

Safety and clinical efficacy of golimumab in the treatment of arthritides

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Abstract: Golimumab is a human anti-tumor necrosis factor (TNF)-alpha monoclonal antibody that was recently approved for the treatment of patients with rheumatoid arthritis, psoriatic arthritis, and ankylosing spondylitis. This review covers the published clinical trial data on the use of golimumab for the approved indications mentioned above with respect to efficacy and safety. The various ongoing trials for golimumab have yielded promising results in terms of efficacy and safety in methotrexate-naive and -resistant patients with rheumatoid arthritis, as well as in patients who were previously treated with other anti-TNF agents. In addition, the efficacy of golimumab in psoriatic arthritis and ankylosing spondylitis has also been demonstrated. The real safety information will be available only once the drug has been used in many more patients, who frequently have comorbid conditions.

Keywords: arthritis, rheumatoid, psoriatic arthritis, ankylosing spondylitis

Introduction

Advances in the treatment of rheumatic diseases have been achieved from an improved understanding of the pathogenesis of these diseases and biotechnological advances that have allowed targeted approaches to the pathological processes.

Tumor necrosis factor (TNF)- α has an important role in inflammatory processes in rheumatoid arthritis (RA) and in other immune-mediated disorders. Consequently, TNF- α has emerged as an important target for the development of therapeutic strategies for treating not only RA but also other inflammatory arthritides as well.¹

RA usually affects hands and feet; psoriatic arthritis (PsA) can affect both peripheral joints and the spine, whereas ankylosing spondylitis (AS) affects the spine predominately. The worldwide prevalence of these conditions is approximately 2% in the adult population.²⁻⁴ Although they are unique conditions, these inflammatory joint diseases share many clinical features and treatment strategies, which have led to the development of agents that target common pathways among the diseases. Since their introduction, the TNF- α inhibitors have become firmly established as effective treatments for several rheumatologic diseases, including RA, AS, and PsA, either alone or in combination with traditional, nonbiologic disease-modifying antirheumatic drugs (DMARDs).⁵⁻⁷

Despite the benefits that these biologic agents have brought since entering the treatment paradigm of these entities, not all patients respond adequately to them and some patients may lose their response over time. Interestingly, the strategy of switching patients who no longer respond to one of the TNF- α blockers to another has often

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turned out to be effective.^{8,9} This insufficient response with current therapy along with the data indicating that switching among the available TNF antagonists is safe and effective has, therefore, led to the development of new TNF- α inhibitors.

Currently available anti-TNF agents include infliximab, adalimumab, etanercept, certolizumab, and golimumab (GM). GM (Simponi™; Centocor), alone or in combination with MTX, was approved by the US Food and Drug Administration on April, 2009 for the treatment of moderate to severe RA, active PsA (alone or with MTX), and active AS.

This review will summarize current evidence covering the pharmacology, efficacy, and safety of GM in RA, AS, and PsA.

Pharmacology and pharmacokinetics

GM, also known as CNTO-148, is a human immunoglobulin G1- κ monoclonal antibody that is specific for TNF- α , which binds to both the soluble and transmembrane forms of human TNF- α . Being a fully human monoclonal antibody, GM resembles adalimumab, which was the first such product to reach the market. However, amino acid sequences of the light and heavy chains of GM are identical to those of infliximab.¹

The pharmacokinetics of GM have been studied mainly in a trial conducted by Zhou et al,¹⁰ whereas several phase 2 and 3 trials in different patient populations provided additional pharmacokinetic data.^{11–14} GM appears to exhibit dose-dependent pharmacokinetics with both intravenous (IV) and subcutaneous (SC) administration; steady-state concentration is reached within 12 weeks. With SC administration, the time to reach maximum serum concentration (2.5 mcg/mL) in healthy participants ranges from 2 to 6 days. Concomitant use of MTX results in a mean steady-state trough serum concentration of 0.4–0.6 mcg/mL, 0.5 mcg/mL, and 0.8 mcg/mL in patients with RA, PsA, and AS, respectively. Patients with RA, PsA, and AS who were treated with GM and MTX had approximately 52%, 36%, and 21% higher mean steady-state trough concentrations compared with those treated without concomitant MTX, suggesting a potential drug interaction between these 2 agents. The median half-life appeared to increase with an increase in dose, with a median of 6.6 days for 0.1 mg/kg and 19.3 days for 10 mg/kg of GM. Based on population pharmacokinetic models, for a patient weighing 70 kg, mean apparent clearance was 1.38–1.91 L/d and apparent volume of distribution was 22.6–26.7 L. Population pharmacokinetic analysis in patients with RA also indicated that concomitant use of MTX could reduce the apparent clearance of GM by 17.1%.

Efficacy

RA

Phase 2 study

GM was investigated in a phase 2, randomized, double-blind, placebo-controlled, dose-ranging study consisting of 172 patients with active RA with an inadequate response to methotrexate (MTX).¹¹ All eligible patients had been unsuccessfully treated with MTX for at least 3 months (≥ 10 mg/wk) and had ≥ 6 swollen, ≥ 6 tender joints, and at least 2 of the following: C-reactive protein (CRP) level ≥ 1.5 mg/dL, erythrocyte sedimentation rate (ESR) ≥ 28 mm/h, and morning stiffness of ≥ 30 minutes. Patients who were on stable doses of nonsteroidal anti-inflammatory drugs (NSAIDs) and corticosteroids (≤ 10 mg/d of prednisone) were allowed to continue their use during the study. Patients were assigned to one of 5 treatment groups: placebo, GM 50 or 100 mg SC every 2 or 4 weeks. All patients continued to receive stable doses of MTX through the end of the study.

To assess GMs efficacy, the primary end point was established as the percentage of individuals fulfilling the American College of Rheumatology (ACR20) criteria after 16 weeks.¹⁵ Secondary end points included the change from baseline in the disease activity score in 28 joints (DAS28) at week 16, numeric index of ACR response (ACR-N), and ACR20/50/70 responses over time through week 52.^{15–17}

The demographics and baseline clinical characteristics were similar to those in the usual RA clinical trials, with a median age of 53.5 years and median duration of disease 7.8 years (Table 1). In all, 87.6% and 82.9% of patients randomized to combined GM plus MTX groups and placebo plus MTX, respectively, completed 16 weeks of study. The discontinuation rates in the individual GM plus MTX dose groups did not vary in a dose-dependent manner.

The study met its primary end point at week 16; the ACR20 response of patients in the combined GM plus MTX group was 61.3% vs 37.1% in patients treated with placebo plus MTX ($P = 0.01$) (Table 2). When compared individually with the placebo group, only the highest dose group (100 mg GM every 2 weeks) showed a significant difference in the proportion of patients achieving an ACR20 response (79.4%; $P < 0.001$ compared with placebo).

The secondary end points of ACR50/70 responses, improvement in DAS28, and ACR-N at week 16 were also significantly improved in the combined GM plus MTX groups as compared with placebo plus MTX (Table 2). Correlated with the favorable clinical outcomes, 26.3% of patients in the combined GM groups achieved remission (DAS28

Table 1 Characteristics of randomized controlled trials of golimumab in rheumatoid arthritis

Reference	No of patients	Age mean (SD) or median [IQR]	Prior MTX failure (yes/no)	Prior biologic failure (yes/no)	HAQ, baseline, mean (SD) or median [IQR]	DAS28-CRP, baseline, mean (SD) or median [IQR]	Disease duration in years, mean (SD) or median [IQR]	Primary end points	Secondary end points
Kay et al ¹¹	172	57 [50,64]	Yes	No	1.7 [1.4,2.0]	5.3 [4.5,6.22]	8.2 [4.1,14.3]	ACR20 at wk 16	ACR50/70 at wk 16 DAS28 improvement at wk 16 ACR-N at wk 16 ACR20/50/70 over time through wk 52
Keystone et al ¹⁸ GO-FORWARD	444	51 [42,59]	Yes	No	1.37 [1.0,1.9]	5.1 [4.0,5.6]	4.5 [2.1,9.7]	ACR20 at wk 14 HAQ-DI at wk 14 ACR20 at wk 24	DAS28 improvement at wk 14 HAQ-DI at wk 24 ACR20 at wk 24
Emery et al ¹⁹ GO-BEFORE	637	51 (11)	Yes	No	1.5 (0.7)	5.1 (1.0)	3.5 (5.7)	ACR50 at wk 24	ACR20 at wk 24
Smolen et al ²⁰ GO-AFTER	461	55 [46,63]	Yes	Yes (TNF-inhibitor)	1.6 [1.1,2.0]	6.3 [5.6,7.2]	9.6 [5.6,17.2]	ACR20 at wk 14	ACR20 at wk 24 ACR50/70/N at wk 14–24 HAQ-DI and DAS28 response/remission
Kremer et al ¹² (IV GM)	643	51 [NR]	Yes	No	1.5 [NR]	NR	6.3 [NR]	ACR50 at wk 14	ACR50 at wk 24 ACR20 and DAS28 at wk 14

Abbreviations: SD, standard deviation; MTX, methotrexate; HAQ-DI, health assessment questionnaire disability index; DAS28, disease activity score employing 28-joint count; CRP, C-reactive protein; ACR, American College of Rheumatology 20/50/70% N response criteria; GO-FORWARD, Golimumab Before Active RA Despite methotrexate; GO-BEFORE, Golimumab Before Employing MTX as the First-line Option in the treatment of Rheumatoid Arthritis Early onset; GO-AFTER, Golimumab in patients with active rheumatoid arthritis after treatment with tumor necrosis factor- α inhibitors; IV, intravenous; GM, golimumab; NR, not reported; IQR, interquartile range.

Table 2 Results from randomized controlled trials of golimumab in rheumatoid arthritis

Reference	Duration	Treatment	ACR20 (%)	ACR50 (%)	ACR70 (%)	DAS28-CRP remission (%)
Kay et al ¹¹	16 wk	Placebo + MTX	37.1	5.7	0.0	5.7
		GM 50 mg q4 wk + MTX	60	37.1*	8.6	20
		GM 50 mg q2 wk + MTX	50	23.5*	14.7*	26.5*
		GM 100 mg q4 wk + MTX	55.9	29.4*	17.6*	32.4*
		GM 100 mg q2 wk + MTX	79.4*	32.4*	8.8	26.5*
		GM combined + MTX	61.3*	30.7*	12.4*	26.3*
		Keystone et al ¹⁸ GO-FORWARD	24 wk	14 wk results		
Placebo + MTX	33.1			9.8	3.8	NR
GM 100 mg q4 wk + placebo	44.4			20.3*	7.5	NR
GM 50 mg q4 wk + MTX	55.1*			34.8*	13.5*	NR
GM 100 mg q4 wk + MTX	56.2*			29.2*	9.0	NR
24 wk results						
Placebo + MTX	27.8			13.5	5.3	NR
GM 100 mg q4 wk + placebo	35.3			19.5	11.3	NR
GM 50 mg q4 wk + MTX	59.6*			37.1*	20.2*	NR
GM 100 mg q4 wk + MTX	59.6*			32.6*	14.6*	NR
Emery et al ¹⁹ GO-BEFORE	24 wk			Placebo + MTX	49.4	29.4
		GM 100 mg q4 wk + placebo	51.6	32.7	13.8	25.2
		GM 50 mg q4 wk + MTX	61.6*	40.3*	23.9	38.4*
		GM 100 mg q4 wk + MTX	61.6*	36.5	18.2	37.7
Smolen et al ²⁰ GO-AFTER	24 wk	14 wk results				
		Placebo + MTX	18	6	2	1
		GM 50 mg q4 wk + DMARD	35*	16*	10*	13*
		GM 100 mg q4 wk + DMARD	38*	20*	9*	12*
		24 wk results				
		Placebo + MTX	17	5	3	3
		GM 50 mg q4 wk + DMARD	34*	18*	12*	10*
		GM 100 mg q4 wk + DMARD	44*	20*	10*	16*
Kremer et al ¹²	48 wk	14 wk results				
		Placebo + MTX	27.9	13.2	4.7	10.1

(Continued)

Table 2 (Continued)

Reference	Duration	Treatment	ACR20 (%)	ACR50 (%)	ACR70 (%)	DAS28-CRP remission (%)
		GM + placebo combined	44.0*	16	4.3	15.2
		GM + MTX combined	53.3*	21.4	6.2	18.3*
		24 wk results				
		Placebo + MTX	24.8	9.3	3.1	7.0
		GM + placebo combined	26.1	10.1	4.7	8.6
		GM + MTX combined	43.6*	21.8*	7.0	18.7*

Note: * $P < 0.05$ vs placebo.

Abbreviations: ACR, American College of Rheumatology 20/50/70% response criteria; DAS28, disease activity score employing 28-joint count; CRP, C-reactive protein; GM, golimumab; MTX, methotrexate; GO-FORWARD, GOLimumab FOR subjects With Active RA Despite methotrexate; NR, not reported; GO-BEFORE, GOLimumab Before Employing MTX as the First-line Option in the treatment of Rheumatoid arthritis Early onset; GO-AFTER, Golimumab in patients with active rheumatoid arthritis after treatment with tumor necrosis factor- α inhibitors; DMARD, disease-modifying antirheumatic drug.

with CRP < 2.6) compared with 5.7% in the placebo group ($P = 0.009$). Although all GM dose regimens had significantly greater proportion of patients achieving an ACR50 response at week 16 compared with placebo, the response was not in a dose-dependent manner. On the other hand, when individual doses of GM compared with the placebo group for all other secondary end points (other than ACR50), different doses of GM for different end points proved to be superior (Table 2). In other words, none of the studied doses of GM was shown to be superior compared with each other. However, the observed lack of dose-response relationship in this study might be due to relatively small number of patients in each dose group.

At 20-weeks follow-up, patients in the placebo group started open-label treatment with IV infliximab at 3 mg/kg followed by maintenance therapy every 8 weeks through week 44. Unfortunately, data regarding head-to-head comparison of GM groups with infliximab group are not available. After week 16, although patients in GM groups continued to receive their assigned dose (50 or 100 mg), their dosing frequency was changed from every 2 weeks to every 4 weeks for all 4 treatment arms. Although specific percentages were not provided, these patients maintained their ACR responses through week 52 despite less frequent dosing.

Overall, this study provided evidence that GM was superior to placebo as add-on MTX in inadequate responders with no clear advantage of more frequent (every 2 weeks) administration.

Phase 3 studies

The efficacy of GM was investigated in four phase 3 trials conducted among different RA populations: the GO-FORWARD

(GOLimumab FOR subjects With Active RA Despite methotrexate) study enrolled patients currently on MTX,^{18,19} the GO-BEFORE (GOLimumab Before Employing MTX as the First-line Option in the treatment of Rheumatoid arthritis Early onset) study included patients who were MTX naïve,¹⁹ and the GO-AFTER (GOLimumab After Former anti-TNF- α Therapy Evaluated in RA) trial examined patients previously treated with TNF- α inhibitors.²⁰ Although the most recent study was similar to GO-FORWARD as investigating the safety and tolerability of GM in patients with active RA that was not adequately controlled with MTX, this study was performed to support the use of or to determine the optimal dosage for maximal safety and effectiveness of GM when administered intravenously.¹²

The GO-FORWARD trial,¹⁸ a 1-year, double-blind, placebo-controlled phase 3 study, enrolled 444 patients who had inadequate response to MTX, was designed to demonstrate 2 coprimary efficacy end points: ACR20 at week 14 and improvement in health assessment questionnaire disability index (HAQ-DI) at week 24 (Table 1). Twenty-four week results of this study that include the primary end points have been published. Keystone and colleagues defined inadequate response to MTX as patients with RA who had been receiving MTX for at least 3 months with a stable dose of 15–25 mg/wk for the last 4 weeks, had active disease manifest by at least 4 joints that were swollen and 4 joints that were tender at the time of enrollment, and 2 of the following: CRP level ≥ 1.5 mg/dL, ESR ≥ 28 mm/h, morning stiffness of ≥ 30 minutes, bone erosion seen on x-ray or magnetic resonance imaging, or anti-cyclic citrillated peptide (CCP) antibody positive or rheumatoid factor (RF) positive. Although the use

of stable doses of NSAIDs and corticosteroids (<10 mg/d of prednisone or equivalent) were allowed, patients were asked to discontinue the use of any DMARDs within 4 weeks of study enrollment or TNF- α inhibitor therapy at any time. Patients were randomized to treatment with placebo plus MTX, GM 100 mg plus placebo, and GM 50 mg or 100 mg every 4 weeks plus MTX. At week 16, patients who had less than 20% improvement in tender and swollen joint counts had their doses adjusted in a double-blind manner, except for the GM 100 mg plus MTX group.

At randomization, patients in this study had shorter disease duration (range of median 4.5–6.7 years), fewer tender (range of median 21–26) and swollen joints (range of median 11–13), and lower disease activity (DAS28 CRP, range of median 4.8–5.1) as compared with those in previous studies of biological agents in patients with active RA despite MTX treatment. Such a difference might be individual or combined result of either less restrictive entry criteria in this study, or overall reduction in the disease activity of patients seen in daily practice, or increased tendency to treat RA with biological agents early in disease course. The median weekly dose of MTX was 15 mg in all of the study arms, and approximately half of the patients had been using MTX for at least 3 years before the enrollment.

At week 14, despite a higher than expected placebo effect, both patients in the GM 50 mg plus MTX and patients in GM 100 mg plus MTX achieved a higher ACR20 response rates than patients receiving placebo plus MTX (55.1%, 56.2% vs 33.1%, $P=0.001$ and $P<0.001$, respectively). No significant difference was detected with respect to ACR20 responses between patients receiving MTX (33.1%) or GM (44.4%) as monotherapy ($P=0.059$). The results were found to show a quite similar pattern for the coprimary end point of change in HAQ-DI at week 24, as patients receiving combination therapy (both of the dosing regimens) exhibited higher improvement than did patients who received MTX or adalimumab monotherapy (Table 2). The outcomes for the secondary end points including ACR50/70, DAS28 remission, and HAQ-DI at week 14, and ACR20/50/70 and DAS28 remission at week 24 were consistent with the primary analysis and disclosed similar superiority of combination therapy (Table 2).

In conclusion, the phase 3 GO-FORWARD study confirmed and extended the findings of a phase 2 study by demonstrating that GM, with background MTX, is more effective than the MTX monotherapy in reducing the signs and symptoms of RA and improving physical function. GM monotherapy, however, was not found to be superior to MTX

monotherapy in this group of patients with RA, similar to all other biologic trials. In addition, no apparent advantage of using higher dose (100 mg) of GM was shown compared with lower dose (50 mg) when used in combination with MTX. The 1-year results of the GO-FORWARD trial has recently been published and indicate that the response rates achieved at week 24 by patients who received the combination of GM and MTX were sustained to week 52. The combination of GM and MTX was more effective than either GM or MTX alone. Furthermore, there was no difference in efficacy of the 50 or 100 mg dose of GM when used in combination with MTX (ACR20 response; 64% vs 58%, respectively).²¹

The GO-BEFORE trial is a double-blind, placebo-controlled, multicenter trial investigating the efficacy of GM in RA. It was designed to last 52 weeks with an open-label extension of 5 years, whereas only the results at the 24 week are currently available.¹⁹ This study evaluated 637 patients who had early disease and were MTX naïve, with the median duration of RA ranging from 1 to 1.8 years across the study groups (Table 1).

Patients were randomized to treatment with placebo plus MTX (group 1), GM 100 mg plus placebo (group 2), GM 50 mg plus MTX (group 3), and GM 100 mg plus MTX (group 4). GM injections were administered every 4 weeks and the average dose of MTX was 20 mg/wk. Although the study reported to have 2 coprimary end points: ACR50 response at week 24 and a change from baseline in the modified Sharp/van der Heijde score at week 52, recent update in the clinical trials database stated that radiologic outcome is no longer the outcome (neither primary nor secondary) of this study.

At week 24, ACR50 responses were found to be similar between the combined group (group 3 and 4) and group 1 according to the prespecified intention to treat (ITT) analysis (38.4% vs 29.4%, respectively, $P=0.053$), but when post hoc modified ITT analysis (excluding 3 randomized but untreated patients) was conducted, the difference between the groups became significant (38.5% vs 29.4%, respectively, $P=0.049$). Using the same post hoc analysis, proportion of patients achieving ACR50 responses in GM 50 mg plus MTX group was found to be higher than those of patients receiving MTX monotherapy (40.5% vs 29.4%, respectively, $P=0.038$), whereas no such difference was detected for patients in group 4 (GM 100 mg plus MTX; 36.5%, $P=0.177$) (Table 2). GM 100 mg without MTX was found to be noninferior statistically to MTX monotherapy for ACR50 response at week 24 (33.1% vs 29.4%, respectively). When examining the ACR20 responses at week 24, there was a clear response both in group 3 (GM 50 mg plus MTX) and group 4

(GM 100 mg plus MTX) with 61.6% improvement in each compared with 49.4% in MTX plus placebo group ($P=0.028$ for both). Furthermore, such a response in ACR20 for both doses of GM combined with MTX became significant as early as week 4 of the study. With regard to other measures of this study including ACR90, ACR-N, and DAS28 CRP remission, GM 50 mg plus MTX group was shown to be superior to MTX monotherapy, whereas no such advantage was shown for GM 100 mg plus MTX group.

Overall study results showed that subcutaneously administered GM with MTX is more effective than MTX monotherapy in patients who had not received MTX previously. In this study, as similar to the results of GO-FORWARD trial which was performed in MTX nonresponders, the regimen of GM 100 mg plus MTX did not appear to provide a greater efficacy than the regimen of GM 50 mg plus MTX.

The GO-AFTER trial is a double-blind, placebo-controlled, multicenter trial investigating the clinical question of whether GM is safe and effective treatment for patients with active RA previously treated with at least 1 anti-TNF- α agent.²⁰ The randomized, double-blind component of the trial was designed to last 52 weeks for which the results are available for 24 weeks, whereas the open extension part (4 years) is still ongoing. To be eligible, patients had to have active disease (≥ 4 swollen and ≥ 4 tender joints), should be treated with at least 1 dose of anti-TNF- α agent, and should have discontinued this agent (for any reason) at least 8–12 weeks before the study entry. Concomitant therapy with MTX, sulfasalazine and/or hydroxychloroquine, was permitted if the patient was on a stable dose for at least 4 weeks before the first administration of the study agent. A total of 461 patients were randomized to treatment with placebo and GM 50 or 100 mg SC every 4 weeks. Patients with $<20\%$ improvement in swollen/tender joint counts in placebo or GM 50-mg groups could enter early escape and received double-blinded rescue therapy. The median disease duration (>8 years) among the recruited patients is longer than the previous studies of GM (Table 1). The disease activity is considerably high (DAS28 ESR > 6), whereas more than 60% of the participants had been treated with MTX (dose not reported). Reasons for the discontinuation of previous anti-TNF- α agents are lack of effectiveness (58%) and intolerance or accessibility problems (53%). The efficacy of GM was evaluated at week 14, based on the ACR20 response (primary end point), which showed that more patients on each of the GM doses (35% for 50 mg and 38% for 100 mg) achieved this response than did those on placebo (18%) (0.0006 and 0.0001, respectively). There is no difference between the GM doses of 50 mg and 100 mg

with regard to ACR20 responses. For weeks 14 and 24, significantly more patients in each of the GM-treated groups achieved ACR50, ACR70, and DAS28 remission (Table 2). At week 14, the difference between the proportion of patients achieving ACR20 on combined GM and placebo groups was higher among patients receiving concomitant DMARDs, had previously received less than 3 anti-TNF- α agents, and had discontinued the previous anti-TNF- α agent due to lack of efficacy. This study provided evidence that GM can be used effectively as an anti-TNF- α agent in patients with RA who have had inadequate responses to other TNF- α inhibitors. Although proportion of patients achieving ACR20 response was lower in this study as compared with previous studies with GM (GO-FORWARD and GO-BEFORE), this findings are compatible with the observational studies suggesting that the probability of response decreases with an increased number of previous DMARDs and anti-TNF- α agents.

Although the pharmacokinetics and safety of IV GM administration were studied in a phase 1 trial in patients with RA,¹⁰ the only phase 3 study evaluating the use of IV route was recently published.¹² The goal of this multicenter, randomized, double-blind, placebo-controlled, 48-week study was to assess the efficacy and safety of IV administration of GM (with and without MTX) in patients with active RA despite concurrent MTX therapy. The study evaluated 643 patients who met almost the same selection criteria as in the trial of SC GM in another MTX-inadequate responder population. The only difference between this trial and the previous trial was the inclusion of those patients with previous anti-TNF therapy. Patients were randomized (1:1:1:1) to receive placebo plus MTX, GM 2 mg/kg with or without MTX, or GM 4 mg/kg with or without MTX. IV infusions of study agent were administered over 30 minutes at week 0 and every 12 weeks thereafter. Baseline demographic and clinical characteristics were similar across treatment groups and were similar to those observed in the GO-FORWARD trial.¹⁸ At randomization, the mean disease duration was more than 7 years, with medians of 23 tender and 13 swollen joints. At study entry, half of the patients had been receiving MTX therapy for 3 or more years (overall median MTX dose was 15 mg/wk), and 80% of them were receiving corticosteroids, whereas approximately 60% of them had a history of DMARD and 5% had a history of anti-TNF use. The primary outcome measure was the percentages of patients who achieved ACR50 response at week 14. Secondary end points were the percentages of patients who achieved ACR50 response at week 24, ACR20 response at week 14, and DAS28 response using CRP at week 14 (Table 1).

The study did not meet its primary end point at week 14, as showing no difference in the proportion of patients achieving ACR50 response between the combined GM (2 and 4 mg/kg) plus MTX group (21.4%) and in the group that received placebo plus MTX (13.2%) ($P = 0.051$). However, by week 24, significantly more GM plus MTX-treated patients achieved an ACR50 response compared with placebo plus MTX (22% vs 9%, $P = 0.002$). There was no difference in the ACR50 response rates at any time point for GM monotherapy compared with placebo plus MTX.

ACR20 responses at week 14 in patients treated with GM 2 and 4 mg/kg plus MTX were 55 and 51.6%, respectively, vs 27.9% in patients treated with placebo plus MTX ($P < 0.001$, each). Although similar findings for ACR20 response were observed for patients treated with GM monotherapy at week 14, the superiority of GM treatment as compared with placebo plus MTX was sustained only among patients receiving GM plus MTX through week 24 (Table 2). There were no significant differences in ACR70 response rates between patients who received GM (both of the doses, either as monotherapy or combined with MTX) compared with those who received placebo plus MTX. Correlated with the other clinical outcomes, at week 14, 18.3% of patients in the combined GM plus MTX groups and 25% in the GM 4 mg/kg plus MTX groups achieved DAS28-CRP remission compared with 10.1% in the placebo plus MTX group ($P = 0.036$ and $P = 0.002$, respectively). Similar trends for DAS28-CRP remission were observed at week 24 for patients in the GM plus MTX groups, and as similar to the results of the week 14, no significant difference was detected in the proportion of patients achieving remission in both doses of GM monotherapy group vs the placebo plus MTX group (Table 2).

Despite the primary study end point (ACR50 response at week 14 was not achieved), these findings suggested that IV GM, when used in combination with MTX, may improve the symptoms and disease activity in patients with RA with incomplete response to MTX monotherapy. IV administration of GM offers the advantage of less frequent dosing (every 12 weeks) compared with SC form (every 4 weeks). However, considering the lack of satisfactory ACR50 response at week 14, further studies investigating different dosing strategy for IV form may be needed.

PsA

The approval of GM for the treatment of PsA was based on the results found in 1 pilot clinical study evaluating the safety and efficacy of GM. Golimumab – A Randomized

Evaluation of Safety and Efficacy in Subjects with Psoriatic Arthritis Using a Human Anti-TNF Monoclonal Antibody (GO-REVEAL) is a phase 3, multicenter, randomized, double-blind, placebo-controlled trial involving 405 patients with active PsA and a history of inadequate response to NSAIDs or DMARDs.¹³ Patients were considered active if they had ≥ 3 swollen and ≥ 3 tender joints in addition to at least 1 psoriasis plaque measuring ≥ 2 cm in diameter. Stable doses of MTX, NSAIDs, and corticosteroids (prednisone 10 mg/d) were allowed. Patients were randomized to receive SC injections of placebo, GM 50 mg, or GM 100 mg every 4 weeks for 24 weeks. At week 16, patients with $< 10\%$ improvement from baseline in both the swollen and tender joint counts entered early escape. Mean age of the patients was 47 years, and 60% were men. Almost half of the patients had polyarticular type PsA with a mean disease duration of more than 8 years. At study entry, half of the patients had been receiving MTX therapy with a median MTX dose of 15 mg/wk, and 20% of them were receiving corticosteroids, whereas approximately 75% of them being treated with NSAIDs.

The primary end point was the proportion of patients meeting the ACR20 response at week 14. Major secondary end points included the ACR20 response at week 24, achievement of at least 75% improvement in the psoriasis area and severity index (PASI),²² at week 14 in the subset of patients in whom at least 3% of the body surface area was affected by psoriasis at baseline, and HAQ scores at week 24.

At week 14, 48% of all patients receiving GM, 51% of patients receiving 50-mg GM, and 45% of patients receiving 100-mg GM achieved an ACR20 response (the primary end point) compared with 9% of patients receiving placebo ($P < 0.001$ for all comparisons). By week 24, 52% of patients in the GM 50-mg group and 61% of patients in the GM 100-mg group achieved an ACR20 response (major secondary end point) compared with 12% of patients in the placebo group ($P < 0.001$ for both comparisons). Indeed, consistent with the primary outcome, patients who received GM (both doses) showed significantly greater ACR50, ACR70, change in the DAS28-CRP, and Psoriatic Arthritis Response Criteria (PsARC) response,²³ at all measured time points as compared with those on placebo.

This study also demonstrated the clinical efficacy of GM in improving the skin and nail lesions of psoriasis. Among those with evaluable skin disease, 40% of the GM 50-mg group and 58% of the GM 100-mg group achieved PASI 75 compared with 3% of the placebo group at week 14 ($P < 0.001$ for each dose). Likewise, both at weeks 14 and 24, the nail psoriasis

severity index²⁴ showed significant improvement from baseline in each GM-dose group vs placebo.

Disability at 24 weeks, as measured by patient responses to the HAQ scores, showed significantly more improvement from baseline in 50-mg- and 100-mg-doses GM group (0.33 ± 0.55 and 0.39 ± 0.50 , respectively) than in the placebo group (-0.01 ± 0.49) ($P < 0.001$ for both comparisons).

In addition to the beneficial effects observed in arthritis measures, the median percentage of improvement in the dactylitis severity score was significantly higher at both time points with 100-mg dose of GM. With respect to enthesitis, those patients in both of the GM arms similarly experienced greater clinical improvement (PsA modified Maastricht Ankylosing Spondylitis Enthesitis Score [MASES]) over those receiving placebo, a response that increased over time.

Finally, results of GO-REVEAL trial imply that GM is effective not only for patients with PsA but also for those patients having skin disease, psoriatic nail disease, enthesitis, and dactylitis. It is of note that differences between the 50-mg and 100-mg doses of GM were modest, whereas some evidence suggests that skin disease may respond better to the higher doses of GM. This study also illustrated that concomitant use of MTX did not result in additional improvement in either joint or skin disease.

AS

The pivotal study to prove the efficacy and safety of GM in AS was the randomized, double-blind, placebo-controlled, multicenter GO-RAISE trial conducted over 24-week period.¹⁴ The inclusion criteria for this trial was similar to the previous trials of biological agents in AS and comprised fulfillment of modified New York criteria for definite AS,²⁵ active disease (as indicated by a Bath AS disease activity index [BASDAI] score > 4), pain score of >4 on visual analogue scale (0–10), and an inadequate response to NSAIDs and DMARDs. Patients were allowed to continue stable doses of concomitant MTX, sulfasalazine, hydroxychloroquine, low-dose corticosteroids, and/or NSAIDs, but the use of other DMARDs is prohibited. Patients with complete spinal ankylosis were also excluded. A total of 356 patients were randomly assigned to placebo, GM 50 mg, or GM 100 mg, given SC every 4 weeks. There was an “early escape” at week 16 in the study whereby patients who meet criteria for having little improvement in their AS symptoms were switched to GM if they were on placebo or have the GM dose increased if they were originally assigned to the GM 50-mg group.

Baseline characteristics of patients resembled the previous studies conducted among patients with AS with different agents: they were predominantly men (70%), white ($>90\%$), with a median age of 40 years and median disease duration of approximately 7 years.

The primary end point was the proportion of patients who achieved at least 20% improvement in the ASsessment in AS International Working Group criteria (ASAS20) at week 14.²⁶ Secondary end points included ASAS 40% improvement (ASAS40),²⁶ ASAS partial remission, and 20% improvement in 5 of 6 ASAS domains (ASAS5/6).²⁷

After week 14, 59.4% of patients in the 50-mg group and 60% of patients in the 100-mg group were ASAS20 responders compared with 21.8% of patients in the placebo group ($P < 0.001$, for each). Of the patients who received GM, 43.5% and 54.3% of patients achieved an ASAS40 response in 50-mg and 100-mg groups, respectively, at week 24 compared with 15.4% in the placebo group ($P < 0.001$, for each). Although significantly more patients receiving GM (50 mg and 100 mg) were reported to achieve an ASAS20, ASAS5/6 response, and partial remission at week 24 as similar to those observed at week 14, no numerical data are available about these end points. Consistent with the other measures, the BASDAI-50 response ($>50\%$ improvement) was seen in half of the GM-treated patients compared with 15% in the placebo arm ($P < 0.001$, for each). Symptom benefit was seen as early as 4 weeks after treatment commencement and sustained throughout week 24.

Taken together, all the data of this trial provide evidence of the short-term clinical efficacy of both the doses of GM, administered SC every 4 weeks in patients with AS refractory to conventional treatment. Furthermore, no clear difference in efficacy was evident between the 50-mg and 100-mg-dose groups through week 24.

Safety

Overall, data obtained from the clinical trials performed in various settings (RA, PsA, AS) suggest that GM appears to be safe and well tolerated. However, it should be kept in mind that none of the studies of GM were designed with safety as primary outcome; therefore, definitive conclusions about the safety cannot be drawn. Furthermore, all of the trials for which the safety data are available are short duration studies.

The incidence of serious (2%–7%) and nonserious (60%–80%) adverse events in the GM-treated groups were similar to those observed in placebo groups with nausea,

headache, and injection site reaction reported most often. There was no notable relationship between overall adverse event rates and GM dose. The proportion of patients who discontinued treatment because of adverse reactions in the controlled phase 3 trials through week 16 in RA, PsA, and AS was 2% for GM-treated patients and 3% for placebo-treated patients. Injection site reactions were observed in a rate ranging from 5% to 25%. They were primarily mild in intensity and consisted most often of injection site erythema, bruising, or warmth. No patient discontinued treatment because of an injection site reaction.^{12-14,18-20} In the only study evaluating IV use of GM, the incidence of infusion reactions among all GM-treated patients was 4% compared with 5% for placebo plus MTX.¹²

Anti-TNF agents may affect host defenses against infections since TNF is involved in modulating this process. In clinical trials of GM, infections are one of the most commonly reported adverse events (30%). In general, the safety profile of GM in patients with RA appears comparable to that of other disease settings (PsA, AS). However, the frequency of infections, in general, was reported to be higher in patients with AS receiving GM (45%) compared with those of the patients with RA.¹⁴ The overall frequency of infections, in general, and nonupper respiratory tract infections in particular were similar in patients treated with GM or placebo. Nonetheless, upper respiratory tract infections were slightly more common in patients treated with GM (12%) than placebo (7%). In different trials, including the trials performed in AS and PsA, excepting a minor increase among patients receiving combination of MTX and high dose of GM (4%–5%), there were no data indicating a significantly higher frequency of serious infections as compared with placebo (1%–4% GM groups vs 0.7%–3% placebo). Among the patients treated with GM, serious infections that have occurred included pneumonia, gastroenteritis, otitis media, urinary tract infection, and sepsis.

Tuberculosis (TB) is the most frequent opportunistic infection that has been reported with TNF- α inhibitors. Indeed, TNF- α plays a role in the host defense against *Mycobacterium tuberculosis* and notably in granuloma formation and in containment of latent disease.²⁸ Considering the previous experience with other TNF- α inhibitors, all patients screened for clinical trials of GM were also screened for TB. In all but 2 studies, patients with positive results for TB screening were allowed to participate but had to start prophylaxis for latent TB. Approximately, 10%–20% of the patients in these 5 studies had latent TB at screening and entered the study receiving prophylaxis.

Overall, TB developed in 3 patients. In GO-BEFORE study, 1 patient was diagnosed TB of the spine after receiving the third dose of GM. A review of the patient's report indicated that the spinal lesion was present before the study entry, whereas no data are available about the patient's prophylaxis status.¹⁹ The other 2 reported cases were from the study investigating IV administration of GM and occurred between weeks 24 and 48 in patients who initially tested negative for TB at screening.¹² At this time, it is reasonable to assume from the existing data that the development of active TB is a class effect that may be expected with the use of any TNF- α inhibitors including GM. Only 1 opportunistic infection (liver histoplasmosis) other than TB has been reported with the use of GM thus far.

Antibodies to GM were detected in a low percentage of patients (approximately 5% and 7%, respectively) following both IV and SC administration. The antibody titers were generally low, and no antibody positive patients exhibited an infusion site reaction or significant lack of efficacy.

In general, GM treatment appeared unassociated with onset of malignancies. However, relatively small number of patients in the controlled trials of GM makes it difficult to interpret differences in the percentage of infrequent events, such as cancer and death.

The safety profile of GM does not bear surprises compared with other TNF- α inhibitors, although conclusive safety data on this compound will have to await postmarketing strategies. As with most of the biologic trials, the way safe data were reported leaves a lot to be desired. No data regarding time to event or what happened after the serious events were provided. Use of patients years and means of event rates are inadequate in any trial for reporting safety data.²⁹

Although concluding statements are still difficult about the safety of GM because of the paucity of data available, the following 7 types of adverse events seem to be of special concern for patients treated with GM therapy considering the experience with other TNF- α inhibitors:

- Infections including sepsis and TB
- Malignancies such as lymphoma
- Hematological disorders such as anemia and pancytopenia
- Demyelinating disorders and neuropathy
- Onset and worsening of congestive heart failure
- Occurrence of autoantibodies and autoimmunity
- Injection/infusion and hypersensitivity reactions

It is possible that GM might differ from other TNF- α inhibitors in terms of adverse reactions. It is, however, pru-

dent to keep the afore-mentioned possible adverse events in mind when treating patients with GM.

Conclusion

The various ongoing trials for GM have yielded promising results in terms of efficacy and safety in MTX-naïve and MTX-resistant patients with RA, as well as in patients with RA who were previously treated with other anti-TNF agents. In addition, the efficacy of GM in PsA and AS has also been demonstrated. The real safety information will only be available once the drug has been used in many more patients, who frequently have comorbid conditions. Some of this data, if collected and analyzed correctly, may be available from the currently active biologic registries.

Although the efficacy of GM was not tested against other TNF- α inhibitors in controlled trials, its efficacy is unlikely to be superior compared with other TNF- α inhibitors available in the market. With respect to molecular structure, it is most similar to adalimumab, but it requires less frequent administration and is labeled for patient self-administration. For all indications, the approved GM dosage is 50 mg administered by SC injection once a month. Thus, the appeal of GM in an already crowded arena is primarily being an option to patients desiring less frequent injections. Though more time is needed to appreciate any long-term consequences, till date GM exhibits a favorable risk-benefit profile, which is quite similar to the other TNF- α inhibitors available in the market.

Although GM therapy has been investigated in controlled trials over 6 months, additional trials are needed to determine long-term safety of this agent and whether the clinical benefits of GM found in the clinical trials reviewed in this study would be sustained over time.

Disclosure

The authors report no conflicts of interest in this work.

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