Golimumab in Patients with Active Rheumatoid Arthritis Despite Methotrexate Therapy: Results Through 2 Years of the GO-FORWARD Study Extension

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ABSTRACT. ***Objective.*** To assess the longterm efficacy and safety of golimumab in patients with active rheumatoid arthritis (RA) despite methotrexate (MTX) therapy.

Methods. We randomized 444 RA patients with inadequate response to MTX (3:3:2:2) to placebo + MTX (Group 1), golimumab 100 mg + placebo (Group 2), golimumab 50 mg + MTX (Group 3), or golimumab 100 mg + MTX (Group 4). Subcutaneous golimumab/placebo was injected every 4 weeks. Patients could escape early (Group 1 added golimumab 50 mg, Group 2 added MTX, Group 3 increased golimumab to 100 mg, Group 4 continued 100 mg) based on Week 16 swollen and tender joint counts. From Week 24, Group 1 patients received golimumab 50 mg + MTX. After the Week 52 database lock, patients in the longterm extension received golimumab 50–100 mg ± MTX. Coprimary endpoints [Week 14 American College of Rheumatology (ACR)20, Week 24 Health Assessment Questionnaire Disability Index (HAQ-DI)] and Week 52 findings have been published; 2-year findings (observed data by randomized group, no imputation) are presented.

Results. Of 444 randomized patients, 392 continued from Week 52 (Group 1: n = 116, Group 2: n = 116, Group 3: n = 84, Group 4: n = 76). Clinical improvement was maintained through Week 104; ~75% and 72% of patients randomized to golimumab 50 mg + MTX and 100 mg + MTX achieved ACR20 response, respectively. The majority [88% (105/120)] of golimumab + MTX–treated patients with Week 24 HAQ-DI improvement ≥ 0.25 maintained improved physical function through Week 104. Group 1 patients with delayed golimumab treatment exhibited more Week 104 radiographic progression (mean change score = 1.15) than golimumab + MTX-randomized patients (0.52). Incidences of serious infections were 2.24, 4.77, 5.78/100 patient-years of followup for golimumab 50 mg + MTX, 100 mg + placebo, and 100 mg + MTX, respectively.

Conclusion. Clinical improvement was maintained and no new safety signals were identified with 2 years of golimumab + MTX. Golimumab efficacy and safety, including serious infections, will continue to be monitored through 5 years (Clinical Trial No. NCT00264550). (First Release May 15 2013; J Rheumatol 2013;40:1097–103; doi:10.3899/jrheum.120584)

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Golimumab is a human monoclonal antibody to tumor necrosis factor-α (TNF-α), indicated for the treatment of rheumatoid arthritis (RA). In patients with active RA despite methotrexate (MTX) therapy, the addition of golimumab in the phase III, randomized, placebo-controlled GO-FORWARD study reduced the signs and symptoms of RA[1]. Clinical response was maintained through 1 year, with 77%–91% of patients exhibiting American College of Rheumatology (ACR)20 response at Week 24 and Week 52, and the golimumab safety profile appeared consistent with those of other TNF antagonists[2]. Minimal radiographic progression was observed in all groups. Although differences in modified Sharp score changes between groups were not statistically significant[3], golimumab + MTX significantly improved magnetic resonance imaging-detected synovitis and osteitis (predictors of future structural damage) versus placebo + MTX through Week 24[4]. We now present findings through Week 104 of the GO-FORWARD study, describing an additional year of golimumab efficacy and safety monitoring.

MATERIALS AND METHODS

Details of the GO-FORWARD (NCT00264550) trial have been reported[1,2]. The study was conducted according to the Declaration of Helsinki and good clinical practices. The protocol was reviewed and approved by each site's institutional review board or ethical committee, and informed consent was obtained prior to any study-related procedures. Patients with active RA[3] despite stable MTX therapy (15–25 mg/week) for ≥ 4 weeks were randomized 3:3:2:2 to placebo injections/MTX capsules (Group 1), golimumab 100 mg injections plus placebo capsules (Group 2), golimumab 50 mg injections plus MTX capsules (Group 3), or golimumab 100 mg injections plus MTX capsules (Group 4). All injections were administered subcutaneously (SC) every 4 weeks. Patients in Groups 1, 3, and 4 continued MTX; patients in Group 2 received sham MTX.

At Week 16, patients in Groups 1–3 with < 20% improvement in tender and swollen joint counts entered early escape (EE) and had study medication adjusted in a double-blind manner. Patients in Group 1 replaced placebo with golimumab 50 mg while continuing MTX; those in Group 2 replaced oral placebo with MTX (at the stable prescreening dose) while continuing golimumab 100 mg; and those in Group 3 increased golimumab from 50 mg to 100 mg while continuing MTX. Patients in Group 4 had no treatment adjustment.

At Week 24, patients in Group 1 who were still receiving placebo initiated blinded golimumab 50 mg injections. Patients in Groups 2, 3, and 4 continued their original or EE-modified treatment. Blinded treatment continued every 4 weeks through Week 52.

After Week 52, patients entered the longterm extension (LTE), during which the blind was broken after all patients completed the visit scheduled for Week 52 and the Week 52 database was locked. During the LTE, at the investigator's discretion, the golimumab dose could be increased from 50 mg to 100 mg and MTX doses could be adjusted or added. LTE visits were scheduled for every 12 weeks. The LTE continues through Week 268, and findings through Week 104 are reported here.

Clinical response was assessed using ACR criteria[5] and European League Against Rheumatism (EULAR) 28-joint Disease Activity Scores using C-reactive protein (DAS28-CRP)[6,7]. A DAS28-CRP score < 2.6 indicated clinical remission[8]. The Health Assessment Questionnaire Disability Index (HAQ-DI)[9] was used to assess physical function. Radiographs of both hands and both feet were obtained at baseline and Weeks 24, 52, and 104. Results for Reading Session 1 (baseline, Week 24, and Week 52) have been published[10]. Results from Reading Session 2 (baseline, Week 52, and Week 104) are now reported. Centrally digitized images were scored, using the Sharp/van der Heijde Score (SHS)[11], as described[10]. Safety was assessed by reported adverse events (AE). The incidences of death, serious infection, and malignancy were calculated per 100 patient-years to account for differences in followup between treatment groups. Observed incidences of malignancy were compared with those expected in the general US population per the Surveillance, Epidemiology, and End Results (SEER) database[12]. Standardized incidence ratios were calculated as "observed" (GO-FORWARD) divided by "expected" (SEER database) cases of malignancy, and exact 95% CI were determined. Nonmelanoma skin cancer is not included in the SEER database and thus is not included in the comparative analyses. Antibodies to golimumab were assessed using a bridging immunoassay[13] on blood samples collected prior to administration of study agent.

Observed clinical efficacy data through Week 104 were summarized by randomized treatment group (despite any protocol-mandated treatment changes) using descriptive statistics; missing data were not imputed. Patients with baseline and ≥ 1 followup SHS were included in radiographic analyses. Patients who discontinued treatment prematurely had images obtained at discontinuation; these scores were carried forward to Week 104. Radiographic scores were not linearly extrapolated. Patients receiving ≥ 1 SC injection were included in safety summaries according to actual treatment received.

RESULTS

Patient disposition and baseline characteristics. Data for this report were collected between December 2005 and March 2009. All 444 randomized patients received ≥ 1 dose of study agent, and 392 patients (88.3%) continued in the study from Week 52. At Week 16, 92 of 355 patients eligible for dose adjustment (25.9%) met the EE criteria and had their study treatment adjusted (Figure 1). During the LTE, 49 patients had the golimumab dose increased to 100 mg. Among these 49 patients, 23 (46.9%) demonstrated a state of low disease activity (DAS28-CRP score < 3.2) at the time of dose escalation. By Week 104, 90 patients (20.3%) discontinued SC therapy, including 44 patients (9.9%) who discontinued treatment because of AE; 18 patients (4.1%) because of unsatisfactory therapeutic effect; and 28 patients (6.3%) because of other reasons such as withdrawal of consent, loss to followup, or protocol violation. Baseline patient and disease characteristics have been reported[1].

Clinical response. As reported[1], golimumab + MTX was significantly more effective than MTX for most assessments of clinical response, including the primary study endpoint of Week 14 ACR20 response rates [55.6% (99/178) vs 33.1% (44/133), respectively; $p < 0.001$]. Among patients continuing treatment, the proportions of patients achieving ACR20 response at Week 104 were 74.7% (62/83) and 71.6% (48/67) for Group 3 and Group 4, respectively. Median improvements in swollen and tender joint counts at

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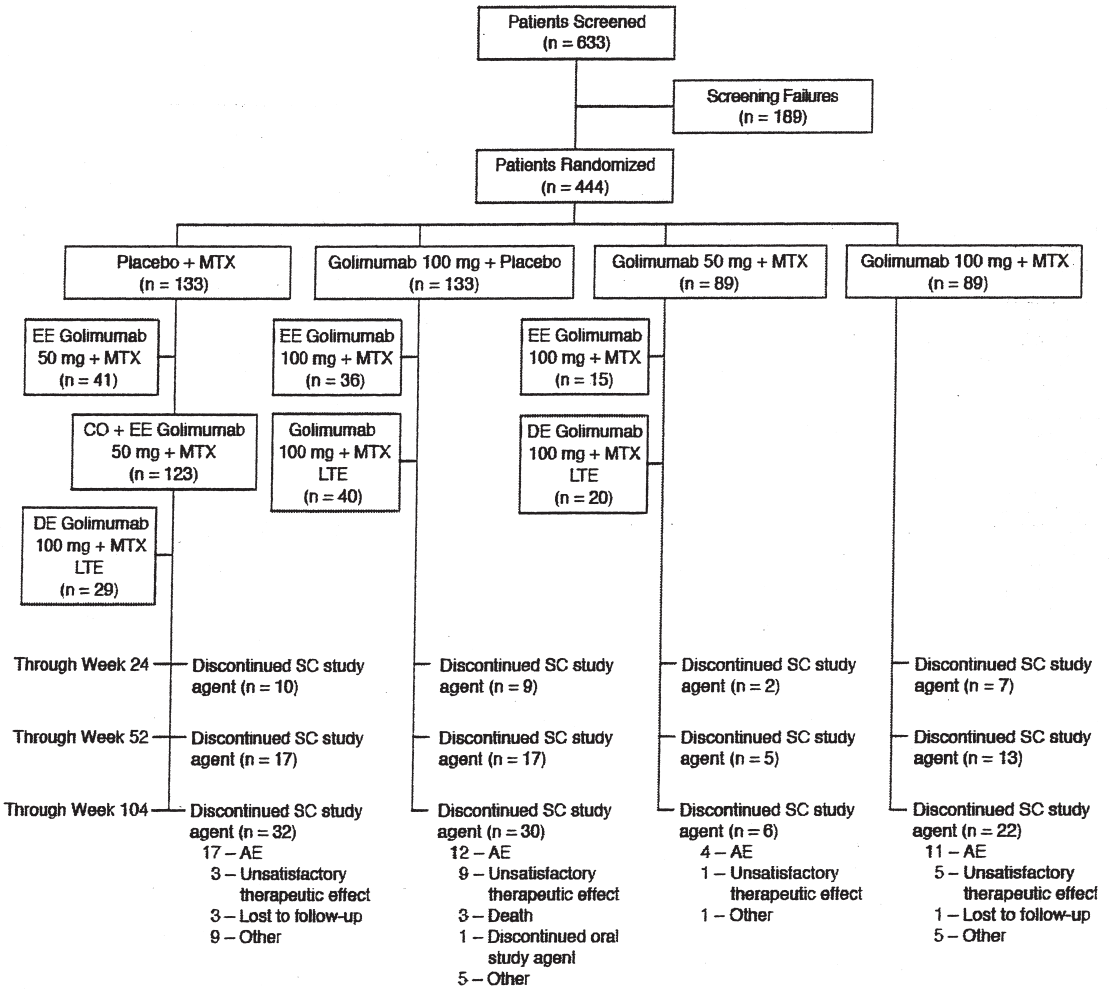

Figure 1. Patient disposition through Week 104; randomized patients. MTX: methotrexate; EE: early escape; CO: crossover; LTE: longterm extension; DE: dose escalation; SC: subcutaneous; AE: adverse event.

Week 104 were –10.0 and –16.5, respectively, in golimumab + MTX-randomized patients (Table 1), representing about 90% improvement from baseline.

Golimumab + MTX was also significantly more effective than MTX in the achievement of Week 24 EULAR/DAS28 response [74.2% (132/178) vs 42.1% (56/133); $p < 0.001$][1]. Among patients continuing treatment, 88.0% (73/83) and 91.0% (61/67) of patients in Group 3 and Group 4, respectively, achieved EULAR/DAS28 response at Week 104 (Table 1).

Physical function. Golimumab + MTX significantly improved Week 24 median HAQ scores (–0.44 vs –0.13 for MTX; $p < 0.001$)[1]. Median improvements in HAQ at Week 104 (0.6 in Group 3, 0.4 in Group 4) yielded a median HAQ score of 0.6 at Week 104 (Table 1), representing about 57% improvement from the baseline median score of 1.4[1].

At Week 104, 72.3% (60/83) and 73.1% (49/67) of patients in Group 3 and Group 4, respectively, had ≥ 0.25-unit improvement from baseline in HAQ scores. Among Week 24 HAQ responders, 86.7% (52/60) and 88.3% (53/60) of patients in Group 3 and Group 4, respectively, maintained improvement through Week 104 (Table 1).

Radiographic response. Mean changes from baseline in total SHS through Week 104 were small, particularly in patients randomized to golimumab + MTX (0.52). Group 1 patients, whose golimumab treatment was delayed, exhibited more progression at Week 104 (mean change = 1.15; Table 1).

Adverse events. Through Week 104, common AE included upper respiratory tract infection, cough, nasopharyngitis, bronchitis, and headache. AE led to discontinuation of SC study agent in 41 (9.4%) golimumab-treated patients (9.8% in 100 mg + placebo group, 6.6% in 50 mg + MTX group, 6.3% in 100 mg + MTX group; Table 2).

Ninety-eight (22.6%) golimumab-treated patients had serious AE (SAE). Serious infections were the most common SAE (6.7% of golimumab-treated patients). The incidences of serious infections per 100 patient-years of

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Table 1. Summary of clinical and radiographic response through Week 104. Data shown are change from baseline or number (%) of patients with response unless noted otherwise. Data are summarized by randomized treatment group.

	Group 1 Placebo + MTX[1]	Group 2 Golimumab 100 mg + Placebo[2]	Group 3 Golimumab 50 mg + MTX[3]	Group 4 Golimumab 100 mg + MTX	Combined Golimumab + MTX
Randomized patients	133	133	89	89	178
ACR20 response	68/104 (65.4%)	74/106 (69.8%)	62/83 (74.7%)	48/67 (71.6%)	110/150 (73.3%)
At Wk 52 and Wk 104	57/73 (78.1%)	59/69 (85.5%)	52/63 (82.5%)	40/46 (87.0%)	92/109 (84.4%)
ACR50 response	38/104 (36.5%)	49/106 (46.2%)	50/83 (60.2%)	34/67 (50.7%)	84/150 (56.0%)
At Wk 52 and Wk 104	28/47 (59.6%)	32/41 (78.0%)	32/41 (78.0%)	27/35 (77.1%)	59/76 (77.6%)
ACR70 response	24/104 (23.1%)	33/106 (31.1%)	26/83 (31.3%)	24/67 (35.8%)	50/150 (33.3%)
At Wk 52 and Wk 104	16/25 (64.0%)	16/23 (69.6%)	17/21 (81.0%)	20/28 (71.4%)	37/49 (75.5%)
Swollen joint count					
Median (IQR) joint count	2.0 (0.0, 5.0)	2.0 (0.0, 6.0)	2.0 (0.0, 6.0)	1.0 (0.0, 4.0)	1.5 (0.0, 4.0)
Median (IQR) change	–8.5 (–13.0, –5.5)	–8.0 (–14.0, –5.0)	–9.0 (–19.0, –5.0)	–10.0 (–15.0, –5.0)	–10.0 (–15.0, –5.0)
Tender joint count					
Median joint count	3.0 (1.0, 9.5)	3.0 (1.0, 9.0)	3.0 (0.0, 12.0)	2.0 (0.0, 9.0)	3.0 (0.0, 9.0)
Median (IQR) change	–15.0 (–23.0, –7.5)	–17.0 (–26.0, –7.0)	–17.0 (–30.0, –8.0)	–16.0 (–27.0, –10.0)	–16.5 (–28.0, –8.0)
DAS28-CRP					
Median (IQR) score	3.0 (1.9, 3.9)	3.0 (2.1, 3.9)	2.7 (1.9, 4.1)	2.5 (1.8, 3.8)	2.7 (1.9, 3.9)
Median (IQR) change	–2.1 (–3.1, –1.3)	–2.1 (–3.2, –1.6)	–2.5 (–3.4, –1.5)	–2.6 (–3.3, –1.9)	–2.6 (–3.4, –1.7)
Responder (Good + Moderate)	89/102 (87.3%)	91/105 (86.7%)	73/83 (88.0%)	61/67 (91.0%)	134/150 (89.3%)
At Wk 52 and 104	77/82 (93.9%)	80/90 (88.9%)	68/75 (90.7%)	56/59 (94.9%)	124/134 (92.5%)
Remission (< 2.6)	42/102 (41.2%)	43/105 (41.0%)	39/83 (47.0%)	35/67 (52.2%)	74/150 (49.3%)
At Wk 52 and Wk 104	22/31 (71.0%)	22/32 (68.8%)	24/34 (70.6%)	25/33 (75.8%)	49/67 (73.1%)
HAQ-DI score					
Median (IQR) score	0.9 (0.3, 1.4)	0.5 (0.1, 1.1)	0.5 (0.3, 1.4)	0.6 (0.3, 1.3)	0.6 (0.3, 1.4)
Median (IQR) change	0.4 (0.0, 0.7)	0.5 (0.1, 1.0)	0.6 (0.1, 1.0)	0.4 (0.1, 0.9)	0.5 (0.1, 0.9)
≥ 0.25–unit improvement	64/104 (61.5%)	75/106 (70.8%)	60/83 (72.3%)	49/67 (73.1%)	109/150 (72.7%)
At Wk 24 and Wk 104	43/47 (91.5%)	50/57 (87.7%)	52/60 (86.7%)	53/60 (88.3%)	105/120 (87.5%)
At Wk 52 and Wk 104	56/68 (82.4%)	60/64 (93.8%)	57/63 (90.5%)	46/50 (92.0%)	103/113 (91.2%)
SHS-Total[4,5]					
Mean (SD) change to Wk 104	1.15 (4.41)	1.87 (5.77)	0.51 (3.32)	0.54 (3.49)	0.52 (3.39)
No radiographic progression* at Wk 52	60/105 (57.1%)	60/106 (56.6%)	51/81 (63.0%)	44/66 (66.7%)	95/147 (64.6%)
No radiographic progression at Wk 104*	54/106 (50.9%)	56/108 (51.9%)	56/83 (67.5%)	46/69 (66.7%)	102/152 (67.1%)

[1] Includes patients who escaped early at Week 16 or crossed over at Week 24 to receive golimumab 50 mg + MTX or whose doses were escalated after Week 52 to receive golimumab 100 mg + MTX. [2] Includes patients who escaped early at Week 16 to receive golimumab 100 mg + MTX or added MTX after Week 52. [3] Includes patients who escaped early at Week 16 or whose doses were escalated after Week 52 to receive golimumab 100 mg + MTX. [4] Includes patients with baseline SHS and ≥ 1 SHS after Week 52. [5] Missing imputation rules were applied. Within type (erosion, joint space narrowing) and region (hand, foot), if ≥ 50% of joint scores were imputed with worst-case scores because of procedure or injection, then change from baseline of this subscore was imputed with worst change score of type-by-region subscores among all other patients. * Change in SHS ≤ 0. ACR: American College of Rheumatology; CRP: C-reactive protein; DAS28: Disease Activity Score using 28-joint count; HAQ-DI: Health Assessment Questionnaire (Disability Index); IQR: interquartile range; MTX: methotrexate; SHS: Sharp/van der Heijde Score.

followup were 2.24 (95% CI 0.90, 4.62) and 5.18 (95% CI 2.83, 8.69) for 50 mg + MTX and 100 mg + MTX, respectively, and 0.00 (95% CI 0.00, 5.83) for placebo (Table 2). Two patients developed active tuberculosis through Week 104 (50 mg + MTX: tuberculosis pleurisy; 100 mg + MTX: peritoneal tuberculosis).

Two patients (100 mg + placebo) died through Week 52 (sepsis, hepatic failure)[1,2]. The patient with hepatic failure experienced a complicated hospitalization including severe intraabdominal hemorrhage following liver biopsy. Two additional patients died through Week 104 (100 mg + placebo: complicated respiratory distress following acute pulmonary edema post-open cholecystectomy; 100 mg + MTX: circulatory insufficiency), yielding overall incidences of 0.53 (95% CI 0.15, 1.37)/100 pt-yrs for golimumab versus 0.00 (95% CI 0.00, 5.83)/100 pt-yrs for placebo (Table 2).

Two placebo-treated [3.89 (95% CI 0.47, 14.05)/100 pt-yrs] and 14 golimumab-treated [1.87 (95% CI 1.02, 3.13)/100 pt-yrs] patients had malignancy diagnosed through Week 104 (Table 2). Four patients (50 mg + MTX: n = 2; 100 mg + MTX: n = 2) had breast cancer, 1 patient (100 mg + MTX) had lymphoma, and 11 patients (placebo + MTX: n = 2; 100 mg + placebo: n = 3; 50 mg + MTX: n = 4; 100 mg + MTX: n = 2) had squamous and/or basal cell carcinoma (basal: n = 6, squamous: n = 3, squamous +

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Table 2. Summary of key safety findings through Week 104. Data presented are number (%) of patients unless specified otherwise.

	Placebo[1], Wks 0–24	Golimumab 100 mg + Placebo	Golimumab 50 mg + MTX	Golimumab + MTX Golimumab 100 mg + MTX	All Golimumab + MTX	All Golimumab
Golimumab-treated pts[2]	125	132	212	239	387	434
Average no. golimumab injections	—	16.4	18.4	14.8	19.4	21.6
Average followup time (wks)	—	66.0	76.6	58.8	78.3	89.9
Average cumulative golimumab dose (mg)	—	1634.5	919.3	1466.8	1407.0	1699.9
Total pt-yrs of followup	51.4	167.6	312.3	270.4	582.7	750.3
AE	—	109 (82.6)	181 (85.4)	154 (64.4)	314 (81.1)	388 (89.4)
Common AE[3]						
Upper respiratory tract infection		21 (15.9)	40 (18.9)	35 (14.6)	74 (19.1)	93 (21.4)
Cough		13 (9.8)	25 (11.8)	20 (8.4)	45 (11.6)	58 (13.4)
Nasopharyngitis		13 (9.8)	20 (9.4)	22 (9.2)	42 (10.9)	55 (12.7)
Bronchitis		11 (8.3)	26 (12.3)	16 (6.7)	42 (10.9)	50 (11.5)
Headache		8 (6.1)	19 (9.0)	19 (7.9)	37 (9.6)	45 (10.4)
Discontinuation of SC study agent because of AE(s)		13 (9.8)	14 (6.6)	15 (6.3)	29 (7.5)	41 (9.4)
Serious AE	—	26 (19.7)	33 (15.6)	41 (17.2)	73 (18.9)	98 (22.6)
Death						
No. patients	0 (0.0)	3 (2.3)	0 (0.0)	1 (0.4)	1 (0.3)	4 (0.9)
Incidence (95% CI) per 100 pt-yrs	0.00 (0.00, 5.83)	1.79 (0.37, 5.23)	0.00 (0.00, 0.96)	0.37 (0.01, 2.06)	0.17 (0.00, 0.96)	0.53 (0.15, 1.37)
Any infection		75 (56.8)	131 (61.8)	103 (43.1)	227 (58.7)	293 (67.5)
Treated infection(s)	—	58 (43.9)	98 (46.2)	83 (34.7)	177 (45.7)	229 (52.8)
Serious infection(s)	0 (0.0)	8 (6.1)	7 (3.3)	14 (5.9)	21 (5.4)	29 (6.7)
Incidence (95% CI) per 100 pt-yrs	0.00 (0.00, 5.83)	4.77 (2.06, 9.41)	2.24 (0.90, 4.62)	5.18 (2.83, 8.69)	3.60 (2.23, 5.51)	3.87 (2.59, 5.55)
Malignancies[4]						
No. patients	2 (1.6)	3 (2.3)	6 (2.8)	5 (2.1)	11 (2.8)	14 (3.2)
Incidence (95% CI) per 100 pt-yrs	3.89 (0.47, 14.05)	1.79 (0.37, 5.23)	1.92 (0.71, 4.18)	1.85 (0.60, 4.32)	1.89 (0.94, 3.38)	1.87 (1.02, 3.13)
SIR (95% CI) vs SEER[5]	0.00 (0.00, 8.40)	0.00 (0.00, 2.91)	1.04 (0.13, 3.76)	1.85 (0.38, 5.41)	1.41 (0.46, 3.29)	1.09 (0.35, 2.54)
Injection site reactions[6]						
Reaction to golimumab injection		14 (10.6)	10 (4.7)	12 (5.0)	22 (5.7)	36 (8.3)
Reaction to placebo injection		9 (6.8)	6 (2.8)	7 (2.9)	13 (3.4)	21 (4.8)

[1] Because of vast differences in length of followup for placebo versus golimumab treatment, incidence by length of followup is provided for AE of interest, i.e., death, serious infection, malignancy. [2] Patients may appear in more than 1 column. Thus, treatment groups are not mutually exclusive. [3] Absolute numbers and percentages of patients with 1 or more AE reported in 10% or more of golimumab-treated patients. The *Medical Dictionary for Regulatory Activities* (MedDRA) preferred terms are sorted by decreasing frequency in the "All Golimumab" group. [4] Two (1.5%) additional patients in the placebo + MTX group had malignancies through Week 52, yielding a total of 16 patients with malignancy. [5] SIR: standardized incidence ratio, i.e., observed/expected incidences of malignancy (excluding nonmelanoma skin cancer). [6] Injection site reactions were defined as any adverse reaction at a subcutaneous study agent injection site. MTX: methotrexate; pt-yrs: patient-years; SC: subcutaneous; SEER: Surveillance, Epidemiology and End Results; AE: adverse events.

basal: n = 2). For both death and malignancy, incidences by length of treatment/followup yielded overlapping 95% CI, suggesting no difference between the golimumab-treated patients treated through Week 104 and patients receiving placebo + MTX therapy through Week 24 (Table 2). Results of an additional analysis indicated that the incidence of malignancy (excluding nonmelanoma skin cancers) in patients receiving golimumab appeared to be similar to that expected in a general population based on the SEER database, because all 95% CI were inclusive of 1 (Table 2).

Injection-site reactions occurred in 8.3% of golimumab-treated and 4.8% of placebo-treated patients, with higher incidences observed in patients receiving golimumab 100 mg + placebo (10.6%) than golimumab + MTX (5.7%; Table 2). Most reactions, mainly erythema, were mild. No injection-site reaction was serious, and 1 patient (50 mg + MTX) discontinued study agent because of moderate injection-site erythema. No golimumab-treated patient experienced an anaphylactic or serum sickness reaction through Week 104.

Antibodies to golimumab. Antibodies to golimumab were detected in 6.3% (27/428) of golimumab-treated patients at Week 104. Patients randomized to golimumab 100 mg + placebo had a higher incidence of antibodies to golimumab (13.1%) than patients who received MTX since Week 0 (4.3%).

DISCUSSION

Our results demonstrate that the majority of patients continuing treatment with golimumab + MTX experienced sustained, significant improvements in disease activity and physical function through Week 104. At Week 24, golimumab (50 mg and 100 mg) + MTX was significantly more effective than MTX monotherapy for most assess-

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ments of clinical response, including ACR20 response at Week 14, which was achieved by about half of golimumab + MTX-treated patients[1]. Among patients who continued golimumab treatment, about three-quarters achieved ACR20 response at Week 104. Also at Week 104, swollen and tender joint counts were improved by about 90%, and about 50% of patients achieved DAS28-CRP remission (score < 2.6). Patients receiving golimumab + MTX also showed sustained, significant improvements from baseline in functional status, as demonstrated by about 60% improvement in the HAQ score from baseline[1]. In addition, > 70% of golimumab + MTX-treated patients had clinically significant improvements in HAQ at Week 104, and most (≥ 87%) who achieved HAQ improvement ≥ 0.25 at Week 24 maintained this clinically significant improvement at Week 104. Note that clinical and functional improvement observed at Week 52 was also observed at Week 104 in the vast majority of golimumab + MTX-treated patients (Table 1). As reported, radiographic progression through Week 24 was minimal in all groups, including the controls[10]. Consistent with these observations, mean changes from baseline in total SHS through Week 104 were small, particularly in patients randomized to golimumab + MTX.

Safety results observed among patients who continued treatment through 2 years were similar to those derived from earlier assessments[1,2]. While no new golimumab safety signals emerged, the higher incidence of serious infections with golimumab 100 mg + MTX than with 50 mg + MTX we observed was consistent with earlier reports of our study and reports from other studies of increased risk of serious infection with higher doses of golimumab[14] and other TNF antagonists[15,16]. The higher incidence of serious infections in the 100 mg + MTX group compared with the 50 mg + MTX group appeared to be driven by events that occurred soon after initiation of golimumab, i.e., 4 serious infections occurred within the first 2 months in the 100 mg + MTX group versus 1 such infection in the 50 mg + MTX group. This finding is consistent with a hypothesis that the indiscriminate randomization process likely leads to the higher dose being given to patients who may not require it and that this may contribute to a higher incidence of serious infection with the higher dose than would be observed in clinical practice, where greater TNF inhibition can be more selectively applied. The START study of infliximab supports this concept[15,17]. In that study, patients who were randomized to 10 mg/kg had a higher incidence of serious infections, while those whose doses were escalated based on clinical response did not. Serious infections were similar in nature to those reported previously in this[1,2] and other golimumab studies[14]. Despite testing performed at screening, 2 cases of active tuberculosis were observed through Week 104, both in areas with relatively higher background tuberculosis rates (Taiwan, Poland). These cases underscore the need for ongoing monitoring of patients receiving anti-TNF therapy for the onset of tuberculous infections[18].

Through Week 104, 4 golimumab-treated patients died (sepsis, hepatic failure, complicated respiratory distress, circulatory insufficiency). The 2 patients who died prior to Week 52 (sepsis, hepatic failure) are described in previous reports[1,2]. Two patients also died between Weeks 52 and 104. One patient underwent open cholecystectomy for cholelithiasis and developed acute pulmonary edema during the procedure. The patient's subsequent hospital course was complicated by hemothorax from subclavian puncture, and the patient eventually succumbed to complicated respiratory distress. The second patient died as a result of circulatory insufficiency. The patient was found dead at home 2 days after being discharged from the hospital for an RA flare. While the underlying cause of death remains unclear because no autopsy was performed, this patient had discontinued golimumab 7 weeks prior to death because of nonserious AE (infectious otitis and pharyngitis). Fourteen golimumab-treated patients had malignancies (breast: n = 4, lymphoma: n = 1, squamous/basal cell carcinoma: n = 9). When incidences of death and malignancy were assessed by length of treatment/followup, overlapping 95% CI suggested no difference between the golimumab-treated patients at Week 104 and patients receiving placebo + MTX therapy through Week 24. Results of an additional analysis indicated that the incidence of malignancy (excluding nonmelanoma skin cancers) in patients receiving golimumab appeared to be similar to that expected based on the SEER database, i.e., all 95% CI were inclusive of 1 (Table 2). It should be remembered that the SEER database is reflective of a general population and not patients with RA, who generally have worse overall health and are at increased risk of certain comorbidities and malignancies such as lymphoma.

Findings reported here are limited by several factors. First, given that no statistical inference testing was planned for the 2-year followup timepoint in the study, observed efficacy data are reported with no imputation of missing data. Therefore, response rates through 2 years could be higher owing to enrichment of the remaining study population with patients responding to treatment. However, most patients who discontinued by Week 104 did so because of AE (44 patients) or other generally administrative reasons (28 patients) and not because of lack of efficacy. As an additional limitation, the relatively short placebo-controlled period (6 months), with an early escape at Week 16 required for ethical reasons, makes comparisons between the active and placebo groups difficult, especially for safety analyses when examining the occurrence of rare safety events that accrue over time, such as malignancy and death.

The majority of patients continuing golimumab + MTX experienced significant improvements in RA signs and

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symptoms and physical function that were maintained, and exhibited only limited radiographic progression, through 2 years. No new golimumab safety signals were identified. Evaluation of longer-term efficacy and safety data, including the incidence of serious infections associated with the higher golimumab dose, for SC golimumab every 4 weeks in combination with MTX will continue through 5 years in these patients with an inadequate response to MTX.

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