International Journal of Medicine and Nanotechnology e ISSN: 2394-4269
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An International Peer Review Journal

Original Article

TO STUDY THE EFFICACY OF GOLIMUMAB PLUS METHOTREXATE IN PATIENTS WITH ACTIVE RHEUMOTOID ARTHRITIS

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Abstract:
Rheumatoid arthritis (RA) is an inflammatory disease which, though systemic, typically involves the small joints of the hands and feet, often symmetrically. It affects approximately 1% of the population and is more common in women. The goal of the study is treat the subjects suffering from rheumatoid arthritis with GOLIMUMAB plus methotrexate DRUGS. TO evaluate the efficacy of the IP in subjects.To evaluate the safety and efficacy of the drug in subjects. To evaluate the pharmacoeconomic analysis in the clinical efficacy evaluable (CEE) and successfully treat patients. Patients were randomized (1:1) to receive subcutaneous placebo, golimumab 50 mg or golimumab 100 mg every 4 weeks. Randomization was stratified by investigational site and baseline MTX use (yes/no). Patients and investigators were masked to study treatment assignment; golimumab and placebo were supplied in identical single-use vials. Concomitant MTX use was permitted, but not required, if continued at a stable dose.The trial demonstrated clinically relevant improvement in disease activity and physical function after switching to golimumab, regardless of which TNF inhibitor had been taken previously. Of particular note, patients who switched from either etanercept or infliximab appeared to exhibit better subsequent responses to golimumab than those that were observed among patients who previously had received adalimumab which, of the three prior TNF inhibitors, is most structurally similar to golimumab. However, further study is required to confirm the current findings.

Keywords: Golimumab, Pharmacoeconomic, Subcutaneous

1. INTRODUCTION

Rheumatoid arthritis (RA) is a long-lasting autoimmune disorder that primarily affects joints. It typically results in warm, swollen, and painful joints. Pain and stiffness often worsen following rest. Most commonly, the wrist and hands are involved, with the same joints typically involved on both sides of the body. The disease may also affect other parts of the body. This may result in a low red blood cell count, inflammation around the lungs, and inflammation around the heart. Fever and low energy may also be present.[1] Often, symptoms come on gradually over weeks to months.[2]

While the cause of rheumatoid arthritis is not clear, it is believed to involve a combination of genetic and environmental factors. The underlying mechanism involves the

body's immune system attacking the joints. This results in inflammation and thickening of the joint capsule. It also affects the underlying bone and cartilage.[1] The diagnosis is made mostly on the basis of a person's signs and symptoms.[2] X-rays and laboratory testing may support a diagnosis or exclude other diseases with similar symptoms.[1] Other diseases that may present similarly include systemic lupus erythematosus,psoriatic arthritis, and fibromyalgia among others.[2]

The goal of treatment is to reduce pain, decrease inflammation, and improve a person's overall functioning. This may be helped by balancing rest and exercise, the use of splints and braces, or the use of assistive devices. Pain medications, steroids, and NSAIDs are frequently used to help with symptoms. A group of medications called disease-modifying antirheumatic drugs (DMARDs) may be used to try to slow the progression of disease. They include the medications hydroxychloroquine and methotrexate.[1] Biological DMARDs may be used when disease does not respond to other treatments.[3] However, they may have a greater rate of adverse effects.[4] Surgery to repair, replace, or fusionjoints may help in certain situations.[1] Most alternative medicine treatments are not supported by evidence.[5][6]

AIM AND OBJECTIVE:

Aim: 1. The goal of the study is treat the subjects suffering from rheumatoid arthritis with GOLIMUMAB plus methotrexate DRUGS.
2. TO evaluate the efficacy of the IP in subjects.

Objective:

- To evaluate the safety and efficacy of the drug in subjects.
- To evaluate the pharmacoeconomic analysis in the clinical efficacy evaluable (CEE) and successfully treat patients.

MATERIALS AND METHODS:

STUDY TYPE : ORAL.

STUDY SITE : Study will be conducted at PRIME HOSPITALS

SAMPLE SIZE : 137 Subjects

STUDY DURATION : study will be of 6 months.From Dec 2016 to May 2017.

WOMAC : Western Ontario and McMaster Universities Osteoarthritis Index (WOMAC)

To assess pain, stiffness, and physical function in patients with hip and / or knee osteoarthritis. The WOMAC consists of 24 items divided into 3 subscales:

- **Pain (5 items):** during walking, using stairs, in bed, sitting or lying, and standing
- **Stiffness (2 items):** after first waking and later in the day
- **Physical Function (17 items):** stair use, rising from sitting, standing, bending, walking, getting in / out of a car, shopping, putting on / taking off socks, rising from bed, lying in bed, getting in / out of bath, sitting, getting on / off toilet, heavy household duties, light household duties.

INCLUSION CRITIERIA:

- Subjects willing to provide informed consent
- Subjects of either sex of age group between ≥ 18 years and ≤ 65 years.
- Subjects must have at least > 4 score on the VAS scale for the inclusion in the study at the time of screening.
- Female subjects of child-bearing potential: subject is not pregnant

EXCLUSION CRITERIA:

- History of gastro esophageal reflux disease (GERD) diagnosed by a physician.
- Evidence of any medical condition that may interfere with the conduct of the study
- Subjects who require continuous use of histamine receptor (H2) blockers, or prokinetics.

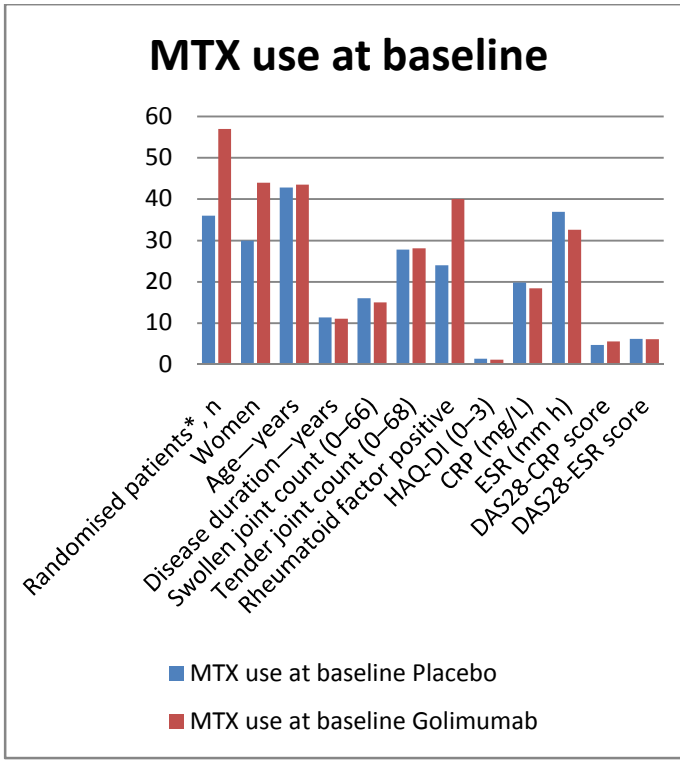
- History of hypersensitivity to non-steroidal ant-inflammatory drugs.
- History of abuse of analgesics.
- Evidence of peritoneal inflammation.
- In the GO-AFTER trial,137 patients were randomly assigned to receive placebo (n=49), golimumab 50 mg (n=44) or golimumab 100 mg (n=44) every 4 weeks.[20] Baseline characteristics for the MTX-treated subgroup of randomised patients (table 1) were generally consistent with those of the overall study population,[20] although fewer MTX-treated patients tested positive for rheumatoid factor at baseline than did patients with no MTX use at baseline.

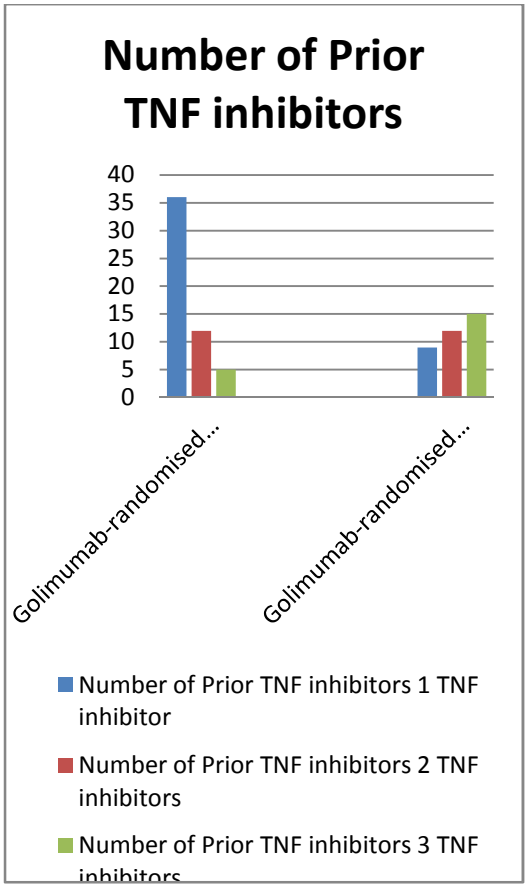
MTX use at baseline		**No MTX use at baseline**		
	Placebo	**Golimumab**	**Placebo**	**Golimumab**
Randomised patients*, n	**36**	**57**	**14**	**30**
Women	30 (83.2%)	44 (78.0%)	12 (89.6%)	22(74.3%)
Age—years	42.8±12.84	43.5±12.03	52.8±12.50	50.14±11.07
Disease duration—years	11.4±8.84	11.1±8.24	11.3±09.96	11.08±9.17
Swollen joint count (0–66)	16.08±10.90	15.0±11.02	17.6±11.37	16.8±11.12
Tender joint count (0–68)	27.8±17.09	28.1±17.20	29.3±15.50	30.4±16.85
Rheumatoid factor positive	24 (67.0%)	40 (69.5%)	12 (85.4%)	23 (77.6%)
HAQ-DI (0–3)	1.4±0.56	1.2±0.61	1.4±0.69	1.5±0.66
CRP (mg/L)	19.8±30.70	18.4±30.52	21.2±30.59	23.6±32.94
ESR (mm h)	36.9±23.94	32.6±27.10	36.3±26.26	38.4±27.97
DAS28-CRP score	4.7±1.02	5.6±1.14	5.6±1.16	5.0±1.05
DAS28-ESR score	6.2±1.10	6.1±1.14	6.0±1.27	6.4±1.14

Table – 1 Summary of baseline characteristics* in randomised patients and previous TNF inhibitor use† among patients receiving MTX at baseline

	Number of Prior TNF inhibitors		
	1 TNF inhibitor	**2 TNF inhibitors**	**3 TNF inhibitors**
Golimumab-randomised MTX-treated patients†, n	**36**	**12**	**5**
	Prior TNF inhibitor		
	Adalimumab only	**Etanercept only**	**Infliximab only**
Golimumab-randomised patients who received only one prior TNF inhibitor†, n	**9**	**12**	**15**
Reason for discontinuation of prior TNF inhibitor			
Lack of efficacy	6 (66.7%)	6 (48.9%)	5 (38.6%)
Intolerance	1 (15.2%)	1 (4.3%)	2 (14.0%)
'Other' reason ‡	2 (18.2%)	5 (46.8%)	8(47.4%)
Distribution by duration of prior treatment, n			
<4 weeks	2	5	2
≥4 to <12 weeks	8	12	4
≥12 to <24 weeks	7	3	4
≥24 to <36 weeks	5	5	3
≥36 to <48 weeks	1	2	8
≥48 weeks	10	20	36
% patients receiving therapy for ≥24 weeks	48.50%	57.40%	82.50%

Table – 2Summary of baseline characteristics* in randomised patients and previous TNF inhibitor use† among patients receiving MTX at baseline


MTX use at baseline
60
50
40
30
20
10
0
Randomised patients*, n
Women
Age—years
Disease duration—years
Swollen joint count (0–66)
Tender joint count (0–68)
Rheumatoid factor positive
HAQ-DI (0–3)
CRP (mg/L)
ESR (mm h)
DAS28-CRP score
DAS28-ESR score
MTX use at baseline Placebo
MTX use at baseline Golimumab


Number of Prior TNF inhibitors
40
35
30
25
20
15
10
5
0
Golimumab-randomised...
Golimumab-randomised...
Number of Prior TNF inhibitors 1 TNF inhibitor
Number of Prior TNF inhibitors 2 TNF inhibitors
Number of Prior TNF inhibitors 3 TNF inhibitors

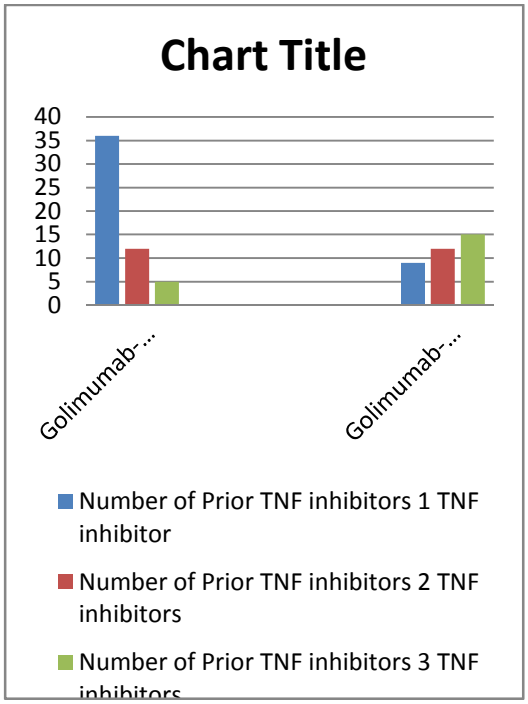
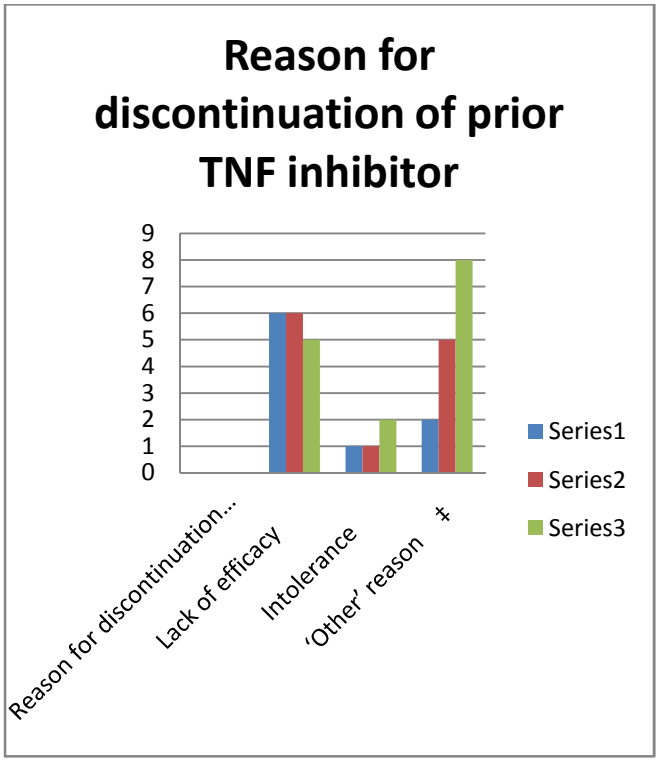


Chart Title
40
35
30
25
20
15
10
5
0
Golimumab-...
Golimumab-...
Number of Prior TNF inhibitors 1 TNF inhibitor
Number of Prior TNF inhibitors 2 TNF inhibitors
Number of Prior TNF inhibitors 3 TNF inhibitors

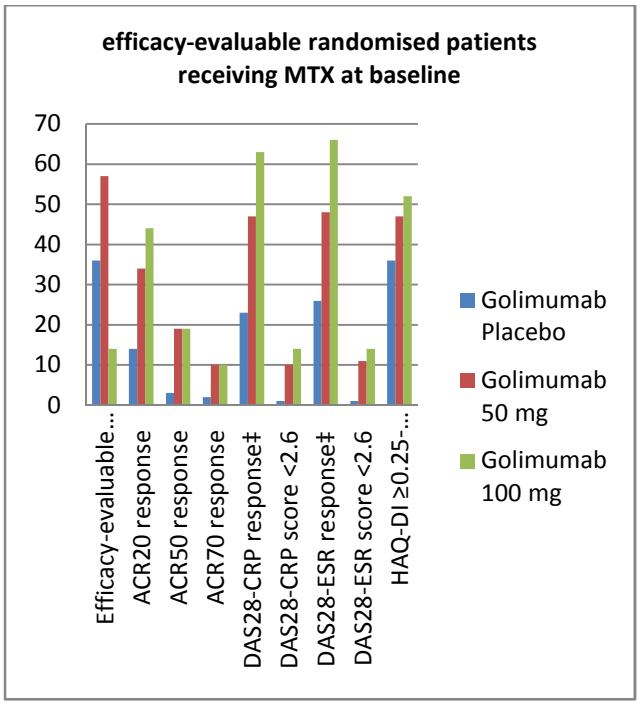

Reason for discontinuation of prior TNF inhibitor
9
8
7
6
5
4
3
2
1
0
Reason for discontinuation...
Lack of efficacy
Intolerance
'Other' reason
Series1
Series2
Series3

With the exception of shorter disease duration (8.1vs 11.6 years, respectively; p=0.023) and more women patients (90.9% vs 70.2%), respectively; p=0.023) among adalimumab-only versus infliximab-only-treated patients, no consistent baseline differences were observed across prior TNF inhibitors (data not shown).

Without the 7 patients treated at the excluded site, 130randomised patients were available for efficacy analyses, 89 of whom were also receiving MTX at baseline. Fifty nine of them were randomised to golimumab and were also receiving MTX (table 2); much smaller proportions of patients were receiving sulfasalazine (4.9%) and/or hydrochloroquine (7.4%) in addition to MTX. Among the efficacy-evaluable golimumab-randomised patients who were also receiving MTX, 36 had previously received only one TNF inhibitor (adalimumab, n=9; etanercept, n=12; and infliximab, n=15). For each prior TNF inhibitor, the proportion of patients who discontinued that agent because of lack of efficacy was 2.5-fold to 11-fold greater than those who discontinued because of intolerance (table 1). Overall, most patients received prior anti-TNF therapy for ≥24 weeks

	Golimumab			
	Placebo	**50 mg**	**100 mg**	**Combined**
Efficacy-evaluable randomised patients receiving study agent+MTX, n	36	57	14	71
ACR20 response	14 (15.6%)	34 (35.6%)	44 (46.0%)	80 (41.8%)
ACR50 response	3 (3.8%)	19 (19.8%)	19 (22.0%)	41 (19.9%)
ACR70 response	2 (2.7%)	10 (11.9%)	10 (11.0%)	21 (10.4%)
DAS28-CRP response‡	23 (23.3%)	47 (48.5%)	63 (65.0%)	112 (56.7%)
DAS28-CRP score <**2.6**	1 (1.9%)	10(11.9%)	14 (14.0%)	26 (12.9%)
DAS28-ESR response‡	26 (26.2%)	48 (48.5%)	66 (67.0%)	114 (57.7%)
DAS28-ESR score <**2.6**	1 (1.0%)	11 (10.9%)	14(16.0%)	26 (13.4%)
HAQ-DI ≥0.25-unit improvement	36 (34.0%)	47 (47.5%)	52(54.0%)	101 (50.7%

Table 3 Summary of clinical efficacy at week 24* among efficacy-evaluable randomised patients receiving MTX at baseline



Clinical improvement

All golimumab-randomised patients who were receiving MTX at baseline

Among patients with active RA who were previously treated with a TNF inhibitor, 41.8% of

golimumab+MTX-treated patients and 15.6% of placebo+MTX-treated patients achieved an ACR20 response at week 24. The ACR50 and ACR70 response rates were also higher among patients who received golimumab+MTX (19.9% and 10.4%, respectively) than among those who received placebo+MTX (3.8% and 2.7%, respectively). Similar patterns of improvement were observed when disease activity was assessed using the DAS28-CRP or the DAS28-ESR and also when using achievement of a ≥0.25-unit reduction in the HAQ-DI score to assess improvement in physical function (table 2).

All golimumab-randomised patients who were receiving MTX at baseline and who had discontinued only one prior TNF inhibitor

Among efficacy-evaluable, golimumab-randomised patients receiving MTX at baseline, 36 had previously received only one prior TNF inhibitor (adalimumab, n= 9; etanercept, n=12; infliximab, n=15). The proportion of patients who achieved an ACR20 response at week 24 was 30.3% among those who previously had been treated only with adalimumab, 46.8% among those who previously had been treated only with etanercept and 50.9% among those who previously had been treated only with infliximab. A similar pattern of clinical response was observed when ACR50 response criteria were appliedAlso at week 24, the proportions of patients achieving DAS28-CRP response (good/moderate) and DAS28-CRP <2.6 were 39.4% and 15.2%, respectively, among those who previously had been treated only with adalimumab, 61.7% and 14.9%, respectively, among those who previously had been treated only with etanercept and 66.7% and 17.5%, respectively, among those who previously had been treated only with infliximab. Similar patterns were observed for DAS28-ESR response (good/moderate) and DAS28-ESR<2.6 (figure 1). Improvement in physical function, as assessed by achievement of a ≥0.25-unit reduction in the HAQ-DI score from baseline to week 24, was fairly consistent across the three TNF inhibitors used previously and was achieved by 48.5%, 53.2% and 56.1% of patients who had received only adalimumab, etanercept or infliximab, respectively

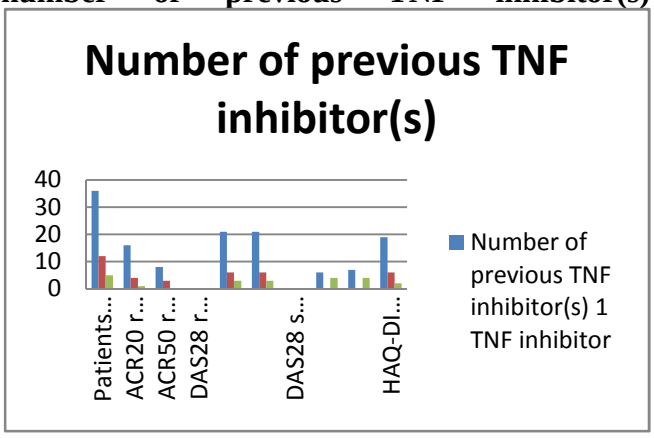
Among patients who discontinued prior TNF inhibitor treatment because of lack of efficacy, ACR20 response rates at week 24 were 36.4% for those who previously had been treated only with adalimumab, 56.5% for those who previously had been treated only with etanercept and 45.5% for those who previously had been treated only with infliximab. Among patients who discontinued previous TNF inhibitor treatment because of intolerance, ACR20 response rates at week 24 were 20.0%, 50.0% and 62.5% for adalimumab, etanercept and infliximab, respectively, but sample sizes were small. Similarly, among those who discontinued previous TNF inhibitor treatment for 'other' reasons, respective ACR20 response rates at week 24 were 16.7%, 36.4% and 51.9% for adalimumab,etanercept and infliximab, respectively (figure 1).

In table 3, clinical responses at week 24 are compared by the number of TNF inhibitors that patients had received prior to study entry. By most measures, improvement in clinical signs and symptoms and in physical function appeared to be more robust among patients who previously had received fewer TNF inhibitors. However, the numbers of patients who had received two (n=12) and three (n=5 prior TNF inhibitors were limited.

Number of previous TNF inhibitor(s)			
	1 TNF inhibitor	**2 TNF inhibitors**	**3 TNF inhibitors**
Patients who discontinued one or more previous TNF-inhibitor for any reason, n	**36**	**12**	**5**
ACR20 response	16 (44.5%)	4 (36.2%)	1(23.5%)
ACR50 response	8 (21.9%)	3 (23.4%)	0 (5.9%)
DAS28 response **(good/moderate)**			
DAS28-CRP	21 (58.4%)	6 (51.1%)	3(58.8%)
DAS28-ESR	21 (59.9%)	6 (51.1%)	3(58.8%)
DAS28 score **<2.6**			

DAS28-CRP	6 (16.1%)	0 (6.4%)	4 (5.9%)
DAS28-ESR	7 (16.8%)	0 (6.4%)	4 (5.9%)
HAQ-DI ≥0.25-unit improvement	19 (53.3%)	6 (46.8%)	2 (41.2%)

Table **4Clinical response at week 24* among golimumab+ MTX-treated patients †by number of previous TNF inhibitor(s)**



Adverse events

Safety findings for all patients enrolled in the GO-AFTER study have been reported through week 24[20] and also through up to 3 years of golimumab therapy.[30] AEs were reported by 62.3% of all MTX-treated patients. Among these, 72.5% of patients who had been intolerant of prior therapy and 56.2% of those who had an inadequate response to treatment with the prior TNF inhibitor(s) reported AEs. The overall proportions of patients developing AEs were similar among those treated with either golimumab or placebo, when grouped by number of prior TNF inhibitors received, specific prior TNF inhibitor received or reason for discontinuation of that previous agent. The incidences of serious AEs and serious infections appeared to be comparable across the subgroups of patients evaluated, with the exception of a higher incidence of serious AEs among patients who had received three (18.8%) prior TNF inhibitors, compared with those who previously had received one (2.5%) or two (3.8%) TNF inhibitors. However, interpretation of these findings is limited by the small numbers of patients who experienced serious AEs or serious infections.

Although data derived from several small case series, open-label studies and registries have suggested that patients with RA switched from one to another TNF inhibitor because of lack of efficacy or intolerance may respond to the second or even third agent,[4–9] such response patterns have not previously been examined in a randomised, controlled study. Using data from the GO-AFTER trial,[20] we evaluated the efficacy and safety of golimumab when switching from another TNF inhibitor among more than 200 patients with active RA who previously received adalimumab, etanercept and/or infliximab and reported MTX use at baseline. Our post-hoc data analyses indicate that among patients taking MTX at baseline, the response rates at week 24 are somewhat higher than those reported previously for all patients at the primary endpoint of week 14.[20] This is consistent with the generally accepted principle that concomitant use of MTX with a TNF inhibitor results in better clinical and functional outcomes.[31–33] Moreover, patients who switch from adalimumab, etanercept or infliximab to golimumab demonstrate clinically relevant responses at week 24, regardless of whether the prior TNF inhibitor was a monoclonal antibody or a soluble receptor fusion protein.

Of note and consistent with results of a comparative meta-analysis,[23]although it is difficult to compare outcomes across clinical trials due to differences in trial design, week 24 ACR response rates among patients who had discontinued prior anti-TNF therapy and received golimumab+MTX in GO-AFTER are comparable to those observed at the same week 24 time point for other biological agents with different mechanisms of action in combination with MTX. For example, week 24 ACR50 response rates for study agent versus placebo, both with concomitant disease-modifying antirheumatic drugs, were 27% and 5% for rituximab[16]; 29% (8 mg/kg), 17% (4 mg/kg) and 4% for tocilizumab[34]; and 20% and 4% for abatacept.[18]

The most straightforward approach to assess effects of switching agents is to analyse data derived from patients previously treated with only one prior TNF inhibitor. Despite our previously

reported observations of clinically relevant responses to golimumab in the overall trial population,[20] patients previously exposed to more than two TNF inhibitors appear to be less likely to demonstrate marked improvement in clinical and functional outcomes. ACR50 response rates were similar among patients who had been treated with one or two prior TNF inhibitors, but were much lower when golimumab was initiated as the fourth TNF inhibitor. Although these findings suggest that such patients might respond better to a biological agent with a different mechanism of action, it should be considered that the rates of response to each of rituximab and abatacept also decrease with previous exposure to increasing numbers of TNF inhibitors.[3536] Future studies employing biomarkers may help to predict which patients are more likely to respond to the different agents, following initial exposure to a TNF inhibitor.

Because patients were not stratified by prior TNF inhibitor use when randomised to treatment arms, the size of some of the subgroups that were evaluated was small, and our subgroup analyses were performed post-hoc, no formal statistical testing was performed. Despite these limitations, the data reveal numerical trends. For example, ACR20 response rates at week 24 for patients treated with golimumab 50 or 100 mg and MTX were numerically higher among those who switched from etanercept (46.8%) or infliximab (50.9%) compared with those who had previously received adalimumab (30.3%), the agent most similar in structure to golimumab.[37]Conversely, the proportion of patients who were previously treated with adalimumab for more than 24 weeks was much lower than that of patients who had previously received treatment with etanercept or infliximab for more than 24 weeks, which could have been due to a larger number of patients with refractory disease among those receiving adalimumab treatment. It is possible that patients previously treated with agents structurally more dissimilar to golimumab developed antibodies to the prior TNF inhibitor that precluded continued response to the previous agent[38]; these antibodies might have been less likely to cross-react with the human golimumab molecule, allowing a better subsequent response to golimumab. The presence of antibodies to prior TNF inhibitor(s) was not assessed in GO-AFTER. However, future studies of switching among TNF inhibitors should include such assessments to better characterise the mechanisms underlying differential responses to subsequent treatment.

Conclusion:

The trial demonstrated clinically relevant improvement in disease activity and physical function after switching to golimumab, regardless of which TNF inhibitor had been taken previously. Of particular note, patients who switched from either etanercept or infliximab appeared to exhibit better subsequent responses to golimumab than those that were observed among patients who previously had received adalimumab which, of the three prior TNF inhibitors, is most structurally similar to golimumab. However, further study is required to confirm the current findings.

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