Five-year Safety Data from 5 Clinical Trials of Subcutaneous Golimumab in Patients with Rheumatoid Arthritis, Psoriatic Arthritis, and Ankylosing Spondylitis

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ABSTRACT. ***Objective.*** Assess 5-year golimumab (GOL) safety in rheumatoid arthritis (RA), psoriatic arthritis (PsA), and ankylosing spondylitis (AS).

Methods. Subcutaneous (SC) GOL (50 mg or 100 mg every 4 weeks) was evaluated in phase 3 trials of patients with active RA, PsA, and AS. Safety data through Year 5 were pooled across 3 RA trials [1 each evaluating methotrexate (MTX)-naive, MTX-experienced, and antitumor necrosis factor (TNF)-experienced patients], 1 PsA trial, and 1 AS trial. Data summarized was derived from both placebo-controlled (through weeks 24–52) and uncontrolled study periods. For adverse events (AE) of special interest [serious infections (SI), opportunistic infections (OI), deaths, malignancies, demyelination, tuberculosis (TB)], incidence per 100 patient-years (pt-yrs) was determined.

Results. Across all trials, 639 patients received placebo and 2228 received SC GOL 50 mg only (n = 671), 50 mg and 100 mg (n = 765), or 100 mg only (n = 792). Safety followup extended for averages of 28.5 and 203.2 weeks for placebo and GOL, respectively. Respective placebo and GOL AE incidence/100 pt-yrs (95% CI) through Year 5 were 4.86 (2.83–7.78) and 3.29 (2.92–3.69) for SI, 0.00 (0.00–0.86) and 0.23 (0.14–0.35) for TB, 0.00 (0.00–0.86) and 0.22 (0.13–0.34) for OI, 0.00 (0.00–0.86) and 0.10 (0.05–0.20) for lymphoma, 0.00 (0.00–0.86) and 0.08 (0.03–0.17) for demyelination, and 0.29 (0.01–1.59) and 0.41 (0.29–0.57) for death. TB, OI, lymphoma, and demyelination incidence appeared to be higher among patients receiving GOL 100 mg only.

Conclusion. SC GOL safety through Year 5 remained consistent with previously reported Year 3 findings and with other TNF antagonists. Numerically higher incidences of TB, OI, lymphoma, and demyelination were observed with 100 mg versus 50 mg. Clinicaltrials.gov identifiers: NCT00264537 (GO-BEFORE), NCT00264550 (GO-FORWARD), NCT00299546 (GO-AFTER), NCT00265096 (GO-REVEAL), and NCT00265083 (GO-RAISE). (J Rheumatol First Release November 1 2016; doi:10.3899/jrheum.160420)

Key Indexing Terms:
ANTITUMOR NECROSIS FACTOR CLINICAL TRIAL ADVERSE EVENTS
MALIGNANCY TUBERCULOSIS LYMPHOMA

Golimumab (GOL) for subcutaneous (SC) injection is a human monoclonal antibody to tumor necrosis factor-α (TNF) that is approved for treating moderately to severely active rheumatoid arthritis (RA) in combination with methotrexate (MTX), active psoriatic arthritis (PsA) alone or in combination with MTX, active ankylosing spondylitis (AS), and moderate to severe active ulcerative colitis among patients with an inadequate response or intolerance to prior treatment or requiring continuous corticosteroid therapy. Across rheumatological indications, the approved SC GOL

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dose is 50 mg monthly; in Europe, a dose increase to 100 mg monthly is approved for patients weighing more than 100 kg who do not respond to initial dosing[1,2].

As a class, anti-TNF agents have a well-characterized and consistent safety profile across rheumatological indications and across agents, including adalimumab (ADA)[3], certolizumab pegol[4], etanercept (ETN)[5], and infliximab (IFX)[6]. GOL safety through 3 years of treatment in the pivotal phase 3 trials of SC GOL in patients with RA, PsA, and AS[7] appeared consistent with other TNF antagonists. The incidence of adverse events (AE) of special interest, including serious infections, demyelinating events, and lymphoma, appeared somewhat higher in patients receiving 100 mg than in those receiving 50 mg of GOL in the previous analysis[7]. These same randomized, double-blind, placebo-controlled trials included longterm extensions designed to evaluate SC GOL safety through 5 years of followup; these data are reported herein.

MATERIALS AND METHODS

Trials and patients. Our current study was a pooled analysis of previously collected safety data from 5 large multicenter trials[8–17,18,19,20,21,22,23,24], each of which was conducted according to the Declaration of Helsinki and the International Committee on Harmonisation Good Clinical Practices. Each of the phase 3 study protocols was approved by central or individual site institutional review boards/ethics committees, and all patients provided written informed consent prior to any study-related procedures. No further ethical approval was required to conduct the additional data analyses reported herein. Patient entrance criteria and study designs for each trial have been reported[8–17,18,19,20,21,22,23,24] and are summarized in Table 1. Additionally, further details of each trial are available at clinicaltrials.gov (GO-BEFORE: NCT00264537, GO-FORWARD: NCT00264550, GO-AFTER: NCT00299546, GO-REVEAL: NCT00265096, GO-RAISE: NCT00265083).

In brief, GO-BEFORE, GO-FORWARD, and GO-AFTER studies enrolled adults (≥ 18 yrs) who had active RA (≥ 4 swollen and ≥ 4 tender joints) according to the revised 1987 American College of Rheumatology (formerly American Rheumatism Association) classification criteria[25] for ≥ 3 months before the initial administration of study drug. In GO-BEFORE, patients with RA could not have received more than 3 weekly doses of oral MTX for RA. In GO-FORWARD, patients with RA must have been receiving MTX for ≥ 3 months, with the dose being stable for ≥ 4 weeks before the start of study treatment. In GO-AFTER, patients with RA must have received ≥ 1 dose of an anti-TNF agent (ETN, ADA, or IFX), the last dose of which must have been given ≥ 8 weeks (ADA or ETN) or ≥ 12 weeks (IFX) before initiating study treatment.

Patients in the GO-REVEAL study were adults who had active PsA, defined by the presence of ≥ 3 swollen and ≥ 3 tender joints, despite treatment with disease-modifying antirheumatic drugs (DMARD) or nonsteroidal antiinflammatory drugs (NSAID); the absence of circulating rheumatoid factor; and the presence of a qualifying plaque psoriasis lesion ≥ 2 cm in diameter. Stable doses of MTX (≤ 25 mg/week) were allowed, but not required.

Patients in the GO-RAISE study were adults who had active AS diagnosed according to the modified New York criteria[26]. Active AS was defined by a Bath AS Disease Activity Index[27] score ≥ 4, a spinal pain assessment score ≥ 4, and an inadequate response to NSAID and/or DMARD.

In all trials, eligible patients met the prespecified tuberculosis (TB) screening criteria. Patients with positive TB skin (per local criteria) and/or whole blood interferon-based QuantiFERON-TB Gold-In-Tube (Cellestis) testing results could participate, but had to begin treatment for latent TB before or with the first dose of study drug.

Data collection and analyses. All treated patients were included in these pooled safety analyses, as were all available followup data for patients who discontinued study agent for any reason. As reported[7], AE were methodically documented and classified by the investigator for seriousness, intensity, causality, action taken, and whether the AE constituted an infection or an injection site reaction (ISR). AE were summarized by system organ class using the Medical Dictionary for Regulatory Activities, version 15.0, and reporting rates were pooled across the trials based on treatment received prior to the AE. Safety events from the first GOL exposure through the end of the 5-year followup period were included.

To provide an overview of longer-term GOL safety, occurrences of AE, serious adverse events (SAE), study drug discontinuation because of AE, infections, and ISR are summarized. To specifically assess AE of interest in the biologic treatment of patients with RA, PsA, and AS, incidence of death, serious infection, TB, opportunistic infection, malignancy, and demyelinating disorder was calculated as the number of events per 100 patient-years (pt-yrs) of followup, along with the corresponding exact 95% CI. In analyses assessing incidence by year of study participation, placebo patients who had neither discontinued study participation nor received active drug at the beginning of the year-long interval were included. Each infection for an individual patient was counted separately. For malignancies, other than nonmelanoma skin cancer (NMSC), incidence was compared with that derived from an age-, sex-, and race-matched population from the 2007 US National Cancer Institute Surveillance, Epidemiology, and End Results (SEER) database[28]. In these analyses, standardized incidence ratios (SIR) with corresponding 95% CI were calculated by dividing the number of events observed in the GOL trials by the number of events that would have been expected based on the SEER database.

RESULTS

Across these 5 phase 3 trials of SC GOL, 639 patients received placebo and 2228 received GOL, including 671 receiving only the 50 mg dose, 792 receiving only the 100 mg dose, and 765 receiving both GOL doses, yielding 8702 and 350 pt-yrs of followup for GOL and placebo, respectively (Table 2). Patients receiving both GOL 50 mg and 100 mg escaped early or had their GOL dose increased or decreased as outlined in Table 1. The majority of treated patients (66.9%, 1537/2297) participated in 1 of the 3 RA trials (Figure 1); GOL exposure in this subgroup was generally similar to that observed among all patients (Table 2). Patient exposure through 5 years of followup has been reported for the individual PsA[21] and AS[24] trials.

The baseline patient demographics have been reported for each of the phase 3 RA[8,11,15], PsA[18], and AS[22] trials, and also in the 3-year pooled safety analysis of these trials[7]. About two-thirds of patients included in our pooled analysis had RA, while about 15% of patients each had PsA or AS.

Through 5 years of GOL treatment and followup, AE were reported by 73.6%, 92.8%, 92.0%, and 95.5% of patients receiving placebo (mean followup 28.5 weeks), GOL 50 mg only (184.0 weeks), GOL 50 mg + 100 mg (227.5 weeks), and GOL 100 mg only (195.9 weeks), respectively (Table 2 and Table 3). Common AE (i.e., those that occurred in ≥ 10% of patients in any treatment group) included infections, constitutional symptoms, hypertension (HTN), injection site erythema, and elevated alanine aminotransferase (ALT)

Table 1. Pivotal phase 3 GOL trials contributing data to 5-year pooled safety analyses.

Indication/Trial Identifier	Patients	Study Design	Study Treatment
RA			
GO-BEFORE[8,9,10]	RA, MTX-naive	Multicenter, randomized (1:1:1:1), double-blind, placebo-controlled through Week 52 with early escape[1] at Week 28, followed by OL GOL after Week 52 DBL.	Fixed SC doses q4wk through Week 52 with early escape[1] at Week 28: placebo + oral MTX, GOL 100 mg + oral placebo, GOL 50 mg + oral MTX, GOL 100 mg + oral MTX. Starting at Week 52, placebo patients crossed over to GOL 50 mg q4wk. During the OLE, the investigator could increase/decrease the OL GOL dose to 100/50 mg q4wk, respectively, and/or adjust the MTX dose.
GO-FORWARD [11,12,13,14]	RA, inadequate response to MTX	Multicenter, randomized (3:3:2:2), double-blind, placebo-controlled through Week 24 with early escape[1] at Week 16, followed by blinded GOL through Week 52 and OL GOL after Week 52 DBL.	Fixed SC doses q4wk through Week 24 with early escape[1] at Week 16: placebo + oral MTX, GOL 100 mg + oral placebo, GOL 50 mg + oral MTX, GOL 100 mg + oral MTX. Starting at Week 24, placebo patients crossed over to double-blind GOL 50 mg q4wk. During the OLE, the investigator could increase/decrease the OL GOL dose to 100/50 mg q4wk, respectively, and/or adjust the MTX dose.
GO-AFTER[15,16,17]	RA, inadequate response to prior TNF antagonist(s)	Multicenter, randomized (1:1:1), double-blind, placebo-controlled through Week 24 with early escape[1] at Week 16, followed by OL GOL after Week 24 DBL (MTX allowed, but not required).	Fixed SC doses q4wk through Week 24 with early escape[1] at Week 16: placebo, GOL 50 mg, GOL 100 mg. Starting at Week 24, placebo patients crossed over to OL GOL 50 mg q4wk. During the OLE, the investigator could increase/decrease the OL GOL dose to 100/50 mg q4wk, respectively.
PsA			
GO-REVEAL [18,19,20,21]	PsA, inadequate response to DMARD/NSAID	Multicenter, randomized (1:1.3:1.3), double-blind, placebo-controlled through Week 24 with early escape[1] at Week 16, followed by blinded GOL from Week 24 through Week 52 DBL and then OL GOL (MTX allowed, but not required).	Fixed SC doses q4wk through Week 24 with early escape[1] at Week 16: placebo, GOL 50 mg, GOL 100 mg. Beginning at Week 24, placebo patients crossed over to GOL 50 mg q4wk. During the OLE, the investigator could increase/decrease the OL GOL dose to 100/50 mg q4wk, respectively.
AS			
GO-RAISE[22,23,24]	AS, inadequate response to DMARD/NSAID	Multicenter, randomized (1:1.8:1.8), double-blind, placebo-controlled through Week 24 with early escape[1] at Week 16, followed by dose-blinded GOL from Week 24 forward. Blinded therapy continued through Week 104 DBL followed by OL GOL.	Fixed SC doses q4wk through Week 24 with early escape[1] at Week 16: placebo, GOL 50 mg, GOL 100 mg. Starting at Week 24, placebo patients crossed over to GOL 50 mg q4wk. During the OLE, the investigator could increase/decrease the OL GOL dose to 100/50 mg q4wk, respectively.

[1] For patients meeting the early escape criteria (i.e., < 20% improvement in tender and swollen joint counts for RA, < 10% improvement in tender and swollen joint counts for PsA, < 20% improvement in total back and morning stiffness for AS), those receiving placebo escaped to GOL 50 mg, those receiving GOL 100 mg + placebo added MTX, those receiving GOL 50 mg increased the GOL dose to 100 mg, and those receiving GOL 100 mg had no change in study medication. GOL: golimumab; RA: rheumatoid arthritis; MTX: methotrexate; TNF: tumor necrosis factor; PsA: psoriatic arthritis; DMARD: disease-modifying antirheumatic drug; NSAID: nonsteroidal antiinflammatory drug; AS: ankylosing spondylitis, OL: open label; DBL: database lock; q4wk: every 4 weeks; OLE: open-label extension; SC: subcutaneous.

levels (Table 3). Although a larger proportion of GOL-treated patients (9.9%) had a serious infection during study participation than did placebo-treated patients (2.7%), the incidence of serious infection was comparable between combined GOL (3.29/100 pt-yrs) and placebo (4.86/100 pt-yrs) treatment when adjusted for length of followup. The incidence of serious infections did not appear to increase with the duration of GOL treatment (Table 4). Findings were consistent among the patients in the safety database with RA (Table 5).

Greater incidence of active TB (0.30 vs 0.17/100 pt-yrs) and opportunistic infections (0.37 vs 0.13/100 pt-yrs) was observed for the GOL 100 mg only group than for the GOL 50 mg only group; the 95% CI for both GOL doses, however, were contained within those for placebo for both of these AE through 5 years of GOL treatment. The 18 patients with opportunistic infection included 13 with RA (6 with esophageal/gastrointestinal candidiasis; 2 with histoplasmosis; and 1 each with aspergilloma, esophageal candidiasis/aspergillosis, *Pneumocystis jirovecii* pneumonia, *Pneumonia legionella*, and ophthalmic herpes zoster), 3 with PsA (toxoplasmal eye infection, histoplasmosis, *P. legionella*), and 2 with AS (coccidioidomycosis, cryptosporidiosis).

Table 2. Extent of exposure and followup through 5 years: pooled data across 5 phase 3 studies of SC GOL (with or without MTX) in RA (3 trials), PsA (1 trial), and AS (1 trial). Values are mean/median unless stated otherwise.

Variables	Placebo	GOL 50 mg Only	GOL 50 and 100 mg	GOL 100 mg Only	GOL Combined
5 trials: 3 RA, 1 PsA, 1 AS					
No. treated patients[1]	639	671	765	792	2228
No. SC injections	6.6/6.0	42.6/57.0	52.9/60.0	45.3/61.0	47.1/58.0
Weeks of safety followup[2]	28.5/24.0	184.0/240.1	227.5/255.7	195.9/257.3	203.2/252.4
Total patient-yrs of followup	350	2374	3346	2982	8702
Cumulative GOL dose, mg	0.0/0.0	2132/2850	4376/4850	4525/6100	3753/3600
3 RA trials					
No. treated patients[1]	449	374	542	565	1481
No. SC injections	7.4/6.0	39.4/51.0	51.5/58.0	43.2/60.0	45.3/57.0
Weeks of safety followup[2]	32.2/24.0	172.0/216.3	223.0/252.1	188.3/257.0	196.9/244.9
Total patient-yrs of followup	278	1237	2323	2044	5604
Cumulative GOL dose, mg	0.0/0.0	1967/2525	4242/4625	4318/6000	3697/3650

[1] Note that some patients received placebo followed by GOL in early escape or following crossover per trial design. [2] Including posttreatment followup. SC: subcutaneous; GOL: golimumab; MTX: methotrexate; RA: rheumatoid arthritis; PsA: psoriatic arthritis; AS: ankylosing spondylitis.

Patients with TB, including 18 with RA, 1 with PsA, and 1 with AS, resided in Asia (n = 12), Europe (n = 6), and South America (n = 2). No increase in the occurrence of either active TB or opportunistic infection was observed over time (Table 4).

Through 5 years, with a much longer period of followup for GOL than for placebo treatment, 58 (9.1%), 177 (26.4%), 230 (30.1%), and 275 patients (34.7%) in the placebo, GOL 50 mg only, GOL 50 mg + 100 mg, and GOL 100 mg only groups, respectively, had ≥ 1 SAE, and 33 (5.2%), 103 (15.4%), 73 (9.5%), and 158 (19.9%) patients, respectively, discontinued the study drug because of an AE (Table 3). Through 5 years, 37 patients died, including 1 (0.2%), 11 (1.6%), 9 (1.2%), and 16 patients (2.0%) in the placebo, GOL 50 mg only, GOL 50 mg + 100 mg, and GOL 100 mg only groups, respectively. The time-adjusted incidence of death was 0.29/100 pt-yrs for the placebo-controlled period and 0.41/100 pt-yrs through 5 years for patients who received GOL (Table 4), the 95% CI for which, however, was contained within that for placebo. The incidence of death appeared to be stable over time (Table 4). Among the 37 deaths, 8 occurred within the first year, 12 occurred during the second and third years, and 17 occurred during the fourth and fifth years of study participation. Four patients whose duration of followup could not be determined were not included in Table 4. Causes of death were malignancy in 13 patients, infection in 8 patients, cerebrovascular/cardiovascular event in 7 patients, an unrelated accident in each of 2 patients, hypoglycemic coma in 1 patient following a suicide attempt, hepatitis in 1 patient, and an overdose of tramadol in 1 patient; the cause of death was not known for 4 patients.

The overall time-adjusted incidence of malignancy through 5 years did not appear to be elevated with GOL versus placebo treatment (1.07 vs 2.59/100 pt-yrs, respectively) or when compared with rates expected in the general US population (SIR 1.08, 95% CI 0.82–1.40); similar findings were observed for NMSC (Table 4). A higher incidence of lymphoma relative to the general US population was observed through 5 years among patients who had received GOL 100 mg only (SIR 7.71, 95% CI 2.83–16.78, not inclusive of 1). This higher incidence of lymphoma among patients who received only GOL 100 mg led to a higher incidence of lymphoma among all GOL-treated patients relative to the general US population (SIR 3.89, 95% CI 1.78–7.38). Conversely, the 95% CI surrounding the SIR for lymphoma among patients who received GOL 50 mg only, i.e., 1.71 (0.04–9.50), was inclusive of 1 (Table 4). Patients with RA mostly drove this higher incidence of lymphoma (Table 5). Among the 9 patients with lymphoma, 8 had RA that ranged in duration from 4.7 to 31.4 years (mean 12.7 yrs). Of the 8 patients with RA, 4 had previously responded inadequately to another TNF inhibitor, 3 had a family history of cancer, and 2 tested positive for Epstein-Barr virus (EBV). These 8 patients, all of whom received GOL 100 mg during study participation, had 28-joint Disease Activity Scores based on C-reactive protein (DAS28-CRP) that ranged from 4.8 to 7.9 (mean 6.3) at study onset and from 1.8 to 6.6 (mean 4.0) at the study visit closest to the time of lymphoma diagnosis (Supplementary Table 1, available online at jrheum.org).

No increase in the occurrence of any malignancy, NMSC, or lymphoma was observed with longer duration of GOL treatment (Table 4). Consistent findings were observed among the subgroups of patients with RA (Table 5).

Through 5 years, demyelination events were reported in 7 patients, including 2 patients with AS (chronic inflammatory demyelinating polyneuropathy, multiple sclerosis) and 5 patients with RA (sclerosis multiplex, demyelination of the central nervous system, autoimmune demyelination, cervical spine lesion/not disc disease/suspected demyelinating process, demyelinating areas of brain). All patients had received GOL 100 mg prior to the event. The highest incidence of demyeli-

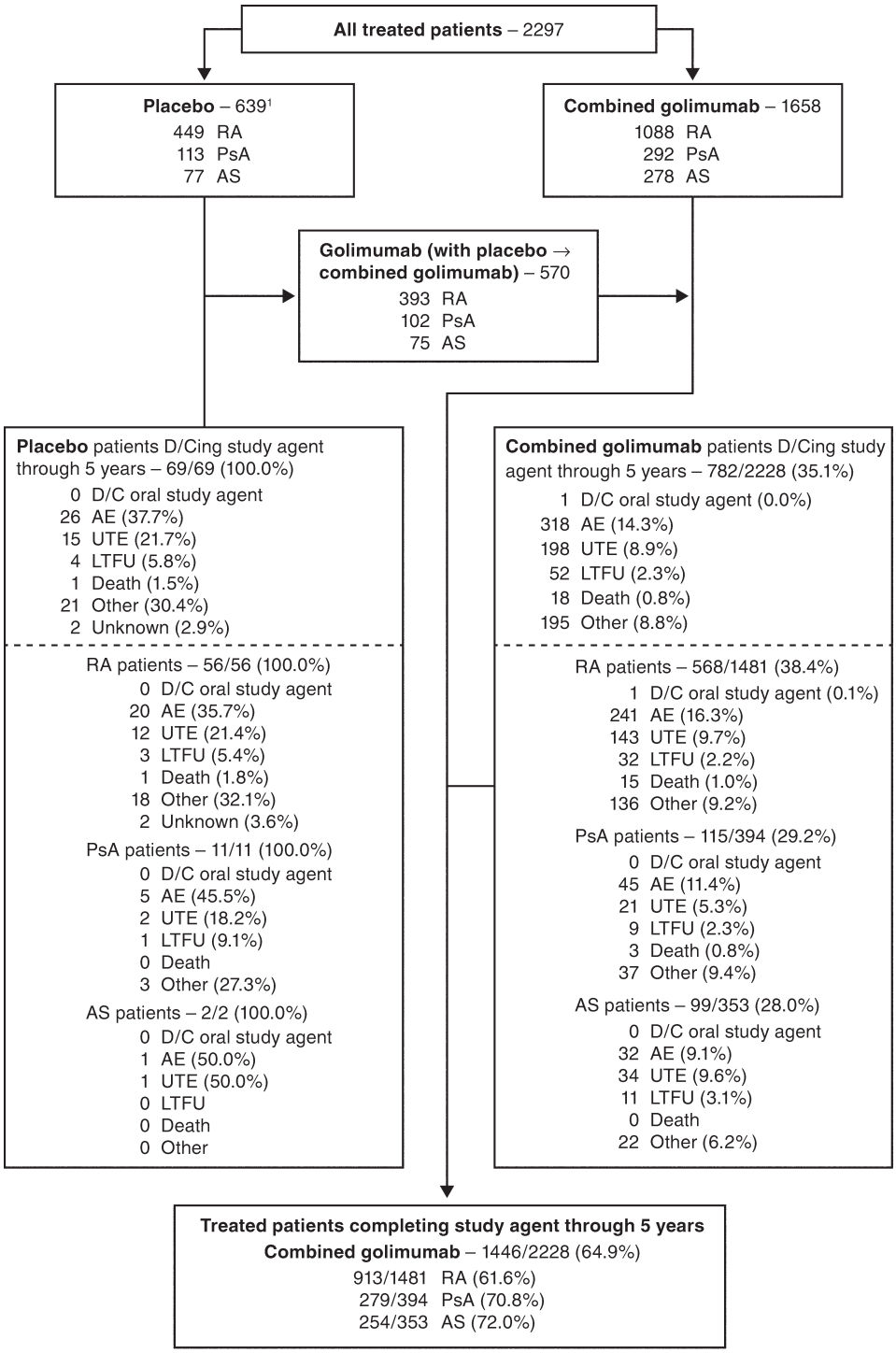

Figure 1. Patient disposition through 5 years of 5 phase 3 clinical trials of subcutaneous golimumab in rheumatological indications. [1] Some patients received placebo followed by golimumab in early escape or following crossover per trial design. RA: rheumatoid arthritis; PsA: psoriatic arthritis; AS: ankylosing spondylitis; D/C: discontinued; AE: adverse event; UTE: unsatisfactory therapeutic effect; LTFU: lost to followup.

nation was observed during the fourth year of GOL treatment (0.19/100 pt-yrs), although during the fifth year (0.06/100 pt-yrs) the incidence was similar to that observed in each of the first 3 years (0.05–0.06/100 pt-yrs). Overall, the highest incidence of demyelination over 5 years was observed among patients who received GOL 100 mg only, i.e., 0.20/100 pt-yrs;

Table 3. Safety findings through 5 years: pooled data from phase 3 studies of SC GOL (with or without MTX) in rheumatological indications. Values are n (%) or n/N (%) of patients.

Variables	Placebo	GOL 50 mg Only	GOL 50 and 100 mg	GOL 100 mg Only	All GOL
Treated patients in 5 trials[1]	639	671	765	792	2228
Patients with ≥ 1 AE	470 (73.6)	623 (92.8)	704 (92.0)	756 (95.5)	2083 (93.5)
Most common AE[2]					
Upper respiratory tract infection	56 (8.8)	215 (32.0)	227 (29.7)	246 (31.1)	688 (30.9)
Nasopharyngitis	41 (6.4)	117 (17.4)	152 (19.9)	164 (20.7)	433 (19.4)
Bronchitis	24 (3.8)	92 (13.7)	114 (14.9)	114 (14.4)	320 (14.4)
Back pain	22 (3.4)	91 (13.6)	116 (15.2)	112 (14.1)	319 (14.3)
Cough	38 (5.9)	93 (13.9)	97 (12.7)	112 (14.1)	302 (13.6)
Headache	39 (6.1)	91 (13.6)	88 (11.5)	114 (14.4)	293 (13.2)
Sinusitis	15 (2.3)	86 (12.8)	108 (14.1)	95 (12.0)	289 (13.0)
Arthralgia	29 (4.5)	87 (13.0)	98 (12.8)	99 (12.5)	284 (12.7)
Nausea	51 (8.0)	63 (9.4)	94 (12.3)	127 (16.0)	284 (12.7)
Hypertension	17 (2.7)	66 (9.8)	112 (14.6)	101 (12.8)	279 (12.5)
Diarrhea	36 (5.6)	69 (10.3)	80 (10.5)	96 (12.1)	245 (11.0)
Urinary tract infection	20 (3.1)	53 (7.9)	75 (9.8)	87 (11.0)	215 (9.6)
RA	26 (4.1)	34 (5.1)	88 (11.5)	75 (9.5)	197 (8.8)
Fatigue	26 (4.1)	48 (7.2)	51 (6.7)	84 (10.6)	183 (8.2)
Injection site erythema	7 (1.1)	39 (5.8)	50 (6.5)	86 (10.9)	175 (7.9)
ALT increased	33 (5.2)	80 (11.9)	65 (8.5)	83 (10.5)	228 (10.2)
Patients with ≥ 1 SAE	58 (9.1)	177 (26.4)	230 (30.1)	275 (34.7)	682 (30.6)
Most common SAE[2]					
Pneumonia	5 (0.8)	11 (1.6)	22 (2.9)	13 (1.6)	46 (2.1)
RA	6 (0.9)	6 (0.9)	14 (1.8)	14 (1.8)	34 (1.5)
Osteoarthritis	0	6 (0.9)	16 (2.1)	8 (1.0)	30 (1.3)
Basal cell carcinoma	3 (0.5)	5 (0.7)	8 (1.0)	13 (1.6)	26 (1.2)
Cholelithiasis	1 (0.2)	4 (0.6)	5 (0.7)	11 (1.4)	20 (0.9)
Sepsis	0	1 (0.1)	7 (0.9)	11 (1.4)	19 (0.9)
Arthralgia	0	2 (0.3)	6 (0.8)	8 (1.0)	16 (0.7)
Patients discontinued due to ≥ 1 AE	33 (5.2)	103 (15.4)	73 (9.5)	158 (19.9)	334 (15.0)
Injection site reactions					
Injections with reactions	31/8403 (0.4)	260/39,944 (0.7)	392/54,005 (0.7)	398/50,999 (0.8)	1050/144,948 (0.7)
Patients with reactions[3]	18 (2.8)	74 (11.0)	89 (11.6)	122 (15.4)	285 (12.8)
Mild	18 (2.8)	68 (10.1)	85 (11.1)	119 (15.0)	272 (12.2)
Moderate	0 (0.0)	9 (1.3)	11 (1.4)	10 (1.3)	30 (1.3)
Severe	0 (0.0)	0 (0.0)	1 (0.1)[4]	0 (0.0)	1 (< 0.1)
Treated patients in 3 RA trials[1]	449	374	542	565	1481
Patients with ≥ 1 AE	341 (75.9)	349 (93.3)	502 (92.6)	541 (95.8)	1392 (94.0)
Patients with ≥ 1 SAE	45 (10.0)	121 (32.4)	182 (33.6)	224 (39.6)	527 (35.6)
Patients discontinued due to ≥ 1 AE	27 (6.0)	70 (18.7)	58 (10.7)	125 (22.1)	253 (17.1)
Injection site reactions					
Injections with reactions	19/6623 (0.3)	78/19,756 (0.4)	284/36,304 (0.8)	313/34,097 (0.9)	675/90,157 (0.7)
Patients with reactions[3]	13 (2.9)	37 (9.9)	64 (11.8)	91 (16.1)	192 (13.0)

[1] Note that some patients received placebo followed by GOL in early escape or following crossover per trial design. [2] Defined as AE and SAE occurring in ≥ 10% and ≥ 1%, respectively, of patients in any treatment group. Common AE and SAE are presented in decreasing order of frequency in the GOL combined group. [3] Patients may have reported ≥ 1 injection reaction. [4] A serious event of erythema on the thigh in a patient with early RA receiving GOL 100 mg at the time of the reaction (Day 368). SC: subcutaneous; GOL: golimumab; MTX: methotrexate; AE: adverse event; ALT: alanine aminotransferase; SAE: serious AE; RA: rheumatoid arthritis.

the surrounding 95% CI (0.07–0.44), however, was contained within that for placebo (Table 4).

The proportions of patients with an ISR were 12.8% for GOL and 2.8% for placebo, and the proportions of injections that resulted in an ISR were 0.7% for GOL and 0.4% for placebo (Table 3). Only 1 patient discontinued study drug because of an ISR. This patient received GOL 100 mg plus MTX and had detectable antibodies to GOL[7].

DISCUSSION

We pooled safety data through 5 years across 5 phase 3 trials of patients with active RA, PsA, and AS who were treated with SC GOL (50 mg or 100 mg every 4 weeks). The 5 trials, consisting of 3 studies in patients with RA (1 each in MTX-naive, MTX-experienced, and anti-TNF–experienced patients), 1 in patients with PsA, and 1 in patients with AS, included both placebo-controlled (extending from Week 0

Table 4. Incidence of safety events of special interest through 5 years: pooled data from 5 phase 3 studies of SC GOL (with or without MTX) in rheumatological indications (RA, PsA, AS). Values are n/N (%), incidence/100 patient-years (95% CI) unless otherwise specified.

Variables	Placebo	GOL 50 mg Only	GOL 50 and 100 mg	GOL 100 mg Only	GOL Combined
No. treated patients	639	671	765	792	2228
Death[1]					
Pts treated at beginning of Yr 1	1/639 (0.2), 0.31 (0.01–1.73)	3/638 (0.5), 0.64 (0.13–1.86)	0/742 (0), 0.00 (0.00–0.48)	4/792 (0.5), 0.54 (0.15–1.37)	7/2172 (0.3), 0.38 (0.15–0.78)
Pts treated at beginning of Yr 2	0/50 (0), 0.00 (0.00–17.83)	3/570 (0.5), 0.58 (0.12–1.69)	0/744 (0), 0.00 (0.00–0.41)	4/674 (0.6), 0.63 (0.17–1.62)	7/1988 (0.4), 0.37 (0.15–0.77)
Pts treated at beginning of Yr 3	0/9 (0), 0.00 (0.00–53.17)	1/484 (0.2), 0.21 (0.01–1.18)	3/709 (0.4), 0.44 (0.09–1.28)	1/594 (0.2), 0.18 (0.00–0.98)	5/1787 (0.3), 0.29 (0.09–0.68)
Pts treated at beginning of Yr 4	0/5 (0), 0.00 (0.00–74.59)	1/457 (0.2), 0.22 (0.01–1.24)	2/659 (0.3), 0.31 (0.04–1.11)	3/543 (0.6), 0.58 (0.12–1.71)	6/1659 (0.4), 0.37 (0.14–0.81)
Pts treated at beginning of Yr 5	0/3 (0), 0.00 (0.00–193.34)	2/437 (0.5), 0.43 (0.05–1.56)	2/627 (0.3), 0.30 (0.04–1.09)	3/489 (0.6), 0.58 (0.12–1.68)	7/1553 (0.5), 0.42 (0.17–0.88)
Pts treated yrs 1–5	1/639 (0.2), 0.29 (0.01–1.59)	11/671 (1.6), 0.46 (0.23–0.83)	9/765 (1.2), 0.27 (0.12–0.51)	16/792 (2.0), 0.54 (0.31–0.87)	36/2228 (1.6), 0.41 (0.29–0.57)
Serious infection					
Pts treated at beginning of Yr 1	16/639 (2.5), 4.97 (2.84–8.08)	15/638 (2.4), 3.18 (1.78–5.24)	13/742 (1.8), 2.23 (1.22–3.75)	42/792 (5.3), 6.56 (4.85–8.67)	70/2172 (3.2), 4.22 (3.34–5.27)
Pts treated at beginning of Yr 2	0/50 (0), 0.00 (0.00–17.83)	17/570 (3.0), 4.05 (2.50–6.18)	22/744 (3.0), 3.45 (2.23–5.09)	22/674 (3.3), 3.96 (2.56–5.84)	61/1988 (3.1), 3.79 (2.96–4.78)
Pts treated at beginning of Yr 3	0/9 (0), 0.00 (0.00–53.17)	8/484 (1.7), 1.70 (0.73–3.35)	23/709 (3.2), 3.80 (2.48–5.57)	19/594 (3.2), 3.87 (2.42–5.85)	50/1787 (2.8), 3.25 (2.45–4.22)
Pts treated at beginning of Yr 4	1/5 (20.0), 24.90 (0.63–138.72)	6/457 (1.3), 1.56 (0.63–3.22)	22/659 (3.3), 4.63 (3.12–6.60)	9/543 (1.7), 1.75 (0.80–3.32)	37/1659 (2.2), 2.86 (2.09–3.81)
Pts treated at beginning of Yr 5	0/3 (0), 0.00 (0.00–193.34)	7/437 (1.6), 1.72 (0.74–3.39)	12/627 (1.9), 2.11 (1.16–3.55)	12/489 (2.5), 2.50 (1.33–4.27)	31/1553 (2.0), 2.12 (1.48–2.95)
Pts treated yrs 1–5	17/639 (2.7), 4.86 (2.83–7.78)	50/671 (7.5), 2.48 (1.89–3.20)	80/765 (10.5), 3.26 (2.67–3.93)	91/792 (11.5), 3.96 (3.27–4.74)	221/2228 (9.9), 3.29 (2.92–3.69)
Tuberculosis					
Pts treated at beginning of Yr 1	0/639 (0), 0.00 (0.00–0.93)	3/638 (0.5), 0.64 (0.13–1.86)	0/742 (0), 0.00 (0.00–0.48)	2/792 (0.3), 0.27 (0.03–0.97)	5/2172 (0.2), 0.27 (0.09–0.63)
Pts treated at beginning of Yr 2	0/50 (0), 0.00 (0.00–17.83)	0/570 (0), 0.00 (0.00–0.58)	3/744 (0.4), 0.41 (0.09–1.21)	6/674 (0.9), 0.95 (0.35–2.07)	9/1988 (0.5), 0.48 (0.22–0.91)
Pts treated at beginning of Yr 3	0/9 (0), 0.00 (0.00–53.17)	0/484 (0), 0.00 (0.00–0.64)	2/709 (0.3), 0.29 (0.04–1.06)	0/594 (0), 0.00 (0.00–0.53)	2/1787 (0.1), 0.12 (0.01–0.42)
Pts treated at beginning of Yr 4	0/5 (0), 0.00 (0.00–74.59)	1/457 (0.2), 0.22 (0.01–1.24)	1/659 (0.2), 0.15 (0.00–0.86)	0/543 (0), 0.00 (0.00–0.58)	2/1659 (0.1), 0.12 (0.02–0.45)
Pts treated at beginning of Yr 5	0/3 (0), 0.00 (0.00–193.34)	0/437 (0), 0.00 (0.00–0.65)	1/627 (0.2), 0.15 (0.00–0.84)	1/489 (0.2), 0.19 (0.00–1.07)	2/1553 (0.1), 0.12 (0.01–0.44)
Pts treated yrs 1–5	0/639 (0), 0.00 (0.00–0.86)	4/671 (0.6), 0.17 (0.05–0.43)	7/765 (0.9), 0.21 (0.08–0.43)	9/792 (1.1), 0.30 (0.14–0.57)	20/2228 (0.9), 0.23 (0.14–0.35)
Opportunistic infection					
Pts treated at beginning of Yr 1	0/639 (0), 0.00 (0.00–0.93)	1/638 (0.2), 0.21 (0.01–1.18)	1/742 (0.1), 0.16 (0.00–0.89)	1/792 (0.1), 0.13 (0.00–0.75)	3/2172 (0.1), 0.16 (0.03–0.47)
Pts treated at beginning of Yr 2	0/50 (0), 0.00 (0.00–17.83)	0/570 (0), 0.00 (0.00–0.58)	2/744 (0.3), 0.28 (0.03–1.00)	2/674 (0.3), 0.32 (0.04–1.14)	4/1988 (0.2), 0.21 (0.06–0.55)
Pts treated at beginning of Yr 3	0/9 (0), 0.00 (0.00–53.17)	1/484 (0.2), 0.21 (0.01–1.18)	0/709 (0), 0.00 (0.00–0.44)	5/594 (0.8), 0.88 (0.29–2.05)	6/1787 (0.3), 0.35 (0.13–0.76)
Pts treated at beginning of Yr 4	0/5 (0), 0.00 (0.00–74.59)	1/457 (0.2), 0.22 (0.01–1.24)	1/659 (0.2), 0.15 (0.00–0.86)	3/543 (0.6), 0.58 (0.12–1.71)	5/1659 (0.3), 0.31 (0.10–0.72)
Pts treated at beginning of Yr 5	0/3 (0), 0.00 (0.00–193.34)	0/437 (0), 0.00 (0.00–0.65)	1/627 (0.2), 0.15 (0.00–0.84)	0/489 (0), 0.00 (0.00–0.57)	1/1553 (0.1), 0.06 (0.00–0.34)
Pts treated yrs 1–5	0/639 (0), 0.00 (0.00–0.86)	3/671 (0.4), 0.13 (0.03–0.37)	5/765 (0.7), 0.15 (0.05–0.35)	10/792 (1.3), 0.37 (0.18–0.66)	18/2228 (0.8), 0.22 (0.13–0.34)
Malignancy					
All malignancies					
Pts treated at beginning of Yr 1	9/639 (1.4), 2.82 (1.29–5.35)	5/638 (0.8), 1.06 (0.34–2.48)	2/742 (0.3), 0.32 (0.04–1.16)	13/792 (1.6), 1.75 (0.93–2.99)	20/2172 (0.9), 1.09 (0.66–1.68)
Pts treated at beginning of Yr 2	0/48 (0), 0.00 (0.00–17.86)	7/568 (1.2), 1.36 (0.54–2.79)	4/742 (0.5), 0.55 (0.15–1.42)	9/669 (1.3), 1.44 (0.66–2.74)	20/1979 (1.0), 1.07 (0.66–1.66)
Pts treated at beginning of Yr 3	0/9 (0), 0.00 (0.00–53.17)	8/484 (1.7), 1.71 (0.74–3.36)	8/706 (1.1), 1.18 (0.51–2.32)	4/584 (0.7), 0.72 (0.20–1.83)	20/1774 (1.1), 1.17 (0.72–1.81)
Pts treated at beginning of Yr 4	0/5 (0), 0.00 (0.00–74.59)	2/453 (0.4), 0.45 (0.05–1.62)	8/653 (1.2), 1.25 (0.54–2.47)	3/532 (0.6), 0.60 (0.12–1.74)	13/1638 (0.8), 0.82 (0.44–1.40)
Pts treated at beginning of Yr 5	0/3 (0), 0.00 (0.00–193.34)	4/437 (0.9), 0.86 (0.24–2.21)	6/617 (1.0), 0.92 (0.34–2.01)	9/481 (1.9), 1.76 (0.81–3.34)	19/1535 (1.2), 1.17 (0.70–1.83)
Pts treated yrs 1–5	9/639 (1.4), 2.59 (1.19–4.92)	26/671 (3.9), 1.10 (0.72–1.61)	28/765 (3.7), 0.84 (0.56–1.22)	38/792 (4.8), 1.29 (0.91–1.77)	92/2228 (4.1), 1.07 (0.86–1.31)
SIR (95% CI) vs SEER database	1.46 (0.30–4.26)	1.55 (0.95–2.40)	0.60 (0.32–1.03)	1.32 (0.84–1.98)	1.08 (0.82–1.40)
Non-melanoma skin cancer					
Pts treated at beginning of Yr 1	6/639 (0.9), 1.88 (0.69–4.09)	1/638 (0.2), 0.21 (0.01–1.18)	2/742 (0.3), 0.32 (0.04–1.16)	7/792 (0.9), 0.94 (0.38–1.94)	10/2172 (0.5), 0.54 (0.26–1.00)
Pts treated at beginning of Yr 2	0/48 (0), 0.00 (0.00–17.86)	2/569 (0.4), 0.39 (0.05–1.40)	3/742 (0.4), 0.42 (0.09–1.21)	3/669 (0.4), 0.48 (0.10–1.40)	8/1980 (0.4), 0.43 (0.19–0.85)
Pts treated at beginning of Yr 3	0/9 (0), 0.00 (0.00–53.17)	2/484 (0.4), 0.42 (0.05–1.53)	3/706 (0.4), 0.44 (0.09–1.29)	3/587 (0.5), 0.54 (0.11–1.57)	8/1777 (0.5), 0.47 (0.20–0.92)
Pts treated at beginning of Yr 4	0/5 (0), 0.00 (0.00–74.59)	0/455 (0), 0.00 (0.00–0.67)	4/653 (0.6), 0.63 (0.17–1.60)	0/533 (0), 0.00 (0.00–0.59)	4/1641 (0.2), 0.25 (0.07–0.64)
Pts treated at beginning of Yr 5	0/3 (0), 0.00 (0.00–193.34)	1/437 (0.2), 0.22 (0.01–1.20)	4/617 (0.6), 0.61 (0.17–1.57)	2/481 (0.4), 0.39 (0.05–1.41)	7/1535 (0.5), 0.43 (0.17–0.89)
Pts treated yrs 1–5	6/639 (0.9), 1.73 (0.63–3.76)	6/671 (0.9), 0.25 (0.09–0.55)	16/765 (2.1), 0.48 (0.28–0.78)	15/792 (1.9), 0.51 (0.28–0.84)	37/2228 (1.7), 0.43 (0.30–0.59)

Table 4. Continued.

Variables	Placebo	GOL 50 mg Only	GOL 50 and 100 mg	GOL 100 mg Only	GOL Combined
Lymphoma					
Pts treated at beginning of Yr 1	0/639 (0), 0.00 (0.00–0.93)	0/638 (0), 0.00 (0.00–0.63)	0/742 (0), 0.00 (0.00–0.48)	2/792 (0.3), 0.27 (0.03–0.97)	2/2172 (0.1), 0.11 (0.01–0.39)
Pts treated at beginning of Yr 2	0/50 (0), 0.00 (0.00–17.83)	0/570 (0), 0.00 (0.00–0.58)	0/744 (0), 0.00 (0.00–0.41)	2/674 (0.3), 0.32 (0.04–1.14)	2/1988 (0.1), 0.11 (0.01–0.39)
Pts treated at beginning of Yr 3	0/9 (0), 0.00 (0.00–53.17)	0/484 (0), 0.00 (0.00–0.64)	1/709 (0.1), 0.15 (0.00–0.81)	0/593 (0), 0.00 (0.00–0.53)	1/1786 (0.1), 0.06 (0.00–0.32)
Pts treated at beginning of Yr 4	0/5 (0), 0.00 (0.00–74.59)	1/457 (0.2), 0.22 (0.01–1.24)	1/659 (0.2), 0.15 (0.00–0.86)	1/543 (0.2), 0.19 (0.00–1.08)	3/1659 (0.2), 0.19 (0.04–0.54)
Pts treated at beginning of Yr 5	0/3 (0), 0.00 (0.00–193.34)	0/437 (0), 0.00 (0.00–0.65)	0/627 (0), 0.00 (0.00–0.45)	1/489 (0.2), 0.19 (0.00–1.07)	1/1553 (0.1), 0.06 (0.00–0.34)
Pts treated yrs 1–5	0/639 (0), 0.00 (0.00–0.86)	1/671 (0.1), 0.04 (0.00–0.23)	2/765 (0.3), 0.06 (0.01–0.22)	6/792 (0.8), 0.20 (0.07–0.44)	9/2228 (0.4), 0.10 (0.05–0.20)
SIR (95% CI)[2] vs SEER database	0.00 (0.00–33.23)	1.71 (0.04–9.50)	2.11 (0.26–7.61)	**7.71 (2.83–16.78)**	**3.89 (1.78–7.38)**
Demyelinating disorder					
Pts treated at beginning of Yr 1	0/639 (0), 0.00 (0.00–0.93)	0/638 (0), 0.00 (0.00–0.63)	0/742 (0), 0.00 (0.00–0.48)	1/792 (0.1), 0.13 (0.00–0.75)	1/2172 (< 0.1), 0.05 (0.00–0.30)
Pts treated at beginning of Yr 2	0/50 (0), 0.00 (0.00–17.83)	0/570 (0), 0.00 (0.00–0.58)	0/744 (0), 0.00 (0.00–0.41)	1/674 (0.1), 0.16 (0.00–0.88)	1/1988 (0.1), 0.05 (0.00–0.30)
Pts treated at beginning of Yr 3	0/9 (0), 0.00 (0.00–53.17)	0/484 (0), 0.00 (0.00–0.64)	0/709 (0), 0.00 (0.00–0.44)	1/593 (0.2), 0.18 (0.00–0.98)	1/1786 (0.1), 0.06 (0.00–0.32)
Pts treated at beginning of Yr 4	0/5 (0), 0.00 (0.00–74.59)	0/457 (0), 0.00 (0.00–0.67)	0/659 (0), 0.00 (0.00–0.46)	3/542 (0.6), 0.59 (0.12–1.71)	3/1658 (0.2), 0.19 (0.04–0.54)
Pts treated at beginning of Yr 5	0/3 (0), 0.00 (0.00–193.34)	0/437 (0), 0.00 (0.00–0.65)	1/627 (0.2), 0.15 (0.00–0.84)	0/489 (0), 0.00 (0.00–0.57)	1/1553 (0.1), 0.06 (0.00–0.34)
Pts treated yrs 1–5	0/639 (0), 0.00 (0.00–0.86)	0/671 (0), 0.00 (0.00–0.13)	1/765 (0.1), 0.03 (0.00–0.17)	6/792 (0.8), 0.20 (0.07–0.44)	7/2228 (0.3), 0.08 (0.03–0.17)

[1] The incidence of death does not include 1 GOL patient who died at the start of Year 4 and 3 GOL patients who died at the start of Year 5, none of whom had exposure data in the year of death. All 4 patients, thus, had an unknown length of followup (required for determination of incidence). [2] 95% CI not containing 1 (in bold face) indicate a significant difference from the SEER database. SC: subcutaneous; GOL: golimumab; MTX: methotrexate; RA: rheumatoid arthritis; PsA: psoriatic arthritis; AS: ankylosing spondylitis; pts: patients; SIR: standardized incidence ratio; SEER: Surveillance, Epidemiology, and End Results.

through weeks 24–52) and uncontrolled study periods. In addition to overall AE and SAE, the incidence of AE of special interest (serious infections including opportunistic infections and TB, deaths, malignancies, and demyelination) per 100 pt-yrs was determined.

Patient retention was substantial, with about 60% of patients with RA, 69% with PsA, and 72% with AS completing 5 years of followup, reflecting the sustained efficacy observed through up to 5 years of GOL treatment[10,14,17,21,24]. This retention, which compares favorably with 5- and 10-year drug survival rates for ETN[29] and ADA[30], respectively, allowed for the analysis of 2228 patients with a mean of 203 weeks of GOL safety followup.

The most common AE included infections, constitutional symptoms, HTN, injection site erythema, and elevated ALT levels. Only 1 ISR led to discontinuation of study drug. These findings were consistent with those observed through 5 years of ETN[29] and 10 years of ADA[30] treatment in patients with RA.

While there were numerically more AE and SAE; cases of TB, demyelination, and ISR; and deaths in the GOL than placebo groups, when adjusted for duration of followup, there were no significant differences between GOL and placebo for the incidence of serious infection, active TB, opportunistic infection, death, demyelination, or malignancy. In addition, the occurrence of these AE did not increase over time. A higher incidence of lymphoma relative to the general US population, however, was observed through 5 years among patients who received GOL 100 mg only, and as a result, also among all GOL-treated patients. Patients with RA largely drove this higher incidence of lymphoma. Among the 8 patients with RA who had lymphoma, disease duration averaged 12.7 years (compared with 7.6 yrs for all the overall safety population assessed)[7] and baseline DAS28-CRP scores averaged 6.2 (compared with 5.7 for all other patients with RA). This indicates longstanding active disease, an important consideration given that patients with RA have a higher lymphoma risk than the general population[31] and this risk increases with longer disease duration and disease activity[32,33]. While most lymphomas developed in patients who received GOL 100 mg, as reported[7], this may be expected given the possibility of dose escalation from 50 mg to 100 mg in patients with persistently active disease and the longer exposure of a greater number of patients to the 100-mg dose. Only 2 patients with lymphoma had evidence of EBV infection, which is noteworthy because the rate of EBV infection is higher among patients with lymphoma associated with immunosuppressive therapy than among patients with other lymphomas[34]. While lymphoma is a known, albeit infrequent, AE that was observed in these studies that were not powered to detect statistical significance of the differential rates of rare AE across dose groups, the potential development of lymphoma with higher doses of GOL requires continued pharmacovigilance.

Table 5. Incidence of safety events of special interest through 5 years: pooled data from 3 phase 3 studies of SC GOL (with or without MTX) in RA. Values are n/N (%), incidence/100 patient-years (95% CI) unless otherwise specified.

Variables	Placebo	GOL 50 mg Only	GOL 50 and 100 mg	GOL 100 mg Only	GOL Combined
No. treated patients	449	374	542	565	1481
Serious infection					
Pts treated at beginning of Yr 1	11/449 (2.4), 4.40 (2.20–7.87)	12/341 (3.5), 5.02 (2.59–8.77)	11/519 (2.1), 2.82 (1.46–4.93)	37/565 (6.5), 8.34 (6.06–11.20)	60/1425 (4.2), 5.71 (4.43–7.24)
Pts treated at beginning of Yr 2	0/50 (0), 0.00 (0.00–17.83)	15/310 (4.8), 6.92 (4.16–10.80)	19/527 (3.6), 4.31 (2.70–6.52)	20/470 (4.3), 5.28 (3.35–7.93)	54/1307 (4.1), 5.24 (4.04–6.69)
Pts treated at beginning of Yr 3	0/9 (0), 0.00 (0.00–53.17)	4/253 (1.6), 1.62 (0.44–4.16)	19/500 (3.8), 4.59 (2.88–6.95)	15/408 (3.7), 4.41 (2.57–7.06)	38/1161 (3.3), 3.87 (2.80–5.21)
Pts treated at beginning of Yr 4	1/5 (20.0), 24.90 (0.63–138.72)	6/238 (2.5), 3.02 (1.22–6.23)	19/458 (4.1), 6.02 (3.97–8.75)	9/367 (2.5), 2.61 (1.20–4.96)	34/1063 (3.2), 4.20 (3.04–5.65)
Pts treated at beginning of Yr 5	0/3 (0), 0.00 (0.00–193.34)	4/227 (1.8), 1.63 (0.44–4.17)	7/434 (1.6), 1.96 (0.89–3.71)	9/328 (2.7), 2.83 (1.36–5.21)	20/989 (2.0), 2.17 (1.38–3.26)
Pts treated yrs 1–5	12/449 (2.7), 4.31 (2.23–7.54)	39/374 (10.4), 3.72 (2.72–4.96)	68/542 (12.5), 3.96 (3.19–4.86)	78/565 (13.8), 5.04 (4.11–6.11)	185/1481 (12.5), 4.30 (3.77–4.88)
Malignancy					
All malignancies					
Pts treated at beginning of Yr 1	8/449 (1.8), 3.23 (1.40–6.37)	3/341 (0.9), 1.26 (0.26–3.68)	2/519 (0.4), 0.47 (0.06–1.70)	9/565 (1.6), 1.72 (0.78–3.26)	14/1425 (1.0), 1.18 (0.65–1.98)
Pts treated at beginning of Yr 2	0/48 (0), 0.00 (0.00–17.86)	6/308 (1.9), 2.20 (0.81–4.79)	3/525 (0.6), 0.59 (0.12–1.73)	7/466 (1.5), 1.63 (0.65–3.36)	16/1299 (1.2), 1.32 (0.76–2.15)
Pts treated at beginning of Yr 3	0/9 (0), 0.00 (0.00–53.17)	5/253 (2.0), 2.04 (0.66–4.77)	8/497 (1.6), 1.69 (0.73–3.32)	4/400 (1.0), 1.06 (0.29–2.72)	17/1150 (1.5), 1.55 (0.90–2.48)
Pts treated at beginning of Yr 4	0/5 (0), 0.00 (0.00–74.59)	0/236 (0), 0.00 (0.00–1.30)	5/452 (1.1), 1.13 (0.37–2.65)	3/358 (0.8), 0.90 (0.18–2.62)	8/1046 (0.8), 0.79 (0.34–1.57)
Pts treated at beginning of Yr 5	0/3 (0), 0.00 (0.00–193.34)	3/227 (1.3), 1.23 (0.25–3.59)	4/425 (0.9), 0.89 (0.24–2.28)	6/321 (1.9), 1.74 (0.64–3.79)	13/973 (1.3), 1.25 (0.67–2.14)
Pts treated yrs 1–5	8/449 (1.8), 2.90 (1.25–5.72)	17/374 (4.5), 1.38 (0.80–2.21)	22/542 (4.1), 0.96 (0.60–1.45)	29/565 (5.1), 1.44 (0.97–2.07)	68/1481 (4.6), 1.23 (0.95–1.56)
SIR (95% CI) vs SEER database	1.70 (0.35–4.97)	1.66 (0.91–2.78)	0.67 (0.34–1.21)	1.42 (0.86–2.22)	1.15 (0.84–1.55)
Lymphoma					
Pts treated at beginning of Yr 1	0/449 (0), 0.00 (0.00–1.20)	0/341 (0), 0.00 (0.00–1.25)	0/519 (0), 0.00 (0.00–0.71)	2/565 (0.4), 0.38 (0.05–1.37)	2/1425 (0.1), 0.17 (0.02–0.61)
Pts treated at beginning of Yr 2	0/50 (0), 0.00 (0.00–17.83)	0/310 (0), 0.00 (0.00–1.09)	0/527 (0), 0.00 (0.00–0.59)	2/470 (0.4), 0.46 (0.06–1.66)	2/1307 (0.2), 0.16 (0.02–0.59)
Pts treated at beginning of Yr 3	0/9 (0), 0.00 (0.00–53.17)	0/253 (0), 0.00 (0.00–1.22)	1/500 (0.2), 0.21 (0.01–1.16)	0/407 (0), 0.00 (0.00–0.78)	1/1160 (0.1), 0.09 (0.00–0.50)
Pts treated at beginning of Yr 4	0/5 (0), 0.00 (0.00–74.59)	0/238 (0), 0.00 (0.00–1.29)	1/458 (0.2), 0.22 (0.01–1.24)	1/367 (0.3), 0.29 (0.01–1.62)	2/1063 (0.2), 0.20 (0.02–0.71
Pts treated at beginning of Yr 5	0/3 (0), 0.00 (0.00–193.34)	0/227 (0), 0.00 (0.00–1.22)	0/434 (0), 0.00 (0.00–0.65)	1/328 (0.3), 0.28 (0.01–1.58)	1/989 (0.1), 0.09 (0.00–0.53)
Pts treated yrs 1–5	0/449 (0), 0.00 (0.00–1.08)	0/374 (0), 0.00 (0.00–0.24)	2/542 (0.4), 0.09 (0.01–0.31)	6/565 (1.1), 0.29 (0.11–0.64)	8/1481 (0.5), 0.14 (0.06–0.28)
SIR (95% CI)[1] vs SEER database	0.00 (0.00–40.12)	0.00 (0.00–8.50)	2.91 (0.35–10.53)	**10.50 (3.85–22.86)**	**4.97 (2.15–9.79)**

[1] 95% CI not containing 1 (in bold face) indicate a significant difference from the SEER database. SC: subcutaneous; GOL: golimumab; MTX: methotrexate; RA: rheumatoid arthritis; pts: patients; SIR: standardized incidence ratio; SEER: Surveillance, Epidemiology, and End Results.

As a limitation to these analyses, the length of placebo followup was relatively short and there was no longterm control group. However, it would have been unethical to continue giving patients in the control group placebo for 5 years. The designs of these clinical trials, which incorporated an early escape option and dose escalation during open-label extension, confound definitive attribution of AE to a single GOL dose in some patients. The ability to adjust the use of concomitant medications during the open-label study extensions also confounds the analyses. Nevertheless, observing 2228 patients treated with GOL over 5 years with 8702 pt-yrs of followup provides considerable insight into the longterm safety profile of GOL.

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ONLINE SUPPLEMENT

Supplementary data for this article are available online at jrheum.org.

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