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Efficacy and Safety of Intravenous Golimumab in Patients With Ankylosing Spondylitis and Complete Spinal Ankylosis

Results Through Week 52 of the GO-ALIVE Study

Atul Deodhar, MD,* Soumya D. Chakravarty, MD, PhD, †‡ Natalie J. Shiff, MD, MHSc, †§
Kim Hung Lo, PhD, || Stephen Xu, MS, || Elizabeth C. Hsia, MD, MSCE, || ¶
Abhijeet Danve, MD, # and John D. Reveille, MD**

Ankylosing spondylitis (AS) is a progressive, chronic, inflammatory arthritis that most commonly affects the spine and sacroiliac joints, entheses, and peripheral joints. As the disease progresses new bone forms along the spine, bridging the vertebrae and reducing mobility. The spine eventually may become fused, or completely ankylosed, leading to limitations in physical activities and impaired health-related quality of life (HRQoL).¹⁻³ In patients with active AS who have an inadequate response to nonsteroidal anti-inflammatory drugs (NSAIDs), biologic therapy with a tumor necrosis factor α inhibitor (TNFi) is recommended.⁴ Despite the availability of several biologic and targeted therapies to treat AS, there is a paucity of data regarding the efficacy of these therapies in patients with complete spinal ankylosis.

The phase 3 GO-ALIVE study assessed the efficacy and safety of the TNFi intravenous IV golimumab in patients with AS, including those with complete spinal ankylosis.^{5,6} A significantly greater proportion of patients receiving IV golimumab achieved at least 20% improvement from baseline in the Assessment of Spondyloarthritis International Society Criteria (ASAS20) at week 16 compared with patients receiving placebo, and response rates were sustained through 52 weeks of IV golimumab treatment.^{5,6} Among patients with complete spinal ankylosis, a greater proportion treated with golimumab achieved ASAS20 response, compared with those receiving placebo.⁵ To further elucidate the effects of IV golimumab in this difficult-to-treat population, we now report results of a post hoc analysis from the GO-ALIVE examining the clinical efficacy, HRQoL, and safety

outcomes through 1 year of golimumab treatment in a subset of patients with AS and complete spinal ankylosis.

METHODS

Study Design

The GO-ALIVE study (NCT02186873) was a phase 3, double-blind, placebo-controlled study, the methods and overall findings of which have been previously reported.⁵ Eligible patients were adults (aged 18 years or older) diagnosed with AS for 3 months or more. Patients were required to have symptoms of active disease at baseline, as assessed by a Bath Ankylosing Spondylitis Disease Activity Index (BASDAI) score of 4 or higher (scale 0–10 cm), a Visual Analog Scale (scale 0–10 cm) score of 4 or higher for total back pain, a C-reactive protein level of 0.3 mg/dL or greater, and either an inadequate response to 2 or more NSAIDs over a 4-week period or inability to receive a full 4 weeks of maximal NSAID therapy due to intolerance, toxicity, or contraindication to NSAIDs.⁷ Patients with complete spinal ankylosis were limited to 10% of the total study population.⁵ Complete spinal ankylosis was defined as bridging syndesmophytes present at all intervertebral levels of the cervical and lumbar spine visualized on lateral-view spinal radiographs, read locally. Patients were permitted to continue concomitant treatment with methotrexate, sulfasalazine, hydroxychloroquine, NSAIDs and other analgesics, and low-dose corticosteroids if the doses were stable.⁵ Prior treatment with no

From the *Oregon Health & Science University, Portland, OR; †Janssen Scientific Affairs, LLC, Horsham, PA; ‡Drexel University College of Medicine, Philadelphia, PA; §Adjunct, Department of Community Health and Epidemiology, College of Medicine, University of Saskatchewan, Saskatoon, Saskatchewan, Canada; ||Janssen Research & Development, LLC, Spring House, PA; ¶University of Pennsylvania, School of Medicine, Philadelphia, PA; #Yale School of Medicine, New Haven, CT; and **University of Texas McGovern Medical School, Houston, TX.

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Correspondence: Atul Deodhar, MD, Oregon Health & Science University, 3181 SW Sam Jackson Park Rd, Portland, OR 97239. E-mail: deodhara@ohsu.edu. These data were presented in part at the 21st Pan American Rheumatology Conference, April 27–30, 2019, Quito, Ecuador.

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more than 1 TNFi other than golimumab was permitted; these patients could not have experienced primary failure to their prior TNFi and were limited to 20% of the study population.

Patients were randomized (1:1) to receive IV golimumab 2 mg/kg at weeks 0, 4, and then every 8 weeks thereafter or placebo at weeks 0, 4, and 12 with crossover to IV golimumab 2 mg/kg every 8 weeks beginning at week 16, both continuing through week 52.

All patients provided written informed consent. The GO-ALIVE study was conducted in accordance with the Declaration of Helsinki and Good Clinical Practices. The protocol was approved by institutional review boards or by local ethics committees.⁵

EndPoints

The primary endpoint was the proportion of patients who achieved ASAS20 at week 16. Additional clinical efficacy assessments included the proportion of patients achieving 40% improvement from baseline ASAS criteria (ASAS40), ASAS 5/6 response (at least 20% improvement in 5 of 6 domains [patient global, total back pain, function, morning stiffness, C-reactive protein, and spinal mobility]), at least 50% improvement in the BASDAI score (BASDAI50), Ankylosing Spondylitis Disease Activity Score (ASDAS) inactive disease (score <1.3), ASDAS clinically important improvement (a decrease of ≥1.1; among patients with a score ≥1.1 at baseline), ASDAS major improvement (a decrease of ≥2.0; among patients with a score ≥2 at baseline), and mean changes in the Bath Ankylosing Spondylitis Metrology Index (BASMI). Improvements in physical function were evaluated using the Bath Ankylosing Spondylitis Functional Index (BASFI), and HRQoL was assessed with the Ankylosing Spondylitis Quality of Life (ASQoL) questionnaire. Night and total back pain were each assessed using a Visual Analog Scale of 0 to 10 cm (0 = no pain; 10 = most severe pain). Entesitis was evaluated using the University of California San Francisco entesitis index. Patients were monitored through week 60 for adverse events (AEs).

Statistical Methods

Only data from patients with complete spinal ankylosis were included in this post hoc analysis. Clinical efficacy for this subgroup of patients was assessed at weeks 16 and 52. Descriptive statistics (eg, number [n], mean, median, and standard deviation [SD] for continuous variables, and counts and percentages for discrete variables) are reported. No formal hypothesis testing for between-group comparisons was performed. Adverse events were summarized through week 60 by treatment received.

RESULTS

Patient Characteristics and Disposition

Of the 208 patients randomized in the GO-ALIVE study, 12 had complete spinal ankylosis (IV golimumab n = 5; placebo n = 7) and were included in this analysis. All 12 patients completed study treatment through week 24; 1 patient (golimumab group) discontinued the study before week 52 because of an AE (pulmonary tuberculosis). The mean ± SD age at baseline was 45.8 ± 9.1 years, and all 12 were White males. The mean ± SD time since diagnosis of AS was 8.7 ± 7.8 years, with a mean ± SD of 17.3 ± 11.4 years since inflammatory back pain first occurred (Supplemental Digital Content 1, <http://links.lww.com/RHU/A449>). In comparison, the total GO-ALIVE study population had a mean age of 38.8 years, 78.4% of patients were male, the mean time since diagnosis of AS was 5.5 years, and the mean duration of inflammatory back pain was 10.9 years.⁵ All 12 patients in the

complete spinal ankylosis subgroup were TNFi naive, compared with 178 patients in the total study population.

Efficacy

In the primary efficacy analysis, 73.3% of IV golimumab-treated patients (77/105) achieved an ASAS20 response at week 16, compared with 26.2% of placebo-treated patients (27/103, *p* < 0.001).⁵ Among the 5 golimumab-treated patients with complete spinal ankylosis, 3 (60.0%) achieved an ASAS20 response at week 16 (Figure, A). Two patients (40.0%) treated with golimumab achieved an ASAS 5/6 response at week 16 (data not shown). Three golimumab-treated patients (60.0%) achieved a clinically important improvement in ASDAS (decrease ≥1.1), and 1 of 4 patients (25.0%) with a baseline ASDAS score of 2 or greater achieved ASDAS major improvement (decrease ≥2.0; Figure, B). One patient (20.0%) achieved a BASDAI50 response and 1 patient (20.0%) achieved an ASAS40 response at week 16 (Figure, C); no golimumab-treated patient in this subgroup with complete spinal ankylosis achieved ASDAS inactive disease at week 16. No patient receiving placebo achieved the assessed ASAS, ASDAS, or BASDAI responses at week 16.

At week 52, 3 of 4 patients (75.0%) in the golimumab group achieved an ASAS20 response, 1 (25.0%) achieved an ASAS40

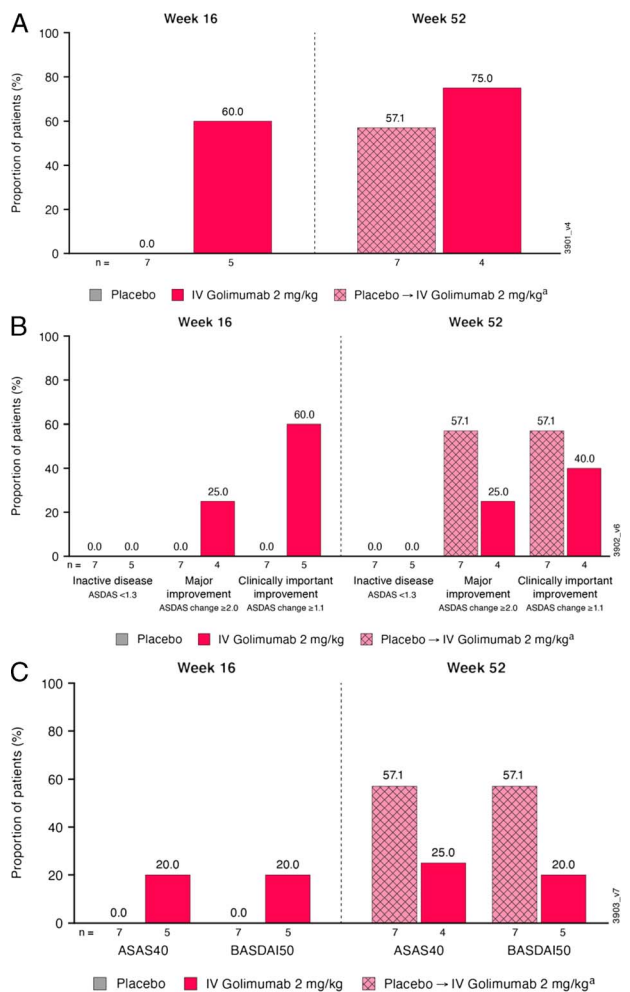


FIGURE 1. Proportions of patients achieving: A, ASAS20 response; B, ASDAS responses; C, ASAS40 and BASDAI50 responses among patients with complete ankylosis. ^aCrossover at week 16.

response, 3 (75.0%) achieved an ASAS 5/6 response (data not shown), 2 (40.0%) achieved ASDAS clinically important improvement, and 1 (25.0%) achieved ASDAS major improvement (Figure, A–C). One golimumab-randomized patient (20.0%) had a BASDAI50 response at week 52 (Figure, C). In the placebo crossover group, ASAS responses, ASDAS clinically important improvement, ASDAS major improvement, and BASDAI50 were each achieved by 4 patients at week 52, when all patients had been receiving golimumab since week 16. No patient in either treatment group achieved ASDAS inactive disease at week 52.

At week 16, the mean \pm SD improvements in BASFI and BASMI, respectively, were numerically greater in the golimumab group (-1.1 ± 2.0 and -0.3 ± 0.4) than in the placebo group (0.7 ± 0.7 and 0.0 ± 0.6). At week 52, the mean improvements were maintained in the golimumab group (BASFI: -1.1 ± 2.0 ; BASMI: -0.7 ± 0.5); after placebo crossover to golimumab, mean improvements in BASFI and BASMI were -2.1 ± 2.3 and -0.3 ± 0.6 , respectively (Table). Four golimumab-treated patients and 7 placebo-treated patients had enthesitis at baseline; the mean \pm SD changes from baseline in enthesitis score were -1.8 ± 3.0 and -0.9 ± 5.8 , respectively, at week 16. At week 52, the mean changes in enthesitis score were -1.0 ± 4.6 in the golimumab group and -0.6 ± 3.7 in the placebo crossover group.

The mean improvements in ASQoL and night and total back pain were numerically higher in golimumab-treated patients compared with placebo-treated patients at week 16 (Table). The mean \pm SD improvements at week 52 were similar for patients randomized to golimumab and for those in the placebo crossover group, respectively, with ASQoL scores of -3.6 ± 5.4 and -3.1 ± 3.7 , night back pain scores of -3.0 ± 1.9 and -3.3 ± 4.3 , and total back pain scores of -2.2 ± 1.8 and -3.4 ± 3.4 .

Safety

Through week 60, 55.4% of all IV golimumab-treated patients (including those who crossed over from placebo) had at least 1 AE, and 3.4% had at least 1 serious AE.⁶ In this post hoc analysis, 7 patients reported 11 AEs. Among placebo-treated patients, 1 AE of hyperuricemia occurred on day 1. Adverse events reported in 4 golimumab-randomized patients were nasopharyngitis ($n = 2$), vertigo ($n = 1$), tendon rupture ($n = 1$), macular rash ($n = 1$), and 1 serious AE of pulmonary tuberculosis (Ukraine; screened negative by QuantiFERON-TB Gold test and chest radiograph).⁶ Adverse events reported among patients who crossed over from placebo to golimumab were increased alanine aminotransferase and aspartate aminotransferase (in the same patient), lymphopenia ($n = 1$), and oral herpes ($n = 1$); none was classified as serious.

DISCUSSION

The GO-ALIVE study demonstrated that IV golimumab 2 mg/kg, administered at week 0, 4, and then every 8 weeks, was efficacious in improving the signs and symptoms of AS in adults with active disease, including those with complete spinal ankylosis.⁵ In this post hoc analysis of the patients with AS and complete spinal ankylosis, numerically greater response rates and mean improvements at week 16 were observed in the patients treated with golimumab versus placebo across measures of global efficacy, physical function, range of motion, back pain, and HRQoL. This was consistent with the overall GO-ALIVE study population in which mean improvements from baseline were significantly higher among patients receiving golimumab than placebo.⁵ The improvements observed among patients with complete ankylosis were maintained through 52 weeks. Patients receiving placebo who crossed over to golimumab at week 16 also demonstrated improvements in disease activity at week 52, although no patient in either treatment group achieved ASDAS inactive disease. In the full study population, significantly more patients treated with golimumab achieved inactive disease at week 16 than those receiving placebo (20.0% vs 2.9%, respectively; $p < 0.001$).⁵ Nevertheless, some patients with complete ankylosis did achieve meaningful improvements in disease activity after treatment with IV golimumab. The gain in physical function patients experienced is notable, although the increase was slight. Improvement in physical function was secondary to improved inflammation in the soft tissue and decreased pain. This analysis demonstrated that inflammation persists in patients with complete spinal ankylosis, and abrogation of inflammation improved several additional outcomes in these patients.

In this subset of patients with complete ankylosis, AEs were consistent with those in the full GO-ALIVE population,^{5,6} as well as previous studies of TNFi therapies in AS.^{8–10} Through week 60 in the GO-ALIVE study, 1 case of tuberculosis (pulmonary) occurred⁶; this patient had complete ankylosis and was included in our subset analysis.

Patients with AS who are fully ankylosed have been largely overlooked in clinical studies of AS treatments. Whereas the GO-ALIVE study included patients with complete spinal ankylosis, other large studies evaluating ixekizumab, certolizumab pegol, secukinumab, and upadacitinib have excluded these patients,^{11–14} missing opportunities to better understand treatment options for this often refractory AS population with substantial unmet need. Studies of ixekizumab and secukinumab, for example, included patients with AS who were naive to biological disease-modifying antirheumatic drugs as well as those who had experience with these therapies, yet patients with complete spinal ankylosis were

TABLE 1. Clinical Response—Mean Changes From Baseline

Measure, Mean (SD)	Week 16		Week 52	
	Placebo (n = 7)	Golimumab (n = 5)	Placebo→Golimumab ^a (n = 7)	Golimumab (n = 5)
BASFI	0.7 (0.7)	-1.1 (2.0)	-2.1 (2.3)	-1.1 (2.0)
BASMI	0.0 (0.6)	-0.3 (0.4)	-0.3 (0.6)	-0.7 (0.5)
UCSF enthesitis index ^b	-0.9 (5.8)	-1.8 (3.0)	-0.6 (3.7)	-1.0 (4.6)
ASQoL	-0.6 (3.6)	-4.0 (3.6)	-3.1 (3.7)	-3.6 (5.4)
Total back pain	0.2 (1.3)	-2.1 (2.1)	-3.4 (3.4)	-2.2 (1.8)
Night back pain	0.9 (0.8)	-3.4 (2.2)	-3.3 (4.3)	-3.0 (1.9)

^aCrossover at week 16.

^bAmong the patients with enthesitis at baseline: placebo ($n = 7$) and golimumab ($n = 4$).

UCSF, University of California San Francisco.

excluded.^{11,15} While long-term efficacy in AS has been reported for certolizumab pegol, studies included patients with radiographic and nonradiographic axial spondyloarthritis and specifically excluded patients with complete spinal ankylosis.^{12,16} Not only were patients with more severe disease excluded, but the investigators also noted that the study was not designed to evaluate whether the treatment could prevent spinal damage associated with disease progression.¹⁶ An exception is the Adalimumab Trial Evaluating Long-term Efficacy and Safety for AS (ATLAS) study, which included 11 patients with complete spinal ankylosis (3.5%, 11/315).¹⁷ In the ATLAS study, TNFi treatment was associated with rapid, sustained improvement in the signs and symptoms of active AS.¹⁷ Results from our exploratory analysis of the GO-ALIVE study are consistent with the ATLAS results and suggest that such patients can experience meaningful improvements in disease activity within 16 weeks of treatment with IV golimumab that are durable through 1 year.

These data should be interpreted with caution because the small sample size limits the generalizability of the results. Although the GO-ALIVE study included patients with complete spinal ankylosis, it was not designed to specifically evaluate the efficacy of golimumab in this subgroup.

In conclusion, IV golimumab provided meaningful and durable clinical benefit across several measures of global disease activity, back pain, enthesitis, and HRQoL in a subset of patients with AS and complete spinal ankylosis. Adverse events were comparable with those reported in the full study population and no unexpected safety concerns were observed in this limited number of patients. Given the paucity of clinical trial data in patients with complete ankylosis, the results of this post hoc analysis provide insight into this patient population. While achieving the most stringent levels of treatment response is more difficult in patients with advanced disease, these patients may still derive notable improvements from therapies such as IV golimumab.

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