

## Golimumab: In Combination with Methotrexate as Once Monthly Treatment for Moderate to Severe Rheumatoid Arthritis

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**Abstract:** Golimumab is the fifth tumor necrosis factor (TNF) alpha inhibitor approved by the Food and Drug Administration for the treatment of rheumatoid arthritis. It is a fully humanized monoclonal antibody which exhibits high affinity for both transmembrane bound and soluble TNF. Based on data from the clinical trials, golimumab is only approved to be used in combination with methotrexate since golimumab monotherapy was not more efficacious than methotrexate monotherapy. Efficacy has been established in three patient populations: methotrexate naïve; methotrexate tolerant; and prior TNF alpha discontinuation. In all patient populations golimumab 50 mg subcutaneous injection every four weeks resulted in an improved patient response. The most common adverse effects are injection site reactions, nausea and liver enzyme increases. Golimumab also has two black box warnings for increased risk of infection and malignancy. Based on the limited indication and lack of long term data, golimumab should be reserved for patients who have failed other TNF alpha inhibitors.

**Keywords:** golimumab, TNF alpha inhibitor, rheumatoid arthritis

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## Introduction

Rheumatoid arthritis (RA) is a chronic autoimmune disorder characterized by joint inflammation and destruction and affects between 0.5 and 1% of the adult population in developing countries.<sup>1,2</sup> The goal of treatment is to prevent joint destruction and disability, and this can be accomplished by initiating disease modifying antirheumatic drugs (DMARDs) as early in the disease process as possible. DMARDs can be classified as nonbiologic (methotrexate, hydroxychloroquine, sulfasalazine, leflunomide) or biologic. Biologic DMARDs can target a variety of pathways including interleukin (IL)-6 inhibition (tocilizumab), IL-1 inhibition (anakinra), T-cell costimulation inhibition (abatacept) and tumor necrosis factor (TNF) alpha inhibition (adalimumab, etanercept, infliximab, certolizumab pegol, and golimumab).

Although the exact cause of RA is unknown, TNF alpha is known to be a key mediator involved in the disease progression. Multiple cells produce TNF alpha including monocytes and macrophages. After being secreted, TNF alpha is transmembrane bound and must be cleaved by TNF-alpha-converting enzyme in order to become soluble. Both the transmembrane bound and soluble forms are active. Upon binding to its receptor, TNF alpha exerts a variety of effects with the predominant effect being stimulation of other proinflammatory cytokines and prostaglandins. This inflammatory response can result in synovial membrane lining inflammation and joint and bone destruction. Therefore, blocking the effects of TNF alpha results in a profound anti-inflammatory effect and decreases the destruction involved in RA.<sup>1,3</sup>

Prior to April 2009, the Food and Drug Administration (FDA) had approved four TNF alpha inhibitors for the treatment of RA. Two of these, infliximab and adalimumab, are specific monoclonal antibodies against TNF alpha with the main difference being that infliximab is chimeric whereas adalimumab is fully humanized. Etanercept is a protein composed of two TNF receptors bound to the Fc portion of a humanized antibody. Certolizumab pegol consists of a Fab' antibody fragment that is pegylated to extend its duration of action. Although differences exist in the agents, the end result is similar in that they all decrease the concentration of TNF alpha resulting in decreased inflammation and disease progression.<sup>3,4</sup>

In April 2009, golimumab was the fifth TNF alpha inhibitor approved by the FDA. Golimumab is indicated to treat adults for moderately to severely active RA in combination with methotrexate, active psoriatic arthritis as monotherapy or in combination with methotrexate and active ankylosing spondylitis.<sup>5</sup> The objective of this article is to review the role of golimumab with methotrexate for the treatment of RA including updating the reader regarding the pharmacology, pharmacokinetics, clinical trials, safety and place in therapy of golimumab.

## Pharmacology

Golimumab shares characteristics with both adalimumab and infliximab. Similar to adalimumab, golimumab is a humanized IgG monoclonal antibody specific for both soluble and transmembrane TNF alpha. Golimumab's amino acid sequence for the heavy and light chain constant regions is identical to infliximab's but golimumab is humanized and infliximab is chimeric.<sup>6</sup> Golimumab has a molecular weight of 150 kDas which is the same as for infliximab, adalimumab and etanercept and higher than the weight of certolizumab pegol (95 kDas).<sup>3</sup>

In order to produce humanized TNF alpha monoclonal antibodies, mice's antibody encoding genes were inactivated and replaced with human encoding genes. These mice were then inoculated with human TNF alpha and produced 100% humanized antibodies. Researchers then created hybridoma cells by fusing the B-cells to multiplier cells and isolated the most potent antibody producing cell line. This technique allows for a humanized monoclonal antibody which decreases the risks of anaphylaxis and injection reactions.<sup>7</sup>

Another important factor to consider is the affinity of golimumab for TNF alpha. The dissociation equilibrium constant ( $K_D$ ) of golimumab for soluble TNF (sTNF) alpha is 18 pM. This is statistically similar to the affinity of infliximab (44 pM) and etanercept (11 pM). However, golimumab has a higher affinity compared to adalimumab (127 pM) for sTNF alpha. When assessing the affinity for the transmembrane bound TNF (tmTNF) alpha, golimumab (1890 pM) was similar to adalimumab (2640 pM) and infliximab (1620 pM), but all three had higher affinity for tmTNF alpha compared to etanercept (15500 pM).<sup>7</sup> The affinity



to tmTNF alpha may contribute to the higher tuberculosis risk observed with adalimumab and infliximab compared to etanercept.<sup>8</sup> Based on golimumab's affinity for tmTNF alpha, it would not be expected to confer a greater tuberculosis risk than that observed with adalimumab and infliximab. However, since golimumab exerts higher affinity for sTNF alpha it can be dosed less frequently than adalimumab and etanercept.

In addition to affinity the inhibitory concentration must also be considered. The half maximal inhibitory concentration (IC50) value for golimumab (6.5 ng/mL) was significantly lower than the IC50 value for infliximab (24.2 ng/mL) and adalimumab (36.4 ng/mL) but was higher than the IC50 value for etanercept (0.8 ng/mL). This indicates that golimumab's doses can be lower than infliximab and adalimumab with similar inhibition.<sup>7</sup> By using lower doses less frequently, patients will have less overall exposure to medication which would theoretically decrease the risk for adverse effects. Overall, these results showed that golimumab has a high affinity and potency for neutralizing TNF alpha.

A subgroup analysis of a phase II clinical trial was done to determine the effect of golimumab on biomarkers for RA disease activity. All patients had to be on a stable dose of methotrexate at baseline and this was continued throughout the study. Patients were then randomized to one of five golimumab treatment arms: placebo; golimumab 50 mg subcutaneously (subQ) every 2 weeks; golimumab 50 mg subQ every 4 weeks; golimumab 100 mg subQ every 2 weeks; golimumab 100 mg subQ every 4 weeks. The biomarkers examined were markers of inflammation (IL-18 and E-selectin), acute phase reactants [C-reactive protein (CRP) and serum amyloid A (SAA)] and collagen breakdown [matrix metalloproteinase (MMP) 9 and tissue inhibitor of matrix metalloproteinase 1 (TIMP-1)]. After four weeks, all doses of golimumab significantly decreased the concentrations of SAA, E-selectin and CRP but only the dose of 50 mg subQ every 2 weeks decreased MMP-9, TIMP-1 and IL-18. When reassessed after 16 weeks, the only concentrations that were decreased from baseline were E-selectin, CRP and SAA for all golimumab doses.<sup>9</sup>

## Pharmacokinetics

Golimumab is indicated as a subQ injection and reaches maximum serum concentrations between two and

four days. However, it takes about 12 weeks to reach steady state when golimumab is given every 4 weeks. When golimumab is taken with methotrexate for RA, the mean steady state trough concentration is 52% higher than golimumab monotherapy. The median terminal half-life is approximately 2 weeks and there are no dose adjustments needed based on renal or hepatic function.<sup>5</sup>

The systemic clearance rate and volume of distribution for golimumab were determined from the intravenous formulation of golimumab which is not currently approved or available. The mean systemic clearance was 4.9 to 6.7 mL/day/kg and the mean volume of distribution was 58 to 126 mL/kg. This volume of distribution indicates that golimumab is hydrophilic and has limited extravascular distribution. Although patients with higher body weight may clear golimumab quicker, there is not data to support adjusting a dose based on a patient's weight.<sup>5</sup>

## Dosage and Administration

The FDA approved dosage of golimumab for the treatment of RA is 50 mg subQ every four weeks in combination with methotrexate. Golimumab must be stored in the refrigerator and be allowed to warm to room temperature (approximately 30 minutes) prior to injection. Golimumab is available as the brand name Simponi® (Centocor Ortho Biotech Inc.) and is available as a prefilled syringe or autoinjector with a concentration of 50 mg per 0.5 mL solution.<sup>5</sup>

## Phase III Clinical Trials

Three phase III clinical trials assessed the use of golimumab with methotrexate for the treatment of RA in different patient populations: methotrexate naive (GO-BEFORE: GOLimumab Before Employing methotrexate as the First-line Option in the treatment of Rheumatoid arthritis); methotrexate resistant (GO-FORWARD: GOLimumab FOR subjects With Active Rheumatoid arthritis Despite methotrexate); prior TNF alpha inhibitor therapy (GO-AFTER: GOLimumab After Former anti-TNF alpha Therapy Evaluated in Rheumatoid arthritis).<sup>10-12</sup> Detailed 24 week efficacy data is presented in Table 1.

The primary endpoint for each of the trials included patients' American College of Rheumatology (ACR) 20 or 50 response. The ACR20 response is a 20%

**Table 1.** 24 week efficacy data from phase III clinical trials.

Trial	Patient population	Treatment group	ACR20 (%)	ACR50 (%)	ACR70 (%)
GO-BEFORE <sup>10</sup>	MTX naïve patients 83% females, mean age 50 years old, 66% had disease duration ≤1 year	Placebo + MTX	49.4	29.4	15.6
		G 100 mg + placebo	51.6	32.7	13.8
		G 50 mg + MTX	61.6 <sup>a</sup>	40.3 <sup>a</sup>	23.9
		G 100 mg + MTX	61.6 <sup>a</sup>	36.5	18.2
GO-FORWARD <sup>11</sup>	MTX treated patients 81% females, mean age 51 years old, median MTX dose 15 mg/week, 47% on MTX for ≥3 years	Placebo + MTX	27.8	13.5	5.3
		G 100 mg + placebo	35.3	19.5	11.3
		G 50 mg + MTX	59.6 <sup>a</sup>	37.1 <sup>a</sup>	20.2 <sup>a</sup>
		G 100 mg + MTX	59.6 <sup>a</sup>	32.6 <sup>a</sup>	14.6 <sup>a</sup>
GO-AFTER <sup>12</sup>	Previous TNF alpha inhibitor treatment 80% females, mean age 55 years old, 66% on concurrent MTX	Placebo	17	5	3
		G 50 mg	34 <sup>b</sup>	18 <sup>b</sup>	12 <sup>b</sup>
		G 100 mg	44 <sup>b</sup>	20 <sup>b</sup>	10 <sup>b</sup>

**Notes:** <sup>a</sup> $P < 0.05$  compared to placebo + MTX group; <sup>b</sup> $P < 0.05$  compared to placebo group.

**Abbreviations:** G, golimumab; MTX, methotrexate.

improvement in number of tender and swollen joints and a 20% improvement in three of the five following measures: patient and physician global assessments; pain; disability; and acute phase reactant. The ACR50 is a 50% improvement in the above criteria, and the ACR70 is a 70% improvement.<sup>13</sup>

In the multicenter, randomized, double-blind, placebo controlled GO-BEFORE trial, 637 patients were randomized to one of the four treatment groups: placebo with methotrexate (group 1); golimumab 100 mg with placebo (group 2); golimumab 50 mg with methotrexate (group 3); and golimumab 100 mg with methotrexate (group 4).<sup>10</sup> Regardless of dose, golimumab was given as a subcutaneous injection every four weeks and methotrexate was given as an oral weekly treatment. Patients included in this study were classified as methotrexate naïve, having received less than 3 weeks of oral methotrexate, and as having active disease for at least 3 months.

The mean age of the patients included was 49.5 years old with the majority of patients being white females. Overall, the study population was considered to have early disease, with a median duration of 1.2, 1.8, 1.0, and 1.3 years for patients in group 1, group 2, group 3 and group 4 respectively and over 50% of patients in each group were previously treated with a non-biologic DMARD. A difference in the ACR50 response at week 24, the co-primary endpoint of the study, was not evident for group 1 compared to the combined groups 3 and 4 (29.4% vs. 38.4%, respectively;  $P = 0.053$ ). However, a difference in the ACR50 response was noted for group 1

compared to group 3 (29.4% vs. 40.3%, respectively;  $P = 0.042$ ). A difference in ACR20 at week 24 was observed for group 1 vs. group 3 ( $P = 0.028$ ) and for group 1 vs. group 4 ( $P = 0.028$ ), suggesting that adding golimumab to methotrexate does have some positive effect. This difference was seen as early as week 4 of treatment. No significant differences were found when comparing group 2 to group 1 for any of the endpoints.<sup>10</sup>

The authors concluded that the combination of golimumab with methotrexate was more effective than methotrexate monotherapy. However, golimumab monotherapy was not more effective than methotrexate monotherapy in this group of patients. When comparing the different dosing regimens, golimumab 50 mg every four weeks appears to be the most effective dose. Overall, this trial showed that golimumab can safely and effectively be initiated with methotrexate in patients with RA who are methotrexate naïve.<sup>10</sup>

The GO-FORWARD study was a 52 week multicenter, randomized, double-blind, placebo controlled trial that compared the same four regimens as the GO-BEFORE study.<sup>11,14</sup> Patients included in this study were on a stable dose of methotrexate of 15 mg to 25 mg per week for 4 weeks prior to screening and had been on at least 15 mg of methotrexate per week for the previous 3 months. Similar to GO-BEFORE, patients had to have RA for at least three months and have active RA at time of enrolment. Patients were excluded if they had received any prior TNF alpha therapy at any time or DMARD therapy other than



methotrexate within the four weeks before enrolment. After 16 weeks of therapy, medications for groups 1, 2 and 3 could be adjusted in a double-blinded manner if they had not achieved a 20% improvement in both tender and swollen joints. After 24 weeks of therapy, patients in group 1 who did not adjust their therapy at week 16 were started on golimumab 50 mg every 4 weeks with methotrexate for the remainder of the study.

Baseline demographics for GO-FORWARD were similar to GO-BEFORE in terms of age, sex and race. The median duration of disease for groups 1–4 was 6.5, 5.9, 4.5 and 6.7 years respectively and 46.6% had been on methotrexate for 3 years or more. The co-primary endpoints of this study were ACR20 response at week 14 and change in health assessment questionnaire—disability index (HAQ-DI) score at week 24. In the combined groups 3 and 4 versus group 1, more patients achieved an ACR20 response at week 14 (55.6% vs. 33.1%, respectively;  $P < 0.001$ ) and had an improvement from baseline in HAQ-DI score at week 24 ( $-0.44$  vs.  $-0.13$ , respectively;  $P < 0.001$ ). When group 3 and group 4 were analyzed independently compared to group 1, both comparisons were statistically significant for both ACR20 response and change in HAQ-DI score. No differences were observed between group 1 and group 2 for any of the endpoints up to week 24.<sup>11</sup> At week 52, 43.6% of group 1 patients, 45.1% of group 2 patients, 64.0% of group 3 patients and 58.4% of group 4 patients achieved an ACR20 response (no  $P$ -values reported). Of the patients who achieved a response at week 24, over 60% maintained that response through week 52.<sup>14</sup>

The authors concluded that the combination of golimumab and methotrexate was superior to methotrexate alone. In addition, the response to therapy was maintained for one year. Lastly, there was not a significant difference between the 50 mg and 100 mg golimumab doses. This has been the longest clinical trial assessing golimumab for RA treatment and proves that adding golimumab to patients failing methotrexate may result in an appropriate response.<sup>11,14</sup>

The GO-AFTER study was a multicenter, randomized, double-blind, placebo-controlled trial that assessed the use of golimumab in patients who had previously received TNF alpha inhibitor therapy.<sup>12</sup> Patients had to have been diagnosed with active RA

at least 3 months before enrolment and their last dose of TNF alpha therapy had to have been at least 8–12 weeks prior to enrolment depending on agent. Patients could have discontinued TNF alpha therapy for any reason but if they had to stop due to serious adverse reactions then they were excluded. Patients included in this study were permitted to concomitantly take a DMARD, including methotrexate as long as they had been on a stable dose for at least 4 weeks; however, this was not a requirement for inclusion. Patients were randomized to three treatment groups: placebo (group 1); golimumab 50 mg (group 2); or golimumab 100 mg (group 3). Each therapy was given as a subcutaneous injection every four weeks. Similar to the GO-FORWARD trial, doses for the placebo and golimumab 50 mg groups could be adjusted after 16 weeks if the patient did not have at least a 20% improvement in tender and swollen joints.

Of the 461 patients enrolled, the majority were females who were in their fifties. The median duration of disease was 9.8 (group 1), 9.6 (group 2) and 8.7 (group 3) years. Approximately one quarter of enrolled patients had been on two TNF alpha inhibitors prior to enrolment and more than 95% of patients had been on a TNF alpha inhibitor for at least four weeks before discontinuing. Fifty eight percent of patients had discontinued previous TNF alpha inhibitor therapy due to lack of effectiveness. Methotrexate was used by 66%, 67%, and 66% of patients in groups 1, 2 and 3 respectively. For the primary endpoint of ACR20 response at week 14, the combined groups 2 and 3 had a greater percentage of response compared to group 1 (37% vs. 18%, respectively;  $P < 0.001$ ). Differences between the combined golimumab groups and the placebo group in ACR50 (18% vs. 6%, respectively;  $P = 0.0005$ ) and ACR70 (10% vs. 2%, respectively;  $P = 0.0017$ ) were also observed at week 14. At week 24, more patients in the combined groups 2 and 3 versus group 1 achieved an ACR20 ( $P < 0.0001$ ), ACR50 ( $P < 0.0001$ ) and ACR70 ( $P = 0.037$ ) response. A subgroup analysis showed that the primary endpoint was significant among patients with DMARD use at baseline ( $P < 0.0001$ ), but was not among patients with no DMARD use at baseline ( $P = 0.1836$ ).<sup>12</sup>

Based on data from this trial, the authors concluded that switching from another TNF alpha inhibitor to



golimumab is effective and well tolerated. In addition, if patients have discontinued a TNF alpha inhibitor due to lack of effectiveness, golimumab with methotrexate may be an effective option.<sup>12</sup>

Two of these trials, GO-BEFORE and GO-FORWARD, also examined the effect of golimumab on radiographic progression of disease.<sup>15</sup> In both analyses, the Sharp score as modified by van der Heijde was used to assess joint erosion and joint space narrowing in the hands, wrists and feet. The range of scores was 0 to 448 which larger scores indicating higher degree of erosion and narrowing. For patients in both trials who entered the early escape or who crossed over from placebo plus MTX to placebo plus golimumab (group 1 of GO-BEFORE), their scores were imputed based on linear extrapolation from the prior scores on the original treatment.

The change in radiographic score at week 52 was one of the co-primary endpoints for the GO-BEFORE trial. When compared to group 1 (1.37), group 3 (0.74,  $P=0.015$ ) and group 4 (0.07,  $P=0.025$ ) had less radiographic progression at week 52. For scores at week 28, the combined group 3 and 4 (0.36,  $P=0.005$ ) and group 4 (0.01,  $P=0.003$ ) had less progression than the group 1 (1.11), but group 3 (0.71,  $P=0.065$ ) was not statistically different. Group 2 did not demonstrate less radiographic progression at either time point. When a subgroup analysis was performed on patients who had disease for greater than 3 years, similar results were seen.<sup>15</sup>

Radiographic progression for the GO-FORWARD trial was a secondary endpoint assessed at week 24 and 52. At both time points, no differences were

observed between any of the four groups. One reason for no observed difference may be due to lack of power for this endpoint and the need for more patients in future trials.<sup>15</sup>

Although radiographic differences were noted in the GO-BEFORE trial in patients on golimumab plus methotrexate, these changes were small in terms of the range of the possible scores (0–448). Based on these small changes, it is hard to determine the clinical relevance. A mean change of less than one is not clinically significant especially when one considers the mean baseline score was less than 20. More information regarding the radiographic progression changes need to be determined.<sup>15</sup>

## Adverse Effects

Overall, golimumab is well tolerated with few serious adverse effects. Adverse effects data from the three phase III clinical trials is summarized in Table 2. The most common adverse effects based on data from the package insert and clinical trials are injection site reactions (6%), alanine aminotransferase increases (4%), and aspartate aminotransferase increases (3%). The most common injection site reaction is erythema and the majority of these reactions are classified as mild.<sup>5</sup>

Golimumab has two black box warnings associated with it that are the same for all of the TNF alpha inhibitors. The first is the risk of serious infections which include tuberculosis, fungal infections and opportunistic infections.<sup>5</sup> Upon combining the 24 week adverse effect data for GO-BEFORE and GO-FORWARD, the rate of any infection for group

**Table 2.** Summary of adverse effects reported in phase III clinical trials.

	Placebo + MTX <sup>10,14</sup>	G 100 mg + placebo <sup>10,14</sup>	G 50 mg + MTX <sup>10,14</sup>	G 100 mg + MTX <sup>10,14</sup>	G 50 ± DMARD <sup>12</sup>	G 100 ± DMARD <sup>12</sup>
N	293	290	370	301	152	152
Any adverse effect	73.0	74.1	80.0	80.7	66.4	78.3
Serious adverse effect	17.0	21.0	27.0	36.0	7.2	4.6
Any infection	32.1	42.8	41.1	41.5	34.9	36.2
Serious infection	1.4	2.4	1.6	5.6	3.3	0.7
Injection site reaction	2.4	11.4	4.6	9.0	5.9	10.5
Malignancies	1.4	0.7	1.1	1.3	0.7	0.7

**Notes:** Adverse events presented as percentages.

**Abbreviations:** G, golimumab; MTX, methotrexate.



1, 2, 3 and 4 was 30.3%, 36.2%, 23.8%, and 33.7% respectively and the rate for serious infection was 1.4%, 2.1%, 1.1% and 4.6% respectively.<sup>10,11</sup> Fifty two week data did show an increase in the rate of infections in these groups especially groups 2, 3 and 4 (31.6%, 51.9%, 46.2%, 52.8%, respectively) and the rate of serious infections increased in all groups at 52 weeks except group 1 (0.8%, 3.8%, 1.9%, 7.0%, respectively).<sup>14</sup> There were more serious infections associated with the 100 mg dose of golimumab combined with methotrexate. In all of the three phase III trials, only one patient developed tuberculosis and no opportunistic infections were reported.<sup>10-12,14</sup>

The other black box warning associated with golimumab is the risk of malignancy particularly lymphoma.<sup>5</sup> When combining the data from all of the golimumab treated patients in the three phase III trials, 11 patients developed malignancy during treatment compared to 4 treated with placebo. For the golimumab treated patients, 2 developed lymphoma, 3 developed basal cell carcinoma, 1 developed squamous cell and basal cell carcinoma, 1 developed squamous cell carcinoma and 4 developed breast cancer.<sup>10-12,14</sup>

Another common concern with monoclonal antibodies is the induction of antibodies against the medication which may then result in decreased clinical effect. This is reduced with fully humanized monoclonal antibodies but the risk is still there. The development of such antibodies was assessed in the GO-BEFORE and the 24 week GO-FORWARD trials.<sup>10,11</sup> In GO-BEFORE, 20 out of the 315 (6.3%) patients sampled had detectable golimumab antibodies.<sup>10</sup> The majority of these patients (14/20) were in the group receiving golimumab 100 mg without methotrexate. In the GO-FORWARD trial, 5 out of the 236 (2.1%) evaluated patients had detectable antibodies and all of these patients were in the group receiving golimumab without methotrexate.<sup>11</sup> Of these five patients, 2 still achieved an ACR20 response and 1 achieved an ACR50 response. From this data, it is apparent that the risk of developing antibodies is low although this is only for 24 weeks of treatment and that the presence of antibodies does not indicate the patient will not respond. Also, patients who were on concomitant methotrexate had a lower risk of antibody development compared to those on golimumab monotherapy.

## Place in Therapy

Currently, golimumab has not been directly compared to any other biologic DMARD therapy for RA making it harder to determine its place in therapy. However, an indirect comparison was done that compared nine biologic agents (abatacept, adalimumab, anakinra, certolizumab pegol, etanercept, golimumab, infliximab, rituximab, and tocilizumab) in patients who had failed methotrexate therapy and had not been on any previous biologic therapy.<sup>16</sup> Comparison was based on the ACR50 response for each agent after 6 months of therapy. Data for the golimumab arm were taken from the GO-FORWARD trial discussed above. All of the biologic agents were more effective than placebo and golimumab was ranked 7th with a median odds ratio of 1.36. When pairwise comparisons were done, there were no statistically significant differences between any of the biologic agents. In addition, the only biologic agent that showed a statistical difference compared to methotrexate was certolizumab. Although a ranking among the biologic agents was determined, the authors concluded that the agents have similar efficacy since none of the pairwise comparisons was significant.

A different analysis used number needed to treat (NNT) and number need to harm (NNH) to compare five new biologic agents for RA.<sup>17</sup> These agents included two TNF alpha inhibitors (golimumab and certolizumab). The NNT was based on the benefit of achieving an ACR50 response and the NNH was based on the percentage of patients who withdrew from the study due to adverse effects. Based on the 6 month data from the GO-FORWARD trial, the NNT for golimumab 50 mg every 4 weeks with methotrexate was five and there were fewer withdrawals in the golimumab group compared to control so there was no increased harm as defined by this analysis. A benefit-to-risk ratio was determined based on 1000 treated patients and this ratio for the golimumab 50 mg every 4 weeks with methotrexate group was 235:1. This indicates that for every 1000 patients treated with golimumab 235 will achieve an ACR50 response and 1 will withdrawal due to adverse events. This was the highest ratio for the medications included with the next closest being certolizumab with a ratio of 13:1 (based on 1 trial with 12 month data). The results of this analysis need to be interpreted cautiously as there are many limitations. First, the data for the golimumab analysis was based



on only one trial for golimumab and included only 6 month data. Also, the risk only included patients who withdrew due to adverse events and did not include patients who experienced adverse events but did not withdraw. This may have led to underestimating the risk of therapy especially in a relatively short follow up period of 6 months. Unfortunately, the analysis did not include the older TNF alpha inhibitors. This analysis confirmed that golimumab 50 mg every 4 weeks with methotrexate is safe and effective for treating RA but due to the limitations comparison to other medications is limited.

The ACR 2008 recommendations for the treatment of RA do not include golimumab since it was not approved at the time. However, they do use all of the TNF alpha inhibitors interchangeable and do not recommend one over another.<sup>18</sup> This indicates that when the recommendations were made the ACR did not feel there was a difference among the agents in efficacy.

Based on the data and the ACR recommendations, the choice of which TNF alpha inhibitor to use is mostly up to patient preference. A few things to consider are that golimumab is only indicated in combination with methotrexate whereas the other TNF alpha inhibitors are indicated as monotherapy. Golimumab's dosing schedule of subcutaneous injection every four weeks may be appealing to patients as they can give the medication at home and less often compared to the other TNF alpha inhibitors. Lastly, golimumab is the only TNF alpha inhibitor that has proven efficacy after a patient has discontinued a different TNF alpha inhibitor. Therefore, golimumab may be the preferred agent in that patient population.

## Conclusions

Golimumab is the newest TNF alpha inhibitor to reach the market and is a fully humanized monoclonal antibody. Although its mechanism of action is not unique, golimumab does have some benefits over the other medications in this class. It is dosed subcutaneously every four weeks and has proven efficacy when other TNF alpha inhibitors have been tried. In addition, based on data from clinical trials, golimumab is well tolerated with minimal adverse effects. However, golimumab must be used in combination with methotrexate and long term data is lacking.

Therefore, golimumab should be reserved for patients who have failed other TNF alpha inhibitors.

## Disclosures

This manuscript has been read and approved by all authors. This paper is unique and not under consideration by any other publication and has not been published elsewhere. The authors and peer reviewers report no conflicts of interest. The authors confirm that they have permission to reproduce any copyrighted material.

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