2015-01-22

Golimumab in patients with active rheumatoid arthritis after treatment with tumor necrosis factor inverted question mark inhibitors: findings with up to five years of treatment in the multicenter, randomized, double-blind, placebo-controlled, phase 3 GO-AFTER study

Josef S. Smolen
Medical University of Vienna

Et al.

Arthritis Research & Therapy

BioMed Central
The Open Access Publisher

Golimumab in patients with active rheumatoid arthritis after treatment with tumor necrosis factor α inhibitors: findings with up to five years of treatment in the multicenter, randomized, double-blind, placebo-controlled, phase 3 GO-AFTER study

Arthritis Research & Therapy

doi:10.1186/s13075-015-0516-6

Josef S Smolen (josef.smolen@wienkav.at)
Jonathan Kay (jonathan.kay@umassmemorial.org)
Mittie Doyle (mittiekdoyle@hotmail.com)
Robert Landewé (landewe@rlandewe.nl)
Eric L Matteson (matteson.eric@mayo.edu)
Norman Gaylis (ngaylis@aol.com)
Jürgen Wollenhaupt (j.wollenhaupt@t-online.de)
Frederick T Murphy (ftmurphy8@gmail.com)
Stephen Xu (sxu2@its.jnj.com)
Yiying Zhou (yzhou45@its.jnj.com)
Elizabeth C Hsia (ehsia@its.jnj.com)

Published online: 22 January 2015

ISSN 1478-6354

Article type Research article

Submission date 20 August 2014

Acceptance date 5 January 2015

Article URL http://dx.doi.org/10.1186/s13075-015-0516-6

Golimumab in patients with active rheumatoid arthritis after treatment with tumor necrosis factor α inhibitors: findings with up to five years of treatment in the multicenter, randomized, double-blind, placebo-controlled, phase 3 GO-AFTER study

Josef S Smolen[1,11,12,*]
Email: josef.smolen@wienkav.at

Jonathan Kay[2]
Email: jonathan.kay@umassmemorial.org

Mittie Doyle[3]
Email: mittiekdoyle@hotmail.com

Robert Landewé[4]
Email: landewe@rlandewe.nl

Eric L Matteson[5]
Email: matteson.eric@mayo.edu

Norman Gaylis[6]
Email: ngaylis@aol.com

Jürgen Wollenhaupt[7]
Email: j.wollenhaupt@t-online.de

Frederick T Murphy[8,9]
Email: ftmurphy8@gmail.com

Stephen Xu[10]
Email: sxu2@its.jnj.com

Yiying Zhou[10]
Email: yzhou45@its.jnj.com

Elizabeth C Hsia[9,10]
Email: ehsia@its.jnj.com

[1] Medical University of Vienna and Hietzing Hospital, Vienna, Austria

[2] University of Massachusetts Medical School and UMass Memorial Center, Worcester, MA, USA

[3] Translational Medicine Group, Alexion Pharmaceuticals, Cambridge, MA, USA

[4] Academic Medical Center/University of Amsterdam & Atrium Medical Center Heerlen, Heerlen, the Netherlands

[5] Mayo Clinic, Rochester, MN, USA

[6] Arthritis & Rheumatic Disease Specialties, Aventura, FL, USA

[7] Schoen Klinik Hamburg Eilbek, Hamburg, Germany

[8] Altoona Center of Clinical Research, Duncansville, PA, USA

[9] University of Pennsylvania Medical School, Philadelphia, PA, USA

[10] Janssen Research & Development, LLC, Spring House, PA, USA

[11] Division of Rheumatology, Medical University of Vienna, Waehringer Guertel 18-20, Vienna A-1090, Austria

[12] Department of Medicine III, Hietzing Hospital, Waehringer Guertel 18-20, Vienna A-1090, Austria

[*] Corresponding author. Division of Rheumatology, Medical University of Vienna, Waehringer Guertel 18-20, Vienna A-1090, Austria

Abstract

Introduction

The aim of this study was to assess long-term golimumab therapy in rheumatoid arthritis (RA) patients who discontinued previous tumor necrosis factor-α (TNF)-inhibitor(s).

Methods

Patients enrolled into this multicenter, randomized, double-blind, placebo-controlled study of active RA (≥4 tender, ≥4 swollen joints) received placebo (Group 1) or golimumab 50 mg (Group 2) or 100 mg (Group 3) injections every 4 weeks. Patients in Groups 1 and 2 with inadequate response at week 16 escaped to golimumab 50 and 100 mg, respectively. At week 24, Group 1 patients crossed-over to golimumab 50 mg, Group 2 continued golimumab 50/100 mg per escape status, and Group 3 maintained dosing. During the long-term-extension (LTE), golimumab 50 mg could be increased to 100 mg, and 100 mg could be decreased to 50 mg. Data through 5 years are reported for all patients (safety) and patients using methotrexate (efficacy, intention-to-treat (ITT) analysis with last-observation-carried-forward for missing data and non-responder imputation for unsatisfactory efficacy discontinuations).

Results

In total, 459 of 461 randomized patients received the study agent, 304 of whom were methotrexate-treated and included in efficacy analyses. Through week 256, the proportions of methotrexate-treated patients achieving American-College-of-Rheumatology (ACR)

responses were 37.6% to 47.0% for ACR20, 21.4% to 35.0% for ACR50, and 7.8% to 17.0% for ACR70 response across randomized groups. Golimumab safety through week 268 was generally consistent with that at week 24 and week 160 and other anti-TNF agents.

Conclusions

In some patients with active RA discontinuing previous TNF-antagonist therapy, golimumab safety and efficacy, assessed conservatively with ITT analyses, was confirmed through 5 years.

Trial registration

Clinicaltrials.gov NCT00299546. Registered 03 March 2006.

Introduction

GO-AFTER (GOlimumab After Former anti-tumor necrosis factor α Therapy Evaluated in Rheumatoid arthritis; Trial registration: Clinicaltrials.gov NCT00299546; registered March 03, 2006) was the first and hitherto only prospective, randomized, phase 3, double-blind, placebo-controlled trial to assess a tumor necrosis factor-α (TNF)-inhibitor exclusively in patients with active rheumatoid arthritis (RA) who previously received TNF-inhibitor(s). Patients had also received several disease-modifying antirheumatic drugs (DMARDs) prior to TNF-inhibitor(s), thereby representing a difficult-to-treat population. As reported previously, treatment with golimumab 50 mg or 100 mg every 4 weeks yielded significantly higher ACR20 (≥20% improvement in the American College of Rheumatology criteria) response rates than treatment with placebo at week 14.[1,2] At week 160 of the GO-AFTER trial, golimumab 50-mg and 100-mg injections every 4 weeks resulted in persistent improvement in signs and symptoms of RA and physical function among patients who continued therapy throughout this observation period of 3 years.[2]

Long-term extension (LTE) phases of clinical trials typically are associated with special concerns in data reporting because of the bias resulting from assessment only of patients who were responding to treatment and who continued study participation [3]. However, both patients and providers can benefit from assessing the outcome of patients who respond to treatment, as well as the outcome in all patients who started a specific therapy. Needless to say, it is particularly challenging for patients with disease refractory to several prior therapies, including biological agents as was the case for the GO-AFTER study population [1,2], to achieve and maintain clinical responses.

The GO-AFTER study was designed to include a LTE phase of golimumab therapy. These 5-year data, which comprise the entire planned trial, are reported herein and include information about long-term safety in this patient population.

Methods

The GO-AFTER study was conducted according to the Declaration of Helsinki. All patients provided written informed consent, and the protocol was approved by each institution's ethical review board (see Acknowledgments for details).

Details of the GO-AFTER (NCT00299546) patients with RA [4] and methods have been reported previously; procedures and analyses specific to the LTE, including assessments of clinical response, quality of life, safety and immunogenicity, [5-14] are summarized in Additional file 1.

Results

Patient disposition and baseline patients and disease characteristics

Patient disposition through week 24 [1] and week 160 [2] of GO-AFTER has been reported previously. Through week 252, 276 (60.1%) patients discontinued study agent (Additional file 1: Figure S1), most commonly because of unsatisfactory therapeutic effect (n = 107), adverse events (n = 86), and "other" reasons (n = 69). The proportions of patients discontinuing study agent due to adverse events or unsatisfactory therapeutic effect increased with greater number of TNF-antagonists taken (data not shown). Baseline methotrexate (MTX) use was reported by 311 treated patients. Among these, 58.2% (181/311) discontinued study agent. In patients receiving golimumab monotherapy, 64.2% (95/148) discontinued study agent. Baseline patient/disease characteristics have been reported [1,2] and are summarized in Additional file 1: Table S1. During the LTE, 139 patients escalated golimumab dose (from 50 mg to100 mg) and 29 patients reduced dose (from 100 mg to 50 mg) at the investigator's discretion (Additional file 1: Figure S1).

Clinical outcomes

As reported previously, at week 24 the proportions of all patients achieving ACR20 response, ACR50 response, 28-joint Disease Activity Score (DAS28) response and DAS28 score < 2.6 among patients who received golimumab 50 mg and 100 mg were significantly higher than for placebo-treated patients (all $p < 0.05$) [1].

Clinical outcomes through 5 years are primarily summarized using an intent-to-treat (ITT) analysis. Given that all patients received golimumab from week 16 or 24, no treatment group comparisons were undertaken. Based on ITT efficacy data, the proportions of MTX-treated patients who achieved ACR20, ACR50, DAS28 employing C-reactive protein (DAS28-CRP) response, and DAS28-CRP scores < 2.6 and < 3.2 were consistent through week 256. At this time, 37.9% (39/103) of patients randomized to receive placebo and then golimumab from week 16 (early escape) or week 24 onward and 42.3% (85/201) of golimumab-randomized patients achieved ACR20 response; 21.4% (22/103) and 29.9% (60/201), respectively, achieved ACR50 response; 56.3% (58/103) and 59.7% (120/201) achieved DAS28-CRP response; 18.4% (19/103) and 15.4% (31/201) achieved DAS28-CRP < 2.6; and 26.2% (27/103) and 29.9% (60/201) achieved DAS28-CRP < 3.2 (Figure 1A-E). Clinical remission, defined as Simplified Disease Activity Index (SDAI) ≤ 3.3, was achieved by 6.8% (7/103) and 8.5% (17/201) of placebo- and golimumab-randomized patients, respectively, at week 256 (Figure 1F). At week 256, 37.9% (39/103) and 43.8% (88/201) of patients, respectively, achieved ≥ 0.25-unit improvement in the Health Assessment Questionnaire Disability Index (HAQ-DI) score (Figure 1G). Similar trends were evident when responses were assessed as observed data, albeit at higher rates due to the 'completer' nature of those analyses (Additional file 1: Figure S2).

Figure 1 Clinical efficacy over time through week 256, including ACR20 (A), ACR50 (B), DAS28-CRP response (C), DAS28-CRP score < 2.6 (D), DAS28-CRP score < 3.2 (E), SDAI score ≤ 3.3 (F), and HAQ-DI improvement ≥ 0.25 (G). Data summarized for randomized patients receiving methotrexate at baseline, excluding one site, using intent-to-treat methodology, with replacement of missing data by last-observation-carried forward methodology and imputation with baseline median values, and non-responder imputation for discontinuations due to unsatisfactory therapeutic effect. *ACR20/50 = at least 20%/50% improvement in the American College of Rheumatology response criteria, CRP = C-reactive protein, DAS28 = 28-joint Disease Activity Score, HAQ-DI = Health Assessment Questionnaire Disability Index, SDAI = Simplified Disease Activity Index.*

Immunogenicity

The overall cumulative incidence of antibodies-to-golimumab through week 268 was low (8.0%) and increased only slightly over time. Most of these patients tested positive for neutralizing antibodies (Table 1).

Table 1 Cumulative summary of golimumab safety and immunogenicity through week 268 of the GO-AFTER trial

	Golimumab			
	50 mg only	**50 and 100 mg**	**100 mg only**	**All patients**
Number of treated patients	98	195	138	431
Mean duration of follow-up (weeks)	129.82	187.45	162.06	166.22
Mean number of injections	29.4	42.9	37.0	37.9
Patients with 1 or more adverse events	90 (91.8%)	186 (95.4%)	132 (95.7%)	408 (94.7%)
Common adverse events[1]				
Upper respiratory tract infection	25 (25.5%)	49 (25.1%)	43 (31.2%)	117 (27.1%)
Rheumatoid arthritis	17 (17.3%)	57 (29.2%)	25 (18.1%)	99 (23.0%)
Nasopharyngitis	10 (10.2%)	37 (19.0%)	26 (18.8%)	73 (16.9%)
Sinusitis	19 (19.4%)	35 (17.9%)	23 (16.7%)	77 (17.9%)
Back pain	8 (8.2%)	36 (18.5%)	18 (13.0%)	62 (14.4%)
Hypertension	10 (10.2%)	34 (17.4%)	17 (12.3%)	61 (14.2%)
Arthrlagia	13 (13.3%)	26 (13.3%)	21 (15.2%)	60 (13.9%)
Bronchitis	12 (12.2%)	24 (12.3%)	22 (15.9%)	58 (13.5%)
Diarrhoea	5 (5.1%)	28 (14.4%)	22 (15.9%)	55 (12.8%)
Urinary tract infection	13 (13.3%)	25 (12.8%)	13 (9.4%)	51 (11.8%)
Nausea	10 (10.2%)	21 (10.8%)	18 (13.0%)	49 (11.4%)
Headache	14 (14.3%)	19 (9.7%)	14 (10.1%)	47 (10.9%)
Cough	10 (10.2%)	24 (12.3%)	13 (9.4%)	47 (10.9%)
Death				
Observed number of patients	2 (2.0%)	6 (3.1%)	1 (0.7%)	9 (2.1%)
Incidence (95% CI)/100 pt-yrs[2]	0.82 (0.10, 2.95)	0.85 (0.31, 1.86)	0.23 (0.01, 1.30)	0.65 (0.30, 1.24)
Discontinuation due to adverse event(s)	24 (24.5%)	33 (16.9%)	24 (17.4%)	81 (18.8%)
Serious adverse events	34 (34.7%)	71 (36.4%)	46 (33.3%)	151 (35.0%)
Common serious adverse events[3]				
Pneumonia	3 (3.1%)	10 (5.1%)	5 (3.6%)	18 (4.2%)
Urinary tract infection	0	5 (2.6%)	2 (1.4%)	7 (1.6%)
Rheumatoid arthritis	4 (4.1%)	8 (4.1%)	2 (1.4%)	14 (3.2%)
Osteoarthritis	2 (2.0%)	8 (4.1%)	1 (0.7%)	11 (2.6%)
Sepsis	0	5 (2.6%)	1 (0.7%)	6 (1.4%)
Arthralgia	1 (1.0%)	1 (0.5%)	2 (1.4%)	4 (0.9%)

Infections	64 (65.3%)	149 (76.4%)	108 (78.3%)	321 (74.5%)
Serious infections				
Observed number of patients	12 (12.2%)	29 (14.9%)	19 (13.8%)	60 (13.9%)
Observed number of serious infections	16	46	35	97
Incidence (95% CI)/100 pt-yrs[4]	6.54 (3.74, 10.62)	6.54 (4.79, 8.73)	8.14 (5.67, 11.32)	7.04 (5.71, 8.59)
Common serious infections[5]				
Pneumonia	3 (3.1%)	10 (5.1%)	5 (3.6%)	18 (4.2%)
Urinary tract infection	0	5 (2.6%)	2 (1.4%)	7 (1.6%)
Sepsis	0	5 (2.6%)	1 (0.7%)	6 (1.4%)
Cellulitis	1 (1.0%)	2 (1.0%)	1 (0.7%)	4 (0.9%)
Diverticulitis	0	1 (0.5%)	2 (1.4%)	3 (0.7%)
Pneumonitis	1 (1.0%)	0	1 (0.7%)	2 (0.5%)
Colitis ulcerative	1 (1.0%)	0	0	1 (0.2%)
Diarrhoea	1 (1.0%)	0	0	1 (0.2%)
Vomiting	1 (1.0%)	0	0	1 (0.2%)
Golimumab injection-site reactions				
Patients with reactions	11 (11.2%)	24 (12.3%)	18 (13.0%)	53 (12.3%)
Injections with reactions	16 (0.6%)	49 (0.6%)	64 (1.3%)	129 (0.8%)
Antibodies to golimumab				
Week 52	5 (5.4%)	9 (5.4%)	6 (4.6%)	20 (5.2%)
% with neutralizing antibodies[6]	3/4 (75.0%)	5/5 (100.0%)	6/6 (100.0%)	14/15 (93.3%)
Week 100	6 (6.5%)	12 (7.2%)	7 (5.4%)	25 (6.4%)
% with neutralizing antibodies[6]	4/5 (80.0%)	10/10 (100.0%)	6/7 (85.7%)	20/22 (90.9%)
Week 268	7 (7.6%)	16 (9.6%)	8 (6.2%)	31 (8.0%)
% with neutralizing antibodies[6]	5/6 (83.3%)	14/14 (100.0%)	6/8 (75.0%)	25/28 (89.3%)

[1] Occurring in ≥ 10% of patients in the combined golimumab group.
[2] The incidence of death for placebo through week 24 was 0.00 (95% CI 0.00, 6.20).
[3] Occurring in ≥ 1% of patients in any golimumab group.
[4] The incidence of serious infections for placebo through week 24 was 2.07 (95% CI 0.05, 11.52).
[5] Occurring in ≥ 1% of patients in any golimumab group.
[6] Among patients with samples evaluable for testing.
CI = confidence interval (based on exact method), pt-yrs = patient-years of follow-up.
Data presented are number (%) of patients unless noted otherwise.

Adverse events

Adverse events through week 24 and week 160 of the GO-AFTER trial have been reported previously [1,2]. Eleven patients died through week 268, including one placebo-treated patient who died of pancreatic cancer during the 24-week study period [1] and 10 golimumab-treated patients who died after week 24 (Table 1). No predominant cause of death was identified throughout the 5-year trial (see Additional file 1).

Serious adverse events were reported for approximately one-third of golimumab-treated patients, with the most common categorized as infections. Infections were also the most common adverse events leading to study agent discontinuation (Table 1). The overall pattern and types of infections observed through week 268 were similar to those reported through week 24 [1]. Through week 268, 13.9% of patients in the combined golimumab group had ≥1 infection identified by the investigator as a serious adverse event (Table 1). One case of active tuberculosis (pulmonary) was reported for a patient who was receiving golimumab 100 mg. Histoplasmosis infection occurred in two patients, each judged to be a serious infectious event (one disseminated, with both patients receiving golimumab 100 mg at event onset). Four patients had opportunistic infections through week 268, including three patients with

esophageal candidiasis (1 patient who was receiving 50 mg, 2 patients who were receiving 100 mg) and one with ophthalmic herpes zoster (100 mg).

Twenty patients in the combined golimumab-treated group had malignancies reported through week 268, including lymphoma (4 patients who were receiving golimumab 100 mg) and nonmelanoma skin cancers. The 95% confidence intervals (CIs) surrounding the incidence/100 pt-yrs of all malignancy categories observed with golimumab were contained within the 95% CI for placebo through week 24 (i.e., 0.00 [0.00, 6.20]). The standardized incidence ratio (SIR) and surrounding 95% CI for lymphoma indicated a higher-than-expected occurrence among patients who received golimumab 100 mg; however, the SIRs (95% CI) for all other malignancies (excluding nonmelanoma skin cancers, which are not captured in the Surveillance, Epidemiology, and End Results database) indicated no increased risk relative to the general US population (Table 2). See Additional file 1 for additional safety findings.

Table 2 Number of patients with 1 or more malignancies through week 268 compared with the expected number of malignancies from the general United States population according to the SEER database

	Golimumab			
	50 mg only	**50 and 100 mg**	**100 mg only**	**All patients**
Treated patients in the study	98	195	138	431
All malignancies				
Observed number of patients	3	11	6	20
Incidence (95% CI)/100 pt-yrs[1]	1.23 (0.25, 3.59)	1.59 (0.79, 2.85)	1.42 (0.52, 3.10)	1.47 (0.90, 2.28)
SIR[2]	1.36	1.20	0.81	1.11
(95% CI)[3]	(0.28, 3.98)	(0.48, 2.47)	(0.17, 2.36)	(0.59, 1.89)
Type of malignancy				
Lymphoma				
Observed number of patients	0	2	2	4
Incidence (95% CI)/100 pt-yrs[1]	0.00 (0.00, 1.22)	0.28 (0.03, 1.03)	0.47 (0.06, 1.68)	0.29 (0.08, 0.74)
SIR[2]	0.00	8.13	12.32	7.96
(95% CI)[3]	(0.00, 31.87)	(0.99, 29.38)	(1.49, 44.49)	(2.17, 20.39)
Other malignancies				
Observed number of patients	3	5	1	9
Incidence (95% CI)/100 pt-yrs[1]	1.23 (0.25, 3.59)	0.71 (0.23, 1.66)	0.23 (0.01, 1.30)	0.65 (0.30, 1.24)
SIR[2]	1.42	0.89	0.28	0.80
(95% CI)[3]	(0.29, 4.15)	(0.29, 2.07)	(0.01, 1.56)	(0.36, 1.51)
Nonmelanoma skin cancer				
Observed number of patients	0	5	3	8
Incidence (95% CI)/100 pt-yrs[1]	0.00 (0.00, 1.22)	0.72 (0.23, 1.69)	0.71 (0.15, 2.08)	0.59 (0.25, 1.16)

[1] The incidences (95% CIs) for placebo through week 24 were 0.00 (0.00, 6.20) for lymphoma, 0.00 (0.00, 6.20) for nonmelanoma skin cancer, 0.00 (0.00, 6.20) for other malignancies, and 0.00 (0.00, 6.20) for all malignancies.

[2] SIR = Standardized Incidence Ratio (observed number of patients with malignancy based on the SEER database [14], adjusted for age, gender, and race divided by expected number of patients with malignancy). SIR (95% CI) for placebo through week 24 were 0.00 (0.00, 175.37) for lymphoma, 0.00 (0.00, 7.82) for other malignancies, and 0.00 (0.00, 7.51) for all malignancies.

[3] Confidence intervals based on an exact method.

CI = confidence interval, pt-yrs = patient-years, SEER = Surveillance, Epidemiology, and End Results.

Discussion

The GO-AFTER trial evaluated patients with active RA despite prior treatment with conventional synthetic DMARDs and ≥ 1 TNF-inhibitor(s) (a particularly treatment-refractory cohort with longstanding disease) for their response to yet another TNF-inhibitor, golimumab. The LTE data presented reveal that, despite refractory disease, 40% of randomized patients continued in the study through 5 years. Among completers, > 50% of patients randomized to golimumab + MTX maintained low disease activity according to DAS28 criteria and 15% attained remission according to stringent ACR-European League Against Rheumatism (EULAR) index-based criteria. Among all randomized patients, > 20% achieved low disease activity and approximately 8% achieved stringent remission criteria. For this treatment-resistant population, among whom approximately one-third had not received MTX and thus were less amenable to responding versus combination therapy [15], this is not necessarily expected. The data show that, indeed, the TNF-inhibitor golimumab can exert sustained significant efficacy in some patients who previously discontinued ≥ 1 TNF-inhibitor.

Similar LTE data have not been published for other biological agents, e.g., tocilizumab, rituximab, abatacept, and other TNF-inhibitors; therefore, indirect comparisons cannot be made. However, we have shown previously that 6-month response rates to golimumab plus MTX were similar to those of other targeted biologics in similar patient populations [1].

There are several limitations to the analyses after week 24. No patients received placebo after week 24, yielding no control group after this time point. Study drug was administered open-label after the week 24 database lock. Patients could change golimumab treatment from 50 mg to 100 mg (n = 139) and from 100 mg to 50 mg (n = 29) during the LTE according to investigator judgment. These uncontrolled dose changes limit conclusions regarding the effect of dose change. These changes in treatment regimens also hinder comparisons between the golimumab 50-mg and 100-mg dose groups. Exposure to golimumab 100 mg was substantially greater, both in number of patients and length of follow-up. Patients with more severe RA disease, who would likely be more difficult-to-treat and more prone to experience adverse events, may have been selectively escalated to the higher dose. These confounding factors preclude drawing definitive conclusions regarding the relative dose comparability.

The safety data revealed no new findings as compared to earlier phases of the GO-AFTER trial [1,2], with serious infections occurring in 14% of the patients. When adjusted for length of follow-up, the incidence of serious infections among all golimumab-treated patients was 7.04/100 pt-yr, which is consistent with those observed in a retrospective observational population-based inception cohort of patients diagnosed with RA between 1995 and 2007, i.e., 6.6/100 pt-yr for all patients and 8.2/100 pt-yr during treatment with biologic agents [16]. Of note, four 100-mg-treated patients developed lymphoma, a rate significantly higher than expected; all occurred within the first 3 years of observation [2]. No patient in the 50-mg group developed lymphoma. Lymphoma is associated with cumulative RA disease activity [17] and registry data have not shown an association between TNF-inhibitor treatment and increased lymphoma risk [18]. When adjusted for length of follow-up, the overall incidence of lymphoma reported herein (0.29/100 pt-yr) was higher than that previously reported based on a longitudinal (1998–2005) study of long-term outcomes of RA patients (0.11/100 pt-yr) [19]. However, due to the relatively small numbers of events and patients in our trial, the accompanying 95% CI was fairly wide (95% CI: 0.08, 0.74) and in fact overlapped that of the longitudinal trial that evaluated 19,591 patients for 89,710 pt-yrs of follow-up (95% CI: 0.09,

0.13) [19]. Whether the increased rate we observed for the 100-mg dose is related to the drug dose itself or to the theoretically higher cumulative disease activity of patients receiving this dose due to dose escalation (see above and as discussed elsewhere [2]) remains unknown.

Conclusion

Golimumab can be an effective therapy over the long term for RA patients who have previously received and discontinued another TNF-inhibitor therapy for reasons including insufficient efficacy. Almost 40% of the patients originally randomized to golimumab continued therapy for 5 years and many achieved low disease activity/remission with this treatment, despite their refractory disease.

Abbreviations

ACR20/50, ≥ 20/50% improvement in the American College of Rheumatology criteria; CI, Confidence interval; DAS28-CRP, 28-joint count disease activity score employing C-reactive protein; DMARD, Disease-modifying antirheumatic drug; EULAR, European League Against Rheumatism; GO-AFTER, GOlimumab After Former anti-tumor necrosis factor α Therapy Evaluated in Rheumatoid arthritis; HAQ-DI, Health assessment questionnaire disability index; ITT, intent-to-treat; LTE, Long-term extension; MTX, Methotrexate; RA, Rheumatoid arthritis; SDAI, Simplified disease activity index; SIR, Standardized incidence ratio; TNF, Tumor necrosis factor-α

Competing interests

JS Smolen has received research grant support from Abbott, BMS, MSD, Pfizer, Roche, and UCB and consultation and/or speaking honoraria from Abbott, Astra-Zeneca, BMS, Celgene, Glaxo, Janssen, MSD, Novo-Nordisk, Pfizer, Roche, Sanofi-Aventis, and UCB.
J Kay has received research grant support paid to the University of Massachusetts Medical School from AbbVie Inc., Ardea Biosciences Inc., Eli Lilly and Company, and Roche Laboratories Inc.; and consultation honoraria from AbbVie Inc., Amgen Inc., AstraZeneca, Bristol Myers Squibb Co., Crescendo BioScience Inc., Epirus Biopharmaceuticals Inc., Genentech Inc., Hospira Inc., Janssen Biotech Inc., PanGenetics B.V., Pfizer Inc., Roche Laboratories Inc., and UCB Inc.
M Doyle was an employee of Janssen Research and Development at the time this study was conducted, and is now employed by Alexion Pharmaceuticals.
R Landewé has received research grant support from Abbott, Pfizer, Roche, and UCB and consultation and/or speaking honoraria from Abbott, Astra-Zeneca, BMS, Glaxo, Janssen, MSD, Pfizer, Roche, and UCB.
EL Matteson has received consultation honoraria from Janssen, and research grant support from Janssen, Mesoblast, Novartis, Pfizer, Roche, and UCB.
N Gaylis has received research grant support and consultation and/or speaking honoraria from Janssen and served as Medical Director Rheumatology Division - Cardinal Health during the time the study was conducted.
J Wollenhaupt has received consultation and/or speaking honoraria from Abbott, Amgen, BMS, Chugai, MSD, Medac, Pfizer, Roche, Sanofi-Aventis, and UCB.
FT Murphy has received speaking honoraria from Abbott Immunology and Janssen.
Y Zhou, S Xu, and EC Hsia are employees of Janssen Research and Development, LLC.

No non-financial conflict of interest exists for any author.

Authors' contribution

JSS, JK, MD, RL, ELM, NG, JW, FTM, and ECH participated in study design/conduct, data interpretation, and manuscript preparation. SX and YZ participated in the design/conduct of statistical analyses, data interpretation, and manuscript preparation. All authors reviewed the paper for critical and substantive content and approved the final manuscript for submission. Thus, all authors met authorship requirements.

Acknowledgments

The authors thank Michelle L. Perate, MS and Mary H. Whitman, PhD of Janssen Scientific Affairs, LLC for their assistance with manuscript preparation and submission.
This study was sponsored by Janssen Research & Development, LLC and Merck/Schering-Plough Research Institute.
The specific ethical bodies that approved the GO-AFTER protocol are as follows:
Australia: Research and Ethics Committee, Daw Park/South Australia; Cabrini Human Research Ethics Committee, Malvern, Victoria; Northside Health Service District - Redcliffe-Caboolture Human Research, Redcliffe, Queensland.
Austria: Ethik-Kommission der Medizinischen, Universität Wien und des Allgemeinen Krankenhauses der Stadt Wien, Vienna.
Canada: IRB Services, Aurora, ON; Sunnybrook Health Science Center REB, Toronto, ON; Mount Sinai Hospital Research Ethics Board, Toronto, ON; Health Research Ethics Authority, St. John's, NL; University Health Network Research, Toronto, ON.
Finland: HUS, Helsingin ja Uudenmaan sairaanhoitopiiri, Medisiininen eettinen toimikunta, Biomedicum Helsinki, HUS.
France: CCPPRB Montpellier, Hôpital St-Eloi, Montpellier Cedex 5.
Germany: Geschäftsstelle der Ethik-Kommission, der Medizinischen Fakultät der Universität zu Köln Gebäude 5, Köln
The Netherlands: Clinical Trial Centre Maastricht, Medische Ethische Commissie AZM/UM/6229 HX Maastricht.
New Zealand: Multi-region Ethics Committee, c/o-Ministry of Health, Wellington.
Spain: Comité Etico de Investigación, Clínica de Cantabria Hospital Universitario Marqués de Valdecilla, Santander; LEC - Comité Ético de investigación Clínica, Hospital Virgen de la Macarena Avda. Sevilla; LEC- Comité Ético de Investigación, Clinica de Andalucía Edificio Arena 1, Dpto. Investigación, Sevilla; Comité Etico de Investigación, Clínica de Cantabria Hospital Universitario Marqués de Valdecilla, Santander; LEC- Comité Ético de Investigación Clínica, Hospital Dr. Peset, C/Gaspar Aguilar, Valencia.
United Kingdom: Newcastle and North Tyneside, Research Ethics Committee 1, Jarrow.
United States of America: Quorum Review, Inc., Seattle, WA; Washington University School of Medicine, Washington University Medical Center Office of Washington, University Medical Center IRB (OWUMC IRB), Human Studies Committee (HSC), St. Louis, MO; UCSD Human Research Protection Program, La Jolla, CA; Mayo Foundation Institutional Review Board, Rochester, MN; University of North Texas Health Science Center at Fort Worth Institutional Review Board, Fort Worth, TX; University of Pittsburgh Institutional Review Board, Pittsburgh, PA; Partners Human Research Committee, Boston, MA; Office of Protection for Research Subjects, Los Angeles, CA.

References

1. Smolen JS, Kay J, Doyle MK, Landewé R, Matteson EL, Wollenhaupt J, et al. GO-AFTER study investigators: Golimumab in patients with active rheumatoid arthritis after treatment with tumour necrosis factor α inhibitors (GO-AFTER study): a multicentre, randomised, double-blind, placebo-controlled, phase III trial. Lancet. 2009;374:210–21.

2. Smolen JS, Kay J, Landewé RB, Matteson EL, Gaylis N, Wollenhaupt J, et al. Golimumab in patients with active rheumatoid arthritis who have previous experience with tumour necrosis factor inhibitors: results of a long-term extension of the randomised, double-blind, placebo-controlled GO-AFTER study through week 160. Ann Rheum Dis. 2012;71:1671–9.

3. Buch MH, Aletaha D, Emery P, Smolen JS. Reporting of long-term extension studies: lack of consistency calls for consensus. Ann Rheum Dis. 2011;70:886–90.

4. Arnett FC, Edworthy SM, Bloch DA, McShane DJ, Fries JF, Cooper NS, et al. The American Rheumatism Association 1987 revised criteria for the classification of rheumatoid arthritis. Arthritis Rheum. 1988;31:315–24.

5. Smolen JS, Landewé R, Breedveld FC, Dougados M, Emery P, Gaujoux-Viala C, et al. EULAR recommendations for the management of rheumatoid arthritis with synthetic and biological disease-modifying antirheumatic drugs: 2013 update. Ann Rheum Dis. 2014;73:492–509.

6. Baecklund E, Iliadou A, Askling J, Ekbom A, Backlin C, Granath F, et al. Association of chronic inflammation, not its treatment, with increased lymphoma risk in rheumatoid arthritis. Arthritis Rheum. 2006;54:692–701.

7. Askling J, van Vollenhoven RF, Granath F, Raaschou P, Fored CM, Baecklund E, et al. Cancer risk in patients with rheumatoid arthritis treated with anti-tumor necrosis factor α therapies: does the risk change with the time since start of treatment? Arthritis Rheum. 2009;60:3180–9.

8. Felson DT, Anderson JJ, Boers M, Bombardier C, Furst D, Goldsmith C, et al. American College of Rheumatology: Preliminary definition of improvement in rheumatoid arthritis. Arthritis Rheum. 1995;38:727–35.

9. Prevoo ML, van't Hof MA, Kuper HH, van Leeuwen MA, van de Putte LB, van Riel PL. Modified disease activity scores that include twenty-eight-joint-counts. Development and validation in a prospective longitudinal study of patients with rheumatoid arthritis. Arthritis Rheum. 1995;38:44–8.

10. Aletaha D, Landewe R, Karonitsch T, Bathon J, Boers M, Bombardier C, et al. Reporting disease activity in clinical trials of patients with rheumatoid arthritis: EULAR/ACR collaborative recommendations. Arthritis Rheum. 2008;59:1371–7.

11. van Riel PL, van Gestel AM, Scott DL. EULAR handbook of clinical assessments in rheumatoid arthritis. Alphen Aan Den Rijn, The Netherlands: Van Zuiden Communications B.V; 2000. p. 1–55.

12. Wells G, Becker JC, Teng J, Dougados M, Schiff M, Smolen J, et al. Validation of the 28-joint Disease Activity Score (DAS28) and European League Against Rheumatism response criteria based on C-reactive protein against disease progression in patients with rheumatoid arthritis, and comparison with the DAS28 based on erythrocyte sedimentation rate. Ann Rheum Dis. 2009;68:954–60.

13. Smolen JS, Breedveld FC, Schiff MH, Kalden JR, Emery P, Eberl G, et al. A simplified disease activity index for rheumatoid arthritis for use in clinical practice. Rheumatology. 2003;42:244–57.

14. Felson DT, Smolen JS, Wells G, Zhang B, van Tuyl LH, Funovits J, et al. American College of Rheumatology/European League Against Rheumatism provisional definition of remission in rheumatoid arthritis for clinical trials. Arthritis Rheum. 2011;63:573–86.

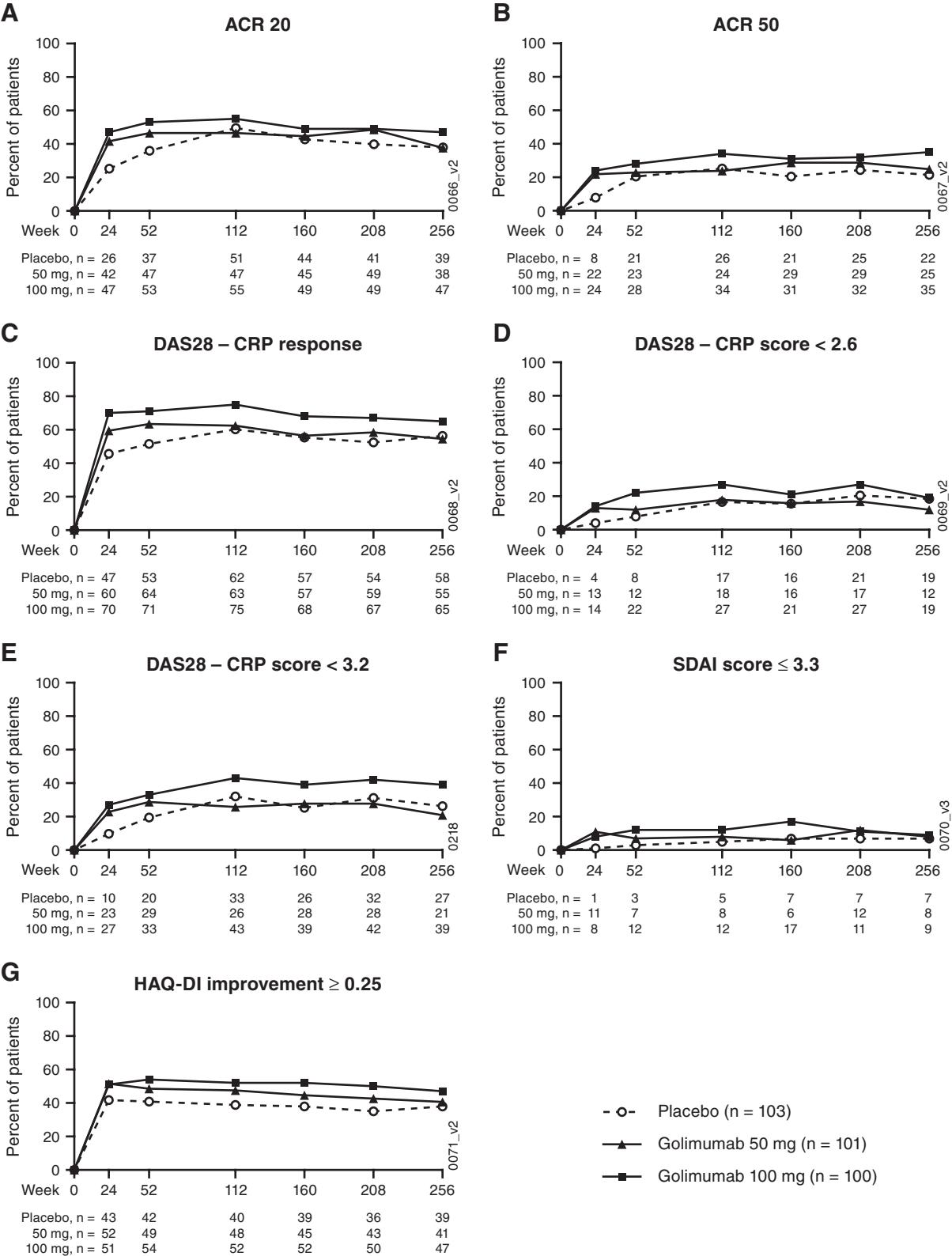
15. Fries JF, Spitz P, Kraines RG, Holman HR. Measurement of patient outcome in arthritis. Arthritis Rheum. 1980;23:137–45.

16. Wells GA, Tugwell P, Kraag GR, Baker PR, Groh J, Redelmeier DA. Minimum important difference between patients with rheumatoid arthritis: the patient's perspective. J Rheumatol. 1993;20:557–60.

17. National Cancer Institute. The Surveillance, Epidemiology, and End Results (SEER). 2004. [http://seer.cancer.gov].

18. Ni Mhuircheartaigh OM, Matteson EL, Green AB, Crowson CS. Trends in serious infections in rheumatoid arthritis. J Rheumatol. 2013;40:611–6.

19. Wolfe F, Michaud K. The effect of methotrexate and anti-tumor necrosis factor therapy on the risk of lymphoma in rheumatoid arthritis in 19,562 patients during 89,710 person-years of observation. Arthritis Rheum. 2007;56:1433–9.


A
ACR 20
Percent of patients
100
80
60
40
20
0
0066_v2
Week 0 24 52 112 160 208 256
Placebo, n = 26 37 51 44 41 39
50 mg, n = 42 47 47 45 49 38
100 mg, n = 47 53 55 49 49 47
B
ACR 50
Percent of patients
0067_v2
Week 0 24 52 112 160 208 256
Placebo, n = 8 21 26 21 25 22
50 mg, n = 22 23 24 29 29 25
100 mg, n = 24 28 34 31 32 35
C
DAS28 – CRP response
Percent of patients
0068_v2
Week 0 24 52 112 160 208 256
Placebo, n = 47 53 62 57 54 58
50 mg, n = 60 64 63 57 59 55
100 mg, n = 70 71 75 68 67 65
D
DAS28 – CRP score < 2.6
Percent of patients
0069_v2
Week 0 24 52 112 160 208 256
Placebo, n = 4 8 17 16 21 19
50 mg, n = 13 12 18 16 17 12
100 mg, n = 14 22 27 21 27 19
E
DAS28 – CRP score < 3.2
Percent of patients
0218
Week 0 24 52 112 160 208 256
Placebo, n = 10 20 33 26 32 27
50 mg, n = 23 29 26 28 28 21
100 mg, n = 27 33 43 39 42 39
F
SDAI score ≤ 3.3
Percent of patients
0070_v3
Week 0 24 52 112 160 208 256
Placebo, n = 1 3 5 7 7 7
50 mg, n = 11 7 8 6 12 8
100 mg, n = 8 12 12 17 11 9
G
HAQ-DI improvement ≥ 0.25
Percent of patients
0071_v2
Week 0 24 52 112 160 208 256
Placebo, n = 43 42 40 39 36 39
50 mg, n = 52 49 48 45 43 41
100 mg, n = 51 54 52 52 50 47
Placebo (n = 103)
Golimumab 50 mg (n = 101)
Golimumab 100 mg (n = 100)

Additional files provided with this submission:

Additional file 1. The additional file provides further details of study methods, patient disposition and baseline characteristics, and additional efficacy and safety findings (827k)
http://arthritis-research.com/content/supplementary/s13075-015-0516-6-s1.docx