Maintenance of Efficacy and Safety with Subcutaneous Golimumab Among Patients with Active Rheumatoid Arthritis Who Previously Received Intravenous Golimumab

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ABSTRACT. ***Objective.*** To evaluate the efficacy/safety of subcutaneous (SC) golimumab in patients with rheumatoid arthritis (RA) who previously received intravenous (IV) golimumab with or without methotrexate (MTX).

Methods. Adult patients with RA (n = 643) with persistent disease despite MTX (≥ 15 mg/wk for ≥ 3 months) were randomized to IV placebo + MTX (n = 129) or IV golimumab 2–4 mg/kg (± MTX) every 12 weeks (n = 514). Patients who completed the study through Week 48 could participate in the longterm extension (LTE), comprising open-label golimumab 50 mg SC every 4 weeks (± MTX) for 24 weeks (LTE-0 to LTE-24) followed by 16 weeks of safety followup (LTE-24 to LTE-40; MTX could be adjusted).

Results. At Week 48, 28% (nominal $p < 0.001$ vs placebo), 11%, and 8% of patients who received IV golimumab + MTX, golimumab alone, and placebo + MTX, respectively, achieved ≥ 50% improvement in the American College of Rheumatology response criteria (ACR50). Among the 505 patients who entered the LTE and were still participating, the proportion of patients treated with golimumab 50 mg SC (± MTX) achieving an ACR50 response increased to 44% at both LTE-14 and LTE-24. ACR20, ACR70, and 28-joint Disease Activity Score using C-reactive protein exhibited similar response patterns as ACR50. Infections were the most commonly reported adverse events through the end of IV golimumab dosing (37% placebo + MTX, 45% golimumab, 51% golimumab + MTX) and with SC golimumab from LTE-0 through LTE-40 (35% golimumab, 36% golimumab + MTX). Concomitant MTX use yielded lower incidences of antibodies to SC golimumab and injection-related reactions.

Conclusion. Clinical improvements observed in golimumab-treated patients were sustained or improved in patients switched from IV (2–4 mg/kg ± MTX) to open-label SC (50 mg ± MTX) golimumab. Both IV and SC golimumab demonstrated acceptable safety profiles (Clinicaltrials.gov NCT00361335). (First Release Nov 15 2011; J Rheumatol 2011;38:2572–80; doi:10.3899/jrheum.110570)

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The role of a key inflammatory mediator, tumor necrosis factor-α (TNF), in rheumatoid arthritis (RA) has been established, whereby TNF is overproduced in the joints of patients with RA[1,2,3]. Clinical trials involving anti-TNF agents have confirmed the key role of TNF in RA[4].

Golimumab, a human anti-TNF monoclonal antibody, inhibits TNF bioactivity. Subcutaneous (SC) golimumab has been studied in patients with RA[5,6,7,8], psoriatic arthritis[9], and ankylosing spondylitis[10]. In patients with RA that did not respond adequately to methotrexate (MTX), SC golimumab + MTX reduced RA signs/symptoms and was generally well tolerated[5,6,7]. SC golimumab also reduces RA signs/symptoms among patients with RA who have taken anti-TNF agents[8]. Intravenous (IV) golimumab has also been evaluated in patients with MTX-refractory RA[11]. While the primary endpoint [≥ 50% improvement in American College of Rheumatology response criteria (ACR50) at Week 14] in our previous study[11] of IV golimumab was not met (golimumab + MTX: 21% vs placebo + MTX: 13%; p = 0.051), at Week 24, significantly more golimumab + MTX-treated patients than placebo + MTX-treated patients achieved an ACR50 response (22% vs 9%, respectively; p = 0.002). Following our study's Week 48 database lock, patients could enter the longterm extension (LTE) and receive SC golimumab. We describe novel findings derived from the LTE that allowed for continuous evaluation of 2 different modes of administration of the same compound (i.e., IV and SC golimumab) in the same patients.

MATERIALS AND METHODS

Institutional review board or ethics committee approval and each patient's written informed consent were obtained before protocol-specific procedures were undertaken. The study was conducted in adherence with the Declaration of Helsinki and International Committee on Harmonization good clinical practices (Clinicaltrials.gov NCT00361335).

Patients. Eligible adults had a diagnosis of RA[12] despite MTX treatment for ≥ 3 months prescreening and stable MTX doses (15–25 mg/week) for ≥ 4 weeks prescreening. Concurrent nonsteroidal antiinflammatory drugs and oral corticosteroids were allowed, as was previous but not current anti-TNF therapy (≤ 20% of study population).

Patients who completed the Week 48 visit of the main study could enter the LTE and switch to open-label SC golimumab 50 mg every 4 weeks for 6 months. Patients who received placebo + MTX through Week 48 of the main trial with a total tender and swollen joint count ≤ 3 were discontinued. No changes in RA concomitant medications were allowed during the LTE enrollment period.

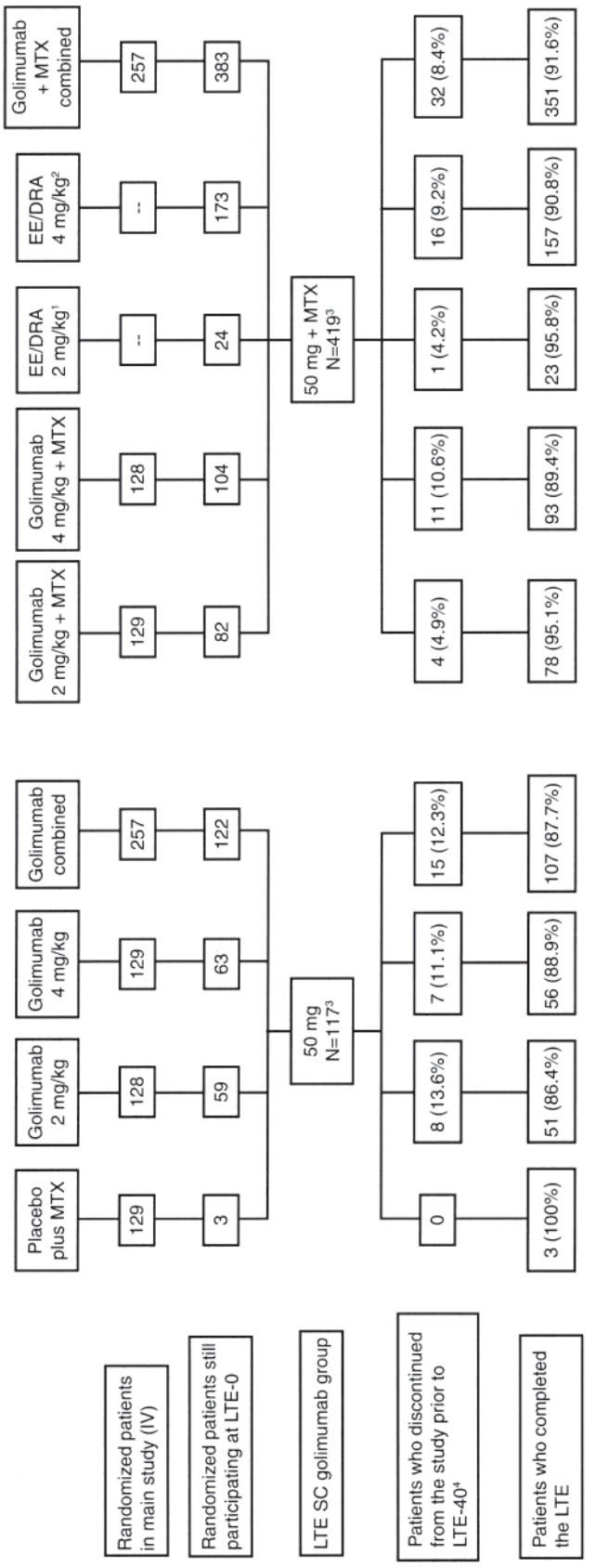

Figure 1. Disposition of patients throughout the longterm study extension in which they switched from intravenous (IV) to subcutaneous (SC) golimumab therapy. Patients received IV golimumab through the start of the longterm extension (i.e., LTE-0), then switched to SC golimumab. [1]Patients who early escaped and/or had a dosage regimen adjustment to 2 mg/kg plus MTX. [2]Patients who early escaped and/or had a dosage regimen adjustment to 4 mg/kg plus MTX. [3]Patients who started MTX during the LTE are counted in both boxes. [4]By treatment assignment at Week 24 of the main study. DRA: dose regimen adjustment; EE: early escape; IV: intravenous; LTE: longterm extension; MTX: methotrexate.

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Study design. As described[11], patients in this phase III study were randomized to receive IV golimumab 2 mg/kg + MTX, 2 mg/kg monotherapy, 4 mg/kg + MTX, 4 mg/kg monotherapy, or MTX monotherapy every 12 weeks through Week 48. During the main study, patients with < 20% improvement in both swollen and tender joint counts at Week 16 and/or Week 24 were eligible for blinded early escape and/or dose regimen adjustment, respectively (Figure 1). During the LTE enrollment period, all patients continued to receive the randomly assigned and blinded treatment of the main study until the Week 48 database was locked such that patients could receive IV golimumab beyond Week 48 of the main study; however, only a limited number of patients did so through Week 96.

In the LTE, patients received open-label SC golimumab (Centocor, Horsham, PA, USA) 50 mg every 4 weeks through LTE-24, beginning 12 weeks after the final IV infusion. Patients receiving MTX through Week 48 of the main study continued receiving the same dose of commercial MTX; patients who received sham MTX discontinued placebo capsules. Beginning at LTE-14, patients were allowed to add, discontinue, or adjust the dose of commercial MTX at the investigator's discretion. A safety followup visit was scheduled for LTE-40.

Study endpoints. The primary endpoint of the main study was ACR50 response at Week 14. ACR20[13], ACR50, and ACR70 responses over time were assessed during the LTE, as were the Disease Activity Score [28-joint using C-reactive protein (DAS28-CRP)][14,15] response (moderate/good) and remission rates (DAS28-CRP score < 2.6)[16]. An independent assessor at each study center, without access to patient medical records, performed the joint assessments. We also determined the numbers of patients who had ≥ 0.30-unit improvement in the disability index of the Health Assessment Questionnaire (HAQ)[17] and achieved US population norms, defined as patients with scores more than half the SD below the US population mean, for the physical and mental component summary (PCS, MCS) scores of the 36-item Short-form Health Survey[18]. Safety evaluations through LTE-0 and LTE-40 included documentation of adverse events. Serum golimumab concentrations were measured using an ELISA capable of quantifying serum golimumab concentrations ≥ 0.1 μg/ml.

Statistical analyses. At Week 48, treatment group comparisons of ACR 20/50/70 and DAS28-CRP response rates were made using the Cochran-Mantel-Haenszel test stratified by previous anti-TNF therapy (yes/no). All statistical testing was 2-sided ($\alpha = 0.05$). P values from these analyses are nominal, because differences in the primary endpoint were not statistically significant. Data collected during the LTE were summarized using descriptive statistics.

Efficacy data are summarized from the start of the main study through the end of the LTE enrollment period (LTE-0), during which patients continued to receive IV golimumab, by IV treatment group and early escape and/or dose regimen adjustment status. Efficacy data were summarized for the 24-week portion of the LTE, during which patients received SC golimumab, for randomized patients by MTX use and response status through LTE-0.

Safety findings through LTE-0 were summarized for all treated patients according to IV treatment received at Week 24 of the main study and accounting for early escape and/or dose regimen adjustment. Safety data pertaining to LTE-0 through LTE-40 were summarized according to MTX use. For all analyses, baseline measurements were defined as the measurement closest to the first IV study infusion at Week 0 of the main study.

RESULTS

Patient disposition and baseline characteristics. The main phase of our study, which evaluated IV golimumab, involved 643 adults. The LTE phase of our study began on September 16, 2008, with the first SC golimumab injection and ended with the final LTE study visit on September 26, 2009.

Among the 643 enrolled patients, 514 were initially randomized to treatment with golimumab (with or without MTX) and 129 were initially randomized to receive placebo plus MTX. Of the 565 patients who completed the main study, 508 were enrolled into the LTE. Most treated patients (91%, 461/508) completed the LTE through Week 40 (Figure 1); the most common reason for study termination was withdrawal of patient consent. The baseline (Week 0 of the main study)

Table 1. Baseline patient and disease characteristics. Baseline measurements were defined as those closest to the measurement taken before the first intravenous infusion of study agent in the main study. Values are mean (median) or n (%) unless otherwise noted.

Characteristics	Placebo	Golimumab Only			Golimumab Plus MTX				
	Plus MTX	2 mg/kg	4 mg/kg	Combined	2 mg/kg	4 mg/kg	EE/DRA to 2 mg/kg	EE/DRA to 4 mg/kg	Combined
Pts randomized in main study	129	128	129	257	129	128	—	—	257
Pts randomized and still participating at LTE-0	3	59	63	122	82	104	24	173	383
Women, n (%)	2 (66.7)	54 (91.5)	52 (82.5)	106 (86.9)	61 (74.4)	86 (82.7)	18 (75.0)	138 (79.8)	303 (79.1)
Race, n (%)									
White	0 (0.0)	39 (66.1)	41 (65.1)	80 (65.6)	54 (65.9)	71 (68.3)	16 (66.7)	130 (75.1)	271 (70.8)
Black	0 (0.0)	0 (0.0)	1 (1.6)	1 (0.8)	0 (0.0)	2 (1.9)	0 (0.0)	4 (2.3)	6 (1.6)
Asian	2 (66.7)	7 (11.9)	9 (14.3)	16 (13.1)	7 (8.5)	8 (7.7)	1 (4.2)	11 (6.4)	27 (7.0)
Other	1 (33.3)	13 (22.0)	12 (19.0)	25 (20.5)	21 (25.6)	23 (22.1)	7 (29.2)	28 (16.2)	79 (20.6)
Age, yrs	49.3 (51.0)	50.7 (51.0)	45.3 (45.0)	47.9 (48.0)	48.9 (50.5)	49.1 (51.0)	50.5 (52.5)	50.3 (51.0)	49.7 (51.0)
RA duration, yrs	8.4 (5.4)	7.0 (3.9)	8.0 (7.1)	7.5 (6.1)	7.9 (4.5)	9.2 (7.2)	7.2 (6.1)	7.6 (5.6)	8.1 (5.8)
No. swollen joints (0-66)	12.7 (13.0)	15.7 (14.0)	15.2 (14.0)	15.4 (14.0)	15.8 (13.0)	14.8 (13.0)	12.5 (13.0)	15.0 (13.0)	14.9 (13.0)
No. tender joints (0–68)	42.7 (48.0)	27.9 (23.0)	26.5 (23.0)	27.2 (23.0)	28.4 (23.5)	26.8 (23.0)	24.0 (22.0)	27.1 (24.0)	27.1 (23.0)
CRP, mg/dl	3.0 (1.9)	2.3 (1.4)	1.5 (0.8)	1.9 (1.0)	1.8 (1.1)	2.0 (1.2)	1.2 (0.7)	1.5 (0.8)	1.7 (0.9)
HAQ (0-3)	2.1 (2.3)	1.6 (1.6)	1.5 (1.5)	1.5 (1.6)	1.6 (1.8)	1.5 (1.6)	1.4 (1.3)	1.4 (1.5)	1.5 (1.5)

CRP: C-reactive protein; DRA: dosage regimen adjustment at Week 24; EE: early escape at Week 16; HAQ: Health Assessment Questionnaire-Disability Index; LTE: longterm extension; MTX: methotrexate; RA: rheumatoid arthritis.

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patient and disease characteristics observed for the LTE participants (Table 1) were consistent with the overall study population[11] and consistent with a diagnosis of moderate to severe RA.

Efficacy. P values reported for treatment group differences at Week 48 of the main study are nominal, because differences in the primary endpoint were not statistically significant.

ACR response. At Week 48 of the main study, significantly larger proportions of patients in the IV golimumab 2 mg/kg + MTX and 4 mg/kg + MTX groups than in the placebo + MTX group achieved ACR20 (45% and 49%, respectively, vs 22%; $p < 0.001$ for both), ACR50 (24% and 33%, vs 8%; $p < 0.001$ for both), and ACR70 (8% and 13%, vs 2%; $p = 0.02$ and $p < 0.001$, respectively) responses. Similar trends were observed for the golimumab monotherapy arms, although response rates were not significantly higher versus placebo + MTX (Table 2).

At LTE-14, when patients had received 4 SC injections of golimumab 50 mg (at LTE-0, -4, -8, and -12), response rates for ACR20, ACR50, and ACR70 were similar between combined golimumab monotherapy (77%, 49%, 26%, respectively) and combined golimumab + MTX (69%, 43%, 26%). Similar findings were observed after receipt of 6 SC golimumab injections at LTE-24. At both timepoints, the highest ACR response rates were generally observed in patients originally randomized to receive golimumab 4 mg/kg + MTX (Table 2).

When assessed by ACR response after IV therapy (2 or 4 mg/kg ± MTX) at LTE-0 (i.e., responder vs nonresponder), ACR responses achieved with IV golimumab (2 or 4 mg/kg ± MTX) were maintained with SC golimumab (50 mg ± MTX) in a majority of patients. Among ACR nonresponders with IV golimumab, about 20% to 50% achieved such a response with SC golimumab (Table 3).

Table 2. Summary of efficacy findings. Efficacy data are summarized as number (%) of randomized patients achieving response at Week 48 of the main study or number (%) of patients participating at LTE-0 achieving response at LTE-14 and LTE-24. Data for Week 48 reflect the effects of IV golimumab during the main study.

	Placebo Plus MTX	Golimumab Only*			Golimumab Plus MTX				
		2 mg/kg	4 mg/kg	Combined	2 mg/kg**	4 mg/kg**	EE/DRA to 2 mg/kg	EE/DRA to 4 mg/kg	Combined
Pts randomized	129	128	129	257	129	128	—	—	257
Pts randomized and still participating at LTE-0	3	53	57	110	83	104	23	163	373
ACR20									
Wk 48 (IV)†	28 (21.7)	31 (24.2)	34 (26.4)	65 (25.3)	58 (45.0)	63 (49.2)	ND	ND	121 (47.1)
p††		0.63	0.38	0.43	< 0.001	< 0.001			< 0.001
LTE-14 (SC)#	2/3 (66.7)	42/53 (79.2)	43/57 (75.4)	85/110 (77.3)	62/83 (74.7)	80/104 (76.9)	13/23 (56.5)	104/163 (63.8)	259/373 (69.4)
LTE-24 (SC)#	2/3 (66.7)	29/40 (72.5)	33/47 (70.2)	62/87 (71.3)	77/98 (78.6)	88/113 (77.9)	16/23 (69.6)	106/165 (64.2)	287/399 (71.9)
ACR50									
Wk 48 (IV)†	10 (7.8)	15 (11.7)	14 (10.9)	29 (11.3)	31 (24.0)	42 (32.8)	ND	ND	73 (28.4)
p††		0.28	0.38	0.27	< 0.001	< 0.001			< 0.001
LTE-14 (SC)#	2/3 (66.7)	25/53 (47.2)	29/57 (50.9)	54/110 (49.1)	42/83 (50.6)	54/104 (51.9)	8/23 (34.8)	55/163 (33.7)	159/373 (42.6)
LTE-24 (SC)#	2/3 (66.7)	19/40 (47.5)	20/47 (42.6)	39/87 (44.8)	51/98 (52.0)	57/113 (50.4)	9/23 (39.1)	57/165 (34.5)	174/399 (43.6)
ACR70									
Wk 48 (IV)†	2 (1.6)	8 (6.3)	7 (5.4)	15 (5.8)	10 (7.8)	16 (12.5)	ND	ND	26 (10.1)
p††		0.05	0.09	0.05	0.02	< 0.001			0.01
LTE-14 (SC)#	2/3 (66.7)	15/53 (28.3)	13/57 (22.8)	28/110 (25.5)	26/83 (31.3)	32/104 (30.8)	5/23 (21.7)	32/163 (19.6)	95/373 (25.5)
LTE-24 (SC)#	2/3 (66.7)	9/40 (22.5)	10/47 (21.3)	19/87 (21.8)	28/98 (28.6)	30/113 (26.5)	4/23 (17.4)	34/165 (20.6)	96/399 (24.1)
DAS28-CRP good/moderate response									
Wk 48 (IV)†	44 (34.1)	44 (34.4)	51 (39.5)	95 (37.0)	75 (58.1)	79 (61.7)	ND	ND	154 (59.9)
p††		0.96	0.37	0.58	< 0.001	< 0.001			< 0.001
LTE-14 (SC)#	3/3 (100.0)	46/53 (86.8)	51/57 (89.5)	97/110 (88.2)	72/82 (87.8)	93/100 (93.0)	18/23 (78.3)	125/163 (76.7)	308/368 (83.7)
LTE-24 (SC)#	3/3 (100.0)	34/40 (85.0)	42/47 (89.4)	76/87 (87.4)	88/98 (89.8)	102/113 (90.3)	20/23 (87.0)	121/163 (74.2)	331/397 (83.4)
DAS28-CRP remission									
LTE-14 (SC)#	2/3 (66.7)	17/53 (32.1)	9/57 (15.8)	26/110 (23.6)	24/82 (29.3)	32/100 (32.0)	5/23 (21.7)	23/163 (14.1)	84/368 (22.8)
LTE-24 (SC)#	2/3 (66.7)	10/40 (25.0)	11/47 (23.4)	21/87 (24.1)	30/98 (30.6)	37/113 (32.7)	6/23 (26.1)	34/163 (20.9)	107/397 (27.0)
HAQ improvement ≥ 0.3									
LTE-14 (SC)#	2/3 (66.7)	32/53 (60.4)	34/57 (59.6)	66/110 (60.0)	55/84 (65.5)	70/104 (67.3)	13/23 (56.5)	92/162 (56.8)	230/373 (61.7)
LTE-24 (SC)#	2/3 (66.7)	23/40 (57.5)	33/47 (70.2)	56/87 (64.4)	66/98 (67.3)	69/113 (61.1)	13/23 (56.5)	91/164 (55.5)	239/398 (60.1)

* Excludes patients who started MTX after LTE-14. ** Includes patients who started and/or adjusted MTX dose after LTE-14. † Among randomized patients in the Main Study. †† For comparison versus placebo + MTX. All p values shown are nominal. # Among randomized patients who remained in the study through the start of the LTE. ACR 20/50/70: 20%/50%/70% improvement in American College of Rheumatology response criteria; CRP: C-reactive protein; DAS28: 28-joint Disease Activity Score; DRA: dose regimen adjustment at Week 24; EE: early escape at Week 16; HAQ: Health Assessment Questionnaire-Disability Index; IV: intravenous; LTE: longterm extension; MTX: methotrexate; ND: not determined; SC: subcutaneous.

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Table 3. Summary of clinical response relative to the start of the LTE. Efficacy data are summarized as number (%) of randomized patients who were still participating at LTE-0 by response status at LTE-0, LTE-14, and LTE-24. Data for LTE-0 reflect the effects of intravenous golimumab during the main study.

	Placebo	Golimumab Only*			Golimumab Plus MTX				
	Plus MTX	2 mg/kg	4 mg/kg	Combined	2 mg/kg**	4 mg/kg**	EE/DRA to 2 mg/kg	EE/DRA to 4 mg/kg	Combined
Pts randomized	129	128	129	257	129	128	—	—	257
Pts randomized and still participating at LTE-0	3	59	63	122	82	104	24	173	383
ACR 20									
Responder at LTE-0 (IV) and Responder at:	1 (33.3)	31 (52.5)	32 (50.8)	63 (51.6)	56 (68.3)	65 (62.5)	14 (58.3)	86 (49.7)	221 (57.7)
LTE-14 (SC)	1 (100.0)	25 (80.6)	29 (90.6)	54 (85.7)	49 (87.5)	60 (92.3)	8 (57.1)	70 (81.4)	187 (84.6)
LTE-24 (SC)	1 (100.0)	27 (87.1)	26 (81.3)	53 (84.1)	48 (85.7)	59 (90.8)	11 (78.6)	73 (84.9)	191 (86.4)
Nonresponder at LTE-0 (IV) and Responder at:	2 (66.7)	28 (47.5)	31 (49.2)	59 (48.4)	26 (31.7)	39 (37.5)	10 (41.7)	87 (50.3)	162 (42.3)
LTE-14 (SC)	1 (50.0)	20 (71.4)	16 (51.6)	36 (61.0)	10 (38.5)	18 (46.2)	5 (50.0)	34 (39.1)	67 (41.4)
LTE-24 (SC)	1 (50.0)	18 (64.3)	14 (45.2)	32 (54.2)	13 (50.0)	22 (56.4)	5 (50.0)	33 (37.9)	73 (45.1)
ACR 50									
Responder at LTE-0 (IV) and Responder at:	0 (0.0)	20 (33.9)	16 (25.4)	36 (29.5)	36 (43.9)	39 (37.5)	5 (20.8)	42 (24.3)	122 (31.7)
LTE-14 (SC)	0 (0.0)	15 (75.0)	12 (75.0)	27 (75.0)	31 (86.1)	35 (89.7)	3 (60.0)	32 (76.2)	101 (82.8)
LTE-24 (SC)	0 (0.0)	14 (70.0)	11 (68.8)	25 (69.4)	28 (77.8)	32 (82.1)	4 (80.0)	28 (66.7)	92 (75.4)
Nonresponder at LTE-0 (IV) and Responder at:	3 (100.0)	39 (66.1)	47 (74.6)	86 (70.5)	46 (56.1)	65 (62.5)	19 (79.2)	131 (75.7)	261 (68.3)
LTE-14 (SC)	2 (66.7)	12 (30.8)	19 (40.4)	31 (36.0)	9 (19.6)	17 (26.2)	5 (26.3)	23 (17.6)	54 (20.7)
LTE-24 (SC)	2 (66.7)	15 (38.5)	15 (31.9)	30 (34.9)	13 (28.3)	19 (29.2)	5 (26.3)	29 (22.1)	66 (25.3)
DAS28-CRP									
Good/moderate Responder at LTE-0 (IV) and Responder at:	3 (100.0)	42 (71.2)	41 (65.1)	83 (68.0)	67 (81.7)	81 (77.9)	17 (70.8)	115 (66.5)	280 (73.1)
LTE-14 (SC)	3 (100.0)	40 (95.2)	37 (90.2)	77 (92.8)	57 (85.1)	76 (93.8)	15 (88.2)	102 (88.7)	250 (89.3)
LTE-24 (SC)	3 (100.0)	38 (90.5)	35 (85.4)	73 (88.0)	63 (94.0)	78 (96.3)	16 (94.1)	101 (87.8)	258 (92.1)
Nonresponder at LTE-0 (IV) and Responder at:	0 (0.0)	17 (28.8)	22 (34.9)	39 (32.0)	13 (15.9)	23 (22.1)	7 (29.2)	57 (32.9)	100 (26.1)
LTE-14 (SC)	0 (0.0)	11 (64.7)	16 (72.7)	27 (69.2)	9 (69.2)	15 (65.2)	3 (42.9)	23 (40.4)	50 (50.0)
LTE-24 (SC)	0 (0.0)	13 (76.5)	18 (81.8)	31 (79.5)	7 (53.8)	13 (56.5)	4 (57.1)	20 (35.1)	44 (44.0)

* Excludes patients who started MTX after LTE-14. ** Includes patients who started and/or adjusted MTX dose after LTE-14. ACR 20/50/70: 20%/50%/70% improvement in American College of Rheumatology response criteria; CRP: C-reactive protein; DAS28: 28-joint Disease Activity Score; DRA: dose regimen adjustment at Week 24; EE: early escape at Week 16; IV: intravenous; LTE: longterm extension; MTX: methotrexate; SC: subcutaneous.

ACR responses over time in patients who did not enter early escape or have a dosage regimen adjustment during the main study illustrate the maintenance of clinical improvement achieved with monthly SC golimumab injections (Figure 2). As noted, limited numbers of patients received IV study agent from Weeks 48 to 96. Also, the 3 patients originally assigned to placebo who continued study participation through LTE-0 are not shown because of limited sample size.

Although evaluation of ACR response among patients who entered early escape at Week 16 and/or adjusted the dose regimen at Week 24 was hindered by the relatively smaller sample sizes per treatment regimen, clinical improvements achieved with IV golimumab through LTE-0 were generally maintained with monthly SC golimumab injections (data not shown). ACR response rates were generally higher among patients who adjusted the dose regimen at Week 24 than among those who met the early escape criteria at Week 16.

DAS28-CRP response and remission. At Week 48 of the main study, DAS28-CRP response rates were significantly higher for IV golimumab 2 mg/kg + MTX and 4 mg/kg + MTX versus the placebo + MTX group (58% and 62% of patients, respectively, vs 34%; $p < 0.001$ for both comparisons). Similar DAS28-CRP response rates were observed for overall golimumab monotherapy (37%) and placebo + MTX (34%; Table 2).

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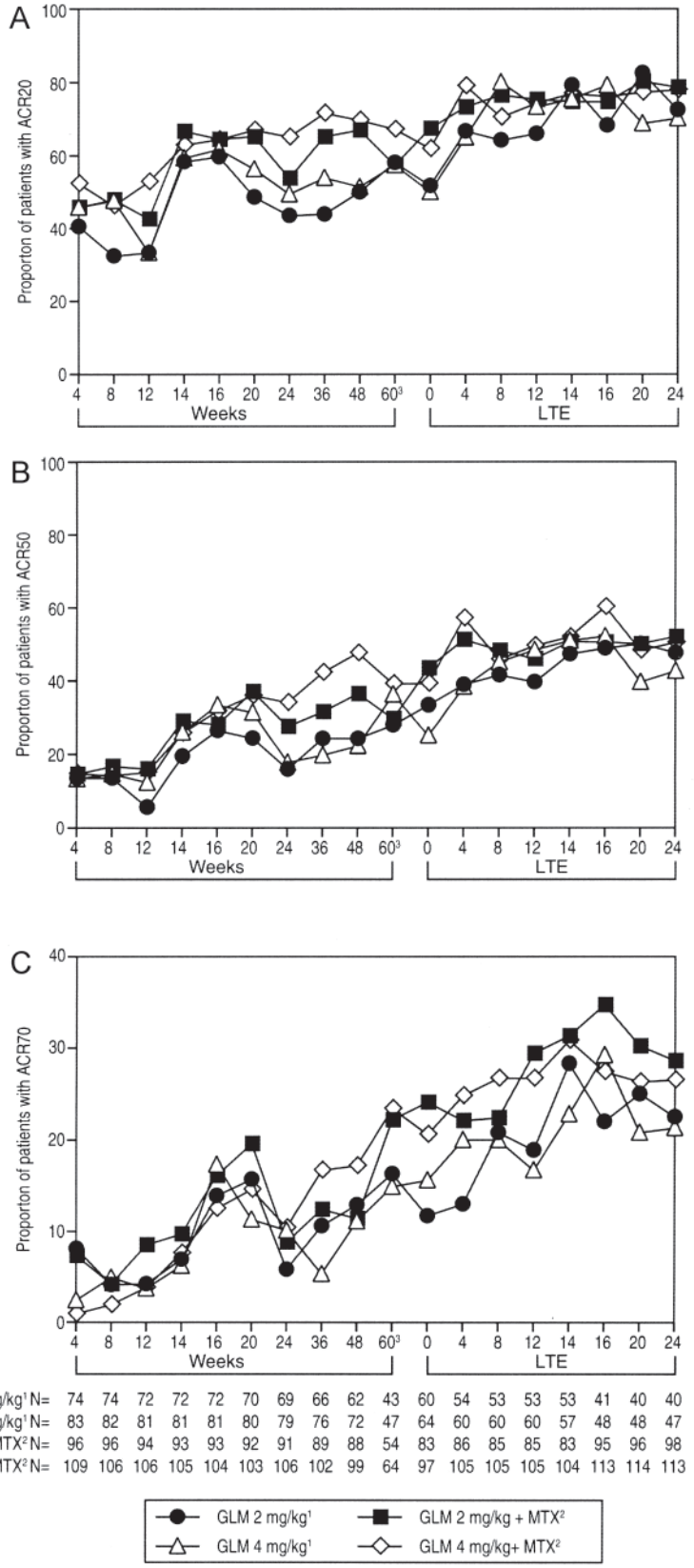

Figure 2. Clinical response as assessed by the American College of Rheumatology (ACR) response criteria among randomized patients who did not enter early escape at Week 16 and/or adjust the dose regimen at Week 24. Patients received IV golimumab through the start of the longterm extension (i.e., LTE-0), then switched to open-label SC golimumab. Note that MTX doses could be adjusted during the LTE. The proportions of patients who achieved ACR20 (A), ACR50 (B), and ACR70 (C) response criteria are shown over time. Only 3 patients originally assigned to placebo continued study participation through LTE-0, and those results are not displayed because of limited sample size. [1]Excludes patients who started MTX after LTE-14. [2]Includes patients who started and/or adjusted MTX doses after LTE-14. [3]Limited numbers of patients continued IV golimumab through Week 72 (n = 70), Week 84 (n = 23), and Week 96 (n = 6), resulting in at least one treatment group with only a single patient, before switching to subcutaneous golimumab. Data for these visits are not shown in the figures due to these small sample sizes. ACR 20/50/70: 20%/50%/70% improvement in American College of Rheumatology response criteria; LTE: longterm extension; MTX: methotrexate.

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At LTE-14, DAS28-CRP response and remission rates were similar for the combined golimumab monotherapy (88% and 24%, respectively) and combined golimumab + MTX groups (84% and 23%). DAS28-CRP response (87% and 83%) and remission (24% and 27%) rates were maintained through LTE-24 in the combined golimumab monotherapy and combined golimumab + MTX groups, respectively. Thus, both SC treatment regimens were effective in maintaining clinical response achieved with IV golimumab. At both timepoints, the highest DAS28-CRP response and remission rates were generally observed in patients originally randomized to golimumab 4 mg/kg + MTX (Table 2).

When assessed by DAS28-CRP response at LTE-0, DAS28-CRP responses achieved with IV golimumab (2 or 4 mg/kg ± MTX) were maintained with SC golimumab (50 mg ± MTX). Among patients who had not achieved a DAS28-CRP response with IV golimumab, 35%–82% achieved response with SC golimumab at LTE-24 (Table 3).

Physical function and quality of life. The proportions of patients who achieved clinically meaningful improvement in the disability index of the HAQ score (i.e., ≥ 0.30-unit improvement) were stable throughout the 24-week period of SC golimumab treatment (Table 2). The proportions of patients who achieved the US population norm for PCS and MCS scores were also stable throughout the 24-week period of SC golimumab treatment (data not shown).

Pharmacokinetics. As described[11], close to dose-proportional mean increases in serum golimumab concentrations were observed at all evaluations during IV therapy in the main study. Median trough serum golimumab concentrations through Week 48 (in association with IV therapy every 12 weeks) were below the limit of quantitation (0.2 μg/ml) for 3 of the 4 golimumab treatment groups (golimumab 2 mg/kg, golimumab 2 mg/kg + MTX, and golimumab 4 mg/kg). Patients receiving golimumab 4 mg/kg + MTX exhibited steady-state trough concentrations of 0.2–0.3 μg/ml[11].

By LTE-12, the time at which serum golimumab concentrations were expected to have achieved a new steady-state status following SC golimumab 50 mg every 4 weeks, median serum trough concentrations ranged from 0.67 to 0.93 μg/ml. The median trough serum golimumab concentrations at this visit and at LTE-16, LTE-20, and LTE-24 were higher than such levels following IV golimumab 2 mg/kg or 4 mg/kg every 12 weeks. By LTE-40 (16 weeks following the last SC injection), serum golimumab concentrations were below the limit of quantitation for most patients.

Adverse events (Table 4). Adverse events through Week 48 of the main study have been described[11]. When assessed through the end of IV treatment preceding the start of SC dosing in the LTE, by which time placebo + MTX, golimumab, and golimumab + MTX patients had been followed for averages of 24, 48, and 60 weeks, respectively, more golimumab and golimumab + MTX than placebo + MTX patients had adverse events (79% and 84% vs 72%, respectively) and serious adverse events (10% and 15% vs 5%). Infections were the most commonly reported adverse events across all treatment groups, occurring in 37%, 45%, and 51% of patients treated with IV placebo + MTX, golimumab, and golimumab + MTX, respectively. Overall, 4162 IV infusions were administered through the end of the LTE enrollment period. The overall proportion of infusions with 1 or more infusion site reactions

Table 4. Safety findings through the end of IV golimumab dosing in the main study and during the LTE enrollment period (including early escape and dose regimen adjustments) and throughout the LTE of SC golimumab. Note that data are summarized by actual treatment received, with adverse events being attributed to the treatment received at the time of the event. Thus, some patients are included in more than 1 column. Data are n (%) unless otherwise indicated.

	IV Study Agent (Main Study Week 0 Through LTE-0)			SC Golimumab (LTE-0 through LTE-40)		
	IV Placebo + MTX	All IV Golimumab Combined	All IV Golimumab + MTX Combined	SC Golimumab 50 mg	SC Golimumab 50 mg + MTX	All SC Golimumab Combined
Patients treated, n	129	254	469	117	419	508
Average duration of followup, wks	24.4	47.6	59.5	33.4	38.2	39.2
Average no. of IV administrations	2.9	5.2	5.4	—	—	—
Average no. of SC administrations	—	—	—	6.0	6.5	6.8
Patients with ≥ 1 AE	93 (72.1)	201 (79.1)	393 (83.8)	78 (66.7)	286 (68.3)	353 (69.5)
Patients with ≥ 1 SAE	7 (5.4)	25 (9.8)	71 (15.1)	8 (6.8)	38 (9.1)	46 (9.1)
Patients who died	0 (0.0)	4 (1.6)	2 (0.4)	0 (0.0)	2 (0.5)	2 (0.4)
Patients who discontinued IV/SC study agent due to AE	4 (3.1)	17 (6.7)	32 (6.8)	5 (4.3)	5 (1.2)	10 (2.0)
Patients with ≥ 1 neoplasm*	2 (1.6)	3 (1.2)	17 (3.6)	0 (0.0)	2 (0.5)	2 (0.4)
Patients with ≥ 1 infection	48 (37.2)	115 (45.3)	238 (50.7)	41 (35.0)	149 (35.6)	187 (36.8)
Patients with ≥ 1 serious infection	2 (1.6)	12 (4.7)	26 (5.5)	2 (1.7)	16 (3.8)	18 (3.5)
Infusions/injections with infusion/injection reaction	7/368 (1.9)	18/1311 (1.4)	24/2483 (1.0)	5/700 (0.7)	14/2743 (0.5)	19/3443 (0.6)
Patients with ≥ 1 infusion/injection reaction	7 (5.4)	15 (5.9)	19 (4.1)	4 (3.4)	8 (1.9)	12 (2.4)

* Including benign, malignant, and unspecified growths (including cysts and polyps). AE: adverse event; IV: intravenous; LTE: longterm extension; MTX: methotrexate; SAE: serious adverse event; SC: subcutaneous.

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was lower among patients treated with IV golimumab (1%) and golimumab plus MTX (1%) versus intravenous placebo + MTX (2%).

Through LTE-40, 70% (353/508) of patients treated with SC golimumab had ≥ 1 adverse event. There was no relationship between overall adverse event rates and MTX use. The most commonly reported adverse events were infections, occurring in 35% and 36% of patients receiving SC golimumab monotherapy and golimumab + MTX, respectively. The most common infections were upper respiratory tract infection, nasopharyngitis, and bronchitis. Among patients who received SC golimumab monotherapy and golimumab + MTX, who were followed for averages of 33 and 38 weeks, respectively, serious adverse events were observed in 7% and 9% of patients; infections requiring antimicrobial treatment were observed in 24% and 27% of patients; and serious infections were observed in 2% and 4% of patients. Two cases of tuberculosis occurring between Weeks 24 and 48 of the main study have been described[11], and there have been no additional reports of tuberculosis. No opportunistic infections were reported.

Throughout the SC treatment period, 3443 injections were administered. The overall proportion of injections with 1 or more injection site reactions was low (0.6%), including 0.7% and 0.5% with SC golimumab monotherapy and golimumab + MTX, respectively. Injection site erythema and pruritus were the most common reactions. There were no cases of serum sickness or anaphylaxis in patients receiving golimumab.

Three patients died (1 patient each receiving IV golimumab 2 mg/kg, 4 mg/kg, and 4 mg/kg + MTX) through Week 48 of myocardial infarction (plus acute cardiac dysfunction in 1 patient)[11]. After Week 48, 3 additional deaths were reported for patients receiving IV study agent: 1 patient receiving golimumab 2 mg/kg died from an unknown cause, 1 patient receiving golimumab 2 mg/kg + MTX died of septic shock following diagnosis of *Staphylococcus aureus*-related septic arthritis, and 1 patient receiving golimumab 4 mg/kg died of respiratory insufficiency following hospital admission for presumptive lung cancer and brain metastases. In addition, 2 patients died after the start of SC golimumab 50 mg + MTX: 1 patient from severe respiratory infection and 1 patient of septicemia caused by methicillin-resistant *S. aureus*.

Throughout the main study and the LTE enrollment period, during receipt of IV golimumab, neoplasms were documented for 2 (1.6%) patients treated with placebo + MTX, 3 (1.2%) patients treated with golimumab monotherapy, and 17 (3.6%) patients treated with golimumab + MTX. Two patients had lung neoplasm (both golimumab 4 mg/kg + MTX) and 2 had melanocytic nevus (1 each golimumab 2 and 4 mg/kg + MTX); all other neoplasms each occurred in 1 patient. From LTE-0 through LTE-40, when all patients received SC golimumab 50 mg ± MTX, 2 (0.5%) patients had a neoplasm. No cases of lymphoma were documented.

DISCUSSION

We detailed efficacy and safety of IV golimumab, administered every 12 weeks with or without MTX, in MTX-experienced patients with RA[11]. Study participants who completed the Week 48 visit of the main study could enter an LTE and switch to open-label SC golimumab 50 mg every 4 weeks for 6 months. We now provide novel evidence of sustained response with 2 different modes of administration of the same compound (i.e., IV and SC golimumab).

Among patients with RA who were switched from IV to open-label SC golimumab, and who could have had their MTX dose adjusted, clinical improvement continued from that observed at Week 48 of the main study, indicating a prolonged effect with IV therapy, and similar or incremental improvement was observed after switching to SC golimumab 50 mg. The ACR20 response rate increased from about 20-50% at Week 48 to about 60-80% at LTE-14. Similar patterns of continued improvement were observed for ACR50, ACR70, and DAS28-CRP response criteria. In addition, the higher response rates observed following 3 months of open-label SC golimumab were generally maintained through Month 6 of SC golimumab. Median trough serum golimumab levels were higher with SC golimumab 50 mg every 4 weeks than with IV golimumab 2 or 4 mg/kg every 12 weeks, providing a pharmacological explanation for the observation that ACR responses induced by IV treatment were well maintained by SC golimumab during the LTE.

IV and SC golimumab, both with or without concomitant MTX, displayed safety profiles consistent with other anti-TNF agents. Based on the limited differences observed between placebo-treated and golimumab-treated patients, some of which might be related to the longer followup periods for golimumab than placebo dosing, and the low incidence of infusion-related and injection site reactions, golimumab appeared to be generally well tolerated by these patients.

Infections were the most commonly reported adverse events in conjunction with both IV and SC golimumab. Two patients who received golimumab plus MTX died as a result of *S. aureus*-related sepsis. These patients were both 59-year-old women with relatively lengthy durations of RA (11 and 19 years).

Patients receiving IV golimumab + MTX were followed for an average of 59.5 weeks, versus 24.4 weeks for patients receiving IV placebo + MTX and 47.6 weeks for patients receiving IV golimumab monotherapy, which may account for the higher incidences of adverse events in most categories observed with IV golimumab + MTX treatment. Indeed, when patients were followed for more similar lengths of time in association with SC dosing (i.e., averages of 33.4 weeks for golimumab 50 mg and 38.2 weeks for golimumab 50 mg + MTX), with the exception of serious infections, incidences of adverse events were generally comparable between patients treated with golimumab monotherapy versus golimumab plus MTX. In the case of serious infections, concomitant SC golimumab and MTX therapy was associated with an incidence of

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3.8%, versus 1.7% of patients who received SC golimumab monotherapy. Despite the longer and higher golimumab exposure in patients who switched from IV to SC golimumab in our study, golimumab safety findings were consistent with those observed in patients with active RA despite prior MTX therapy for whom SC dosing was the sole route of golimumab administration[6].

A range of protein-based, highly targeted RA therapies are available for delivery by parenteral administration. While many patients welcome the relative freedom that self-administered SC injection provides, others may prefer IV delivery, especially in circumstances where patients/caregivers cannot administer SC injections, patient compliance is an issue, hospital visits for drug infusion permit other evaluations on a regular basis, or even when social contact is an important part of patient well-being. Thus, the potential for choice in the mode of golimumab delivery is advantageous. This flexibility in dosing route raises questions regarding the extent to which golimumab dose can be optimized to equate the dose and/or mode of delivery to the most favorable efficacy/toxicity ratio. Future golimumab trials will address such questions.

Thus, these novel data evaluating 2 different modes of administration of the same compound have demonstrated that response to golimumab is maintained or improved, without penalty in toxicity/tolerability, following a switch from IV to SC delivery. The reverse circumstance (switching from SC to IV golimumab) is being studied in an ongoing phase IIIb study.

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