Golimumab: a new anti-TNF agent on the horizon for inflammatory arthritis

Rheumatoid arthritis (RA), psoriatic arthritis, and ankylosing spondylitis are highly prevalent inflammatory arthritides. Various conventional therapies are currently in use, and biologic therapies have also been introduced into the treatment armamentarium. Despite the remarkable efficacy of the anti-tumor necrosis factor (TNF) agents, there still remains an unmet need for newer anti-TNF agents. A substantial number of patients do not respond to an initial anti-TNF agent, but may respond to a second one. The modes of administration of currently marketed anti-TNF agents are not particularly convenient and risk-free for all patients. An anti-TNF agent with a better safety profile is also highly desirable. Golimumab (CNTO-148) is a high affinity, human monoclonal antibody to TNF-α. The various ongoing trials for golimumab have shown promising results in terms of efficacy and safety in methotrexate-naive and -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 golimumab in psoriatic arthritis and ankylosing spondylitis has also been demonstrated.

KEYWORDS: golimumab, human monoclonal antibody, new anti-TNF

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Rheumatoid arthritis (RA), psoriatic arthritis (PsA) and ankylosing spondylitis (AS) form the majority of the inflammatory arthritides causing long-term morbidity and need protracted treatment. In the UK, RA affects approximately 1% of the population [1]. There is a significant difference in prevalence estimates between northern European and American countries and developing countries [2]. There is a wide variation of annual incidence of PsA (median: 6.4, range: 0.1–23.1 cases per 105 inhabitants) according to a recently published systematic review of studies from around the world. The prevalence estimates vary from one case per 105 individuals in a Japanese study to 420 cases per 105 population in an Italian study (median: 180) [3]. NICE estimated the prevalence of clinically significant AS at 0.15% of the population, and an annual incidence of 6.9 per 100,000 [4]. Thus, inflammatory arthritides constitute a huge disease burden.

Existing nonbiologic treatments have included analgesics, corticosteroids, NSAIDs and DMARDs. Biologic therapies, specifically tumor necrosis factor-α (TNF-α) inhibitors, have been used in a wide variety of immune-mediated inflammatory diseases and have been approved by the US FDA and EMEA. Adalimumab, etanercept and infliximab have been approved to treat RA, PsA and AS. Current NICE guidlines have approved the use of infliximab, etanercept and adalimumab for the treatment of RA, and other biologics like rituximab have been approved for refractory RA if one anti-TNF agent has failed, while abatacept and anakinra have not been recommended. Etanercept and adalimumab have been recommended for PsA if an anti-TNF agent is needed, and infliximab should be used only if there are problems with the other two anti-TNF agents. NICE recommends adalimumab or etanercept as possible treatment for people with severe AS who have active spinal disease as assessed on two separate occasions, 12 weeks apart, and who have tried at least two NSAIDs without success.

Etanercept is a recombinant, dimeric fusion protein composed of two extracellular domains of the human p75 TNF receptor linked to the Fc portion of human immunoglobulin G1 (IgG1) that binds to soluble and transmembrane forms of TNF-α and lymphotoxin (TNF-β). Adalimumab is a human IgG1 monoclonal antibody (mAb) directed against TNF-α that binds to soluble and transmembrane forms of TNF-α. Infliximab is a chimeric mAb, composed of human constant regions of IgG and murine hypervariable regions. It binds to both soluble and transmembrane TNF-α. The hypervariable region segments of infliximab and adalimumab can lead to the development of human anti-adalimumab and anti-infliximab antibodies, which in some patients leads to decreased efficacy and increased chances of infusion and injection site reaction. However, the majority of patients with antibodies do not have any clinical consequences [5,6].

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Despite their efficacy in randomized clinical trials, there are some limiting factors of individual agents contributing to both restriction in therapeutic efficacy and treatment-limiting adverse effects. Even in diseases where anti-TNF treatments have been proven to be successful, more than a third of patients do not respond adequately to treatment [7]. This may be due to differing mechanisms of disease, different binding properties of each of the antagonists to TNF molecules and different dissociation rates [8,9]. The binding to soluble and transmembrane TNF receptors may also activate several different cascades. Finally, the genetic makeup of individuals may dictate response to biological treatments. When an individual fails to respond to one biologic treatment, a switch to another biologic is often successful [10].

Despite being highly effective and generally well-tolerated, anti-TNF agents can lead to serious adverse reactions (serious infections including sepsis), TB immunogenic reactions (lupus-like syndromes) and hypersensitivity-type reactions (including infusion and injection-site reactions). The current modes of delivery of these biologic anti-TNF agents remain extremely inconvenient for patients. While oral administration of such large protein molecules (approximately 150 kD) does not seem to be feasible in the near future, other modes of administration, including less frequent subcutaneous injections, could provide substantial relief for patients.

Clearly, there is a need for future research aimed at innovations to improve and extend the therapeutic use and safety of biological agents. Golimumab, with monthly subcutaneous administration, is one such newer anti-TNF agent developed for use in the inflammatory arthritides.

Introduction to the compound: chemistry & formulation

Golimumab (CNTO-148) is a high affinity, human mAb to TNF-α. The constant regions of the heavy and light chains of golimumab are identical in amino acid sequence to the corresponding human constant regions of infliximab. The antibody neutralizes both soluble and membrane-bound forms of TNF-α.

Golimumab is the first anti-TNF agent with both subcutaneous and intravenous formulations, requiring less frequent administration compared with current anti-TNF products. Golimumab is intended to be used as monotherapy or in combination with methotrexate (MTX).

Pharmacokinetics & metabolism

The first in-human Phase I study published in 2007 was a randomized, double-blind, placebo-controlled, parallel-group, dose-escalating study conducted at two sites in the USA. Six groups of adult subjects with RA were randomly assigned to receive a single intravenous infusion dose of golimumab of 0.1, 0.3, 1, 3, 6 or 10 mg/kg. Following intravenous administration, serum concentrations of golimumab declined biexponentially, with a median t½ of 19.3 days for the 10 mg/kg group. The median half-life appeared to increase with an increase in dose [11]. No dose adjustment according to body weight appeared to be necessary based on the findings of this study. Detectable concentrations of golimumab were observed in the majority of subjects through week 4, even those in the lower dose groups. Estimates based on a population pharmacokinetics model also suggest that the t½ of golimumab ranges from 2 to 3 weeks.

Another multicenter, randomized, double-blind, placebo-controlled, dose-ranging study reported similar results. Median trough concentrations increased as the dose increased, and attained steady state by week 12 for all golimumab dosage groups (50 mg every 4 weeks, 50 mg every 2 weeks, 100 mg every 4 weeks and 100 mg every 2 weeks) [12]. However, there was much variability between patients. A study of golimumab in PsA patients identified several co-variates that affected the apparent clearance of golimumab. Of these, weight, antibody to golimumab status, baseline C-reactive protein (CRP) and smoking status were identified as significant co-variates [13].

Clinical efficacy of golimumab in trials

Phase II trial in RA

This was the first study reporting the efficacy of golimumab in humans. This study enrolled patients with active RA despite treatment with MTX [12]. This was a dose-finding study that evaluated four dosing regimens of golimumab in combination with MTX, compared with MTX alone. A total of 172 adult patients with RA that had been active for at least 3 months while on MTX, and were on a stable dose of MTX during the 4 weeks prior to study entry, were randomly assigned to one of five treatment groups: placebo plus MTX, 50 mg golimumab every 4 weeks plus MTX, 50 mg every 2 weeks plus MTX, 100 mg every 4 weeks plus MTX and 100 mg every 2 weeks plus MTX. The primary end point of a greater proportion of patients in

the combined golimumab plus MTX groups, and at least one of the individual golimumab plus MTX groups achieving ACR20 at week 16 compared with the placebo plus MTX group was achieved. ACR20 response at week 16 was achieved in a significantly greater proportion of patients in the combined golimumab plus MTX groups, 61.3% (p = 0.010), and in the group receiving 100 mg golimumab every 2 weeks plus MTX, 79.4% (p < 0.001), compared with the placebo plus MTX group, 37.1%.

The study was not powered to detect a difference between individual golimumab plus MTX treatment groups. When compared individually with the placebo group, the other three golimumab treatment groups did not show a statistically significant difference in the proportions of patients achieving an ACR20 response. However, each individual dose regimen had a statistically significant greater proportion of ACR50 responders; 37.1% (p = 0.001) in the 50 mg golimumab every 4 weeks group, 23.5% (p = 0.036) in the 50 mg every 2 weeks group, 29.4% (p = 0.009) in the 100 mg every 4 weeks group, and 32.4% (p = 0.005) in the 100 mg golimumab every 2 weeks group (Table 1).

Greater proportions of patients in the combined golimumab plus MTX group and at least one of the individual golimumab plus MTX groups achieved ACR20 at week 16 compared with the placebo plus MTX group. Significantly greater proportions of patients in the combined group also achieved ACR50, 30.7% (p = 0.003), and ACR70, 12.4% (p = 0.028), responses at week 16 compared with those in the placebo plus MTX group. They also demonstrated a significantly greater improvement in the Disease Activity Score (DAS) 28 score (-1.8 ± 1.3). ACR20, ACR50 and ACR70 responses were observed as early as week 2 and were maintained through week 52.

No clear dose response was evident; however, the 50 mg golimumab plus MTX every 4 weeks dose group had relatively less suppression of serum CRP concentration compared with the other three dose groups. Both the 50 and 100 mg every 4 weeks dosing demonstrated adequate efficacy. Thus, 50 and 100 mg golimumab every 4 weeks were selected for further study in the Phase III program.

Phase III studies in RA, PsA & AS

Five Phase III studies with the subcutaneous formulation, and one study with the intravenous formulation, are ongoing. Three trials are being conducted with the subcutaneous formulation in three different subpopulations of patients with RA. These subpopulations included MTX-naive patients, patients with active RA despite MTX treatment, and patients with active RA despite prior or current anti-TNF-α therapy. One trial with the subcutaneous formulation is being conducted in both PsA and AS. The only intravenous formulation trial is being conducted in patients with RA.

The results of several ongoing trials of golimumab were presented at the EULAR 2008 meeting, and some have been recently published. These are reviewed below (Table 2).

Active RA, MTX-naive: GO-BEFORE study

The GO-BEFORE study was a multicenter, double-blind, placebo-controlled study of 637 MTX-naive adult patients with active RA (predominantly early RA). This study showed that those treated with 50 mg golimumab plus 20 mg MTX per week by subcutaneous injections every 4 weeks had a significantly greater improvement in signs and symptoms of RA through week 24, as compared with the MTX alone group, in a modified intent-to-treat (mITT) analysis (excluding the three patients who did not receive study treatment). In the combined golimumab population of 50 and 100 mg plus MTX, 38.5% of patients achieved ACR50 (p = 0.049) by mITT analysis, compared with 29.4% in the MTX-alone group.

Table 1. Efficacy results at week 16 in a Phase II trial.

Response criteria	Placebo + MTX	50 mg every 4 weeks + MTX	50 mg every 2 weeks + MTX	100 mg every 4 weeks + MTX	100 mg every 2 weeks + MTX	Combined golimumab + MTX
ACR20	37.1%	60% (p = 0.056)	50% (p = 0.281)	55.9% (p = 0.119)	79.4% (p < 0.001)	61.3% (p = 0.010)
ACR50	5.7%	37.1% (p = 0.001)	23.5% (p = 0.036)	29.4% (p = 0.009)	32.4% (p = 0.005)	30.7% (p = 0.003)
ACR70	0.0%	8.6% (p = 0.077)	14.7% (p = 0.018)	17.6% (p = 0.009)	8.8% (p = 0.072)	12.4% (p = 0.028)
DAS28 CRP (mean ± SD change)	-0.9 ± 1.0	-1.9 ± 1.3	-1.4 ± 1.3	-1.9 ± 1.5	-1.9 ± 1.1	-1.8 ± 1.3

CRP: C-reactive protein; DAS28: Disease activity score 28; MTX: Methotrexate.

Table 2. Summary of efficacy in trials for rheumatoid arthritis.

RA trials	Placebo + MTX 20 mg/week	100 mg GLM 4-weekly + placebo	50 mg GLM 4-weekly + 20 mg/week MTX	100 mg GLM 4-weekly + MTX 20 mg/week	50 mg GLM + 100 mg combined
GO-BEFORE					
Week 24 ACR50 (mITT)	29.4%	33.1% (p = 0.473)	40.5% (p = 0.038)	36.5% (p = 0.177)	38.5% (p = 0.049)
Week 24 DAS28 responders	60.6%	66% (p = 0.310)	75.5% (p = 0.005)	75.5% (p = 0.004)	75.5% (p < 0.001)
GO-FORWARD					
Week 14 ACR20	33.1%	44.4%	55.1% (p < 0.01)	56.2% (p < 0.001)	55.6% (p < 0.001)
Week 14 ACR50	9.8%	20.3% (p < 0.05)	34.8% (p < 0.001)	29.2% (p < 0.001)	32% (p < 0.001)
Week 24 ACR20	27.8%	35.3%	59.6% (p < 0.001)	59.6% (p < 0.001)	59.6% (p < 0.001)
Week 24 ACR50	13.5%	19.5%	37.1% (p < 0.001)	32.6% (p < 0.001)	34.8% (p < 0.001)
RA trials	**Placebo**	**50 mg GLM 4-weekly**	**100 mg GLM 4-weekly**	**Combined 50 and 100mg**	
GO-AFTER					
Week 14 ACR20	17.7%	35.7% (p = 0.006)	42.7% (p < 0.001)	36.6%	

GLM: Golimumab; mITT: Modified intent-to-treat analysis; MTX: Methotrexate; RA: Rheumatoid arthritis.

DAS28 CRP response was achieved in 75.5% of patients (p = 0.005) compared with 60.6% in the MTX-alone group. The study was powered to detect superiority of 50 and 100 mg golimumab plus MTX versus MTX alone, and non-inferiority of golimumab alone versus MTX alone. Golimumab alone was not found to be statistically inferior to MTX alone by mITT analysis, and numerically it was shown to be better [14].

Active RA despite MTX: GO-FORWARD study

This was the study of the efficacy of golimumab with or without MTX in patients with active RA despite MTX therapy. This study of 444 patients demonstrated through week 24 that 50 or 100 mg golimumab subcutaneous injections plus MTX every 4 weeks significantly reduced signs and symptoms of RA [15]. In the 50 mg golimumab plus MTX group, 55.1% of patients (p < 0.01) achieved ACR20 and 34.8% (p < 0.001) of patients achieved ACR50 at week 14, as compared with 33.1 and 9.8%, respectively, in the MTX plus placebo arm. The 100 mg golimumab plus MTX group achieved ACR20 in 56.2% of patients (p < 0.001) and ACR50 in 29.2% of patients (p < 0.001). In the 100 mg golimumab plus placebo group, 44.4% of patients achieved ACR20, and 20.3% of patients (p < 0.05) achieved ACR50. At week 24, ACR20 was achieved in 59.6% of patients (p < 0.001) in both the 100 and 50 mg golimumab plus MTX groups, 35.3% of patients in the 100 mg golimumab only group and 27.8% in the MTX-alone group. In this study, the comparison with the golimumab-only group was a superiority comparison, which showed a numerically higher ACR20 response for the 100 mg golimumab-alone group.

Active RA despite previous treatment with anti-TNF agents: GO-AFTER study

Several publications have reported that a large proportion of patients who do not respond to one anti-TNF agent respond to a second anti-TNF agent. However, all these reports are retrospective chart reviews, registries or otherwise open-label anecdotal case series [7]. This is the first prospective, placebo-controlled, double-blind study of an anti-TNF agent (golimumab) in patients with active RA who were previously or are currently being treated with anti-TNF agents. All 461 patients had received at least one anti-TNF agent, 115 (24.9%) had received two anti-TNF agents and 43 (9.3%) had received three anti-TNF agents. Prior anti-TNF treatment had been discontinued due to lack of efficacy (58.4%), intolerance (16.5%) and other reasons (39.7%).

Among those who discontinued anti-TNF treatment due to lack of efficacy, 35.7 and 42.7% of patients in the 50 and 100 mg golimumab group had an ACR20 response at week 14, compared with 17.7% in the placebo group (p = 0.006 and p < 0.001, respectively). At week 24, 34% of patients (p < 0.001) in the 50 mg golimumab

and 43.8% of patients ($p < 0.001$) in the 100 mg golimumab group, achieved ACR20, as compared with 16.8% of patients in the placebo group. Thus, in patients with active RA who had received anti-TNF therapy and discontinued for any reason, golimumab significantly reduced RA signs and symptoms and improved physical function [16].

Trials of golimumab in PsA: GO-REVEAL study

The efficacy and safety of golimumab in PsA were assessed in the GO-REVEAL study. A total of 405 patients were randomized to three groups receiving either placebo, 50 mg golimumab or 100 mg golimumab subcutaneously every 4 weeks. Golimumab was significantly better than placebo in improving PsA signs and symptoms at week 24, and efficacy was maintained through week 52. At week 24, ACR20 was achieved in 52.1% of the 50 mg golimumab group and 61% of the 100 mg golimumab group, as compared with 12.4% in the placebo group. In addition, a reduction of at least 75% in the Psoriasis Area and Severity Index (PASI75) was obtained in 55.9% of patients in the 50 mg golimumab group, and 66% of patients in the 100 mg golimumab group, compared with 1.4% in the placebo group [17] (**Table 3**).

Sera of patients from the GO-REVEAL study were collected at weeks 0, 4 and 14. Samples were tested for selected inflammatory, bone and cartilage markers after injections of golimumab. In the golimumab-treated patients, levels of acute-phase proteins, inflammatory cytokines and other proteins were significantly decreased as early as week 4, and continued to show a decrease at week 14. Treatment also resulted in significantly increased markers of bone formation and decreases in markers of bone degradation [18].

Nail changes and enthesitis also improved significantly with golimumab treatment, both with monthly 50 and 100 mg golimumab subcutaneous injections. However, statistically significant improvement in dactylitis was achieved only with 100 mg golimumab [19].

Trials of golimumab in AS: GO-RAISE study

Golimumab has also been studied in AS. In the GO-RAISE study, doses of 50 or 100 mg golimumab were administered subcutaneously every 4 weeks in 356 patients. The primary end point, that is the proportion of patients with at least a 20% improvement in the Assessment in AS working group criteria at week 14, was achieved in 59.4% of patients in the 50 mg golimumab group ($p < 0.001$), and 60% of patients in the 100 mg golimumab group ($p < 0.001$), as compared with 21.8% in the placebo group. Clinical benefit was observed as early as 4 weeks after golimumab treatment and was maintained through week 24 [20] (**Table 3**). Similar to the PsA study, sera from patients with AS were tested for

Table 3. Summary of efficacy in psoriatic arthritis and ankylosing spondylitis.

Response criteria	Placebo	GLM 50 mg 4 weekly	GLM 100 mg 4 weekly	Combined
Psoriatic arthritis (GO-REVEAL)				
Week 24 ACR20	12.4%	52.1%	61%	–
ACR50	3.5%	32.2%	37.7%	–
PASI75 response	1.4%	55.9%	66.0%	–
Week 52 ACR20	–	78.4%	74.1%	–
ACR50	–	56.9%	52.6%	–
PASI75 response	–	62.0%	69.3%	–
Ankylosing spondylitis (GO-RAISE)				
Week 14 ASAS20	21.8%	59.4% ($p < 0.001$)	60.0% ($p < 0.001$)	59.7% ($p < 0.001$)
Week 24 ASAS20	23.1%	55.8% ($p < 0.001$)	65.7% ($p < 0.001$)	60.8% ($p < 0.001$)
Week 24 ASAS40	15.4%	43.5%	54.3%	–

ASAS: Assessment in ankylosing spondylitis; GLM: Golimumab; PASI75: Psoriasis area severity index 75.

acute phase, inflammatory, bone and cartilage markers. Baseline levels and early changes in levels of select markers were associated with clinical response to golimumab in AS patients [21].

Health-related quality of life was found to be significantly improved with 50 and 100 mg golimumab as early as week 14, and was maintained through week 24 as assessed using Physical Component Summary and Mental Component Summary scores of the Short Form 36 (SF-36®) Health Survey [22]. Significant improvement in functionality and self-reported productivity in patients with active AS was also found at week 24 [23]. In addition, sleep was significantly improved after treatment [24].

As measured by the 13-point Maastricht AS Enthesitis Score and University of California San Francisco indices for measuring enthesitis, significant improvement was found at week 24 [25]. The results from the GO-RAISE trial have recently been published, as summarized in Table 3. Patients receiving golimumab also showed significant improvement in the physical and mental component summary scores of the SF-36 Health Survey, the Jenkins Sleep Evaluation Questionnaire score, the Bath Ankylosing Spondylitis Disease Activity Index score, and the Bath AS Functional Index score, but not the Bath AS Metrology Index score [26]. Thus, evidence is being consolidated for the use of golimumab in RA, PsA and AS.

Safety & tolerability

The first human study of golimumab pharmacokinetics also looked at the safety profile of the drug [11]. Adverse events were generally mild-to-moderate, and there was no clear dose-related trend in their incidence. In addition, antibodies to golimumab were detected in a small number of patients in each of the dose cohorts, and their presence did not correlate with the incidence of any adverse event.

The study by Kay *et al.* [12] reported mild-to-moderate adverse events that were comparable between the placebo group (85.3%) and the combined golimumab groups (86.1%). Nausea, headaches, injection-site erythema and worsening of RA disease activity were the most common in the combined groups. Patients who received 100 mg golimumab every 2 weeks had an increased incidence of injection-site reactions, but no patient discontinued treatment due to injection site reaction. The overall rate of infection in each of the golimumab groups was not greater than that observed in the placebo group.

Serious adverse events were reported by 5.9% of patients in the placebo group and by 8.8% of patients in the combined treatment group. Adverse events included pneumonia, congestive heart failure, cardiac tamponade, lung cancer, squamous cell carcinoma and basal cell carcinoma. The safety profile during the follow-up period through week 52 was similar in all groups. There were no cases of TB or lymphoma. No deaths occurred during the 52-week study period. This study reported antibodies to golimumab in 6.5% of patients at week 48. However, there was no association of antibodies with nonresponse or serious adverse events. Through week 52, 21% of patients in the combined treatment group developed antinuclear antibodies as compared with 18% of patients in the placebo group, and no lupus-like syndrome was reported [12].

The results of the GO-RAISE, GO-BEFORE, GO-FORWARD and GO-REVEAL studies, as presented at the EULAR 2008 meeting, all showed the safety profile of golimumab to be similar to the other three marketed anti-TNF agents.

Conclusion

Data have been emerging concerning the benefits of switching anti-TNF agents. Based on treatment continuation rates, there is a strong case for switching patients to a second anti-TNF agent when failure to respond to the first agent occurs. Studies from a large dataset from the UK (the British Society for Rheumatology Biologics Register) showed that more than 70% of patients with RA, PsA and AS continued on a second agent for at least 6 months [7].

The anti-TNF agents bind with different affinity and avidity and to different epitopes, which could mean different efficacy in individual patients. It may actually be the genetic factors of the individuals and the phenotype of the disease that lead to differential response. Other minor differences, such as the development of antibodies and small differences in adverse events, for example, infusion reactions with infliximab and injection site reactions with etanercept and adalimumab, also exist. Hence, there is an unmet need for newer anti-TNF agents.

Golimumab has shown promising results in terms of efficacy and safety, and should be considered as an alternative treatment for RA, PsA and AS. In MTX-naive patients, golimumab has been found to be noninferior to MTX alone and superior when used in combination with MTX. In patients previously treated with MTX, the study

detected superiority of the MTX plus golimumab combination. ACR20 response was achieved in 59.6% patients, which is comparable with results from large trials for other anti-TNF agents. The first randomized, double-blind, placebo-controlled trial on patients failing anti-TNF therapy has shown statistically significant improvement after treatment with golimumab. This offers a useful evidence-based option for patients who have failed anti-TNF therapy. In addition, the results of the GO-REVEAL study and the GO-RAISE trial have achieved statistical significance and confirmed the versatility of golimumab.

The 4-weekly subcutaneous administration offers more convenience to patients, as compared with the weekly or fortnightly administration of etanercept and adalimumab. Golimumab has also been found to be safe, and in particular, no cases of TB or lymphoma were found after 1 year of follow-up. No deaths have been reported. In addition, the minor adverse events were the same as in the placebo group and were not dose-dependent.

Despite the initial promising results, long-term data are needed to further consolidate the long-term efficacy and safety. The effects on radiographic progression have not yet been reported. Nevertheless, golimumab is a useful, effective and safe alternative therapy for RA, PsA and AS.

Regulatory affairs

In February 2008, Centocor (PA, USA) submitted a Marketing Authorisation Application to EMEA, and has submitted application for approval to the US FDA for marketing of golimumab in June 2008.

Future perspective

Biological therapy for rheumatoid arthritis has changed the outcomes for this condition in a very short time. However, it is now clear that not all patients respond to a single biological therapeutic agent and the response in many cases is either not sustained or remains partial. Clearly, there is a need for better therapeutic agents with more convenient routes of administration, greater efficacy and perhaps lesser immunogenicity. Golimumab represents one such therapeutic formulation with these required features. Long-term data regarding the safety and efficacy of golimumab is needed. Other anti-TNF agents, like certolizumab (pegylated human anti-TNF monoclonal antibody), CDP-571, pegsunercept (pegylated natural TNF p55 type I receptor molecule), and onercept (recombinant TNF binding protein) are being developed with different mechanisms of action to add to the armamentarium of biologic agents to treat inflammatory arthritis.

Executive summary

Mechanism of action

- Golimumab is a human monoclonal antibody directed against circulating and membrane-bound TNF-α.

Pharmacokinetic properties

- Detectable concentrations of golimumab were observed in the majority of patients through week 4 in pharmacokinetic studies.
- Median trough concentrations increased as the dose increased and attained steady state by week 12 for all dosage groups.

Clinical efficacy

- The Phase III dose finding (randomized, double-blind, placebo-controlled, dose-ranging study of golimumab in active rheumatoid arthritis despite methotrexate [MTX]) demonstrated the efficacy and preliminary safety of 50 and 100 mg golimumab administered subcutaneously every 2 or 4 weeks with concomitant MTX. A total of 61% of the combined golimumab plus MTX dose groups achieved an ACR20 response at week 16, compared with 37% of the placebo plus MTX group.
- Subsequent Phase III trials confirmed the efficacy of golimumab administered monthly in MTX-naive, MTX-inadequate responders, and after anti-TNF patient groups with active rheumatoid arthritis have also reported significant improvement.
- In a randomized, placebo-controlled trial in psoriatic arthritis, active psoriatic arthritis and skin disease improved through week 52 at doses of 50 mg every 4 weeks and 100 mg every 4 weeks.
- In a randomized, placebo-controlled trial in ankylosing spondylitis, signs, symptoms and physical functions improved in patients with ankylosing spondylitis through week 24. Productivity, health-related quality of life and sleep have also been shown to significantly improve.

Safety & tolerability

- Safety analysis has shown minimal difference between treatment groups and placebo groups. Serious adverse events have been reported in 9% of the combined golimumab groups versus 6% of placebo groups.

Dosage & administration

- Golimumab is administered subcutaneously at a dose of 50 or 100 mg every 4 weeks. It is also being developed for intravenous use.

Financial & competing interests disclosure

Dr Bhagat has no interests to declare. Professor Dasgupta has received honoraria from Roche, Servier and Merck for various advisory board meetings and speaking engagements. He is a member of the Trial Stearing Group of a Phase II study of golimumab in RA. Dr Mahboob Rahman is an employee of Johnson & Johnson/Centocor R&D Inc. and owns Johnson & Johnson stock. The authors have no other relevant affiliations or financial involvement with any organization or entity with a financial interest in or financial conflict with the subject matter or materials discussed in the manuscript apart from those disclosed.

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▪▪ **Serum antibodies to adalimumab against adalimumab are associated with lower serum concentrations of adalimumab and nonresponse to adalimumab therapy.**

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