ORIGINAL ARTICLE

Maintenance of Clinical and Radiographic Benefit With Intravenous Golimumab Therapy in Patients With Active Rheumatoid Arthritis Despite Methotrexate Therapy: Week-112 Efficacy and Safety Results of the Open-Label Long-Term Extension of a Phase III, Double-Blind, Randomized, Placebo-Controlled Trial

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Objective. To evaluate the safety, efficacy, pharmacokinetics, immunogenicity, and radiographic progression through 2 years of treatment with intravenous (IV) golimumab plus methotrexate (MTX) in an open-label extension of a phase III trial of patients with active rheumatoid arthritis (RA) despite MTX therapy.

Methods. In the phase III, double-blind, randomized, placebo-controlled GO-FURTHER trial, 592 patients with active RA were randomized (2:1) to intravenous golimumab 2 mg/kg plus MTX (Group 1) or placebo plus MTX (Group 2) at weeks 0 and 4, then every 8 weeks thereafter; placebo patients crossed over to golimumab at week 16 (early escape) or week 24 (crossover). The final golimumab infusion was at week 100. Assessments included American College of Rheumatology 20%, 50%, 70% (ACR20, ACR50, ACR70) response criteria, 28-joint count disease activity score using the C-reactive protein level (DAS28-CRP), physical function and quality of life measures, and changes in the modified Sharp/van der Heijde scores (SHS). Safety was monitored through week 112.

Results. In total, 486 patients (82.1%) continued treatment through week 100, and 68.1%, 43.8%, and 23.5% had an ACR20/50/70 response, respectively, at week 100. Clinical response and improvements in physical function and quality of life were generally maintained from week 24 through 2 years. Mean change from baseline to week 100 in SHS score was 0.74 in Group 1 and 2.10 in Group 2 ($P = 0.005$); progression from week 52 to week 100 was clinically insignificant in both groups. A total of 481 patients completed the safety followup through week 112; 79.1% had an adverse event, and 18.2% had a serious adverse event.

Conclusion. Clinical response to IV golimumab plus MTX was maintained through week 100. Radiographic progression following golimumab treatment was clinically insignificant between week 52 and week 100. No unexpected adverse events occurred through week 112, and the safety profile was consistent with anti–tumor necrosis factor therapy.

INTRODUCTION

The phase III GO-FURTHER trial investigated the safety and efficacy of intravenous (IV) infusions of golimumab 2 mg/kg at weeks 0, 4, and every 8 weeks thereafter in patients with active rheumatoid arthritis (RA) despite prior treatment with methotrexate (MTX) (1). Through 24 weeks, significantly greater proportions of patients treated

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Significance and Innovations

- The efficacy of intravenous golimumab 2 mg/kg in combination with methotrexate in patients with active rheumatoid arthritis despite prior methotrexate therapy was maintained through 2 years of therapy.
- Radiographic progression was clinically insignificant from week 52 through week 100, when all patients had been receiving intravenous golimumab plus methotrexate for several months.

with golimumab 2 mg/kg infusions plus MTX achieved improvement in the American College of Rheumatology (ACR) 20%, 50%, 70% (ACR20, ACR50, ACR70) response criteria (2) when compared with those who received MTX monotherapy (1). Clinical response to IV golimumab plus MTX was rapid, often occurring as early as week 2, and the majority of patients who were responders at week 24 had a sustained response through week 52 (1,3). Patients treated with IV golimumab plus MTX also had significantly less radiographic progression through 24 weeks than did patients who were treated with MTX monotherapy, and radiographic progression was minimal between weeks 24 and 52 (3). Safety results through 1 year of the GO-FURTHER trial were comparable to those observed for subcutaneous golimumab and other anti–tumor necrosis factor (anti-TNF) therapies (1,3). Here we report the final safety, efficacy, pharmacokinetic, and immunogenicity results of the GO-FURTHER trial through 2 years.

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PATIENTS AND METHODS

Patients and study design. The GO-FURTHER patient population and study design have been previously described in detail (1). Adult patients (≥18 years) with active RA for ≥3 months despite MTX therapy were eligible. All enrolled patients were on a stable dose of MTX (15–25 mg/week) for ≥4 weeks before screening. Eligibility criteria included ≥6 of 66 swollen joints and ≥6 of 68 tender joints, C-reactive protein (CRP) level ≥1.0 mg/dl (upper limit of normal [ULN] 1.0 mg/dl), and a positive anti–cyclic citrullinated peptide antibody and/or rheumatoid factor result at screening. All patients were screened for signs of latent or active tuberculosis (TB) using the QuantiFeron-TB Gold (QFT; Qiagen) test and chest radiographs; patients were also screened using tuberculin skin testing if the QFT test was not approved or registered in that country. Eligible patients were randomized (2:1) to receive weekly MTX and IV infusions of either golimumab 2 mg/kg (Group 1) or placebo (Group 2) at weeks 0, 4, and every 8 weeks thereafter. Infusions were administered over 30 ± 10 minutes. Patients were stratified by investigational site and CRP level (< or ≥1.5 mg/dl). At week 16, patients in Group 2 with <10% improvement in both swollen and tender joint counts entered blinded early escape and received IV golimumab 2 mg/kg at weeks 16, 20, and every 8 weeks thereafter. No changes to the golimumab dose were permitted for patients in Group 1, regardless of their early escape status. At week 24, all patients in Group 2 who were still receiving placebo crossed over to receive IV golimumab 2 mg/kg at weeks 24, 28, and every 8 weeks thereafter. An additional placebo infusion was administered at week 24 to patients initially randomized to golimumab to maintain the blind. The final golimumab infusions were at week 100.

Concomitant use of nonsteroidal antiinflammatory drugs or other analgesics for RA and oral corticosteroids (≤10 mg prednisone/day) was permitted. Patients were to remain on stable doses of permitted concomitant medications (including MTX); however, temporary reductions in dose or discontinuation were permitted if medically necessary (e.g., abnormal laboratory values, adverse effects, concurrent illness). After week 52, MTX could be substituted with another disease-modifying antirheumatic drug (e.g., sulfasalazine) if the patient was intolerant to MTX. Prior treatment with anti-TNF therapies was prohibited, and throughout the entire study, treatment with other anti-TNF agents, any cytotoxic agents, or investigational drugs was prohibited.

Assessments. The primary endpoint was the proportion of patients who achieved an ACR20 response at week 14 (1). Other efficacy assessments included ACR50 and ACR70 responses, changes from baseline in the 28-joint count disease activity score using the CRP level (DAS28-CRP) (4), and the proportions of patients with a good or moderate DAS28-CRP (European League Against Rheumatism [EULAR]) response (5) or DAS28-CRP level <2.6. In a post hoc analysis, the Simplified Disease Activity Index (6) and the Clinical Disease Activity Index (7) scores were determined at weeks 24, 52, and 100. Physical function

was assessed with the health assessment questionnaire disability index (HAQ DI) (8), with a minimum clinically important difference defined as an improvement ≥0.25 (9). Radiographs of the hands and feet were acquired at baseline and weeks 24, 52, and 100. Radiographic progression was evaluated using the modified Sharp/van der Heijde score (SHS) (10).

Patient-reported quality of life outcomes were collected at weeks 0, 12, 16, 24, 52, and 112. Health-related quality of life was evaluated with the Short Form 36 (SF-36) physical component summary (PCS) and mental component summary (MCS) scores. Overall health status was measured using the EuroQol 5-domain visual analog scale (EQ-5D VAS), which ranges from 100 (best imaginable health state) to 0 (worst imaginable health state) (11,12). Fatigue was assessed using the Functional Assessment of Chronic Illness Therapy-Fatigue (FACIT-F) score, a 13-item questionnaire that assesses a patient's level of fatigue and tiredness over the previous 7 days (13). The impact of disease on daily productivity at work, school, or home in the previous 4 weeks was self-reported using a VAS (where 0 = productivity not affected at all and 10 = productivity affected very much), with lower scores and negative changes indicating improvement.

Safety was assessed by monitoring vital signs and laboratory investigations as well as adverse event (AE) reporting through week 112. Serum samples were collected at weeks 0, 20, 52, 76, and 100 for evaluation of the presence of antibodies to golimumab using a validated antigen bridging enzyme immunoassay that was previously described by Zhou et al (14).

Serum samples for determination of golimumab concentrations were collected at weeks 0, 2, 4, 8, 12, 14, 16, 20, 36, 52, 76, and 100. Patients were included in the pharmacokinetic analysis if they had ≥1 golimumab infusion and ≥1 reported serum concentration value.

Statistical analysis. Results were summarized using descriptive statistics. For efficacy analyses, patients were analyzed by randomized treatment group. Analyses of the primary and secondary endpoints through week 52 have been previously described (1,3). All clinical efficacy results were analyzed based on the intent-to-treat principle. For analyses of the ACR20/ACR50/ACR70, DAS28-CRP EULAR, and HAQ DI response after week 24, patients who discontinued the study agent due to unsatisfactory therapeutic effect were considered to be treatment failures and counted as nonresponders at the time of treatment discontinuation and at all subsequent time points, and missing data were imputed using last observation carried forward (LOCF) methodology. For continuous variables, if the baseline value was missing, the median change for all patients in the same CRP stratum (< or ≥1.5 mg/dl) was applied, and missing data at nonbaseline time points were imputed using LOCF.

Radiographic results through week 52 have been previously described and included scores from baseline, week 16/24, and week 52 (3). The current analysis included radiographs obtained at baseline, week 52, and week 100 conducted in a separate reading session; radiographs from baseline and week 52 were re-read for the current analysis.
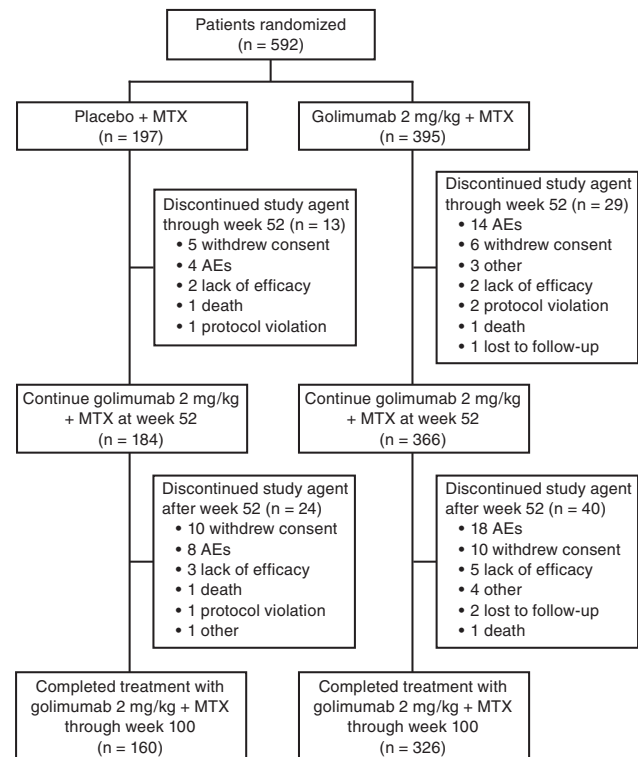
Figure 1. Patient disposition through week 100. AE = adverse event; MTX = methotrexate.

The change from baseline to week 100 in SHS was summarized by randomized treatment group, and differences between treatment groups were tested using an analysis of variance on the van der Waerden normal scores test with a 2-sided significance level of 0.05. The change in SHS score from week 52 to week 100 was summarized by randomized treatment group. The proportion of patients with radiographic progression at week 100 based on the smallest detectable change (3.22) (15) was reported by randomized treatment group, and differences between groups were tested using a 2-sided (α = 0.05) Cochran-Mantel-Haenszel test stratified by baseline CRP level (< or ≥1.5 mg/dl).

RESULTS

Patient disposition. A total of 592 patients were randomized to receive IV infusions of golimumab 2 mg/kg (Group 1, n = 395) or placebo (Group 2, n = 197). Patient disposition through week 52 has been previously described (1,3). At week 16, 68 patients in Group 2 met the early escape criteria and began receiving golimumab 2 mg/kg, and at week 24, another 121 patients from Group 2 crossed over to golimumab as specified in the protocol. Through week 52, a total of 42 patients (Group 1, n = 29; Group 2, n = 13) discontinued the study agent (3) (Figure 1). After week 52, an additional 64 patients discontinued the study agent (Group 1, n = 40; Group 2, n = 24); the most common reasons were AEs (n = 21) and withdrawal of consent (n = 16). Thus, through week 100, a total of 69

Table 1. Clinical efficacy and radiographic results at week 100*			
	Placebo + MTX → golimumab 2 mg/kg	Golimumab 2 mg/kg + MTX	All patients
Clinical efficacy			
ACR response week 100			
ACR20	130/197 (66.0)	273/395 (69.1)	403/592 (68.1)
ACR50	81/197 (41.1)	178/395 (45.1)	259/592 (43.8)
ACR70	47/197 (23.9)	92/395 (23.3)	139/592 (23.5)
Maintenance of ACR response week 52–100			
ACR20	106/120 (88.3)	218/249 (87.6)	324/369 (87.8)
ACR50	49/62 (79.0)	125/150 (83.3)	174/212 (82.1)
ACR70	20/29 (69.0)	52/71 (73.2)	72/100 (72.0)
DAS28-CRP score			
Improvement from baseline to week 100, mean ± SD	2.2 ± 1.5	2.4 ± 1.5	2.3 ± 1.5
Patients with good/moderate response at week 100	153/197 (77.7)	332/395 (84.1)	485/592 (81.9)
Maintenance of DAS28-CRP response week 52–100	132/146 (90.4)	290/304 (95.4)	422/450 (93.8)
Patients in remission at week 100	50/197 (25.4)	114/395 (28.9)	164/592 (27.7)
SDAI score			
No. of patients	197	395	592
Improvement from baseline to week 100, mean ± SD	24.2 ± 15.8	25.1 ± 15.5	24.8 ± 15.6
Range	(−14.4, 62.3)	(−29.9, 73.0)	(−29.9, 73.0)
CDAI score			
No. of patients	197	395	592
Improvement from baseline to week 100, mean ± SD	23.2 ± 15.2	23.6 ± 14.6	23.5 ± 14.8
Range	(−16.8, 60.3)	(−23.1, 65.3)	(−23.1, 65.3)
HAQ DI			
No. of patients	197	395	592
Improvement from baseline to week 100, mean ± SD	0.47 ± 0.62	0.53 ± 0.66	0.51 ± 0.65
Range	(−1.5, 2.1)	(−1.3, 2.5)	(−1.5, 2.5)
Patients with improvement ≥0.25	131 (66.5)	266 (67.3)	397 (67.1)
Radiographic results			
No. of patients	197	395	592
Change from baseline to week 100 in total SHS, mean ± SD	2.10 ± 7.42	0.74 ± 6.32†	1.19 ± 6.73
Change from baseline to week 100 in joint space narrowing score, mean ± SD	1.67 ± 3.91	0.81 ± 3.56	1.09 ± 3.67
Change from baseline to week 100 in erosion score, mean ± SD	0.43 ± 4.62	−0.07 ± 3.68	0.10 ± 4.02
Change from week 52 to week 100 in total SHS, mean ± SD	0.80 ± 3.03	0.56 ± 3.07	0.64 ± 3.06
Patients with change from baseline to week 100 in total SHS ≤0	108/197 (54.8)	244/395 (61.8)	352/592 (59.5)
Patients with progression at week 100 based on the SDC‡	47/197 (23.9)	66/395 (16.7)	113/592 (19.1)

* Values are the no. of patients/total (%) unless indicated otherwise. MTX = methotrexate; ACR 20/50/70 = American College of Rheumatology 20%, 50%, 70% response criteria; DAS28-CRP = 28-joint count disease activity score using C-reactive protein; SDAI = simplified disease activity index; CDAI = clinical disease activity index; HAQ DI = health assessment questionnaire-disability index; SHS = modified Sharp/van der Heijde score; SDC = smallest detectable change.
† *P* = 0.005.
‡ SDC = 3.22 for change in total SHS from baseline to week 100.

patients (17.5%) in Group 1 discontinued the study agent, with the most common reasons being AEs (n = 32) and withdrawal of consent (n = 16) (Figure 1); only 7 patients (1.8%) discontinued for lack of efficacy through week 100.

In Group 2, a total of 37 patients (18.8%) discontinued the study agent through week 100; 15 patients withdrew consent, and 12 discontinued due to AEs. In total, 486 patients continued golimumab treatment through week

Table 2.	Patient-reported outcomes through week 112*		
Improvement from baseline	**Placebo + MTX → golimumab 2 mg/kg (n = 197)**	**Golimumab 2 mg/kg + MTX (n = 395)**	**All patients (n = 592)**
SF-36 PCS			
Week 24	3.8 ± 7.3	8.3 ± 8.3†	–
Week 52	6.9 ± 8.0	8.1 ± 8.8	7.7 ± 8.6
Week 112	7.0 ± 8.5	7.6 ± 9.1	7.4 ± 8.9
SF-36 MCS			
Week 24	1.2 ± 10.1	6.9 ± 10.3†	–
Week 52	3.9 ± 11.2	6.9 ± 11.2	5.9 ± 11.3
Week 112	3.7 ± 11.3	5.7 ± 11.2	5.1 ± 11.2
FACIT-F			
Week 24	2.5 ± 10.2	8.0 ± 10.8†	–
Week 52	6.2 ± 10.3	8.4 ± 11.1	7.6 ± 10.8
No. patients	183	360	543
Week 112	6.1 ± 10.6	7.0 ± 11.0	6.7 ± 10.9
No. patients	164	330	494
EQ-5D VAS (scale 0–100)			
Week 24	8.3 ± 24.6	19.1 ± 29.9†	–
Week 52	15.0 ± 26.7	21.4 ± 27.4	19.2 ± 27.3
No. patients	181	356	537
Week 112	15.3 ± 28.2	19.9 ± 29.6	18.4 ± 29.2
No. patients	163	326	489
Impact of disease on daily productivity at work, school, or home (VAS scale 0–10)			
Week 24	1.0 ± 3.0	2.8 ± 2.9†	–
Week 52	1.9 ± 3.1	2.6 ± 3.4	2.3 ± 3.3
No. patients	117	237	354
Week 112	1.3 ± 4.0	2.2 ± 3.2	1.9 ± 3.5
No. patients	112	230	342

* Values are mean ± SD unless indicated otherwise. MTX = methotrexate; SF-36 PCS = Short Form 36 physical component summary; MCS = mental component summary; FACIT-F = Functional Assessment of chronic Illness Therapy-Fatigue; EQ-5D VAS = EuroQol 5-domain visual analog scale.
† $P = 0.001$ versus placebo.

100, and 481 patients completed the safety followup through week 112.

Clinical efficacy. The primary endpoint (ACR20 at week 14) was achieved, with 58.5% of patients in Group 1 achieving an ACR20 response versus 24.9% of patients in Group 2 (1). Through the placebo-controlled period of the study, patients in Group 1 had significantly greater improvements in clinical efficacy endpoints when compared with Group 2 (1), and clinical response was maintained through week 52 (3). At week 100, ACR20, ACR50, and ACR70 response rates in Group 1 were 69.1%, 45.1%, and 23.3%, respectively; response rates at week 100 among patients in Group 2, who initially received placebo and crossed over to golimumab at week 16 or 24, were 66.0%, 41.1%, and 23.9%, respectively (Table 1). More than 80% of all patients had a good or moderate DAS28-CRP response at week 100, and approximately 28% of patients achieved DAS28-CRP < 2.6 (Table 1). The mean improvement in HAQ DI score from baseline to week 100 among all patients was 0.51, and 67.1% of patients had an improvement in HAQ DI exceeding the minimum clinically important difference of 0.25 (Table 1).

Maintenance of response from week 52 to week 100 was observed for those patients who were responders at week 52 (Table 1). Among patients who were ACR20, ACR50, or ACR70 responders at week 52, 87.8% (n = 324 of 369), 82.1% (n = 174 of 212), and 72.0% (n = 72 of 100), respectively, maintained this response at week 100. Likewise, DAS28-CRP response was maintained by nearly all (93.8%, n = 422 of 450) patients who had a good or moderate response at week 52.

Patient-reported outcomes. Patients in Group 1 had significantly greater improvements from baseline to week 24 in health-related quality of life compared with patients in Group 2 (16). Improvements in SF-36 PCS and MCS scores, FACIT-Fatigue, EQ-5D VAS, and the impact of disease on productivity were maintained through week 52 and week 112 in Group 1 (Table 2). For patients in Group 2, improvements in health-related quality of life increased from week 24 to week 52 and were sustained through week 112.

Radiographic results. Patients in Group 1 had significantly less radiographic progression from baseline to week
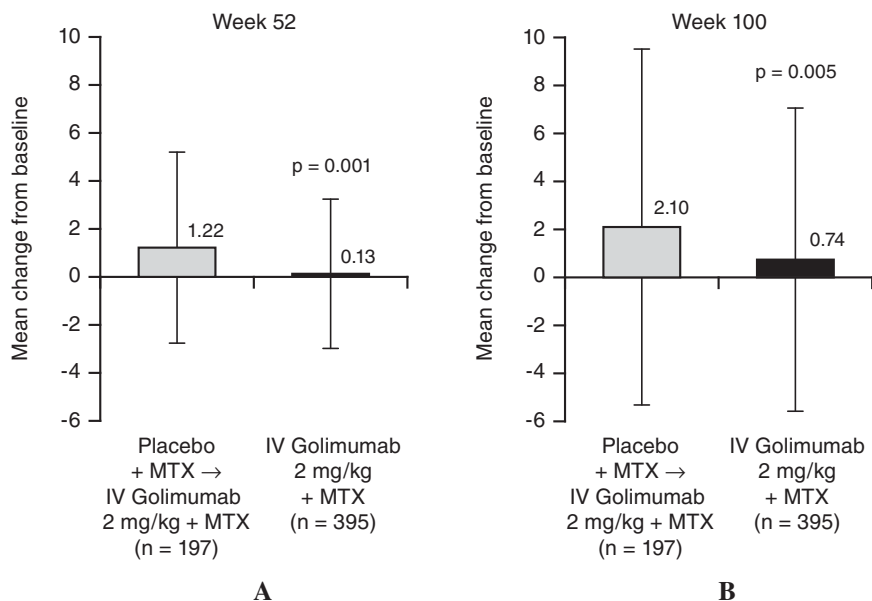
Figure 2. Mean change from baseline in **A,** total modified Sharp/van der Heijde score (SHS) at week 52 **B,** and week 100. IV = intravenous; MTX = methotrexate.

24 and week 52 compared with those in Group 2 (3) (Figure 2A). At week 100, the mean change from baseline in total SHS score was significantly lower in Group 1 than in Group 2 (0.74 versus 2.10; $P = 0.005$) (Figure 2B), and 61.8% (n = 244 of 395) of patients in Group 1 and 54.8% (n = 108 of 197) of patients in Group 2 had a change from baseline in total SHS of ≤0 (Table 1). When evaluated by progression beyond the smallest detectable change (3.22) in total SHS, 16.7% (n = 66 of 395) of patients in Group 1 and 23.9% (n = 47 of 197) in Group 2 demonstrated radiographic progression from baseline to week 100. The mean change in total SHS score from week 52 to week 100 when
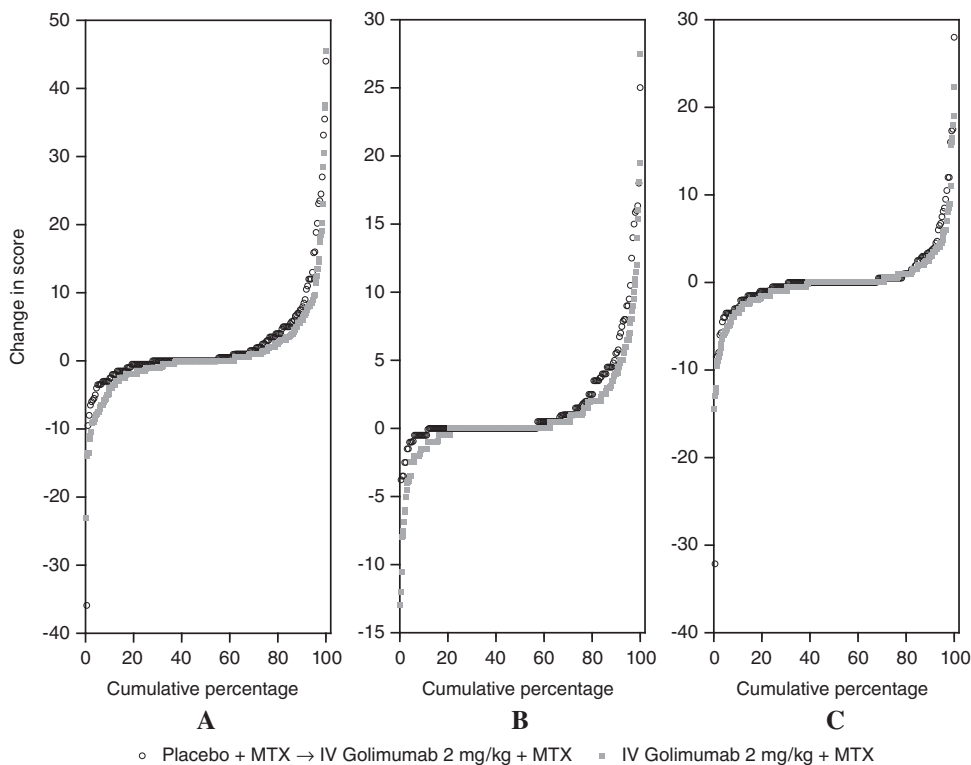
Figure 3. Cumulative probability plot of changes from baseline in **A,** total modified Sharp/van der Heijde scores, **B,** joint space narrowing scores, and **C,** erosion scores. MTX = methotrexate; IV = intravenous.

	Placebo + MTX → Golimumab 2 mg/kg				
	Placebo + MTX	Golimumab 2 mg/kg week 16 (early escape)	Golimumab 2 mg/kg week 24 (crossover)	Golimumab 2 mg/kg + MTX	Combined golimumab 2 mg/kg + MTX
No. patients treated	197	68	121	395	584
Mean followup duration, weeks	21.0	88.5	81.7	101.5	95.9
Mean no. infusions	4.2	11.0	10.2	12.6	11.9
Patients with ≥1 AE	98 (49.7)	54 (79.4)	88 (72.7)	320 (81.0)	462 (79.1)
Upper respiratory tract infection	15 (7.6)	5 (7.4)	8 (6.6)	54 (13.7)	67 (11.5)
Bronchitis	2 (1.0)	6 (8.8)	9 (7.4)	37 (9.4)	52 (8.9)
RA	12 (6.1)	9 (13.2)	3 (2.5)	39 (9.9)	51 (8.7)
Hypertension	5 (2.5)	8 (11.8)	4 (3.3)	27 (6.8)	39 (6.7)
Nasopharyngitis	5 (2.5)	3 (4.4)	8 (6.6)	28 (7.1)	39 (6.7)
Patients with ≥1 infusion reaction	1 (0.5)	5 (7.4)	0	18 (4.6)	23 (3.9)
No. infusions	829	748	1235	4972	6955
Infusions with infusion reactions	2 (0.2)	8 (1.1)	0	22 (0.4)	30 (0.4)
Patients with ≥1 SAE	6 (3.0)	11 (16.2)	17 (14.0)	78 (19.7)	106 (18.2)
Patients with ≥1 serious infection	1 (0.5)	3 (4.4)	5 (4.1)	28 (7.1)	36 (6.2)
Deaths	1 (0.5)	0	2 (1.7)	3 (0.8)	5 (0.9)

Table 3. Adverse events (AEs) through week 112.

*Values are the number (%) unless indicated otherwise. MTX = methotrexate; RA = rheumatoid arthritis; SAE = serious adverse event.

all patients were receiving golimumab was numerically lower in Group 1 (0.56) than in Group 2 (0.80) (Table 1); the median change was 0 in both groups. In both groups, changes in total SHS appeared to be largely due to changes in joint space narrowing scores rather than erosion scores. As shown in Figure 3, radiographic progression through week 100 was limited in both treatment groups when assessed by both the total SHS score and the erosion and joint space narrowing component scores, with a slightly greater benefit observed among patients in Group 1 (in terms of fewer patients demonstrating progression).

Pharmacokinetics. Steady state levels of golimumab were achieved at week 12, and trough serum concentrations suggested maintenance of golimumab exposure through week 52 (3). Median serum golimumab concentrations were maintained through week 100 with median pre- and postinfusion golimumab concentrations of 0.31 μg/ml and 45.73 μg/ml, respectively (mean ± SD 0.44 ± 0.49 and 47.61 ± 10.57 μg/ml, respectively), corresponding to the observed sustained clinical efficacy with golimumab 2 mg/kg administered intravenously every 8 weeks.

Safety. Through week 112, a total of 584 patients received ≥1 golimumab infusion, with a mean followup duration of 95.9 weeks (Table 3). Of these patients, 462 (79.1%) had ≥1 AE, with infections being the most common type. The most commonly reported AEs among golimumab-treated patients were upper respiratory tract infection (n = 67, 11.5%), bronchitis (n = 52, 8.9%), worsening of RA (n = 51, 8.7%), hypertension (n = 39, 6.7%), and nasopharyngitis (n = 39, 6.7%). Twenty-three patients (3.9%) treated with golimumab had ≥1 infusion reaction through week 112. Of the 6,955 golimumab infusions administered during the trial, 30 (0.4%) were

complicated by an infusion reaction. All infusion reactions were considered to be mild or moderate in severity. One patient who tested positive for antibodies to golimumab had a non-serious, non-severe infusion reaction that led to discontinuation of the study agent. There were no reports of anaphylactic or serum sickness reactions.

One-hundred-six patients treated with golimumab (18.2%) had ≥1 serious AE through week 112. Serious infections were reported by 6.2% (n = 36 of 584) of all golimumab-treated patients and included pneumonia (n = 5, 0.9%), urinary tract infection (n = 4, 0.7%), and erysipelas (n = 2, 0.3%). Two serious opportunistic infections (localized vertebral candidal infection and uncomplicated cryptococcal pneumonia) occurred in golimumab-treated patients; however, no case was considered severe.

Three cases of active TB were reported through week 112, with 1 case of abdominal TB being fatal. All three cases occurred in patients who had no history of active TB or signs of TB at screening (by QFT, chest radiograph, or optional tuberculin skin test), and were in countries endemic for TB (Malaysia [patient initially randomized to placebo, diagnosed after week 28], Mexico [patient randomized to golimumab, diagnosed after week 44], and Argentina [patient initially randomized to placebo, diagnosed after week 84]). At baseline, all 3 patients had negative QFT tests; only the patient in Argentina received the tuberculin skin test, which was also negative. Two patients had received the BCG vaccine before study enrollment.

One malignancy (lung adenocarcinoma) occurred in a patient receiving placebo plus MTX and has been previously reported (1). Six malignancies were reported in the combined golimumab group; 3 (breast cancer, basal cell carcinoma, and cervical carcinoma) occurred before week 52 and were previously reported (1,3). The 3 malignancies

that occurred after week 52 were basal cell carcinoma, Bowen's disease, and chronic lymphocytic leukemia (CLL) in a patient with a strong family history of CLL. No cases of lymphoma were reported.

Two deaths occurred prior to week 52 and have been previously described (1,3). Four additional deaths occurred after week 52. A 48-year-old woman died from acute abdominal syndrome due to previously undiagnosed abdominal TB at week 54, a 58-year-old woman died from septic shock secondary to pyogenic lung abscess at week 66, a 58-year-old man died of unknown causes at week 79, and a 66-year-old woman died of dehydration due to *Clostridium difficile* colitis at week 106.

Laboratory abnormalities. Among all golimumab-treated patients who did not receive TB prophylaxis and who had a normal (i.e., ≤ULN) baseline alanine aminotransferase (ALT) level, 45.4% (n = 204 of 449) had at least 1 increased (>ULN) postbaseline value through week 112. Of these patients, 186 had an increase in ALT <3 times the ULN, and no patient had an increase in ALT ≥8 times the ULN.

Among golimumab-treated patients who received TB prophylaxis and had a normal baseline ALT level, 44.4% (n = 36 of 81) had at least 1 postbaseline increase in ALT through week 112. Twenty-eight of these patients had an increase in ALT <3 times the ULN, and 3 patients had an increase ≥8 times the ULN.

None of the increases in ALT was associated with an increase in bilirubin, infectious hepatitis, or any clinical symptomatology consistent with hepatic failure. All of the cases of increased ALT improved with modifications in treatment (mostly MTX and/or anti-TB medications; few with changes to golimumab), and no long-term toxicity was observed. One patient with an ALT level >8 times ULN was discontinued from the trial.

Antibodies to golimumab. Among golimumab-treated patients with appropriate serum samples (i.e., ≥1 sample after receiving golimumab), 3.0% (n = 13 of 440) tested positive for antibodies to golimumab through week 24 (3) and 4.6% (n = 26 of 560) tested positive through week 52 (3). Consistent with these findings, a small number of patients developed antibodies to golimumab through week 100 (6.7%, [n = 37 of 553]). Among the 37 patients who were positive for antibodies to golimumab at week 100, 86.5% were positive for neutralizing antibodies, and neutralizing, 3 patients (8.1%) had an infusion reaction, with 1 patient (2.7%) discontinuing the study agent as a result. Of the 516 patients who were negative for antibodies to golimumab, 22 (4.3%) had infusion reactions, none leading to discontinuation.

DISCUSSION

The multicenter, randomized, placebo-controlled GO-FURTHER trial evaluated the safety and efficacy of IV golimumab 2mg/kg plus MTX through 112 weeks in patients with RA despite prior MTX therapy. Golimumab-treated patients had significantly greater improvements in the

signs and symptoms of RA through week 24 when compared with placebo, with some patients experiencing a rapid onset of response as early as 2 weeks after initiating golimumab therapy (1), and efficacy was maintained through 1 year (3). Results through week 100 of the GO-FURTHER trial demonstrate that the observed clinical response to IV golimumab 2mg/kg plus MTX was sustained through 2 years of treatment.

Of the 592 patients who received treatment, approximately 82% completed golimumab therapy through week 100. The rate of discontinuation due to lack of efficacy among patients randomized to golimumab was relatively low (1.8%). Among all patients, 68.1%, 43.8%, and 23.5% had an ACR20, ACR50, and ACR70 response at week 100, respectively, and 81.9% had either a moderate or good DAS28-CRP response. In addition, the majority of patients who had an ACR20, ACR50, ACR70, or DAS28-CRP response at week 52 maintained that response at week 100. Taken together with earlier results (1,3), the GO-FURTHER trial demonstrated that clinical response to IV golimumab 2mg/kg plus MTX can occur as early as week 2, and once achieved, is often sustained through 1 and 2 years for patients with active RA who previously had an insufficient response with MTX monotherapy. Improvements in health-related quality of life, fatigue, and the impact of disease on productivity that were observed among golimumab plus MTX-treated patients at week 24 (16) were also maintained through 1 and 2 years in the GO-FURTHER trial.

Patients treated with IV golimumab plus MTX from baseline had significantly less radiographic progression from baseline to weeks 24, 52, and 100 when compared with patients who had initially received placebo plus MTX. Evaluation of the radiographic component scores indicated that the increases from baseline among patients in Group 2 were largely due to changes in joint space narrowing rather than erosions. It should be noted, however, that at all time points, including week 100, the median change from baseline in total SHS was 0, indicating that the majority of patients in both treatment groups demonstrated no radiographic progression through 2 years. The very low rate of radiographic progression over 2 years in both treatment groups, a finding also encountered in other, similar studies of biologic therapies in RA, highlights the need for more modern and innovative assessments in the future, as recently proposed by Landewe et al (17).

The changes in total SHS from week 52 to 100, when all patients had been receiving golimumab plus MTX for several months, were generally similar between the 2 treatment groups, which suggests that much of the radiographic progression observed among patients in Group 2 occurred primarily during the first 24 weeks of the trial, when most patients in Group 2 were receiving placebo plus MTX. These results support the treatment recommendations made by both the ACR and EULAR that promote treating RA patients with the goal of reaching remission or low disease activity as soon as possible (18,19). Achieving the lowest disease state possible has been shown to provide long-term benefits in preventing radiographic damage and loss of physical function, with earlier control of disease activity leading to better outcomes (17,20–22).

The safety results of this trial were consistent with the safety profile of other trials of anti-TNF therapies administered either as IV infusion or subcutaneous injection (23–27), and no unexpected safety events occurred through week 112. As seen with other anti-TNF agents, infections were the most common type of AE reported. Serious infections occurred in 6.2% of golimumab plus MTX-treated patients. Three cases of active TB (1 fatal) occurred during the trial; all 3 patients were living in countries endemic for TB and had negative QFT blood tests at screening. One of the 3 patients received the optional tuberculin skin test, which was also negative. None of these patients had been diagnosed with latent TB and therefore were not receiving TB prophylaxis during the trial. A total of 6 deaths occurred during the trial; 4 were related to infections.

Limited transaminitis was observed following treatment with IV golimumab plus MTX through 2 years. Most abnormalities were <3 times the ULN, and the few cases that were ≥8 times the ULN occurred among patients receiving TB prophylaxis during the trial. No patient presented with clinical symptoms of hepatotoxicity or liver failure through week 112 of the trial, and there were no associated changes in bilirubin. All abnormalities in ALT levels responded to adjustments in treatments such as decreases in MTX, changes in the types of anti-TB medications, and/or discontinuation of golimumab (in the majority of cases, treatment with the study agent continued uninterrupted).

A total of 37 (6.7%) patients tested positive for antibodies to golimumab through week 100. The incidence of antibodies to golimumab through week 100 was similar to that through week 52 (4.6%) (3) and to the rates previously reported through 2 years in trials of subcutaneous golimumab plus MTX in patients with RA (GO-BEFORE, 7.1%; GO-FORWARD, 6.3%) (25,26). Because the overall incidence of antibodies to golimumab was low in the GO-FURTHER trial, it is difficult to make conclusions about the possible effect of antibodies to golimumab on efficacy and safety.

It should be noted that our safety and efficacy findings following 2 years of treatment with IV golimumab 2 mg/kg plus MTX in MTX-experienced patients with active RA should be interpreted in the context of certain limitations. As determined by the protocol, all patients received open-label IV golimumab after week 24, resulting in the lack of an active comparator group. Selection bias is also a concern in long-term trials as patients who have an inadequate response to treatment are more likely to discontinue the study agent. In conclusion, MTX-experienced patients with active RA had improvements in the signs and symptoms of RA and slowing of radiographic progression that were sustained through 2 years of treatment with IV golimumab 2 mg/kg plus MTX. These patients also experienced sustained improvements in measures of health-related quality of life, fatigue, and productivity. No unexpected safety events were observed through 112 weeks, and the safety profile of IV golimumab plus MTX was similar to that for subcutaneous golimumab as well as for other anti-TNF agents in patients with RA.

AUTHOR CONTRIBUTIONS

All authors were involved in drafting the article or revising it critically for important intellectual content, and all authors approved the final version to be submitted for publication. Dr. Bingham 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 conception and design. Bingham, Mendelsohn, Kim, Xu, Leu, Han, Westhovens, Weinblatt
Acquisition of data. Mendelsohn, Kim, Xu, Han, Weinblatt
Analysis and interpretation of data. Bingham, Mendelsohn, Kim, Xu, Leu, Han, Lo Westhovens, Weinblatt

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Authors who are or were employees of Janssen Research & Development, LLC were involved in the study design and in the collection, analysis, and interpretation of the data, the writing of the manuscript, and the decision to submit the manuscript for publication. All authors approved the manuscript for submission. Lenore Noonan (Janssen Research & Development, LLC) provided support for clinical data collection and Rebecca Clemente and Mary Whitman (Janssen Scientific Affairs, LLC) provided writing support.

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