20. At Week 16, patients with < 10% improvement from baseline in both swollen and tender joint counts entered early escape in a blinded fashion, with crossover from placebo to golimumab 50 mg or dose escalation from golimumab 50 mg to 100 mg. Patients in the golimumab 100 mg group who met the early escape criteria continued to receive the 100 mg dose. Beginning at Week 24, patients originally randomized to placebo who did not meet the early escape criteria crossed over to active treatment (golimumab 50 mg), such that all study participants received blinded golimumab 50 or 100 mg every 4 weeks from Week 24 forward. Janssen Biotech Inc. [Malvern, PA, USA; Merck/Schering-Plough (Kenilworth, NJ, USA)] sponsored our study and supplied golimumab and placebo as sterile liquids. The planned duration of the study was 5 years.

Evaluations. Entheses tenderness was scored in 15 body sites using the PsA-modified (left and right insertion of the plantar fascia added) Maastricht Ankylosing Spondylitis Enthesitis Score (MASES)[4]. The 15 entheses sites were evaluated as tender (scored as 1) or not tender (scored as 0), with application of local pressure. The total MASES is the sum of the site scores and can range from 0 to 15. Scores > 0 indicate the presence of enthesitis.

Dactylitis was assessed in each of the 20 digits of the hands and feet on a scale of 0 to 3 (0 = no dactylitis; 1 = mild dactylitis, 2 = moderate dactylitis, 3 = severe dactylitis). The dactylitis score is calculated as the sum of scores for all 20 digits and thus can range from 0 to 60. Scores > 0 indicate the presence of dactylitis.

Statistical analyses. Efficacy data from all randomized patients were analyzed by assigned treatment group. Treatment group differences in the percentage of improvement from baseline in the MASES and dactylitis score at Week 24 were assessed with ANOVA on the van der Waerden normal scores. All such analyses included treatment, and patients' baseline MTX usage as factors and were performed at a 0.05 level of significance. Differences between the combined golimumab and placebo groups had to be statistically significant before subsequent comparisons were made between the individual golimumab dose and placebo groups. No comparisons between the golimumab 50 mg and 100 mg doses were performed. For Week 24 efficacy analyses, placebo and golimumab 50-mg patients who met the early escape criteria at Week 16 had Week 16 observations carried forward. For patients randomized to golimumab 100 mg who met the early escape criteria, observed Week 24 values were used.

RESULTS

Patient disposition and baseline characteristics. A total of 405 patients, enrolled at 58 investigational sites (18 United States, 18 Canada, 22 Europe), were randomized to treatment and received the study agent. As shown in Table 1, baseline components of the American College of Rheumatology response criteria[5], 28-joint Disease Activity Score and C-reactive protein[6,7], and body surface area with psoriasis involvement indicated active disease. There were no relevant differences between randomized treatment groups in these disease-specific or general demographic characteristics at baseline (Table 1). Among randomized patients, 77% and 34% had enthesitis and dactylitis at baseline, respectively, with no relevant differences among treatment groups, with the exception of slight differences in mean baseline dactylitis score (3.1 for placebo vs 6.3 for golimumab 50 mg and 5.4 for golimumab 100 mg; Table 1).

Enthesitis. Among patients with enthesitis at baseline, the mean percent changes from baseline in the PsA-modified MASES were significantly greater in the combined golimumab group and in each of the individual golimumab 50-mg and 100-mg groups than in the placebo group at Week 24 (49%, 46%, and 52%, respectively, vs 13%; $p < 0.001$ for all comparisons vs placebo; Table 2). Results of a posthoc analysis using the original MASES, i.e., excluding the plantar fascia, were consistent with those obtained using the PsA-modified MASES (Table 2).

The initial improvements in enthesitis severity observed in golimumab-treated patients were maintained with additional golimumab treatment, with overall mean percent improvements in the PsA-modified MASES of 54% at Week 52 (Table 2). Placebo patients who started treatment with golimumab 50 mg at Week 16 or Week 24 achieved somewhat less improvement in the PsA-modified MASES at Week 52 (39%) relative to patients who received a full year of golimumab (Table 2).

Dactylitis. Among patients with dactylitis at baseline, mean percent improvements from baseline to Week 24 were 74% in the combined golimumab group versus 28% in the placebo group ($p = 0.002$). Mean percent improvements from baseline in the dactylitis score were also significantly larger in the golimumab 100-mg group than in the placebo group at Week 24 (82% vs 28%, $p < 0.001$; Table 2). The numerical difference observed between the golimumab 50-mg and placebo groups at Week 24 was not statistically significant (66% vs 28%; $p = 0.09$).

Improvements in dactylitis severity observed through the first 6 months of golimumab treatment were maintained through Week 52, with overall mean improvements in the dactylitis score of 77% (Table 2). Placebo patients who started treatment with golimumab 50 mg at Week 16 or Week 24 achieved somewhat less mean improvement in the dactylitis score by Week 52 (57%; Table 2).

DISCUSSION

The recent surge of interest in PsA has been partly stimulated by improved therapeutic options, particularly the introduction of TNF inhibitors[1,2]. Progress in therapy, in turn, has driven intense and diverse research into optimal methods of assessment of disease activity. Given the heterogeneous nature of PsA, and its predilection to involve not only peripheral joints and skin and nails, but also entheses, the axial spine, and other extraarticular areas, this has presented a challenge. Groups such as the Group for Research and Assessment in Psoriasis and Psoriatic Arthritis have involved rheumatologists and dermatologists from around the globe to define optimal assessment and therapy of disease activity across these diverse domains of PsA[8,9]. Contemporary recommendations for treating PsA require consideration of these various areas of clinical involvement[10]. In addition, categorizing various levels of disease activity such as minimal disease activity or remission will require that all areas potentially involved be evaluated[11]. Focus on areas of involvement such as enthesitis has also stimulated research into newer methods of assessment, including highly sensitive imaging techniques such as ultrasound and magnetic resonance imaging[1,12,13].

In this report, we highlight longer-term efficacy data about

Table 1. Baseline patient characteristics. Values are mean (SD) or n (%) unless otherwise noted. Adapted from Kavanaugh, *et al*[3].

Characteristics	Placebo	Golimumab 50 mg	Golimumab 100 mg
No. patients randomized	113	146	146
Men	69 (61)	89 (61)	86 (59)
White	110 (97)	141 (97)	142 (97)
Age, yrs	47.0 (10.6)	45.7 (10.7)	48.2 (10.9)
PsA duration, yrs	7.6 (7.9)	7.2 (6.8)	7.7 (7.8)
No. swollen joints (0–66)	13.4 (9.8)	14.1 (11.4)	12.0 (8.4)
No. tender joints (0–68)	21.9 (14.7)	24.0 (17.1)	22.5 (15.7)
HAQ (0–3)	1.0 (0.55)	1.0 (0.65)	1.1 (0.62)
CRP, mg/dl	1.3 (1.6)	1.3 (1.6)	1.4 (1.8)
DAS28 using CRP	4.3 (1.0)	4.4 (1.1)	4.3 (1.0)
Patients with enthesitis	88 (78)	109 (75)	115 (79)
PsA-modified MASES score (1–15)	5.0 (4.1)	5.7 (4.0)	6.1 (4.1)
Patients with dactylitis	38 (34)	50 (34)	49 (34)
Dactylitis score (0–60)	3.1 (2.1)	6.3 (6.1)	5.4 (6.7)
Patients with ≥ 3% BSA	79 (70)	109 (75)	108 (74)
BSA (%)	14.7 (15.7)	16.2 (17.7)	17.7 (18.3)
PASI score (0–72)	8.4 (7.4)	9.8 (8.6)	11.1 (9.5)

PsA: psoriatic arthritis; BSA: body surface area; CRP: C-reactive protein; DAS28: 28-joint Disease Acivity Score; HAQ: Health Assessment Questionnaire; MASES: Maastricht Ankylosing Spondylitis Enthesitis Score; PASI: psoriasis area and severity index.

Table 2. Summary of enthesitis and dactylitis findings through Week 52; randomized patients with enthesitis and/or dactylitis at baseline. Data are number (%) of patients or mean (SD)/median [IQR] percent change from baseline. Adapted from Kavanaugh, *et al*[3].

No. randomized patients	Placebo 113	Golimumab 50 mg 146	Golimumab 100 mg 146	Combined 292
Enthesitis				
Randomized patients with enthesitis at baseline	88	109	115	224
Percent change in PsA-modified MASES at:				
Week 24, n	84	103	114	217
	–12.9 (112.1)	46.1 (65.5)	52.4 (62.6)	49.4 (63.9)
	11.7 [–50.0, 77.5]	60.0 [0.0, 100.0]	66.7 [25.0, 100.0]	66.7 [14.3, 100.0]
p value vs placebo		< 0.001	< 0.001	< 0.001
Week 52	39.1 (76.1)	56.3 (62.4)	51.9 (64.1)	54.1 (63.2)
	60.0 [12.9, 100.0]	87.5 [35.0, 100.0]	75.0 [25.0, 100.0]	80.0 [25.0, 100.0]
Percentage change in MASES at:				
Week 24, n	81	100	111	211
	–10.8 (112.1)	43.6 (71.2)	49.3 (70.3)	46.6 (70.6)
	0.0 [–33.3, 80.0]	58.6 [0.0, 100.0]	66.7 [0.0, 100.0]	66.7 [0.0, 100.0]
p value vs placebo		< 0.001	< 0.001	< 0.001
Dactylitis				
Randomized patients with dactylitis at baseline	38	50	49	99
Percent change in dactylitis at:				
Week 24, n	34	46	49	95
	27.7 (97.6)	65.5 (52.1)	82.1 (29.1)	74.1 (42.4)
	41.7 [0.0, 100.0]	100.0 [33.3, 100.0]	100.0 [66.7, 100.0]	100.0 [63.6, 100.0]
p value vs placebo		0.09	< 0.001	0.002
Week 52	57.2 (81.2)	70.4 (59.9)	83.0 (45.9)	76.6 (53.5)
	100 [20.0, 100.0]	100.0 [66.7, 100.0]	100.0 [100.0, 100.0]	100.0 [80.0, 100.0]

IQR: interquartile range; PsA: psoriatic arthritis; MASES: Maastricht Ankylosing Spondylitis Enthesitis Score.

the TNF inhibitor golimumab regarding enthesitis and dactylitis in patients with active PsA. Golimumab achieved substantial and significant clinical efficacy, and the clinical benefit was sustained over a year of therapy. Interestingly, although patients initially randomized to placebo achieved benefit over 6 or more months of active golimumab treatment, they did not

achieve as much benefit as those patients receiving golimumab for the whole year. This suggests that improvement in these areas may take longer for the benefit to become apparent. Alternatively, earlier therapy, even for patients with largely established disease, may be more effective in reversing disease activity in these domains. Longer-term followup of these groups will be of great interest.

Golimumab therapy improved multiple facets of PsA, including enthesitis and dactylitis, and efficacy was sustained over a longer period of followup.

ACKNOWLEDGMENT

The authors thank Anna Beutler, MD (Janssen Biotech Inc., Malvern, PA, USA), for excellent and helpful discussions.

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