

Efficacy and Safety of Golimumab in Patients With Ankylosing Spondylitis

Results of a Randomized, Double-Blind, Placebo-Controlled, Phase III Trial

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Objective. To evaluate the efficacy and safety of golimumab in patients with ankylosing spondylitis (AS) in the GO-RAISE study.

Methods. Patients with active AS, a Bath AS Disease Activity Index (BASDAI) score ≥ 4 , and a back pain score of ≥ 4 were randomly assigned in a 1.8:1.8:1 ratio to receive subcutaneous injections of golimumab (50 mg or 100 mg) or placebo every 4 weeks. The

primary end point was the proportion of patients with at least 20% improvement in the AS assessment in AS (ASAS20) criteria at week 14.

Results. At randomization, 138, 140, and 78 patients were assigned to the 50-mg, 100-mg, and placebo groups, respectively. After 14 weeks, 59.4%, 60.0%, and 21.8% of patients, respectively, were ASAS20 responders ($P < 0.001$). A 40% improvement in the ASAS criteria at week 24 occurred in 43.5%, 54.3%, and 15.4% of patients, respectively. Patients receiving golimumab also showed significant improvement in the physical and mental component summary scores of the Short Form 36 Health Survey, the Jenkins Sleep Evaluation Questionnaire score, the BASDAI score, and the Bath AS Functional Index score, but not the Bath AS Metrology Index score. Through week 24, 85.6% of golimumab-treated patients and 76.6% of patients in the placebo group had ≥ 1 adverse event, and 5.4% and 6.5% of patients, respectively, had ≥ 1 serious adverse event. Eight golimumab-treated patients and 1 placebo-treated patient had markedly abnormal liver enzyme values ($\geq 100\%$ increase from baseline and a value >150 IU/liter), which were transient.

Conclusion. Golimumab was effective and well tolerated in a large cohort of patients with AS during a 24-week study period.

Ankylosing spondylitis (AS) is a chronic inflammatory disease of unknown etiology that involves the sacroiliac joints, axial skeleton, entheses, and peripheral joints. Chronic inflammation of entheses potentially leads to new bone formation in the form of syndesmophytes and ankylosis of vertebrae and joints, primarily in the axial skeleton. Patients may also have extraarticular

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manifestations and comorbidities, including acute anterior uveitis, psoriasis, colitis, aortitis, and cardiac conduction abnormalities.

Tumor necrosis factor α (TNF α) is a major therapeutic target in AS (1), and several biologic agents that target this proinflammatory cytokine have been shown to significantly improve the signs and symptoms of AS in patients with moderate-to-severe disease (2–4). Golimumab is a new human anti-TNF α monoclonal antibody with pharmacologic properties that allow for monthly subcutaneous dosing. Golimumab has been studied in patients with rheumatoid arthritis (5) and patients with psoriatic arthritis (6), and more studies are ongoing. In the GO-RAISE study, we evaluated the efficacy and safety of golimumab in reducing signs and symptoms of active AS.

PATIENTS AND METHODS

Patients. Adult patients who had AS (diagnosed according to the modified New York Criteria [7]) for ≥ 3 months before the first administration of the study agent, a Bath AS Disease Activity Index (BASDAI) score of ≥ 4 (0–10-point scale), a spinal pain assessment score of ≥ 4 on a visual analog scale (VAS; 0–10-cm scale), and an inadequate response to current or previous nonsteroidal antiinflammatory drugs (NSAIDs) or disease-modifying antirheumatic drugs (DMARDs) were eligible for participation in the study. Patients who were receiving NSAIDs had to have received continuous therapy for 3 months at the highest recommended doses or had to have been unable to receive a full 3-month course of full-dose NSAID therapy because of intolerance, toxicity, or contraindications. Patients were also required to have normal results of a chest radiograph within 3 months before randomization and to have undergone screening for latent tuberculosis (TB) using a purified protein derivative skin test and the QuantiFERON TB Gold test. Patients in whom latent TB was discovered were required to initiate therapy for TB prior to or simultaneously with the first dose of the study agent. Patients were excluded from the study if they had any of the following: complete ankylosis of the spine, any other inflammatory rheumatic disease, a serious infection within 2 months before randomization, active or latent TB or positive results of a tuberculin skin test before screening or recent contact with a person with active TB, an opportunistic infection within 6 months of screening, hepatitis, human immunodeficiency virus, a transplanted organ, malignancy, multiple sclerosis, or congestive heart failure.

Patients were allowed to continue concurrent treatment with methotrexate (MTX), sulfasalazine, hydroxychloroquine, corticosteroids, and NSAIDs at stable doses during the study. The following treatments were not permitted: systemic immunosuppressives, DMARDs (other than MTX, sulfasalazine, or hydroxychloroquine), or leflunomide within 4 weeks before the first administration of the study agent; alefacept or efalizumab within 3 months before the first administration of

the study agent; or any previous use of anti-TNF therapy, rituximab, natalizumab, or cytotoxic drugs.

The study was conducted at 57 centers in the US, Canada, Europe, and Asia. The protocol was reviewed and approved by the institutional review board or independent ethics committee at each site. All patients provided written informed consent. A list of the principal investigators and their locations is shown in Appendix A.

Study agent. Golimumab is a human IgG1 κ monoclonal antibody that specifically binds to both the soluble and membrane-bound forms of TNF α . Both golimumab and placebo were supplied as sterile liquid for subcutaneous injection in single-use, 2-ml vials. Each patient received 2 injections (0.5 ml and 1.0 ml) every 4 weeks. To maintain blinding, patients in the 50-mg group received active golimumab in the 0.5-ml syringe and placebo in the 1.0-ml syringe; patients in the 100-mg group received placebo in the 0.5-ml syringe and active golimumab in the 1.0-ml syringe; and patients in the placebo group received placebo in both syringes.

Study protocol. In this 24-week, double-blind, placebo-controlled study, patients were randomly assigned in a 1:1.8:1.8 ratio to receive placebo or golimumab at a dose of 50 mg or 100 mg. An interactive voice-response system with adaptive treatment allocation was used to assign patients to treatment. Randomization was stratified by investigational site and C-reactive protein (CRP) level (≤ 1.5 mg/dl or > 1.5 mg/dl). At week 16, patients who achieved $< 20\%$ improvement from baseline in both the total back pain and morning stiffness measures entered early escape in a double-blinded manner: patients in the placebo group received golimumab 50 mg, patients in the golimumab 50-mg group had a dose escalation to 100 mg, and patients in the 100-mg group continued to receive 100 mg.

Evaluations. The primary end point was the proportion of patients who achieved at least 20% improvement in the ASessment in AS International Working Group criteria (ASAS20) (8) at week 14. Secondary end points included ASAS 40% improvement (ASAS40) (9), ASAS partial remission (8), and 20% improvement in 5 of 6 ASAS domains (ASAS5/6) (9). Disease activity was evaluated using the BASDAI (10), the back pain VAS, the night pain VAS, the patient's global assessment, and the CRP level. Physical function was evaluated using the Bath AS Functional Index (BASFI) (11). Range of motion was assessed using the Bath AS Metrology Index (BASMI) (3-point scale) (12) and chest expansion. Health-related quality of life was measured using the Short Form 36 (SF-36) Health Survey (13). Sleep disturbance was assessed using the Jenkins Sleep Evaluation Questionnaire (JSEQ) (14), in which patients indicated the number of days they experienced problems falling asleep, staying asleep, early awakening, and awakening tired in the previous 30 days. The numbers of days were grouped according to predefined categories, and each category was given a score of 0–5, for a possible total score of 0–20.

Serum samples collected before each injection of study agent were used to measure the trough golimumab concentration. Serum samples obtained at baseline and at week 24 were assessed for the presence of antibodies to golimumab, using a previously described assay (5).

Statistical analysis. When designing the study, we assumed that 20% of patients in the placebo group (regardless

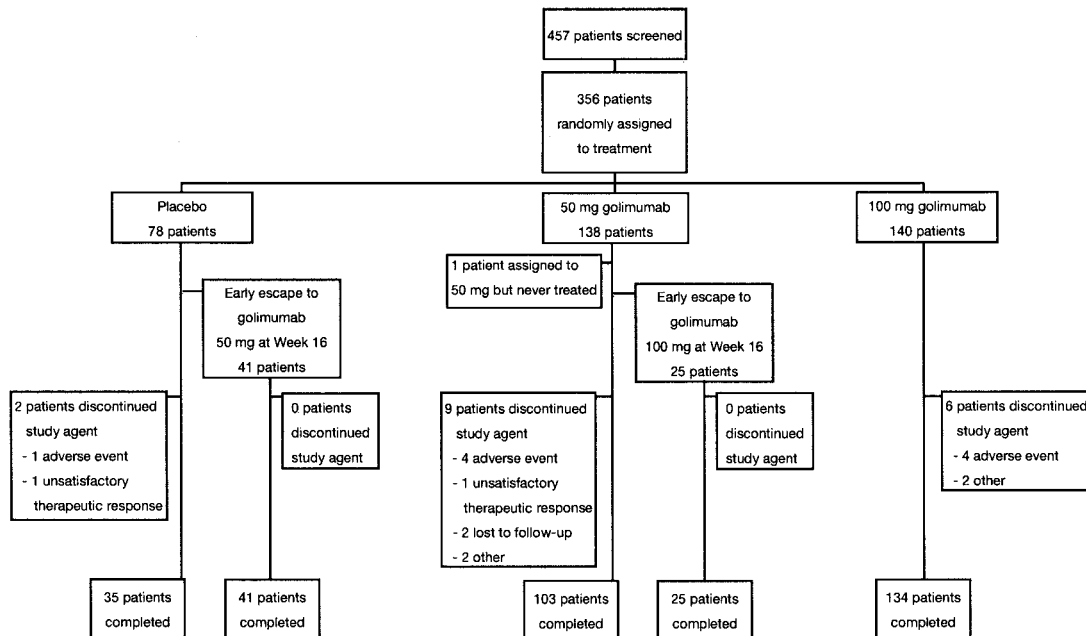


Figure 1. Patient disposition through week 24.

of CRP level), 35% of patients in the combined-golimumab group with a CRP level ≤ 1.5 mg/dl, and 60% of patients in the combined-golimumab group with a CRP level > 1.5 mg/dl would achieve the primary end point. Under these assumptions, a sample size of 135 patients in each golimumab group and 75 patients in the placebo group had $> 99\%$ power to detect a significant difference in the proportion of patients achieving the primary end point between the golimumab-treated groups and the placebo-treated group at the 0.05 level of significance. There was also $> 99\%$ power for the comparison between each individual golimumab treatment group and the placebo group.

In the primary efficacy analysis, data from all randomized patients were analyzed according to their assigned treatment group. A last observation carried forward procedure was used to impute any missing ASAS components for patients who had data for at least 1 ASAS component at week 14. Patients without data for any of the ASAS components at week 14 were considered not to have achieved the primary end point. In addition, patients who met any 1 of the following criteria before week 14 were considered not to have achieved the primary end point: initiated new DMARDs, biologic agents, or systemic immunosuppressives; increased the MTX, sulfasalazine, or hydroxychloroquine dose above the baseline level; initiated treatment with or increased the dose of corticosteroids; or discontinued study treatment due to an unsatisfactory therapeutic effect.

The proportions of patients who achieved the primary end point were compared between treatment groups using the Cochrane-Mantel-Haenszel test with stratification by the screening CRP level (≤ 1.5 mg/dl or > 1.5 mg/dl). For secondary end points, the proportions of patients were compared

using the Cochrane-Mantel-Haenszel test with the same stratification criteria as for the primary end point. Changes from baseline in continuous variables were compared between treatment groups using an analysis of variance on the normal van der Waerden test scores.

Patients in the placebo or 50-mg groups who met the criteria for early escape at week 16 were considered to be nonresponders at week 24. The actual observed week 24 values were used for patients in the 100-mg group who met the criteria for early escape at week 16.

A logistic regression analysis of the ASAS20 response at week 14 was performed based on the following factors: treatment group (placebo or golimumab at either dose), screening CRP level (≤ 1.5 mg/dl or > 1.5 mg/dl), DMARD use (yes or no), and the continuous variables body weight and duration of AS.

RESULTS

Data for this analysis were collected between December 2005 and May 2007. A total of 356 patients were randomly assigned to treatment (Figure 1). One patient was assigned to golimumab 50 mg but never received any study treatment before withdrawing from participation. One patient in the placebo group received a 50-mg dose of golimumab in error. As per the pre-specified data-handling rules, this patient was included in the placebo group for all efficacy analyses and in the golimumab 50 mg group for all safety analyses.

Table 1. Summary of demographics and baseline disease characteristics*

Characteristic	Placebo (n = 78)	Golimumab		
		50 mg (n = 138)	100 mg (n = 140)	Combined (n = 278)
Male sex, no. (%)	55 (70.5)	102 (73.9)	98 (70.0)	200 (71.9)
Race, no. (%)				
White	57 (73.1)	103 (74.6)	102 (72.9)	205 (73.7)
Black	1 (1.3)	0 (0.0)	2 (1.4)	2 (0.7)
Asian	18 (23.1)	32 (23.2)	35 (25.0)	67 (24.1)
Other	2 (2.6)	3 (2.2)	1 (0.7)	4 (1.4)
Age, years	41.0 (31.0–50.0)	38.0 (30.0–47.0)	38.0 (29.0–46.0)	38.0 (29.0–46.0)
Years since inflammatory back pain first occurred	16.0 (6.0–24.0)	11.0 (6.0–19.0)	11.0 (5.0–18.5)	11.0 (6.0–19.0)
Years since symptoms of SpA first occurred†	16.0 (5.0–25.0)	11.0 (6.0–18.0)	9.5 (4.0–18.0)	11.0 (5.0–18.0)
Years since diagnosis of ankylosing spondylitis	7.25 (2.80–18.60)	5.15 (1.60–11.60)	5.20 (1.50–13.25)	5.20 (1.50–12.30)
HLA-B27 positive, no. (%)	66 (84.6)	112 (81.8)	118 (84.3)	230 (83.0)
CRP, mg/dl	1.15 (0.30–2.40)	1.10 (0.50–2.50)	0.90 (0.40–2.50)	1.00 (0.40–2.50)
CRP ≤1.5 mg/dl, no. (%)	46 (59.0)	79 (57.2)	81 (57.9)	160 (57.6)
CRP >1.5 mg/dl, no. (%)	32 (41.0)	59 (42.8)	59 (42.1)	118 (42.4)
Patient's global assessment of disease activity (0–10-cm VAS)	7.2 (6.2–8.4)	7.0 (5.9–8.0)	7.2 (6.0–8.6)	7.1 (6.0–8.2)
Patient's assessment of total back pain (0–10-cm VAS)	7.6 (6.6–8.8)	7.5 (6.7–8.2)	7.9 (6.5–8.8)	7.6 (6.1–8.5)
Inflammation, overall morning stiffness (0–10-cm VAS)	7.1 (5.5–8.3)	7.1 (5.4–8.1)	7.6 (6.1–9.0)	7.3 (5.7–8.5)
Duration of morning stiffness, minutes	77.4 (45.6–104.4)	77.4 (52.8–99.6)	90.0 (60.0–117.6)	90.0 (60.0–112.8)
Chest expansion, cm	3.5 (2.3–4.5)	3.5 (2.5–5.5)	3.0 (2.0–5.0)	3.5 (2.5–5.2)
Night back pain (0–10-cm VAS)	7.4 (6.0–8.6)	7.1 (5.2–8.1)	7.6 (6.5–8.8)	7.4 (5.7–8.5)
BASDAI (0–10 scale)	6.6 (5.7–7.7)	6.6 (5.6–7.6)	7.0 (6.0–7.9)	6.8 (5.7–7.7)
BASF1 (0–10 scale)	4.9 (3.5–6.8)	5.0 (3.2–6.7)	5.4 (3.4–7.3)	5.2 (3.2–6.9)
BASMI (0–10 scale)	4.0 (2.0–5.0)	3.0 (2.0–4.0)	3.0 (2.0–5.0)	3.0 (2.0–5.0)
Short Form 36 Health Survey				
Physical component summary score (0–50 scale)	28.3 (23.8–34.1)	29.7 (22.5–35.3)	29.8 (25.2–35.5)	29.7 (24.0–35.5)
Mental component summary score (0–50 scale)	46.2 (37.1–54.8)	46.5 (36.8–54.1)	43.1 (33.5–53.5)	45.0 (34.8–53.9)
Jenkins Sleep Evaluation Questionnaire (0–20 scale)	9.0 (6.0–14.0)	10.0 (7.0–14.0)	11.0 (8.0–15.0)	11.0 (8.0–14.0)
History of extraaxial involvement, no. (%)				
Uveitis	25 (32.1)	28 (20.3)	30 (21.4)	58 (20.9)
Psoriasis	8 (10.3)	7 (5.1)	16 (11.4)	23 (8.3)
Inflammatory bowel disease	8 (10.3)	11 (8.0)	7 (5.0)	18 (6.5)
Dactylitis	1 (1.3)	9 (6.5)	13 (9.3)	22 (7.9)
Enthesitis	24 (30.8)	50 (36.2)	57 (40.7)	107 (38.5)
Peripheral arthritis	28 (35.9)	49 (35.5)	44 (31.4)	93 (33.5)
Patients taking methotrexate, no. (%)	15 (19.2)	29 (21.0)	28 (20.0)	57 (20.5)
Methotrexate dosage, mg/week	15.0 (12.5–15.0)	12.5 (10.0–15.0)	12.5 (10.0–15.0)	12.5 (10.0–15.0)
Patients taking sulfasalazine, no. (%)	24 (30.8)	33 (23.9)	37 (26.4)	70 (25.2)
Sulfasalazine dosage, gm/day	2.0 (1.3–2.0)	2.0 (1.0–2.0)	2.0 (1.0–2.0)	2.0 (1.0–2.0)
Patients taking hydroxychloroquine, no. (%)	2 (2.6)	2 (1.4)	1 (0.7)	3 (1.1)
Hydroxychloroquine dosage, mg/day	250 (200–300)	300 (200–400)	400 (400–400)	400 (200–400)
Patients taking corticosteroids, no. (%)	13 (16.7)	26 (18.8)	18 (12.9)	44 (15.8)
Prednisone or equivalent dosage, mg/day	7.5 (5.0–10.0)	6.3 (5.0–7.5)	5.0 (2.5–7.5)	5.0 (5.0–7.5)
Patients taking NSAIDs, no. (%)	72 (92.3)	124 (89.9)	123 (87.9)	247 (88.8)

* Except where indicated otherwise, values are the median (interquartile range). CRP = C-reactive protein; VAS = visual analog scale; BASDAI = Bath Ankylosing Spondylitis Disease Activity Index; BASFI = Bath Ankylosing Spondylitis Functional Index; BASMI = Bath Ankylosing Spondylitis Metrology Index; NSAIDs = nonsteroidal antiinflammatory drugs.

† Symptoms of spondylarthritis (SpA) include back pain, uveitis, psoriasis, dactylitis, enthesitis, peripheral arthritis, or inflammatory bowel disease.

The demographic and baseline disease characteristics were generally well balanced across treatment groups, except for disease duration (Table 1), which was shorter in the golimumab groups. The treatment groups were not balanced for the proportions of patients with some extraaxial manifestations. Baseline disease activity values indicated that patients had a moderately high level of pain and inflammation (Table 1).

Efficacy. The primary end point was achieved. Of the patients who received golimumab, 59.4% in the 50-mg group and 60.0% in the 100-mg group achieved an ASAS20 response at week 14 compared with 21.8% in the placebo group ($P < 0.001$) (Figure 2). Sensitivity analyses indicated that the primary end point was robust when patients who discontinued treatment because of adverse events were considered to be nonresponders,

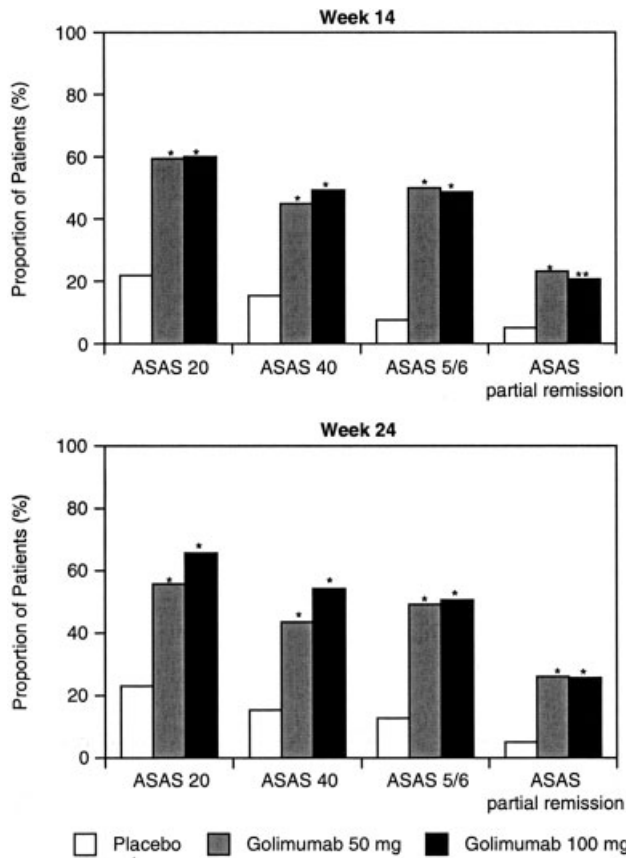


Figure 2. Proportions of patients achieving improvement in the ASessment in Ankylosing Spondylitis (ASAS) International Working Group criteria (20% improvement [ASAS20], 40% improvement [ASAS40], 20% improvement in 5 of 6 ASAS domains [ASAS5/6], and ASAS partial remission) at weeks 14 and 24. * = $P < 0.001$; ** = $P < 0.01$, versus placebo.

when patients with insufficient data to determine the ASAS20 response were considered to be nonresponders, and when the analysis was based on observed data only. The logistic regression analysis indicated that effects attributable to treatment group ($P < 0.001$), screening CRP level ($P = 0.0062$), and body weight ($P = 0.0140$) were significantly associated with ASAS20 responses, while use of DMARDs and duration of AS were not significantly associated.

The benefit of golimumab treatment was also consistent across subgroups of sex, race, age, geographic region, and body weight, except for patients in the 50-mg group in the weight quartile >87 kg and those in the 100-mg group in the weight quartile >75.15 kg to ≤ 87 kg; for both of these groups, the percent of patients with an ASAS20 response was not statistically significantly different from that observed in the placebo group (data

not shown). The response at week 14 in the combined-golimumab group was greater in patients with a CRP level >0.6 mg/dl (66.1%) compared with the response in those with a CRP level ≤ 0.6 mg/dl (49.5%), and in patients with a CRP level >1.5 mg/dl (70.3%) compared with those with a CRP level ≤ 1.5 mg/dl (51.9%).

Greater proportions of patients in the golimumab groups achieved an ASAS20 response at the first assessment, 4 weeks after the first injection (Figure 3A). The mean BASDAI and BASFI scores were lower in the golimumab groups through week 24 compared with the scores in the placebo group (Figures 3B and C). In addition, 43.5%, 54.3%, and 15.4% of patients in the

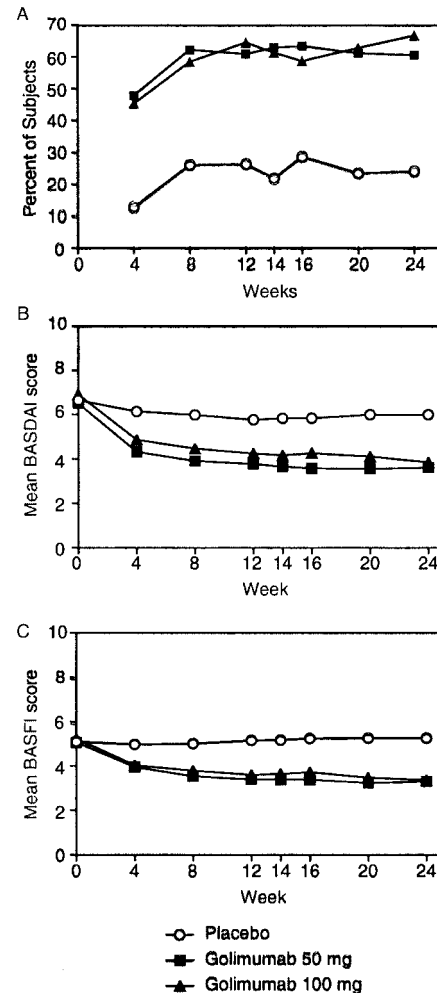


Figure 3. A, Proportion of patients achieving a 20% improvement in the ASessment in Ankylosing Spondylitis International Working Group criteria through week 24. B, Mean Bath Ankylosing Spondylitis Disease Activity Index (BASDAI) score through week 24. C, Mean Bath Ankylosing Spondylitis Functional Index (BASFI) score through week 24.

Table 2. Summary of changes in clinical signs and symptoms from baseline to week 14 and week 24*

Assessment	Placebo (n = 78)	Golimumab		
		50 mg (n = 138)	100 mg (n = 140)	Combined (n = 278)
Changes from baseline to week 14				
Patient's global assessment of disease activity (0–10-cm VAS)	−0.8 (−2.3, 0.30)	−2.8 (−5.0, −1.0)†	−3.4 (−5.3, −0.6)†	−3.0 (−5.2, −0.8)†
Patient's assessment of total back pain (0–10-cm VAS)	−0.8 (−3.1, 0.3)	−3.5 (−5.5, −0.8)†	−3.6 (−5.9, −0.9)†	−3.5 (−5.8, −0.9)†
Inflammation (overall morning stiffness) (0–10-cm VAS)	−0.5 (−1.9, 0.7)	−3.2 (−5.4, −1.2)†	−3.3 (−5.7, −0.8)†	−3.3 (−5.6, −1.0)†
BASFI (0–10 scale)	0.1 (−1.1, 1.1)	−1.4 (−3.1, −0.1)†	−1.5 (−3.0, −0.1)†	−1.4 (−3.1, −0.1)†
BASDAI50, no. (%)	12 (15.4)	61 (45.9)†	56 (40.9)†	117 (43.3)†
Night back pain (0–10-cm VAS)	−0.3 (−2.9, 0.5)	−3.0 (−5.3, −0.5)†	−3.1 (−5.9, −0.8)†	−3.0 (−5.7, −0.6)†
C-reactive protein, gm/dl	0.0 (−0.6, 0.2)	−0.7 (−2.0, 0.0)†	−0.5 (−2.2, 0.0)†	−0.6 (−2.0, 0.0)†
BASMI (0–10 scale)	0.0 (−1.0, 0.0)	0.0 (−1.0, 0.0)	0.0 (−1.0, 0.0)	0.0 (−1.0, 0.0)
Patients with ≥1-unit improvement in the BASMI, no. (%)	22 (29.3)	57 (44.2)‡	63 (48.1)†	120 (46.2)‡
Tragus-to-wall, cm	0.0 (−0.5, 1.0)	0.0 (−1.0, 0.5)	0.0 (−1.0, 1.0)	0.0 (−1.0, 0.8)
Lumbar flexion, cm	0.0 (−0.5, 0.5)	0.2 (0.0, 1.0)§	0.0 (−0.5, 0.6)	0.0 (−0.2, 1.0)‡
Cervical rotation, degrees	1.0 (−3.0, 10.0)	4.0 (0.0, 11.0)	5.0 (−1.0, 11.5)	5.0 (0.0, 11.0)
Lumbar side flexion, cm	0.5 (−0.7, 2.0)	1.0 (−0.5, 3.0)	1.0 (−0.5, 3.5)	1.0 (−0.5, 3.2)
Intermalleolar distance, cm	−1.3 (−7.0, 6.0)	2.5 (−2.0, 10.0)‡	3.7 (−3.3, 12.0)‡	2.8 (−2.0, 11.0)§
Chest expansion, cm	0.0 (−0.5, 0.60)	0.0 (−0.5, 1.0)	0.0 (−0.5, 0.9)	0.0 (−0.5, 1.0)
Short Form 36 Health Survey				
Physical component summary score (0–50 scale)	2.4 (−1.4, 7.8)	7.3 (1.5, 15.3)†	8.4 (2.3, 14.1)†	7.8 (1.9, 14.5)†
Mental component summary score (0–50 scale)	0.1 (−4.3, 5.3)	1.5 (−2.2, 7.8)‡	3.7 (−3.2, 12.1)§	2.5 (−2.6, 9.4)§
JSEQ (0–20 scale)	0.0 (−3.0, 1.0)	−3.0 (−5.0, 0.0)†	−3.0 (−6.0, 0.0)†	−3.0 (−6.0, 0.0)†
Changes from baseline to week 24				
Patient's global assessment of disease activity (0–10-cm VAS)	−0.2 (−2.2, 1.0)	−2.6 (−5.2, −1.0)†	−3.6 (−5.9, −0.6)†	−3.3 (−5.6, −1.0)†
Patient's assessment of total back pain (0–10-cm VAS)	−0.40 (−2.0, 1.0)	−3.5 (−5.6, −0.8)†	−3.9 (−6.4, −1.2)†	−3.7 (−6.3, −1.0)†
Inflammation (overall morning stiffness) (0–10-cm VAS)	−0.2 (−2.3, 0.8)	−3.5 (−5.4, −1.1)†	−3.7 (−6.2, −1.4)†	−3.6 (−5.8, −1.2)†
BASFI (0–10 scale)	0.4 (−1.1, 1.3)	−1.6 (−3.4, 0.0)†	−1.6 (−3.5, −0.3)†	−1.6 (−3.5, −0.2)†
BASDAI50, no. (%)	11 (14.7)	66 (50.8)†	66 (47.8)†	132 (49.3)†
Night back pain (0–10-cm VAS)	−0.4 (−1.9, 0.9)	−3.1 (−5.6, −0.8)†	−3.5 (−6.7, −0.8)†	−3.3 (−6.2, −0.8)†
C-reactive protein, gm/dl	0.0 (−0.6, 0.3)	−0.7 (−2.0, 0.0)†	−0.5 (−1.8, 0.0)†	−0.6 (−1.9, 0.0)†
BASMI (0–10 scale)	0.0 (−1.0, 0.0)	0.0 (−1.0, 0.0)	−0.2 (−1.0, 0.0)	0.0 (−1.0, 0.0)
Patients with ≥1-unit improvement in the BASMI, no. (%)	25 (34.2)	59 (47.2)	67 (51.1)‡	126 (49.2)‡
Tragus-to-wall, cm	0.0 (−1.0, 1.0)	0.0 (−1.5, 1.0)	0.0 (−1.3, 0.5)	0.0 (−1.5, 0.5)
Lumbar flexion, cm	0.0 (−0.5, 0.5)	0.5 (−0.2, 1.0)‡	0.3 (−0.3, 1.0)	0.4 (−0.2, 1.0)‡
Cervical rotation, degrees	4.0 (−2.0, 14.0)	5.5 (−2.0, 15.5)	5.0 (−2.0, 12.0)	5.0 (−2.0, 13.0)
Lumbar side flexion, cm	1.0 (−0.7, 2.5)	2.0 (0.0, 3.8)‡	1.0 (−0.5, 3.9)	1.5 (−0.2, 3.9)‡
Intermalleolar distance, cm	−2.0 (−8.0, 9.0)	6.0 (−2.0, 16.0)§	5.3 (−2.0, 15.0)§	6.0 (−2.0, 16.0)†
Chest expansion, cm	0.0 (−0.5, 0.7)	0.5 (−0.5, 1.3)‡	0.2 (−0.5, 1.0)	0.3 (−0.5, 1.0)‡
Short Form 36 Health Survey				
Physical component summary score (0–50 scale)	2.0 (−2.4, 7.7)	7.9 (1.1, 17.6)†	8.1 (2.1, 15.0)†	8.1 (2.0, 16.6)†
Mental component summary score (0–50 scale)	−0.3 (−3.2, 6.3)	1.4 (−3.3, 6.6)	5.2 (−2.3, 12.8)§	2.9 (−2.8, 9.7)‡
JSEQ (0–20 scale)	−1.0 (−3.0, 1.0)	−3.0 (−6.0, 0.0)†	−4.0 (−7.0, 0.0)†	−3.0 (−6.0, 0.0)†

* Except where indicated otherwise, values are the median (interquartile range). VAS = visual analog scale; BASFI = Bath Ankylosing Spondylitis Functional Index; BASDAI50 = at least 50% improvement from baseline in the baseline Bath Ankylosing Spondylitis Disease Activity Index score; BASMI = Bath Ankylosing Spondylitis Metrology Index; JSEQ = Jenkins Sleep Evaluation Questionnaire.

† $P < 0.001$ versus placebo.

‡ $P < 0.05$ versus placebo.

§ $P < 0.01$ versus placebo.

50-mg, 100-mg, and placebo groups, respectively, achieved an ASAS40 response at week 24. The proportions of patients achieving an ASAS20 response, an ASAS40 response, an ASAS5/6 response, or partial remission at week 24 were similar to those at week 14 (Figure 2).

Of the 41 patients who entered early escape at week 16, changing from placebo to golimumab at a dose of 50 mg, 50.0% showed an ASAS20 response at week

24. Of the 25 patients who entered early escape at week 16, changing from golimumab at a dose of 50 mg to a 100-mg dose of golimumab, 16.0% showed an ASAS20 response at week 24.

At both week 14 and week 24, patients who received golimumab showed statistically significant improvements in all components of the ASAS20 (Table 2). In addition, significantly more golimumab-treated patients achieved ≥50% improvement in the BASDAI

score compared with patients who received placebo (Table 2). Significant improvements in night back pain and the CRP level were observed in the golimumab groups from baseline to week 14 and week 24.

The median changes from baseline in BASMI scores at weeks 14 and 24 were similar between the treatment groups (Table 2). However, significantly more patients in the 50-mg and 100-mg golimumab groups showed ≥ 1 unit improvement from baseline in the BASMI score at week 14. In addition, 3 of the 5 component assessments of the BASMI (lumbar flexion, lumbar side flexion, and intermalleolar distance) improved at week 14 or week 24 for golimumab-treated patients. Although no improvement in chest expansion was observed at week 14, the median improvement in chest expansion at week 24 was significantly greater in the 50-mg and combined-golimumab groups compared with the placebo group ($P = 0.013$ and $P = 0.016$, respectively).

The SF-36 physical component summary scores and JSEQ scores improved significantly from baseline to weeks 14 and 24 in all golimumab groups compared with the placebo group (Table 2). The SF-36 mental component summary scores improved from baseline to week 14 in all golimumab groups compared with the placebo group, with sustained and significant improvement through week 24 in the 100-mg and combined-golimumab groups.

Golimumab serum concentration. Golimumab-treated patients demonstrated an approximately dose-proportional increase in serum golimumab concentrations (data not shown). Serum golimumab concentrations generally achieved steady state by week 12. Patients in the 50-mg group who met the criteria for early escape had lower median serum golimumab concentrations ($0.36 \mu\text{g/ml}$) before week 16 than did those who did not require early escape ($0.59 \mu\text{g/ml}$). The median serum concentration for the 21 patients who did not achieve an ASAS20 response after early escape ($1.04 \mu\text{g/ml}$) was similar to that for the 4 patients who did achieve an ASAS20 response ($0.90 \mu\text{g/ml}$). There was large variability in serum golimumab concentrations. However, patients with a heavier body weight tended to have lower serum golimumab concentrations.

Antibodies to golimumab. The incidence of antibodies to golimumab was low (4.1% of patients originally assigned to golimumab). None of the patients with antibodies were receiving concomitant MTX. The highest titer (1:2,560) was measured in a patient in the 50-mg group who entered early escape to the 100-mg dose.

Antibody-positive patients generally had low serum golimumab concentrations.

Safety. Through week 16, before patients had the possibility of entering early escape, 77.3% of those in the combined-golimumab group and 74.0% in the placebo group had ≥ 1 adverse event, with similar proportions in the 50-mg (79.0%) and 100-mg (75.7%) groups. Five patients (3.6%) in the 50-mg group, 7 patients (5.0%) in the 100-mg group, and 4 patients (5.2%) in the placebo group had serious adverse events through week 16.

Through week 24, the proportion of patients who had at least 1 adverse event was 79.9% in the all-golimumab group (which includes patients in the placebo group who met the criteria for early escape) and 85.6% in the combined-golimumab group (which includes only patients who were originally assigned to golimumab at the time of randomization), with similar proportions in the 50-mg (84.8%) and 100-mg (85.7%) groups (Table 3). Of the adverse events that occurred in $\geq 5\%$ of patients in the combined-golimumab group, nasopharyngitis, upper respiratory tract infections, fatigue, headache, diarrhea, injection-site erythema, and increases in alanine aminotransferase (ALT) or aspartate aminotransferase (AST) levels occurred more frequently in the combined-golimumab group than in the placebo group. Patients receiving DMARDs at baseline (MTX, sulfasalazine, or hydroxychloroquine) had lower incidences of adverse events compared with patients who were not receiving DMARDs at baseline.

The proportion of patients who had at least 1 serious adverse event through week 24 was 3.6% in the 50-mg group, 6.4% in the 100-mg group, 5.4% in the combined-golimumab group, and 6.5% in the placebo group (Table 3). One patient in the 50-mg group had a myocardial infarction on day 67, despite a normal screening cardiac evaluation 4 months prior. One patient in the 100-mg group experienced severe fatigue, depression, and hypertension. There were no deaths, opportunistic infections, or cases of TB.

Nine patients (2.9% of the 50-mg group, 2.9% of the 100-mg group, and 1.3% of the placebo group) discontinued study treatment because of an adverse event, including 1 patient in the 50-mg group and 2 patients in the 100-mg group who had increases in liver transaminase levels; 1 patient in the 50-mg group who had alcohol withdrawal syndrome, hallucination, and a suicide attempt; 1 patient in the 50-mg group with chest pain; 1 patient in the 50-mg group with blepharitis, nausea, and vomiting; 1 patient in the 100-mg group with hepatitis (noninfectious); 1 patient in the 100-mg group with depression and hypertension; and 1 patient in the

Table 3. Summary of adverse events and antibodies to golimumab through week 24*

	Placebo → golimumab		Golimumab				All golimumab (n = 319)
	Placebo (n = 77)	50 mg (n = 41)	50 mg (n = 138)	50 mg → 100 mg (n = 25)	100 mg (n = 140)	Combined (n = 278)	
Average number of injections	4.8	2.0	5.4	1.9	5.8	5.8	5.3
Median cumulative dose, mg	0.0	100	300	200	600	400	400
Any adverse event	59 (76.6)	17 (41.5)	117 (84.8)	14 (56.0)	120 (85.7)	238 (85.6)	255 (79.9)
Receiving DMARDs at baseline	19 (67.9)	4 (30.8)	34 (79.1)	3 (37.5)	34 (77.3)	69 (79.3)	73 (73.0)
No DMARDs at baseline	40 (81.6)	13 (46.4)	83 (87.4)	11 (64.7)	86 (89.6)	169 (88.5)	182 (83.1)
Any serious adverse event	5 (6.5)	0 (0.0)	5 (3.6)	1 (4.0)	9 (6.4)	15 (5.4)	15 (4.7)
Discontinued study agent because of an adverse event	1 (1.3)	0 (0.0)	4 (2.9)	0 (0.0)	4 (2.9)	8 (2.9)	8 (2.5)
Injection-site reaction	2 (2.6)	0 (0.0)	12 (8.7)	3 (12.0)	9 (6.4)	23 (8.3)	23 (7.2)
Any infection	28 (36.4)	9 (22.0)	64 (46.4)	5 (20.0)	68 (48.6)	135 (48.6)	144 (45.1)
Any serious infection	1 (1.3)	0 (0.0)	0 (0.0)	0 (0.0)	2 (1.4)	2 (0.7)	2 (0.6)
Any malignancy	1 (1.3)	0 (0.0)	0 (0.0)	0 (0.0)	1 (0.7)	0 (0.0)	1 (0.3)
Adverse event occurring in ≥5% of patients in the combined-golimumab group							
Nasopharyngitis	9 (11.7)	2 (4.9)	18 (13.0)	1 (4.0)	21 (15.0)	40 (14.4)	42 (13.2)
Upper respiratory tract infection	6 (7.8)	2 (4.9)	19 (13.8)	2 (8.0)	16 (11.4)	37 (13.3)	39 (12.2)
Fatigue	5 (6.5)	1 (2.4)	14 (10.1)	0 (0.0)	20 (14.3)	34 (12.2)	35 (11.0)
Arthralgia	8 (10.4)	0 (0.0)	13 (9.4)	1 (4.0)	10 (7.1)	23 (8.3)	23 (7.2)
Headache	2 (2.6)	0 (0.0)	11 (8.0)	0 (0.0)	11 (7.9)	22 (7.9)	22 (6.9)
ALT level increased	2 (2.6)	0 (0.0)	6 (4.3)	0 (0.0)	13 (9.3)	19 (6.8)	19 (6.0)
Cough	5 (6.5)	1 (2.4)	13 (9.4)	0 (0.0)	5 (3.6)	18 (6.5)	19 (6.0)
Diarrhea	3 (3.9)	0 (0.0)	11 (8.0)	2 (8.0)	6 (4.3)	18 (6.5)	18 (5.6)
Nausea	4 (5.2)	0 (0.0)	8 (5.8)	0 (0.0)	10 (7.1)	18 (6.5)	18 (5.6)
AST level increased	1 (1.3)	1 (2.4)	5 (3.6)	0 (0.0)	11 (7.9)	16 (5.8)	17 (5.3)
Injection-site erythema	0 (0.0)	0 (0.0)	5 (3.6)	3 (12.0)	8 (5.7)	15 (5.4)	15 (4.7)
Pharyngolaryngeal pain	4 (5.2)	1 (2.4)	10 (7.2)	2 (8.0)	4 (2.9)	15 (5.4)	16 (5.0)
Antibodies to golimumab	NA	0 (0.0)	5 (4.6)	3 (12.5)	3 (2.2)	11 (4.1)	11 (3.5)

* Except where indicated otherwise, values are the number (%) of patients. DMARDs = disease-modifying antirheumatic drugs; ALT = alanine aminotransferase; AST = aspartate aminotransferase; NA = not applicable.

placebo group who had headache, influenza-like illness, pain in the extremities, and increased body weight.

Nine patients had markedly abnormal postbaseline ALT or AST values ($\geq 100\%$ increase from baseline and a value >150 IU/liter), including 1 patient in the placebo group, 2 patients who were originally in the placebo group and then received 50 mg of golimumab, 2 patients in the 50-mg golimumab group, and 5 patients in the 100-mg golimumab group (2 patients in the 100-mg group had markedly abnormal levels of both ALT and AST). Three patients (all in the 100-mg group) discontinued the study agent because of elevations in their ALT or AST level. Some of the 6 patients who continued to receive treatment had concomitant medication adjustments. None of the 9 patients with a markedly abnormal ALT or AST value, including the patient with hepatitis, demonstrated symptoms of liver toxicity, and none had a concurrent markedly abnormal bilirubin value. Transaminase levels decreased to normal or to <3 -fold the upper limit of normal by week 24 in 8 of the 9 patients with

markedly abnormal ALT or AST values. The remaining patient had the markedly abnormal value at week 24, 8 weeks after receiving golimumab 50 mg as early escape, and this value had normalized after followup. Some of the patients with markedly abnormal ALT or AST values were receiving concomitant hepatotoxic medications (e.g., isoniazid, indomethacin, MTX, or sulfasalazine), were consuming alcohol, or had evidence of fatty liver (1 patient).

Prophylaxis for latent TB consisted of isoniazid monotherapy or a combination of isoniazid and rifampin. The proportions of patients with abnormal ALT or AST values were generally higher among those who received TB prophylaxis compared with those who did not receive prophylaxis (data not shown).

A greater proportion of patients in the golimumab groups (46.4% and 48.6% in the 50-mg and 100-mg groups, respectively) had at least 1 infection through week 24 compared with the placebo group (36.4%). Three patients had serious infections through week 24: 1 patient in the 100-mg group had infectious

mononucleosis, 1 patient in the 100-mg group had chronic otitis media, and 1 patient in the placebo group had gastrointestinal inflammation. Through week 24, 2 patients (1 in the placebo group and 1 in the 100-mg golimumab group) had a malignancy; both had basal cell carcinoma.

Through week 24, 8.7% and 6.4% of patients in the 50-mg and 100-mg groups, respectively, had at least 1 injection-site reaction compared with 2.6% of patients in the placebo group. The most common injection-site reaction was erythema. No injection-site reactions were serious. One patient in the early escape group who began treatment with 50 mg and then received 100 mg of golimumab experienced a severe injection-site reaction (erythema over a 7.5×6.5 -inch area on the arm). No patients discontinued the study agent because of injection-site reactions.

Through week 14, 10 (10.1%) of 99 patients in the 50-mg group, 16 (14.8%) of 108 patients in the 100-mg group, and 8 (12.9%) of 62 patients in the placebo group had newly positive test results for antinuclear antibodies. Of these, 1 patient (6.3%) in the 100-mg group also became positive for anti-double-stranded DNA antibodies. No patient had clinical features suggestive of drug-induced lupus.

DISCUSSION

This phase III study was the first to evaluate the efficacy and safety of subcutaneous injections of golimumab in patients with AS. The study population, consisting of patients with moderate-to-severe symptoms of back pain, was similar to that in previous studies of anti-TNF α agents in patients with AS, except that this was the first study to include a sizable proportion of Asian patients (24%).

Injections of golimumab (50 mg or 100 mg) every 4 weeks resulted in rapid, significant, and sustained improvement in the signs and symptoms of AS through week 24. No clear difference in efficacy was evident between the 50-mg and 100-mg dose groups through week 24. The primary efficacy end point was robust to sensitivity analyses, even when the longer disease duration in the placebo group was accounted for in a logistic regression analysis. Results of other outcomes, including the ASAS40 response, ASAS partial remission, the ASAS5/6 response, back pain, inflammation, 50% improvement in the BASDAI, and the BASFI, provided further evidence that golimumab-treated patients showed significant and clinically meaningful improvement.

The efficacy results of this study were similar in magnitude to those of previous studies of anti-TNF α agents in AS (2–4), although no data are available from direct comparisons in a single head-to-head study. However, currently available subcutaneous anti-TNF α agents are administered either twice weekly or once every 2 weeks. Thus, monthly dosing with golimumab would provide a more convenient dosing schedule compared with these agents. In addition, recent observational studies have shown that patients with spondylarthritis respond well to treatment with a second anti-TNF α agent (15,16), although golimumab was not evaluated in these studies.

A recent study showed that patients with elevated CRP levels and extensive spinal inflammation detected by magnetic resonance imaging were likely to respond to anti-TNF therapy (17). In our study, a greater proportion of patients with high screening CRP values achieved ASAS20 responses compared with those with lower screening CRP levels. However, significantly more golimumab-treated patients achieved an ASAS20 response compared with patients in the placebo group, regardless of the baseline CRP level.

No statistically significant differences in median BASMI scores at week 14 or week 24 were observed between the treatment groups. However, improvements in individual BASMI components (lumbar flexion, lumbar side flexion, intermalleolar distance), the proportions of patients with ≥ 1 -unit improvement in the BASMI, and the improvement in chest expansion suggest that golimumab may have provided some improvement in range of motion to patients in this study. In addition, we used a 3-point scale for the BASMI, which was recently shown to be less sensitive to change than the 11-point or linear method (18).

Fatigue is a well-described symptom in patients with AS (19,20); however, few studies have systematically evaluated sleep. This was the first study to evaluate the effect of an anti-TNF agent on sleep in patients with AS. The results show that golimumab-treated patients had a significantly greater reduction in sleep disturbance, as measured by the JSEQ, than patients in the placebo group. Patients receiving golimumab also demonstrated improved health-related quality of life as measured by the physical and mental component summary scores of the SF-36 Health Survey.

Trough serum golimumab concentrations achieved steady state at week 12 and generally increased in a dose-proportional manner through week 24. Although there was not a clear relationship between the trough serum golimumab concentration and the

ASAS20 response, it is possible that the lower serum golimumab concentration observed in heavier patients (e.g., patients in the 50-mg group weighing >87 kg) might partially account for the lower ASAS20 response in these patients. Patients who met the criteria for early escape from 50 mg to 100 mg of golimumab at week 16 generally had lower trough concentrations than those who did not require early escape. However, considering the large interpatient variability, it is not clear whether this difference between the groups was clinically meaningful. Only 4 of 25 patients (16%) who had dose escalations from 50 mg to 100 mg were ASAS20 responders after 8 weeks. The median serum trough concentrations at week 24 were similar for responders and nonresponders in this group. Thus, the inadequate response in most of these patients at week 16 was likely attributable to factors other than trough serum concentrations. Serum golimumab concentrations were generally low in patients who were positive for antibodies to golimumab. The incidence of antibodies to golimumab was low (4.1%), and thus there were too few antibody-positive patients to properly discern whether antibodies to golimumab affected efficacy and safety.

Golimumab was generally well tolerated by patients in this study, and the pattern of adverse events was consistent with the known safety profile of TNF α inhibitors. Patients receiving golimumab had a slightly greater proportion of infections than those in the placebo group. The most common infections were nasopharyngitis and upper respiratory tract infection. Serious infections were uncommon, occurring in 1 patient in the placebo group and 2 patients in the golimumab group. Serious adverse events were also infrequent and occurred in similar proportions in the golimumab and placebo groups through weeks 16 and 24. Overall, adverse events occurred more frequently in patients who were not receiving DMARDs at baseline compared with those who were receiving concomitant DMARDs at baseline, regardless of treatment group assignment. There were no deaths, cases of TB, or opportunistic infections. Injection-site reactions were infrequent and mostly mild, consisting primarily of injection-site erythema.

Nine patients had transient, markedly abnormal liver enzyme values ($\geq 100\%$ increase from baseline and a value >150 IU/liter), which have been previously reported in patients with AS who receive anti-TNF α agents (3,4). Levels subsequently decreased in all patients, including those who continued to receive the study agent. None of these patients had symptoms of liver toxicity.

Identifying treatments that provide safe and ef-

fective blockade of proinflammatory cytokines via an acceptable route of administration is a priority for the management of AS. Golimumab doses of 50 mg or 100 mg administered subcutaneously every 4 weeks were effective and well tolerated. Additional studies are planned to determine the long-term efficacy and safety of golimumab.

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AUTHOR CONTRIBUTIONS

Dr. Inman 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. Inman, Davis, van der Heijde, Mack, Han, Hsu, Beutler, Braun.

Acquisition of data. Inman, Davis Diekman, Sieper, Kim, Hsu, Braun. **Analysis and interpretation of data.** Inman, Davis van der Heijde, Mack, Han, Visvanathan, Xu, Hsu, Beutler, Braun.

Manuscript preparation. Inman, Davis van der Heijde, Sieper, Mack, Han, Xu, Hsu, Beutler, Braun, and Scott Newcomer (nonauthor; Centocor).

Statistical analysis. Mack, Han.

Trial coordination. Mischa Engel, Renato Gusinu, Andrea Bevis, Sean Murphy, Cecile Spiertz, Angela Rommens (nonauthors; Centocor).

ROLE OF THE STUDY SPONSOR

The conduct of the study was managed by a steering committee consisting of Drs. Inman, Davis, Braun, van der Heijde, and Hsu. This committee also designed the study, with input from the Centocor clinical trial team. Clinical data were collected by the investigators and/or study-site personnel and analyzed by Centocor statisticians and programmers, led by Drs. Mack and Han. An independent data-monitoring committee, paid for by Centocor, conducted periodic safety reviews. The study data were interpreted primarily by the steering committee, with contributions from the other authors. All authors reviewed the manuscript during its development, agreed to submit the manuscript, and approved the content of the final manuscript prior to submission.

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APPENDIX A: PRINCIPAL INVESTIGATORS AND STUDY CENTERS

The investigators who participated in this trial are as follows: Piet Geusens (Diepenbeek, Belgium), Frank Raeman (Merksem, Belgium), Serge Steinfeld (Brussels, Belgium), Thierry Appelboom (Brussels, Belgium), Kurt de Vlam (Leuven, Belgium), Christopher Atkins (Victoria, British Columbia, Canada), Andre Beaulieu (Sainte Foy, Quebec, Canada), Mary Bell (Toronto, Ontario, Canada), Robert Inman (Toronto, Ontario, Canada), Majed Khraishi (St. John’s, Newfoundland, Canada), Walter Maksymowych (Edmonton, Alberta, Canada), Proton Rahman (St. John’s, Newfoundland, Canada), Glen Thomson (Winnipeg, Manitoba, Canada), Kamran Shojania (Vancouver, British Columbia, Canada), Marjatta Leirisalo-Repo (Helsinki, Finland), Eero Jukka (Rauma, Finland), Yves Maugars (Nantes, France), Jürgen Braun (Herne, Germany), Christoph Fiehn (Baden-Baden, Germany), Mathias Gruenke (Erlangen, Germany), Michael Bäuerle (Erlangen, Germany), Herbert Kellner (Munich, Germany), Stefan Schewe (Munich, Germany), Joachim Sieper (Berlin, Germany), Henning Zeidler (Hannover, Germany), Reinhold Schmidt (Hannover, Germany), Ulf Müller-Ladner (Bad Nauheim, Germany), Piet van Riel (Nijmegen, The Netherlands), Désirée van der Heijde (Maastricht, The Netherlands), Sjeff van der Linden (Maastricht, The Netherlands), Won Tae Chung (Busan, South Korea), Sung Il Kim (Busan, South Korea), Tae-Hwan Kim (Seoul, South Korea), Sung Hwan Park (Seoul, South Korea), Gwan Gyu Song (Seoul, South Korea), Yeong Wook Song (Seoul, South Korea), Chung-Ming Huang (Taichung, Taiwan), Joung-Liang Lan (Taichung, Taiwan), Wen-Chan Tsai (Kaohsiung City, Taiwan), John Davis, Jr. (San Francisco, CA), Atul Deodhar (Portland, OR), Guy Fiocco (La Crosse, WI), Richard Jimenez (Edmonds, WA), Philip Mease (Seattle, WA), Frederick Murphy (North Duncansville, PA), Mark Pearson (Brookfield, WI), Eric Peters (Paradise Valley, AZ), John Reveille (Houston, TX), Yong Tsai (Ormond Beach, FL), Michael Weisman (Los Angeles, CA).