ARTHRITIS & RHEUMATISM
Vol. 60, No. 4, April 2009, pp 976–986
DOI 10.1002/art.24403

Golimumab, a New Human Tumor Necrosis Factor α Antibody, Administered Every Four Weeks as a Subcutaneous Injection in Psoriatic Arthritis

Twenty-Four–Week Efficacy and Safety Results of a Randomized, Placebo-Controlled Study

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Objective. **To assess the efficacy and safety of golimumab in patients with active psoriatic arthritis (PsA).**

Methods. **Adult patients with PsA who had at least 3 swollen and 3 tender joints and active psoriasis were randomly assigned 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. Efficacy assessments through week 24 included the American College of Rheumatology 20% improvement criteria (ACR20), the Psoriasis Area and Severity Index (PASI) in patients in whom at least 3% of the body surface area was affected by psoriasis at baseline, the Short Form 36 Health Survey (SF-36), the disability index of the Health Assessment Questionnaire (HAQ), the Nail Psoriasis Severity Index (NAPSI), the physician's global assessment of psoriatic nail disease, and enthesitis (using the PsA-modified Maastricht Ankylosing Spondylitis Enthesitis Score [MASES] index).**

Results. **At week 14, 48% of all patients receiving golimumab, 51% of patients receiving golimumab 50 mg, and 45% of patients receiving golimumab 100 mg achieved an ACR20 response (the primary end point), compared with 9% of patients receiving placebo ($P < 0.001$ for all comparisons). Among the 74% of patients in whom at least 3% of the body surface area was affected by psoriasis at baseline, 40% of those in the golimumab 50 mg group and 58% of those in the golimumab 100 mg group had at least 75% improvement in the PASI at week 14 (major secondary end point), compared with 3% of placebo-treated patients ($P < 0.001$ for both doses). Significant improvement was observed for other major secondary end points (the HAQ and the SF-36), the NAPSI, the physician's global assessment of psoriatric nail disease, and the PsA-**

ClinicalTrials.gov identifier: NCT00265096.

Supported by Centocor Research and Development, Inc. and Schering-Plough Corporation.

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Dr. Kavanaugh has received research funding from Centocor. Dr. McInnes has received research grants from Schering-Plough. Dr. Mease has received consulting fees, speaking fees, and/or honoraria from Centocor (less than $10,000). Dr. Krueger has received fees as a consultant or advisory board member at Abbott, Almirall, Alza, Amgen, Anacor, Astellas, Barrier Therapeutics, Boehringer Ingleheim, Bristol Myers Squibb, Centocor, CombinatoRx, Elelixis, Gaderma, Genentech, Genzyme, lsis, Lilly, L'Oreal, Lupin Limited, Magen Biosciences, MedaCorp, Medicis, Novartis, Nova Nordisk, Pfizer, Schering-Plough, Somagenics, theDerm.org, Synvista, Warner Chilcot, UCB, USANA Health Sciences, and ZARS (less than $10,000 each). Dr. Gladman has received consulting fees, speaking fees, and/or honoraria from Centocor and Schering-Plough (less than $10,000 each). Dr. Gomez-Reino has received consulting fees, speaking fees, and/or honoraria from Roche, Schering-Plough, and Bristol-Myers Squibb (less than $10,000 each). Drs. Mudivarthy, Mack, Visvanathan, and Beutler own stock or stock options in Johnson & Johnson, of which Centocor is a subsidiary.

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Submitted for publication July 31, 2008; accepted in revised form December 30, 2008.

modified MASES index in each golimumab group compared with placebo. This efficacy was maintained through week 24. Golimumab was generally well tolerated.

Conclusion. **Treatment with golimumab at doses of 50 mg and 100 mg significantly improved active PsA and associated skin and nail psoriasis through week 24.**

Psoriatic arthritis (PsA), a chronic, inflammatory arthropathy, occurs in ~11% of patients with psoriasis (1). Anti–tumor necrosis factor α (anti-TNFα) agents improve the arthritic and psoriatic manifestations of PsA (2–4). Golimumab is a new human monoclonal antibody against TNFα that binds with high affinity and specificity to soluble and transmembrane TNFα and has a median terminal half-life of ~2 weeks (5). In a phase II rheumatoid arthritis trial, subcutaneous golimumab provided benefit within 2 weeks of administration of the first dose (6).

We now report the efficacy and safety of golimumab through week 24 in the psoriatic arthritis study, Golimumab—A Randomized Evaluation of Safety and Efficacy in Subjects with Psoriatic Arthritis Using a Human Anti-TNF Monoclonal Antibody (GO-REVEAL), a phase III, multicenter, randomized, double-blind, placebo-controlled trial that is the largest of its kind yet completed with a biologic agent in PsA. The efficacy of golimumab in psoriatic nail disease, which is commonly associated with PsA but seldom studied (7), is also reported.

PATIENTS AND METHODS

Patients. Patients enrolled in the study had active PsA despite therapy with disease-modifying antirheumatic drugs or nonsteroidal antiinflammatory drugs (NSAIDs). Active PsA was defined by the presence of at least 3 swollen and 3 tender joints, negative rheumatoid factor, at least 1 subset of PsA, and the presence of plaque psoriasis with a qualifying lesion at least 2 cm in diameter.

Previous use of anti-TNF agents, rituximab, natalizumab, or cytotoxic agents was prohibited. Stable doses of methotrexate (MTX), NSAIDs, and corticosteroids (prednisone ≤10 mg/day) were allowed. Patients in whom latent tuberculosis was diagnosed during screening via the purified protein derivative (PPD) skin test or whole blood interferon-γ–based QuantiFERON-TB Gold (Cellestis, Valencia, CA) testing could participate if they were treated for latent tuberculosis prior to or concurrent with administration of the study agent.

Institutional review board or ethics committee approval and patient written informed consent were obtained prior to study procedures.

Study design. In this multicenter, randomized, double-blind, placebo-controlled trial, 405 patients were randomized in a blinded manner (1:1.3:1.3) by a centralized interactive voice response system (ClinPhone, Princeton, NJ) to receive subcutaneous injections of placebo, golimumab 50 mg, or golimumab 100 mg at weeks 0, 4, 8, 12, 16, and 20. Randomization was stratified by baseline MTX use (yes/no). Golimumab (provided by Centocor, Malvern, PA) and placebo were supplied as sterile liquid. At week 16, patients with <10% improvement from baseline in both the swollen and tender joint counts entered early escape, with dose escalation from placebo to golimumab 50 mg or from golimumab 50 mg to golimumab 100 mg. Patients in the golimumab 100 mg group meeting early escape criteria continued with the 100-mg dose in a blinded manner. Beginning at week 24, all patients received golimumab and continued to receive subcutaneous treatment every 4 weeks. The last evaluation for this study was performed at week 24.

Study end points. The primary end point was the proportion of patients meeting the American College of Rheumatology 20% improvement criteria (ACR20 response) (8) at week 14. An ACR20 response was defined as ≥20% improvement in the swollen joint count (66 joints), the tender joint count (68 joints), and at least 3 of the following 5 assessments: patient's assessment of pain, patient's global assessment of disease activity, physician's global assessment of disease activity, patient's assessment of physical function using the Health Assessment Questionnaire (HAQ) (9), and the C-reactive protein (CRP) level. ACR50 and ACR70 responses were defined similarly, using ≥50% and ≥70% improvements, respectively. Independent assessors at each study center, who had no access to patient records, performed joint, enthesitis, and dactylitis assessments.

The extent and severity of psoriasis were assessed by the Psoriasis Area and Severity Index (PASI) score (0–72-point scale) (10) among patients in whom at least 3% of the body surface area (BSA) was affected by psoriatic skin involvement at baseline. Irrespective of the percent BSA affected at baseline, a prospectively identified target psoriatic skin lesion was assessed for erythema, plaque induration, and scaling (range 0–4 for each). The Nail Psoriasis Severity Index (NAPSI) (11) was used to assess the severity of a target fingernail representing the worst nail psoriasis at baseline. Fingernail psoriasis was also evaluated using the physician's global assessment of psoriatic nail disease, where 1 = absent and 5 = very severe.

The Psoriatic Arthritis Response Criteria (PsARC) (12) and Disease Activity Score in 28 joints (DAS28) using the CRP level (DAS28-CRP) (13,14) were employed; dactylitis, enthesitis, and morning stiffness were also assessed. The presence and severity of dactylitis were scored on a scale of 0–3, where 0 = no dactylitis and 3 = severe dactylitis, in each digit of the hands and feet. Enthesitis was assessed using the Maastricht Ankylosing Spondylitis Enthesitis Score (MASES) index (15), modified for PsA to include plantar fascia, with scores of 0–15.

Physical function and health-related quality of life were measured at weeks 14 and 24 using the disability index of the HAQ and the Short Form 36 Health Survey (SF-36) (16), respectively.

Safety evaluations included adverse events, routine laboratory analyses, and the presence of antibodies to golimumab (6). The incidence of malignancies was determined

Table 1. Characteristics of the patients at baseline*

Characteristic	Placebo (n = 113)	Golimumab 50 mg (n = 146)	Golimumab 100 mg (n = 146)
Male sex, no. (%)	69 (61)	89 (61)	86 (59)
Caucasian race, no. (%)	110 (97)	141 (97)	142 (97)
Age, years	47.0 ± 10.6	45.7 ± 10.7	48.2 ± 10.9
PsA duration, years	7.6 ± 7.9	7.2 ± 6.8	7.7 ± 7.8
No. of swollen joints, 0–66	13.4 ± 9.8	14.1 ± 11.4	12.0 ± 8.4
No. of tender joints, 0–68	21.9 ± 14.7	24.0 ± 17.1	22.5 ± 15.7
CRP, mg/dl	1.3 ± 1.6	1.3 ± 1.6	1.4 ± 1.8
Morning stiffness duration, minutes (0–1,440)	131.1 ± 264.9	124.7 ± 262.3	117.8 ± 234.1
PsA subtype, no. (%) of patients			
Distal interphalangeal joint arthritis	16 (14)	24 (16)	22 (15)
Arthritis mutilans	0 (0)	2 (1)	1 (1)
Asymmetric peripheral arthritis	27 (24)	44 (30)	49 (34)
Polyarticular arthritis with no rheumatoid nodules	58 (51)	62 (43)	56 (38)
Spondylitis with peripheral arthritis	12 (11)	14 (10)	18 (12)
DAS28-CRP, 0–10	4.3 ± 1.0	4.4 ± 1.1	4.3 ± 1.0
Dactylitis, no. (%) of patients	38 (34)	50 (34)	49 (34)
Dactylitis score, 0–60	3.1 ± 2.1	6.3 ± 6.0	5.4 ± 6.7
Enthesitis, no. (%) of patients	88 (78)	109 (75)	115 (79)
Enthesitis score, 0–15	5.0 ± 4.1	5.7 ± 4.0	6.1 ± 4.1
Target lesion score, 0–12	6.1 ± 2.0	6.2 ± 2.1	6.3 ± 2.4
≥3% BSA affected by psoriasis, no. (%) of patients	79 (70)	109 (75)	108 (74)
BSA affected by psoriasis, %	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
Patients with nail psoriasis, no. (%)	83 (74)	95 (65)	109 (75)
NAPSI score for target nail, 0–8	4.4 ± 2.2	4.7 ± 2.2	4.6 ± 2.1
Physician's global assessment of target nail, no. (%) of patients			
Very severe	1 (1)	3 (3)	5 (5)
Severe	10 (12)	16 (17)	15 (14)
Moderate	29 (35)	37 (39)	35 (32)
Mild	43 (52)	39 (41)	54 (50)
Patients taking MTX, no. (%)	54 (48)	71 (49)	69 (47)
MTX dosage, mean (median) mg/week	15.0 (15.0)	14.8 (15.0)	15.5 (15.0)
Total duration of prior MTX use in patients taking MTX, no. (%)			
Never used	37 (33)	49 (34)	40 (27)
<3 months	3 (3)	9 (6)	10 (7)
≥3–<6 months	9 (8)	16 (11)	10 (7)
≥6 months	64 (57)	72 (49)	86 (59)
Patients taking oral corticosteroids, no. (%)	19 (17)	19 (13)	27 (18)
Prednisone or equivalent dosage, mean (median) mg/day	5.8 (5.0)	7.6 (7.5)	6.0 (5.0)
Patients taking NSAIDs, no. (%)	88 (78)	110 (75)	110 (75)

* Except where indicated otherwise, values are the mean ± SD. PsA = psoriatric arthritis; DAS28-CRP = Disease Activity Score in 28 joints as assessed with the C-reactive protein (CRP) level; BSA = body surface area; PASI = Psoriasis Area and Severity Index; NAPSI = Nail Psoriasis and Severity Index; MTX = methotrexate; NSAIDs = nonsteroidal antiinflammatory drugs.

based on 100 patient-years of followup, with corresponding 95% confidence intervals (95% CIs). Trough golimumab concentrations were determined from serum samples collected before each injection was administered.

Statistical analysis. The planned sample size (n = 396 [110 in the placebo group and 286 in the combined golimumab group]) provided >98% power to detect a significant difference ($\alpha = 0.05$) between the placebo and combined golimumab groups in the primary efficacy end point, assuming equal proportions of patients in each group received MTX at baseline and the following proportions of patients achieved an ACR20 response at week 14: 15% of patients receiving placebo, 25% of patients receiving placebo plus MTX, 42% of patients receiving both golimumab doses combined, and 42% of patients receiving both golimumab doses combined plus MTX. Greater than usual power resulted from basing calculations on radiographic changes and International Committee on Harmonization requirements for the numbers of patients exposed to treatment.

The primary end point was the proportion of patients

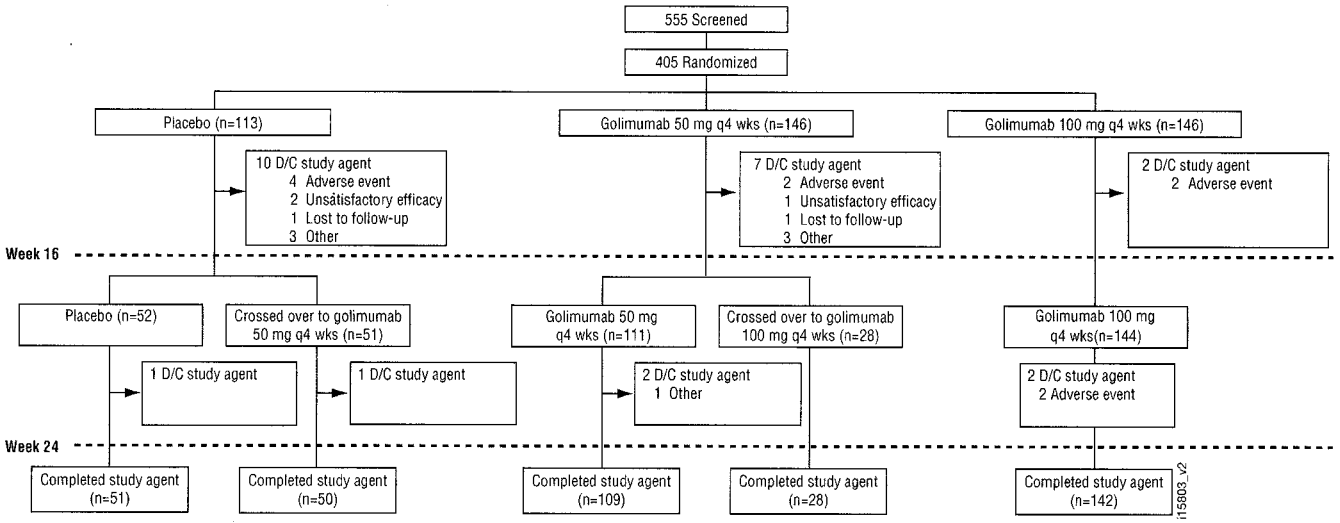

Figure 1. Patient disposition through week 24. Through week 14, adverse events that were responsible for patients discontinuing (D/C) the study agent included vertigo/headache, urosepsis, headache/nausea/chills, and isoniazid-induced hepatitis in the placebo group; acute abscess and elevated aspartate aminotransferase and alanine aminotransferase levels in the golimumab 50 mg group; and fatigue and prostate cancer in the golimumab 100 mg group. After week 14, adverse events leading to discontinuation included an elevated creatinine level in the placebo group and mumps/sialoadenitis and numbness/tingling/muscle weakness in the golimumab 100 mg group.

achieving an ACR20 response at week 14. Major secondary end points included the ACR20 response at week 24, achievement of at least 75% improvement in the PASI at week 14 in the subset of patients in whom at least 3% of the BSA was affected by psoriasis at baseline, HAQ scores at week 24, and SF-36 physical component summary (PCS) scores at week 14. Efficacy data from all randomized patients were analyzed according to assigned treatment group. Treatment group differences were assessed with a 2-sided Cochran-Mantel-Haenszel test for discrete variables or 2-sided analysis of variance on van der Waerden normal scores for continuous parameters. All analyses included treatment and patients' use of MTX at baseline as factors and were performed at a 0.05 level of significance. Because most sites enrolled only a few patients, analyses were not stratified by center. For patients who discontinued treatment but continued to be followed up and for whom some ACR component data were missing, the last observation was carried forward to week 14 or week 24.

Differences between the combined golimumab and placebo groups had to be statistically significant before subsequent comparisons were made for individual golimumab dose groups versus placebo. No comparisons between golimumab 50 mg and golimumab 100 mg were made. For efficacy analyses, patients assigned to placebo and patients assigned to golimumab 50 mg who met the early escape criteria at week 16 had week 16 observations carried forward to week 24. For patients randomized to receive golimumab 100 mg who met the criteria, observed values were used at week 24. Post hoc analyses were performed to evaluate the impact of MTX on the ACR and PASI responses. Safety analyses were based on all treated patients.

RESULTS

Patient disposition and baseline characteristics. Of the 555 adults screened at 58 investigational sites (18 in the US, 18 in Canada, and 22 in Europe), 405 were randomized and received study agent. Consent was obtained for the first patient on December 12, 2005; the last patient completed the final visit for the week 24 reporting period on May 14, 2007. Baseline ACR components and BSA psoriasis involvement indicated active disease, with no relevant differences between groups (Table 1). Twelve (11%) of 113 patients randomized to the placebo group and 13 (4%) of 292 patients randomized to the golimumab groups discontinued treatment (Figure 1). One of 12 patients in the placebo group discontinued treatment after receiving golimumab 50 mg in early escape. Followup continued for these patients, and they were included in the analyses of primary and major secondary end points.

Efficacy results. *ACR response.* At the primary end point evaluation (week 14), 48% of patients (140 of 292) in the combined golimumab group achieved an ACR20 response, compared with 9% of patients (10 of 113) in the placebo group ($P < 0.001$). Benefit at week 14 was observed with both the 50-mg dose (74 [51%] of 146 patients) and the 100-mg dose (66 [45%] of 146

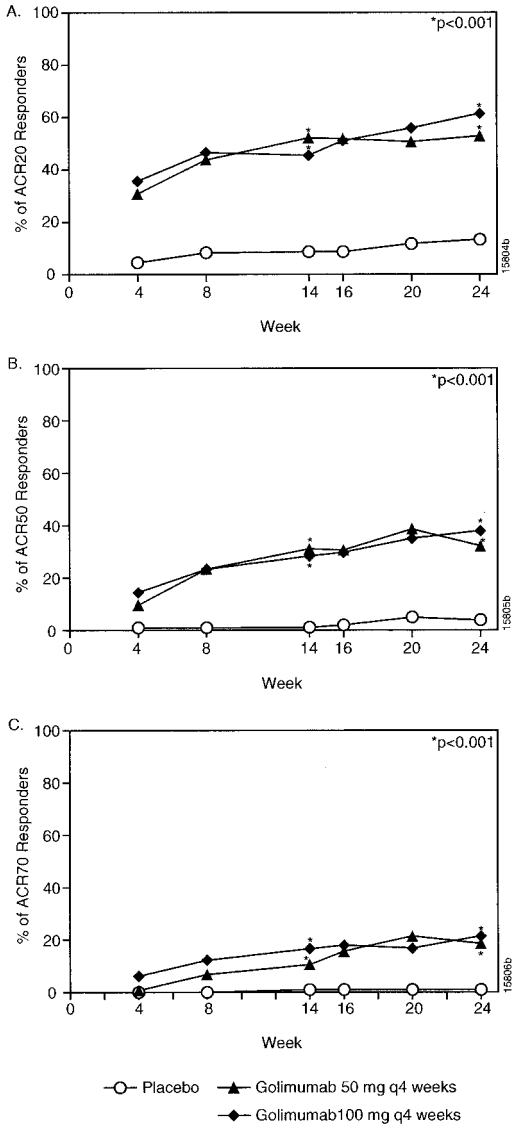

Figure 2. Proportions of patients achieving at least 20% improvement according to the American College of Rheumatology criteria (ACR20 response) (**A**), ACR50 response (**B**), and ACR70 response (**C**) through week 24.

patients) (both $P < 0.001$ versus placebo) (Figure 2) and was seen irrespective of MTX use ($P = 0.66$). By week 24, 52% of patients in the golimumab 50 mg group (76 of 146) and 61% of patients in the golimumab 100 mg group (89 of 146) achieved an ACR20 response (major secondary end point), compared with 12% of patients in the placebo group (14 of 113) ($P < 0.001$ for both comparisons). Consistent findings were observed for the ACR50 and ACR70 responses at weeks 14 and 24 (Figure 2). Among patients randomized to receive golimumab 50 mg who met the early escape criteria and received golimumab 100 mg at weeks 16 and 20, 14% (4 of 28) achieved an ACR20 response, 4% (1 of 28) achieved an ACR50 response, and none achieved an ACR70 response at week 24. A larger proportion of placebo-treated patients who switched to golimumab 50 mg in early escape achieved ACR responses at week 24 (for ACR20, 47% [24 of 51]; for ACR50, 14% [7 of 51]; for ACR70, 6% [3 of 51]). Among patients randomized to receive golimumab 100 mg who met the early escape criteria, ACR20, ACR50, and ACR70 responses were achieved at week 24 by 16% (4 of 25), 8% (2 of 25), and 4% (1 of 25) of patients, respectively.

Physical function and quality of life. Patients in both golimumab groups had significantly improved HAQ scores at week 24 (major secondary end point), with a mean ± SD change from baseline of 0.33 ± 0.55 and 0.39 ± 0.50 for golimumab 50 mg and golimumab 100 mg, respectively, versus –0.01 ± 0.49 for patients in the placebo group ($P < 0.001$ for both comparisons). Patients in the golimumab 50 mg group and patients in the golimumab 100 mg group also had significant improvement in the PCS component of the SF-36 at week 14 (major secondary end point) ($P < 0.001$), with respective mean ± SD changes of 6.53 ± 8.88 and 7.85 ± 9.55 versus 0.63 ± 7.68 for placebo.

Other measures of arthritis and assessments of enthesitis and dactylitis. Significantly greater improvement from baseline to weeks 14 and 24 was generally observed in each golimumab dose group versus placebo for each supportive arthritis efficacy parameter, including the PsARC, the European League Against Rheumatism (EULAR) response, change in the DAS28-CRP, and assessments of enthesitis and morning stiffness (Table 2). No significant difference between placebo and golimumab was seen in the proportion of patients with dactylitis at week 14 or week 24; however, there was significantly greater improvement in the dactylitis severity score at both time points with golimumab 100 mg. Significantly smaller proportions of patients in the golimumab 50 mg and 100 mg groups had enthesitis at week 24 compared with patients in the placebo group (Table 2), and significantly greater improvement in the PsA-modified MASES enthesitis score was observed in the golimumab 50 mg and 100 mg groups compared with the placebo group at weeks 14 and 24.

Skin and nail responses. Among the 74% of patients (217 of 292) in whom at least 3% of the BSA was affected by psoriasis at baseline, 40% of those in the golimumab 50 mg group (44 of 109) and 58% of those in the golimumab 100 mg group (63 of 108) had at least

Table 2. Summary of supportive efficacy findings*

	Week 14			Week 24		
		Golimumab			Golimumab	
	Placebo (n = 113)	50 mg (n = 146)	100 mg (n = 146)	Placebo (n = 113)	50 mg (n = 146)	100 mg (n = 146)
Psoriatic Arthritis Response Criteria, no. (%) achieving response [*P*]	24 (21)	107 (73) [<0.001]	105 (72) [<0.001]	33 (29)	102 (70) [<0.001]	124 (85) [<0.001]
DAS28-CRP						
Mean ± SD change	−0.18 ± 0.78	−1.38 ± 1.16	−1.29 ± 1.16	−0.12 ± 0.97	−1.43 ± 1.34	−1.56 ± 1.10
No. (%) achieving EULAR response [*P*]	27 (24)	96 (66) [<0.001]	98 (67) [<0.001]	27 (24)	94 (64) [<0.001]	114 (78) [<0.001]
Dactylitis						
No. of patients with dactylitis/no. assessed (%) [*P*]	27/105 (26)	31/142 (22) [0.46]	25/145 (17) [0.10]	23/105 (22)	22/139 (16) [0.21]	20/145 (14) [0.09]
Median % change in score [*P*]	0	76 [0.10]	100 [0.009]	42	100 [0.09]	100 [<0.001]
Enthesitis						
No. of patients with enthesitis/no. assessed (%) [*P*]	75/105 (71)	78/142 (55) [0.008]	89/145 (61) [0.10]	72/105 (69)	68/139 (49) [0.002]	72/145 (50) [0.003]
Median % change in PsA-modified MASES [*P*]	0	50 [<0.001]	50 [<0.001]	12	60 [<0.001]	67 [<0.001]
Morning stiffness, mean ± SD change [*P*]	23.4 ± 299.9	−72.4 ± 201.3 [<0.001]	−86.3 ± 238.3 [<0.001]	−20.4 ± 257.7	−67.2 ± 231.1 [<0.001]	−90.1 ± 234.5 [<0.001]
No. of patients with ≥3% BSA affected by psoriasis at baseline	79	109	108	79	109	108
PASI50, no. of patients/no. assessed (%) [*P*]	7/73 (10)	63/106 (59) [<0.001]	83/107 (78) [<0.001]	6/73 (8)	77/102 (76) [<0.001]	87/106 (82) [<0.001]
PASI75, no. of patients/no. assessed (%) [*P*]	2/79 (2.5)	44/109 (40) [<0.001]	63/108 (58) [<0.001]	1/73 (1)	57/102 (56) [<0.001]	70/106 (66) [<0.001]
PASI90, no. of patients/no. assessed (%) [*P*]	0/73 (0)	22/106 (21) [<0.001]	26/107 (24) [<0.001]	0/73 (0)	33/102 (32) [<0.001]	34/106 (32) [<0.001]
Target lesion score, median % improvement [*P*]	0	50 [<0.001]	68 [<0.001]	0	60 [<0.001]	83 [<0.001]
No. of patients with fingernail involvement at baseline	83	95	109	83	95	109
NAPSI, median % change [*P*]	0	25 [0.015]	43 [<0.001]	0	33 [<0.001]	54 [<0.001]
PGA of nail psoriasis, no. of patients with improvement/no. assessed (%) [*P*]	11/81 (14)	43/91 (47) [<0.001]	52/108 (48) [<0.001]	14/79 (18)	53/89 (60) [<0.001]	68/108 (63) [<0.001]

* All *P* values are versus placebo. *P* values for the Psoriasis Area and Severity Index criteria for 50% improvement (PASI50) and the PASI90 are from post hoc analyses. The PASI50, PASI75, and PASI90 were determined for patients in whom at least 3% of the body surface area was affected with psoriatic skin involvement at baseline. To determine the Nail Psoriasis Severity Index score (NAPSI), the target nail is divided into quadrants and graded for nail matrix psoriasis and nail bed psoriasis; the sum of these scores, ranging from 1 to 8, is the NAPSI score. DAS28-CRP = Disease Activity Score in 28 joints as assessed with the C-reactive protein level; EULAR = European League Against Rheumatism; PsA = psoriatic arthritis; MASES = Maastricht Ankylosing Spondylitis Enthesitis Score; BSA = body surface area; PGA = physician's global assessment.

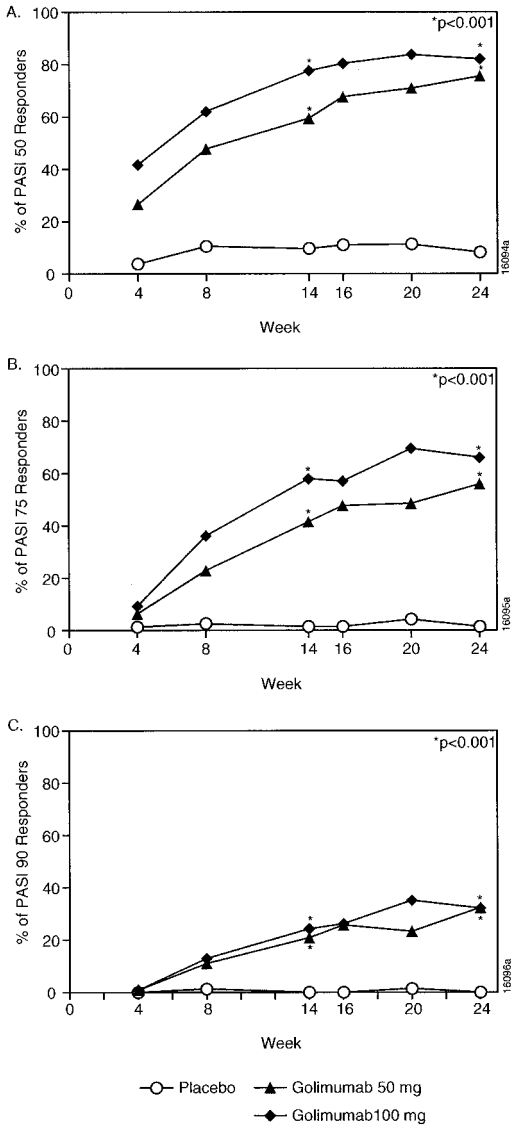

Figure 3. Proportions of patients achieving at least 50% improvement according to the Psoriasis Area and Severity Index (PASI50 response) (**A**), PASI75 response (**B**), and PASI90 response (**C**) through week 24.

75% improvement in the PASI at week 14 (major secondary end point), compared with 3% of patients in the placebo group (2 of 79) ($P < 0.001$ for each dose) (Figure 3). Benefit of golimumab at week 14 was observed irrespective of MTX use ($P = 0.32$). A target psoriatic lesion was also assessed for each patient. The median percent improvements in the target lesion score from baseline to weeks 14 and 24 were significantly greater ($P < 0.001$) in each golimumab dose group versus the placebo group (Table 2). For the assessment of a single target fingernail using the NAPSI and the physician's global assessment of psoriatic nail disease, significantly greater improvement from baseline to weeks 14 and 24 was observed in each golimumab dose group versus placebo (Table 2).

Safety results. *Adverse events.* Through week 24, 65% (222 of 343) and 59% (67 of 113) of all golimumab-treated and placebo-treated patients, respectively, had adverse events. The most frequently reported adverse events in the golimumab groups were nasopharyngitis and upper respiratory tract infection (Table 3). No differences in the types or frequency of adverse events were observed between the 2 golimumab dose groups, with the exception of infections, which occurred more often with the higher dose (33% in the group receiving golimumab 50 mg, 41% in the group receiving golimumab 100 mg, and 24% in the placebo group). Serious adverse events were reported for 2% (7 of 343) of all golimumab-treated patients versus 6% (7 of 113) of placebo-treated patients. More placebo-treated patients had serious infections (2 cases of pneumonia, 1 case of cellulitis, and 1 case of urosepsis) than did patients receiving golimumab 50 mg (1 case of abscess) and those receiving golimumab 100 mg (1 case of sepsis/cholecystitis). No cases of active tuberculosis were observed. Eight golimumab-treated patients (3%) and 5 placebo-treated patients (4%) discontinued the study agent due to adverse events occurring prior to week 24. Three malignancies were reported, all in the golimumab 100 mg group (2 cases of basal cell carcinoma and 1 case of prostate cancer), representing an incidence of 2.32 (95% CI 0.48–6.78) per 100 patient-years versus 0.00 (95% CI 0.00–7.13) per 100 patient-years for placebo, with the 95% CI for golimumab fully contained within that for placebo.

Reactions to injections, most commonly erythema, occurred in 3% of patients in the combined golimumab group (10 of 292) and 3% of placebo-treated patients (3 of 113). No injection-site reaction was severe, serious, or resulted in discontinuation of treatment. No patient experienced anaphylactic or serum sickness–like reactions.

Additional safety events reported after week 24 (including during the long-term extension after week 52 of treatment) are important to note, including 2 deaths (both in the golimumab 50 mg group [1 due to a climbing accident and 1 resulting from small cell lung cancer]), 1 case of colon cancer (a patient assigned to golimumab 50 mg who entered early escape), 1 case of small cell lung cancer (in the golimumab 100 mg group), 2 cases of basal cell carcinomas (1 in the golimumab 50 mg group and 1 in a patient in the golimumab 50 mg group who

Table 3. Safety findings through week 24*

	Patients randomized to placebo group		Patients randomized to golimumab group				
	Placebo (n = 113)	Placebo → golimumab 50 mg (n = 51)	50 mg (n = 146)	50 mg → 100 mg (n = 28)	100 mg (n = 146)	Combined 50 mg and 100 mg (n = 292)	All golimumab (n = 343)
Average duration of followup, weeks	19	8	22	8	24	24	22
Adverse events	67 (59)	26 (51)	99 (68)	4 (14)	95 (65)	196 (67)	222 (65)
Common adverse events†							
Upper respiratory tract infection	7 (6)	1 (2)	17 (12)	0 (0)	13 (9)	30 (10)	31 (9)
Nasopharyngitis	5 (4)	3 (6)	10 (7)	0 (0)	19 (13)	29 (10)	32 (9)
Headache	8 (7)	3 (6)	7 (5)	1 (4)	8 (6)	16 (6)	19 (6)
Back pain	5 (4)	0 (0)	6 (4)	0 (0)	7 (5)	13 (4)	13 (4)
Diarrhea	4 (4)	0 (0)	5 (3)	0 (0)	7 (5)	12 (4)	12 (4)
Hypertension	5 (4)	0 (0)	10 (7)	0 (0)	2 (1)	12 (4)	12 (4)
Cough	5 (4)	3 (6)	7 (5)	0 (0)	4 (3)	11 (4)	14 (4)
Injection-site erythema	2 (2)	0 (0)	4 (3)	0 (0)	6 (4)	10 (3)	10 (3)
Nausea	5 (4)	1 (2)	4 (3)	0 (0)	6 (4)	10 (3)	11 (3)
Elevated ALT level	4 (4)	0 (0)	4 (3)	0 (0)	5 (3)	9 (3)	9 (3)
Serious adverse events	7 (6)	0 (0)	3 (2)	0 (0)	4 (3)	7 (2)	7 (2)
Serious infections	4 (4)	0 (0)	1 (<1)	0 (0)	1 (<1)	2 (<1)	2 (<1)
Injection-site reactions‡	3 (3)	0 (0)	4 (3)	0 (0)	6 (4)	10 (3)	10 (3)
Markedly abnormal ALT level§	4 (4)	0 (0)	3 (2)	0 (0)	0 (0)	3 (1)	3 (1)
Markedly abnormal AST level§	3 (3)	0 (0)	2 (1)	0 (0)	0 (0)	2 (<1)	2 (<1)
Markedly abnormal total bilirubin level§	2 (2)	1 (2)	4 (3)	0 (0)	2 (1)	6 (2)	7 (2)
Antibodies to golimumab¶	—	0/51 (0)	5/114 (4)	1/28 (4)	7/143 (5)	13/285 (5)	13/336 (4)

* Except where indicated otherwise, values are the number (%) of patients.
† Absolute number (%) of patients with ≥1 adverse events reported in at least 3% of the patients in any treatment group. The preferred World Health Organization Adverse Reactions Terminology terms are sorted by decreasing frequency in the "all golimumab" group.
‡ Injection-site reactions were defined as any adverse reaction at the site of a subcutaneous injection of placebo or golimumab.
§ Any markedly abnormal postbaseline value through week 24. Criteria for abnormal alanine aminotransferase (ALT) and aspartate aminotransferase (AST) levels were an increase of at least 100% and a value in excess of 150 IU/liter; criteria for an abnormal total bilirubin level were an increase of at least 100% and a value in excess of 1.5 mg/dl.
¶ Among patients with appropriate samples.

was escalated to 100 mg of golimumab), and a case of liver histoplasmosis (in the golimumab 100 mg group). Analyses comparing the incidence of malignancies in this study with those in the Surveillance, Epidemiology, and End Results database (17) suggest no difference between the number of observed and expected cases (data not shown).

Laboratory values. In general, there was no difference in hematology and chemistry values between the golimumab and placebo groups, with the exception of postbaseline liver transaminase (alanine aminotransferase [ALT] and aspartate aminotransferase [AST]) elevations in patients with normal ALT/AST levels at baseline, which occurred more frequently in golimumab-treated patients compared with placebo-treated patients. Elevations in the ALT level occurred in 24% of patients receiving golimumab 50 mg (33 of 135), 35% of patients receiving golimumab 100 mg (47 of 133), and 18% of placebo-treated patients (18 of 98), and elevations in the AST level occurred in 18% (26 of 143), 13% (18 of 142), and 10% (11 of 107) of patients in these groups, respectively. Clinically significant elevations in the ALT and total bilirubin levels (Table 3) occurred in 2% and 3% of patients in the golimumab 50 mg group (3 of 146 and 4 of 146), respectively, 0% (0/146) and 1% (2/146) of patients in the golimumab 100 mg group, and 4% (4/112) and 2% (2/112) of patients receiving placebo. Two patients (1 in the placebo group and 1 receiving golimumab 50 mg) experienced transient, asymptomatic, concomitant elevations in the ALT level (194 IU/liter and 298 IU/liter, respectively) and the total bilirubin level (2.8 mg/dl and 2.6 mg/dl, respectively). Concomitant treatment with MTX did not appear to affect transaminase levels.

Tuberculosis screening. Eleven patients in the placebo group (10%) and 33 patients in the golimumab group (11%) required treatment (usually isoniazid) for latent tuberculosis based on positive screening PPD or QuantiFERON-TB Gold testing. Patients treated for latent tuberculosis were more likely to have had liver transaminase abnormalities compared with those who were not treated. The elevations were generally mild to

moderate, and no increased risk of serious transaminase abnormalities with concomitant administration of golimumab and tuberculosis prophylaxis was noted.

Golimumab pharmacokinetics and antibodies to golimumab. Dose-proportional pharmacokinetic effects were observed, with steady-state golimumab concentrations achieved by week 12. The incidence of antibodies to golimumab was low (4.6% of patients assigned to golimumab; highest titer 1:2,560 in the patient who required early escape from 50 mg to 100 mg). No patient receiving MTX at baseline developed antibodies to golimumab. In the small number of antibody-positive patients, the presence of antibodies had no apparent impact on ACR responses or injection-site reactions.

DISCUSSION

Golimumab, a human monoclonal antibody against TNFα, was demonstrated to be efficacious and generally well tolerated when administered subcutaneously every 4 weeks during 24 weeks of treatment. An ACR20 response was achieved at week 14 by 51% of patients receiving golimumab 50 mg and 45% of patients receiving golimumab 100 mg, compared with 9% of placebo-treated patients ($P < 0.001$ for both comparisons). Significantly more golimumab-treated patients than placebo-treated patients achieved ACR50 and ACR70 responses and demonstrated improvement in other arthritis efficacy end points, including the EULAR response, change in the DAS28-CRP, and the PsARC. Differences between the 50-mg and 100-mg doses of golimumab were modest, with no evidence of increased benefit with background MTX treatment. Golimumab-treated patients had significant improvement in physical function and health-related quality of life, as measured by the HAQ and the SF-36, and also had significant improvement in enthesitis.

Patients receiving golimumab also demonstrated significant improvement in psoriasis compared with patients receiving placebo. Among the 74% of patients in whom at least 3% of the BSA was affected by psoriasis at baseline, 40% of those in the golimumab 50 mg group and 58% of those in the golimumab 100 mg group had at least 75% improvement in the PASI at week 14, compared with 3% of patients in the placebo group ($P < 0.001$ for both comparisons).

In GO-REVEAL, the first placebo-controlled study evaluating the effect of an anti-TNFα biologic agent on nail psoriasis (18), ~70% of patients had baseline nail involvement. Significant improvements in nail symptoms (as assessed by the NAPSI and the physician's global assessment of psoriatic nail disease) were observed in golimumab-treated patients as early as week 14 and were maintained or improved through week 24.

Although the study was not powered to detect differences between golimumab doses, there appeared to be more evidence of a golimumab dose-response in terms of the skin/nail outcomes compared with the arthritis outcomes. Since these findings could be related to the performance of the arthritis instruments versus the skin/nail instruments, different biologic responses, or the speed of responses in affected organs, further study is needed.

The safety profile of golimumab in PsA is consistent with that of other anti-TNF agents (19,20). Injection-site reactions occurred in a small proportion of patients and were mild in most cases. Malignancies were reported for 3 patients receiving golimumab 100 mg (2 cases of basal cell malignancies and 1 case of prostate cancer) through week 24. Certain safety events reported after week 24, after which all patients switched from the control arm to receive active treatment, are important to note, including 2 deaths (a climbing accident and a case of small cell lung cancer) and 1 report of liver histoplasmosis. One-year golimumab efficacy and safety data are forthcoming.

Elevations of the transaminase level were more common in the golimumab groups compared with the placebo group; patients with elevated transaminase levels were generally asymptomatic. These findings are consistent with observations with other biologic agents (20,21). Transaminase abnormalities were more frequent in patients treated with isoniazid for latent tuberculosis than in those who were not treated; the elevations were generally mild to moderate. Concomitant treatment with golimumab and isoniazid did not appear to increase the risk of serious transaminase abnormalities.

In summary, subcutaneous golimumab (at doses of 50 mg and 100 mg) administered every 4 weeks significantly improved active PsA and associated skin disease. Similar responses for the arthritis end points were observed with both doses, and responses were numerically higher with the 100-mg dose across the psoriasis end points. The proportion of patients responding to golimumab generally increased through week 24. Golimumab is the first subcutaneously administered anti-TNF agent to show efficacy in PsA-associated enthesitis, dactylitis, and psoriatic nail disease. The safety of golimumab is similar to that of other anti-TNF agents. Longer-term data are forthcoming.

ACKNOWLEDGMENTS

We thank Dr. Richard Cook for providing comments on the statistical aspects of this manuscript. We also thank the following study investigators who enrolled patients into the study: T. Appelboom (Brussels, Belgium), C. Atkins (Victoria, British Columbia, Canada), D. R. Baker (Lake Oswego, OR), A. Beaulieu (Sainte Foy, Quebec, Canada), C. Birbara (Worcester, MA), J. Brzezicki (Elblag, Poland), M. S. Brzosko (Szczecin, Poland), C. Chattopadhyay (Wigan, UK), H. Chwalińska-Sadowska (Warsaw, Poland), A. Cividino (Hamilton, Ontario, Canada), A. Deodhar (Portland, OR), K. L. F. de Vlam (Leuven, Belgium), A. Fillipowicz-Sosnowska (Warsaw, Poland), M. A. Fitzcharles (Pointe-Claire, Quebec, Canada), N. B. Gaylis (Aventura, FL), R. M. Griffin (West Reading, PA), W. Gulliver (St. John's, Newfoundland, Canada), D. G. Halter (Houston, TX), B. Haraoui (Montreal, Quebec, Canada), A. Hou, E. Boling (Upland, CA), P. Z. Hrycaj (Proznań, Poland), J. A. R. Ivorra (Valencia, Spain), S. F. Jeka (Torun, Poland), R. A. H. Jimenez (Edmonds, WA), E. Keystone (Toronto, Ontario, Canada), M. Khraishi (St. John's, Newfoundland, Canada), A. Klinkhoff (Vancouver, British Columbia, Canada), K. M. Latinis (Kansas City, KS), M. Malaize (Liége, Belgium), M. Luggen (Cincinnati, OH), D. R. Mandel (Mayfield Village, OH), R. McKendry (Ottawa, Ontario, Canada), Z. A. Mencel (Kalisz, Poland), F. T. Murphy (Duncansville, PA), W. P. Olszynski (Saskatoon, Saskatchewan, Canada), W. Palmer (Omaha, NE), J. A. Pazdur (Warsaw, Poland), M. J. Plant (Middlesborough, UK), Y. Poulin (Sainte-Foy, Quebec, Canada), A. Racewicz (Bialystok, Poland), F. Raeman (Merksem, Belgium), P. Rahman (St. John's, Newfoundland, Canada), L. A. Rosoph (North Bay, Ontario, Canada), F. N. Sarabia (Serville, Spain), W. J. Shergy (Huntsville, AL), E. L. Siegel (Wheaton, MD), S. J. Sierakowski (Bialystok, Poland), H. Tahir (London, UK), G. Thomson (Winnipeg, Manitoba, Canada), C. Thorne (Newmarket, Ontario, Canada), F. E. J. van den Bosch (Ghent, Belgium), C. Wiesenhutter (Coeur D'Alene, ID).

AUTHOR CONTRIBUTIONS

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

Study design. Kavanaugh, McInnes, Mease, Krueger, Gladman, Mudivarthy, Mack, Beutler.

Acquisition of data. Kavanaugh, Mease, Gladman, Gomez-Reino, Papp, Zrubek, Mudivarthy, Mack.

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Manuscript preparation. Kavanaugh, Mease, Krueger, Gladman, Gomez-Reino, Papp, Zrubek, Mudivarthy, Mack, Beutler, and Michelle Perate and Mary Whitman (nonauthors, Centocor, Inc.).

Statistical analysis. McInnes, Mudivarthy, Mack.

ROLE OF THE STUDY SPONSOR

This study was funded by Centocor Research and Development, Inc. and Schering-Plough. Schering-Plough was involved in the study design and the interpretation of data. The study was managed by a steering committee (AK, IM, PM, GK, and DG) and A. Beutler of Centocor. The study was designed by the Steering Committee members and scientists at Centocor and Schering-Plough, with input from the study investigators. Data were collected by the investigators and were entered into a database that was maintained by Centocor. The analyses were conducted by Centocor statisticians and programmers. All authors reviewed and approved the content of the manuscript before submission and jointly agreed to submit the final version of the manuscript. Publication was not contingent on approval from Centocor and/or Schering-Plough.

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