Clinical Medicine Reviews in Therapeutics

REVIEW

Golimumab-A Review of its Therapeutic Efficacy in Rheumatoid Arthritis

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Abstract: The advent of monoclonal antibodies to Tumor necrosis factor-α (TNF), has revolutionized the treatment in rheumatoid arthritis (RA). These agents have proved to be highly efficacious, making remission an achievable goal in RA. Golimumab is a human monoclonal antibody to TNF, which is approved by the US FDA for the treatment of RA, psoriatic arthritis and ankylosing spondylitis since April 2009. Golimumab is a useful addition to the therapeutic armamentarium against rheumatoid arthritis. It has proven efficacy in RA patients with active disease, despite treatment with methotrexate and also found to be useful in patients who have failed on a prior anti-TNF agent. It offers a reasonable alternative to other anti-TNF drugs like infliximab, adalimumab or etanercept. The short-term safety profile, based on short-term RCTs, is reasonable with no differences in total adverse events, serious infections, cancer, tuberculosis or deaths. However, Long-term surveillance studies are needed for safety assessment.

Keywords: rheumatoid arthritis, golimumab, TNF

Clinical Medicine Reviews in Therapeutics 2010:2 229–237

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Introduction

The management of rheumatoid arthritis (RA) has evolved greatly from use of broad immunomodulatory agents to specifically targeted cytokines and molecules in the inflammatory cascade involved in the pathogenesis of RA. Tumour necrosis factor (TNF) is an important mediator of articular inflammation. The monoclonal antibodies to TNF, have revolutionized the treatment in RA.[1–4] The TNF antagonists currently approved for the treatment of RA are infliximab—a chimeric mouse human monoclonal antibody against TNF, adalimumab—a humanized monoclonal antibody against TNF and etanercept—soluble type 2 receptor fused to Fc fraction of immunoglobulin. These agents have proved to be highly efficacious, making remission an achievable goal in RA. Although associated with a higher incidence of infections, especially tuberculosis, they are safe if used with caution.[5] Two additional TNF antagonists have recently come into the market, certolizumab pegol[6] and golimumab. Golimumab is approved by the US FDA for the treatment of RA, psoriatic arthritis and ankylosing spondylitis since April 2009.[7] Golimumab known as CNTO 148 is a human monoclonal antibody to TNF developed using the Humab Mouse technology (Medarex, Princeton, NJ). The recent approval of SIMPONI (golimumab) by the FDA has added one more anti TNF agent in our armamentarium, in the fight against RA. Also with the emergence of anti-TNF refractory RA, the availability of Golimumab offers additional option for patients. At the writing of this review, four RCT and a meta analysis were already published and a recent RCT data on use of intravenous golimumab in refractory RA has been recently published. This review attempts to look at the evidence for the, efficacy of Golimumab in the management of RA and tries to look at the safety issues associated with the drug.

Mechanism of Action

Golimumab is a fully humanized bivalent immunoglobulin (Ig) G1 monoclonal antibody similar to adalimumab. It is produced by immunizing genetically engineered mice with human TNF, resulting in an antibody with human-derived variable and constant regions. Preclinical studies have demonstrated it to have a high affinity and specificity for human TNFα with effective neutralization of TNFα bioactivity.[8] Golimumab binds to both the soluble and transmembrane bioactive forms of human TNF, preventing the binding of TNF to its receptors and thereby inhibiting the biological activity of TNF. Being similar to adalimumab, the first humanized antiTNF antibody, it elicits less immunogenic response than infliximab.

Pharmacokinetics

Golimumab is administered either by the subcutaneous or intravenous (IV) route. When given by IV infusion it has a linear pharmacokinetics. Following a single IV infusion, serum concentrations of golimumab decline biexponentially. The median $t_{1/2}$ was 19.3 days for the 10-mg/kg dose group.[9] The median $t_{1/2}$ increases with an increase in dose, with a median $t_{1/2}$ of 6.6 days for 0.1 mg/kg, 7.3 days for 0.3 mg/kg and, 8.6 days for 1 mg/kg. It increased to11.2 days for 3 mg/kg, 14.5 days for 6 mg/kg, and 19.3 days for 10 mg/kg. Population pharmacokinetics show that the mean C_{max} and AUC increased in a dose proportional manner. A 10-fold increase in dose resulted in an approximately 8- to 11-fold increase in mean C_{max} and an approximately 8- to 13-fold increase in mean area under the curve (AUC). The mean clearance (CL) after IV administration of golimumab ranged from 4.89 to 6.72 mL/d/kg; the CL of golimumab appeared to be independent of dose at a range of 0.1 to 10 mg/kg. There appeared to be positive correlation between CL, volume of distribution in central compartment (V_c) and body weight.[9]

When compared with intravenous administration, the absolute bioavailability of subcutaneously administered golimumab is 53%.[10] After a subcutaneous injection, the maximum concentration is reached in 2–6 days and steady-state is achieved by week 12. The mean steady state concentration for patients with RA receiving golimumab 50 mg subcutaneously every 4 weeks is 0.4–0.6 µg/mL. Nevertheless only 4 ng/mL is required to inhibit 50% of TNFα, this concentration is adequate to successfully inhibit the effects of TNFα. The terminal half-life of golimumab is approximately 2 weeks in healthy subjects. No dosage adjustments based on age, weight, ethnicity, or sex is necessary.

Dosage and Mode of Administration

The FDA approved Golimumab in April 2009 for the treatment of moderately to severely active RA in adults, in combination with methotrexate, active psoriatic arthritis in adults alone or in combination with methotrexate and in ankylosing spondylitis in adults. The FDA-approved dose for all of these conditions is 50 mg injected subcutaneously once a month. It is available as Simponi and manufactured by Centocor Ortho/Biotech Inc. But trials have also used 100 mg of Golimumab which can be given subcutaneously SC. However current data did not show significant difference between 50 mg and 100 mg dosage. Golimumab is available in 2 single-use forms: a prefilled syringe and a prefilled SmartJect autoinjector. It is provided in one strength, 50 mg/0.5 mL, and does not contain preservatives. With autoinjector, patients should inject at a 90-degree angle, whereas the prefilled syringes should be injected at a 45-degree angle. The average wholesale price of 50 mg sc once a month is about 1518 $ for a 70 kg patient.

Clinical Studies

Till now 4 RCTs have been published which have studied the efficacy of golimumab in RA. These studies include both phase II and phase III trials. (Table 1)

The study by kay et al,[11] was a multicenter, randomized, double-blind, placebo-controlled, 5-arm, dose-ranging study. It assessed the efficacy, safety, and pharmacology of golimumab plus methotrexate (MTX) versus placebo plus MTX in active RA patients. 172 patients were randomly assigned to 1 of 5 treatment groups in approximately equal proportions: placebo, 50 mg golimumab q4wks, 50 mg golimumab q2wks, 100 mg golimumab q4wks, 100 mg golimumab q2wks. The drug was administered subcutaneously (SC). The primary end point i.e. ACR 20 response at week 16 was achieved in significantly greater proportion of patients in the combined golimumab plus MTX groups (61.3%) compared with patients in the placebo plus MTX group (37.1%), ($P = 0.010$). 79.4% of patients of the 100 mg golimumab q2wks group had an ACR 20 response at week 16, which was significant. Also significant proportions of patients in the combined golimumab plus MTX groups achieved ACR 50/70 responses at week 16, compared with the placebo plus MTX group. American College of Rheumatology Criteria (ACR 20/50/70) responses were observed as early as week 2 and maintained through week 52. The Disease activity score 28 (DAS-28) also significantly improved in the combined golimumab plus MTX group compared to placebo plus MTX group. Serious adverse events occurred in 8.8% of the golimumab group compared to 5.9% in the placebo group. This study was the first to demonstrate that the new TNFα inhibitor golimumab is effective in controlling disease activity in RA among patients who had active disease despite MTX therapy. More phase 3 trials followed after the results of this study.

The GO-FORWARD study by keystone et al[12] is one of the first large randomized, double blind, placebo controlled phase III trial. It evaluated the efficacy and safety of golimumab in patients with persistent RA despite stable methotrexate doses between 15 and 25 mg per week for at least 4 weeks. Persistent RA was defined as at least 4 tender and swollen joints and 2 of the following: C-reactive protein greater than or equal to 1.5 mg/dL or erythrocyte sedimentation rate greater than or equal to 28 mm/h, morning stiffness for at least 30 minutes, bone erosion seen on X-ray or magnetic resonance imaging, or anti-CCP antibody or rheumatoid factor positivity. Patients were excluded if they had received previous TNF-α inhibitor therapy at any time or anakinra or DMARDs other than methotrexate within 4 weeks of study enrollment. Patients with latent tuberculosis were allowed in the trial, but required appropriate treatment. A total of 444 patients with active RA were randomized to receive placebo injections plus methotrexate (group 1), golimumab 100 mg injections plus placebo capsules (group 2), golimumab 50 mg injections plus methotrexate (group 3), or golimumab 100 mg injections plus methotrexate (group 4). The injections of golimumab/placebo were administered subcutaneously every 4 weeks. Significant proportion of patients in the golimumab + MTX groups achieved the ACR 20 response compared with the placebo + MTX or golimumab alone. At week 16, the ACR 20 response was achieved by only 33% in group 1 (placebo + MTX) compared with 55.6% in the combined groups 3 and 4 (golimumab 50 mg + MTX and golimumab 100 mg + MTX), $P < 0.001$. The proportion of ACR 20 responders in group 2 (golimumab + placebo) was not statistically significantly different from that of group 1 (44.4%

Table 1. A brief summary of clinical trials of golimumab.

Trials	Study population	Arms	Sample size	Study duration	ACR 20	ACR 50	ACR 70	Serious adverse events
The CNTO 148 study	Active RA for at least 3 months Primary efficacy parameter was proportion of patients achieving ACR 20 response at week 16	Placebo + MTX	172	52 weeks	37%	5.7%	0%	• Pneumonia (3 patients) • Malignancies (4 patients)
		GMB 50 mg every 4 weeks + MTX			60%	37.1%	8.6%	
		GMB 50 mg every 2 weeks + MTX			50%	23.5%	14.7%	
		GMB 100 mg every 4 weeks + MTX			55.9%	29.4%	17.6%	
		GMB 100 m every 2 weeks + MTX			79.4%	32.4%	8.8%	
		Combined GMB + MTX			61.3%	30.7%	12.4%	
GO-FORWARD	Active RA for at least 3 months, despite being on MTX. Should not have been on a biologic previously Primary efficacy parameter were 1. Proportion of patients achieving ACR 20 response at week 14 2. Improvement in HAQ-DI from baseline at week 24	Placebo + MTX (Group 1)	444	24 weeks	33.1%	9.8%	3.8%	• SAE and serious infections were greater in GMB 100 mg + MTX group (9%) • 1 death in GMB 100 mg + placebo group • 4 malignancies equally distributed in the 4 groups
		GMB 100 mg + Placebo (Group 2)			44.4%	20.3%	7.5%	
		GMB 50 mg + MTX (Group 3)			55.1%	34.8%	13.5%	
		GMB 100 mg + MTX (Group 4)			56.2%	29.2%	9%	
		Group 3 and 4 combined			55.6%	32%	11.2%	
GO-BEFORE	MTX- naïve patients with active RA Primary end point was the difference in ACR 50 response at week 24 between groups 3 and 4 combined versus group 1 and group 2	Placebo + MTX (group 1)	637	24 weeks	49.4%	29.4%	15.6%	• 2 deaths (1 suicide, gluteal abscess) • 4 malignancies (groups 1, 3 and 4)
		GMB 100 mg + Placebo (Group 2)			51.6%	33.1%	13.8%	
		GMB 50 + MTX (Group 3)			61.6%	40.5%	23.9%	
		GMB 100 mg + MTX (Group 4)			61.6%	36.5%	18.2%	
		Group 3 and 4 combined			61.6%	38.5%	21.1%	
GO-AFTER	Active RA for at least 3 months who have been treated with at least 1 TNFα inhibitor in the past. Concomitant DMARDSs were permitted. Primary end point is ACR 20 at week 14	Placebo	461	24 weeks	18%	6%	2%	• Worsened activity of RA (3 patients placebo group) • 3 malignancies (2 patients on GMB, 1 placebo)
		GMB 50 mg			35%	16%	10%	
		GMB 100 mg			38%	20%	9%	
		Combined GMB			37%	18%	10%	

Abbreviations: GMB, Golimumab; MTX, Methotrexate; RA, Rheumatoid arthritis; SAE, Serious adverse events.

versus 33.1%) ($P = 0.059$). At week 24, patients in the combined groups 3 and 4 also showed significantly greater improvement in the median HAQ-DI score (–0.44, $P < 0.001$) compared with group 1 (–0.13). The percentage of patients who achieved a 0.25 or more reduction in Health assessment questionnaire disability index (HAQ-DI) were 38.6% in group 1; 45.3% in group 2; 68.2% in group 3 ($P < 0.001$); 72.1% in group 4 ($P < 0.001$). The ACR 20 response in the golimumab groups were observed as early as week 4 with a gradual increase up to week 24. Additionally the patients in groups 3 and 4 combined achieved a significant European League against Rheumatism (EULAR) response, DAS 28 remission, ACR 50 and ACR 70 responses.

There were almost equal number of adverse events in all the four groups (60.9% in group 1, 63.2% in group 2, 68.5% in group 3 and 69.7% in group 4). The number of serious adverse events was higher in the golimumab 100 mg + MTX group (2.3%, 3.8%, 5.6% and 9.0% of patients in group 1, group 2, group 3 and group 4, respectively). One patient in group 2 died of sepsis after receiving 2 infusions of golimumab at week 8. Ninety-two (20.7%) patients had latent tuberculosis at study entry were receiving isoniazid, none of these patients developed active tuberculosis.

The GO-BEFORE (*Go*limumab *B*efore *E*mploying methotrexate as *F*irst line *O*ption in the treatment of *R*heumatoid arthritis of *E*arly onset) by Emery et al[13] is a large study conducted in 90 centers across Europe, Asia, Australia and New Zealand. In this study 637 MTX-naïve patients with early (<3 years) active RA were randomized to 1 of 4 treatment groups: placebo plus MTX (group 1), golimumab 100 mg plus placebo (group 2), golimumab 50 mg plus MTX (group 3), or golimumab 100 mg plus MTX (group 4). The primary end point was the proportion of patients achieving ACR 50 response at week 24. The other efficacy parameters were ACR 20, ACR 70 and ACR 90 responses. The ACR-N, DAS 28, disability index of the Health assessment questionnaire was also assessed. The study medication (golimumab or placebo) was administered every 4 weeks by the subcutaneous route. At week 24, an intent-to-treat (ITT) analysis of the ACR 50 response did not show a significant difference between the combined group (combined group 3 and group 4) and group 1 (38.4% and 29.4%, respectively; $P = 0.053$). But when 3 untreated patients were excluded, a post hoc modified ITT analysis of the primary endpoint showed that 38.5% of patients in the combined group versus 29.4% in group 1 achieved ACR 50 responses, $P = 0.049$. The ACR 20 response at week 24 was achieved by 61.6% of patients in-group 3 and 61.6% of patients in group 4 compared with 49.4% of patients in group 1, $P = 0.028$. More patients' in-group 3 and 4 achieved an ACR 20 response as early as week 4. Additionally disease activity as measured by DAS 28 either using ESR or CRP was significantly reduced in the golimumab 50 mg + MTX and golimumab100 mg + MTX group at week 24, and also more patients in these two groups achieved remission (defined by DAS 28 < 2.6) by week 24. Therefore, golimumab with methotrexate was more effective than methotrexate monotherapy, and golimumab monotherapy is noninferior to methotrexate monotherapy with no unexpected safety concerns.

In the GO-AFTER GOlimumab After Former anti-tumour necrosis factor α Therapy Evaluated in Rheumatoid arthritis) trial by smolen et al,[14] the efficacy and safety of golimumab for patients with active RA who had previously received one or more TNFα inhibitors was assessed. So far, this is the only study that assessed whether patients who discontinued one of the existing TNFα inhibitors would respond to golimumab. This trial recruited patients with active RA from 82 centers in Austria, Australia, Canada, Finland, Germany, Netherlands, New Zealand, Spain, UK, and USA. Four hundred and sixty one (461) patients were randomly assigned in a 1:1:1 ratio to receive SC injections of placebo, 50 mg golimumab, or 100 mg golimumab every 4 weeks. Patients continued concomitant DMARD treatment with MTX, sulfasalazine, and hydroxychloroquine, corticosteroid and non-steroidal anti-inflammatory drugs. Patients must have tolerated these drugs for at least 12 weeks and dose must have been stable for 4 weeks before randomization. The primary endpoint was achievement of ACR 20 response at week 14. At week 16, patients who had less than 20% improvement in tender and swollen joint counts were given rescue therapy and changed treatment from placebo to 50 mg golimumab or from 50 mg to 100 mg golimumab. The reason for discontinuation of previous TNFα

inhibitors in 269 (58%) patients was lack of effectiveness and in 246 (53%) patients it was intolerance and accessibility issues (reasons unrelated to effectiveness). All patients had active disease, and more than 95% of patients had been treated for 4 weeks or more with at least one TNFα inhibitor. One hundred and fifteen (25%) patients had received two and 43 (9%) had received three TNFα inhibitors previously.

At week 14 the ACR 20 response was achieved by 28 (18%) patients on placebo, 54 (35%) patients on 50 mg golimumab (OR 2.5, [95% CI 1.5–4.2], $P = 0.0006$), 58 (38%) patients on 100 mg golimumab (OR 2.8, [CI 1.6–4.7], $P = 0.0001$). Similarly, the ACR 50 and ACR 70 response was achieved by a significantly larger number of patients in the golimumab 50 mg and golimumab 100 mg group compared to placebo. Remission by DAS 28 score (<2.6) was achieved by 1 (1%) patient in the placebo group, 13 (8%) patients in the golimumab 50 mg group ($P < 0.0009$), and by 19 (12%) patients in the golimumab 100 mg group ($P < 0.0001$). DAS 28 scores <3.2 was achieved by higher number of patients in the combined golimumab group, 83 patients (29%) compared to placebo 21 patients (15%), $P = 0.0033$. Golimumab therapy significantly improved the signs and symptoms of RA (reduction in the number of swollen and tender joints) and the quality of life related to physical function. The mean change in HAQ-DI scores: –13.4%, $P < 0.0005$; –17.6%, $P < 0.0001$; vs. 0% respectively for golimumab 50 mg, golimumab 100 mg vs. placebo. Additionally golimumab was found to be quite safe with similar number of adverse events in placebo and golimumab groups. Serious adverse events were recorded in 11 (7%) patients on placebo, 8 (5%) on 50 mg golimumab, and 4 (3%) on 100 mg golimumab during weeks 1–16. Subsequently after some patients were given rescue therapy, serious adverse events were recorded in 15 (10%) patients on placebo, 14 (5%) on 50 mg golimumab, and 8 (4%) on 100 mg golimumab.

Efficacy

A recent systematic review from Cochrane database by Singh JA et al[15] had looked in to all major RCTs published until august 2009. The Meta analysis included 1714 patients out of which 1231 received golimumab and 483 received placebo. The primary outcome, the ACR 50 response and safety of the drug was analyzed, apart from other secondary outcome measures like ACR 20/70 response, DAS 28, good EULAR response, disease remission, quality of life and radiological progression. The study tried to analyze the efficacy and safety of golimumab (alone or in combination with DMARDs or biologics) in comparison with the placebo (alone or in combination with DMARDs or biologics).

Data analysis from the RCTs was done for patients who received 50 mg of golimumab q4wks with MTX versus placebo and MTX alone. It was found that golimumab treated patients were 2.6 times more likely to reach ACR 50 response (95% confidence interval: 1.34 to 4.94), at 14–24 weeks compared to placebo. There was no significant difference in the safety outcome measures like serious infections, tuberculosis, lung infections, cancer and death. The golimumab treated patients were 2.8 times more likely to reach ACR 70, and 5.1 times more likely to reach DAS remission. However, there was lack of data on radiological progression.

In the next group where 100 mg golimumab q4wks with MTX versus placebo and MTX, the Golimumab treated patients were 2.4 times more likely to reach ACR 50 (95% CI: 1.25 to 4.74; $P = 0.009$) at 14–24 weeks. There was no significant difference in the safety outcome measures. How ever, there was no significant difference in ACR 70 response, where as all other secondary outcome measures showed a significant response in favor of Golimumab.

For patients who received 50 mg golimumab q2wks with MTX versus placebo and MTX, it was found that there was no significant difference in ACR 50 response from each other ($P = 0.06$). Even the secondary outcome measures showed no significant change between golimumab and the placebo.

However, patients who received 100 mg q2wks and MTX versus placebo and MTX golimumab treated patients were 5.7 times more likely to reach ACR 50 response than placebo (95% CI: 1.35, 23.7; $P = 0.02$) at 16 weeks. No significant difference was observed in safety outcome measures. There was no significant improvement in ACR 70 response, DAS remission but rest of the parameter showed a significant improvement with golimumab.

On comparison of Golimumab to methotrexate (golimumab 100 mg q4wks and placebo versus

placebo and MTX), the data from two studies (Emery 2009, keystone 2009) showed no significant difference between the two in ACR 20/50/70 response, Das remission, good EULAR response and proportion achieving HADMCID. However, golimumab treated patients achieved a significantly lower HAQ score compared to MTX-treated patients. The safety profile of golimumab was similar to that of MTX in terms of number of adverse events, serious adverse events, infections, serious infections and cancer. Withdrawals rates overall and due to adverse events were similar. However it's only a subgroup analysis and there is a possibility of type II error due to small sample size. Also in one study (Keystone 2009), patients had already failed MTX before being randomized to MTX or golimumab, thereby providing an efficacy advantage to the golimumab group.

The metanalysis failed to answer several important issues like role of golimumab in early RA versus established RA vs. late RA, its role in single biologic DAMRD agent versus combination biological agents and role of treatment duration with biologic DMARD, due to lack of data on these issues. Its use in patients who have MTX-failure versus biologic failure a detailed comparison was not done since there was only one study in patients with biologic-failure (Smolen 2009), also in DMARD-naive versus not naive: Only one study (Emery 2009) recruited methotrexate naive patients, therefore this comparison was not done.

Patient Preference

The metanalysis found that those treated with golimumab 50 mg q4 wks were 0.5 times less likely to withdraw compared to placebo (95% CI: 0.31 to 0.81; $P = 0.005$) and those on 100 mg q4wks were 0.7 times less likely to withdraw compared to placebo.

Adverse Events

The clinical trials done till now has reported one case of tuberculosis and 2 patients developed lymphoma while on golimumab therapy. The most common adverse effects associated with golimumab were nausea[11,13] and injection site reactions manifesting as erythema. In addition, the recent metanalysis did not find any significant difference in the safety outcome measures between golimumab and placebo group. The golimumab label warns against the risk of serious infection like tuberculosis, bacterial sepsis, invasive fungal and other opportunistic infection. There is possibility of reactivation of hepatitis B, new onset psoriasis and increased risk of malignancies including lymphoma especially in children and adolescents, so careful monitoring and discontinuation is advised if patient develops any infections. FDA also warns of worsening or new onset of heart failure and worsening or new onset of demylenating disease. Since none of the RCTs had safety as the primary outcome and all RCTs were of short duration therefore, adverse events that are uncommon and/or occur with long-term treatment with golimumab are unknown at this time. Long-term surveillance studies and RCTs with safety as primary outcome are needed. In addition, development of antibodies to golimumab is still being investigated in most clinical trials.

Place in Therapy

The metanalysis found a significant impact of golimumab in FDA-approved dose on both lowering RA disease activity (DAS 28) as well as improving RA disease activity (ACR 20/50/70). Four RCTs with 1,231 patients treated with golimumab and 483 patients treated with placebo were included. Of these, 436 were treated with the FDA-approved dose of golimumab 50 mg every four weeks. Compared to patients treated with placebo + methotrexate, patients treated with the FDA-approved dose of golimumab + methotrexate were 2.6 times more likely to reach ACR 50 (95% confidence interval (CI) 1.3 to 4.9; $P = 0.005$ and NNT = 5, 95% confidence interval 2 to 20). No more likely to have any adverse event (relative risk 1.1, 95% Cl 0.9 to 1.2; $P = 0.44$), and 0.5 times as likely to have overall withdrawals (95% Cl 0.3 to 0.8; $P = 0.005$). Golimumab-treated patients were significantly more likely to achieve remission, low disease activity and improvement in functional ability compared to placebo (all statistically significant).

The ACR 50 rates are similar to those reported in the systematic reviews of other TNF-blockers like etanercept (Lethaby 2003),[16] infliximab (Blumenauer 2002)[17] and Adalimumab (Navarro-Sarabia 2005)[18] and to other current approved biologics for the treatment of RA. Thus, in absence of direct comparison

studies, based on these data, golimumab seems to have an efficacy similar to the other biologics currently used for the treatment of RA, it may be preferred by the patient in view of convenience of administration (once in a month by sc). Some rheumatologist may prefer in patients who had inadequate response to Ist anti TNF therapy.

Golimubab in Other Diseases

Two phase III trials, the GO REVEAL[19] study which looked at the twenty four week efficacy and safety results of golimumab in psoriatic arthritis (PsA) and GO-RAISE study, which evaluated the efficacy and safety of golimumab in reducing signs and symptoms of active Ankylosing Spondylitis (AS) has been published. In GO REVEAL study the adult patients with PsA who had at least 3 swollen and 3 tender joints and active psoriasis were randomly assigned to receive subcutaneous injections of placebo (n–113), golimumab 50 mg (n–146), or golimumab 100 mg (n–146) every 4 weeks through week 20. An ACR 20 response was achieved at week 14 by 51% of patients receiving golimumab 50 mg and 45% of patients receiving golimumab 100 mg, compared with 9% of placebo-treated patients ($P \leq 0.001$ for both comparisons), which was the primary end point. However, differences between the 50-mg and 100-mg doses of golimumab were modest, with no evidence of increased benefit with background MTX treatment. Patients-receiving golimumab also demonstrated significant improvement in psoriasis compared with patients receiving placebo. Among the 74% of patients in whom at least 3% of the BSA was affected by psoriasis at baseline, 40% of those in the golimumab 50 mg groupand 58% of those in the golimumab 100 mg group had at least 75% improvement in the Psoriasis Area and Severity Index (PASI) score at week 14, compared with 3% of patients in the placebo group ($P \leq 0.001$ for both comparisons). Out of 70% of patients who had baseline nail involvement, significant improvements in nail symptoms were observed in golimumab-treated patients as early as week 14 and were maintained or improved through week 24. However, the study was not powered to detect differences between golimumab doses, there appeared to be more evidence of a golimumab dose-response in terms of the skin/nail outcomes compared with the arthritis outcomes. Since these findings could be related to the performance of the arthritis instruments versus the skin/nail instruments, different biologic responses, or the speed of responses in affected organs, further study is needed. Malignancies were reported for 3 patients receiving golimumab 100 mg (2 cases of basal cell malignancies and 1 case of prostate cancer) through week 24, and elevation of transaminases were some of the adverse events that were reported.

The GO RAISE 20 study is a 24-week, double-blind, placebo controlled study, were patients who had active AS (Bath Ankylosing Spondylitis Disease Activity Index > 4, spinal pain VAS > 4) were randomly assigned in a 1:1.8:1.8 ratio to receive placebo or golimumab at a dose of 50 mg or 100 mg. Of the patients who received golimumab, 59.4% in the 50-mg group and 60.0% in the 100-mg group achieved an ASsessment in AS International Working Group criteria (ASAS 20) response at week 14 compared with 21.8% in the placebo group ($P < 0.001$) which was the primary end point of the study. Results of other outcomes, including the ASAS 40 response, ASAS partial remission, the ASAS 5/6 response, back pain, inflammation, 50% improvement in the Bath Ankylosing Spondylitis Disease Activity Index (BASDAI), and the Bath Ankylosing Spondylitis Functional Index (BASFI), provided further evidence that golimumab-treated patients Showed significant and clinically meaningful improvement. However, there were no direct comparisons in a single head-to-head study between Golimumab and other TNF-α inibitors currently in AS patients. So further comparison studies and data may be required in AS patients before endorsing Golimumab as a primary biological agent in treating AS.

Conclusion

Golimumab is a useful addition to the therapeutic armamentarium against rheumatoid arthritis. It has proven efficacy in patients of RA with active disease despite treatment with methotrexate and has been found to be useful in patients who have failed on a prior anti-TNF agent. It offers a reasonable alternative to other anti-TNF drugs like infliximab, adalimumab or etanercept. The short-term safety profile, based on short-term RCTs, is reasonable with no differences in total adverse events, serious infections, cancer, tuber-

culosis or deaths. However, Long-term surveillance studies are needed for safety assessment.

Disclosures

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

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