Drug Evaluation

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Role of golimumab for the treatment of rheumatoid arthritis

Golimumab, a fully humanized anti-TNFα monoclonal antibody, is a recent addition to this class of biological agents used in the treatment of rheumatoid arthritis (RA). Phase II and III trials have shown that subcutaneous and intravenous administration of golimumab alongside methotrexate is both efficacious and well tolerated in treating RA. As with other TNF inhibitors, studies have shown no increased risk of death or malignancy with its use, although there is potentially an increased risk of serious infection. Golimumab is a safe and effective treatment in RA and, uniquely within this class, has been shown to be effective in patients who have failed previous anti-TNFα treatment.

Keywords: golimumab • TNFα inhibitor • rheumatoid arthritis

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Rheumatoid arthritis (RA) is a chronic autoimmune inflammatory disease, resulting in synovial damage and bone destruction. Its worldwide prevalence varies between 0.1% in developing countries up to 1.1% in Northern Europe and Northern America, with an estimated annual incidence of between 20 and 50 per 100 000 [1]. Furthermore, patients with RA have a reduced life expectancy of between 3 and 10 years, a trend that has remained unchanged over the last four to five decades [2]. The socioeconomic burden of RA is large, with the total economic costs estimated at over €40 billion in Northern America and Europe. RA also has a significant impact on the quality of life, with health utility values comparable to those patients suffering from multiple sclerosis [3].

Current treatment options for RA include conventional standard disease-modifying antirheumatic drugs (DMARDs) such as methotrexate, sulfasalazine, leflunomide and hydroxychloroquine, as well as biological DMARDs such as TNFα inhibitors. A recent addition to this class of drug is golimumab. The objective is this article is to evaluate the efficacy and safety profile of this drug, as well as provide an insight into its clinical use.

Overview of the market

Over the last decade, the therapeutic options in treating RA have dramatically evolved and the introduction of biological agents has significantly altered the clinical course of the disease. Drugs targeting TNFα have been shown to reduce radiological progression [4], induce remission [5] and improve function and work participation [6]. The first three TNF inhibitors to emerge were infliximab (a chimeric human/murine monoclonal antibody), etanercept (a fusion protein of the TNF receptor 2 and Fc portion of human immunoglobulin gamma 1) and the fully humanized antibody, adalimumab. Recently, there have been two further additions: certolizumab (a human Fab fragment linked to polyethylene glycol) and golimumab, a fully humanized antibody.

Introduction to the drug

Among the inflammatory cytokines involved in RA, TNFα plays a prominent role. Patients with active arthritis have been shown to have high levels of TNFα and TNFR in serum and synovial samples [7,8]. Furthermore, in animal models expressing transgenic human TNFα, an inflammatory arthritis phenotype has been observed [9]. Finally, the revolutionary role of TNF inhibitors in improving patient

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outcomes, particularly in patients who have failed conventional standard DMARDs, has demonstrated the importance this cytokine plays in the pathogenesis of RA [10,11].

TNFα exerts a potent effect on a variety cells and in particular plays a key proinflammatory role via activation of downstream mediators and inducing apoptosis. TNF is a transmembrane homotrimeric protein that can be proteolytically cleaved to form a soluble protein. Both the membrane and soluble forms are biologically active. TNF binding to two different receptors, TNFR1 and TNFR2, results in a downstream cascade of activating MAPK and NF-κB, which are both key proinflammatory mediators [12]. Furthermore, activation of TNFR1 results in the activation of proapoptotic proteins via the FADD pathway.

Golimumab is a humanized monoclonal antibody directed against TNFα, which was approved for clinical use in combination with methotrexate in Europe and the USA in 2009. Transgenic mice were developed to express human IgG having been exposed to human TNFα. The resulting hybridoma cell lines led to four human antibodies with a high affinity and neutralizing ability to TNFα. The most potent of these, golimumab, was put forward for further evaluation [13]. Golimumab is licensed in the USA and EU for the treatment of RA, to be given subcutaneously at doses of either 50 or 100 mg once a month, and should be used in combination with methotrexate [14,15].

Pharmocokinetics & pharmocodynamics

Golimumab binds to soluble TNFα with the dissociation equilibrium constant at 18 pM. Its affinity for transmembrane TNFα was significantly less at 1890 pM. The IC50 on soluble TNFα was shown to be 6.5 ng/ml and 162 ng/ml for transmembrane TNFα when measured using cytotoxicity assay. This was significantly lower when compared with infliximab (24.2 ng/ml) and adalimumab (36.4 ng/ml), suggesting a lower serum concentration of golimumab could provide a similar effect [13].

The pharmacokinetic properties of a single intravenous (iv.) golimumab infusion was evaluated at varying doses from 0.1 to 10 mg/kg [16]. The median half-life was found to be proportional to the dose administered and ranged from 6.6 to 19.3 days, although this variation was thought to be due to a result of assay detection limitation at the lower doses. In a separate study, the mean half-life was 11.8 days in those receiving a single dose of 100 mg golimumab iv. [17]. Studies have shown that clearance ranged from 4.89 to 7.5 ml/d/kg and this was independent of dose [14,18]. The volume of distribution ranged from 58 to 126 ml/kg [14]. 100 mg iv. golimumab has shown a mean maximum serum concentration of 29.53 μg/ml [17]. For iv. administration of 2 mg/kg, the maximum concentration was 44.4 μg/ml at first dose and 45.7 μg/ml 12 weeks later [18]. In a Phase III trial, a dose-dependent increase in median serum golimumab concentration was observed, with those receiving combination with methotrexate having higher levels compared with golimumab monotherapy [19].

The median time to maximum concentration in subcutaneous administration was found to be 4 days, with a mean maximum serum concentration value of 6.3 μg/ml in healthy adults receiving 100 mg golimumab [17]. The half-life was found to be 10.9 days and the bioavailability was 51.1% in those receiving golimumab [17]. In a further study in RA patients receiving six 100 mg subcutaneous injections every 4 weeks, a steady serum golimumab concentration was maintained by week 12 with a trough concentration of 1.15–1.24 μg/ml and a mean half-life of 13.1 days and bioavailability of 53% [18]. It has been shown that the median time from maximum serum concentration in subcutaneous administration ranges from 2 to 6 days, with a mean maximum serum concentration of 2.5 μg/ml [14]. In a different study, differences in maximum serum concentrations were found between the first (5.13 μg/ml) and last dose (6.13 μg/ml) [18]. The time to peak serum concentration was 3.5 days after the first dose and 3.0 days after the last dose [18]. In patients receiving subcutaneous golimumab at 50 and 100 mg every 4 weeks alongside methotrexate, the steady-state tough serum concentrations at week 16 were 0.5 and 1.2 μg/ml, respectively [20].

Phase I study

In addition to the pharmacokinetics and pharmocodynamic properties, further studies have evaluated the effect of golimumab on inflammatory markers.

The administration of 100 mg subcutaneous golimumab every 4 weeks or 2 mg/kg iv. golimumab 12 weeks apart in RA patients has demonstrated reduced levels of the inflammatory markers CRP, IL-6, serum amyloid A (SAA), TNFRII, MMP-3, haptoglobin and serum/urine hepcidin [21]. These were shown to be reduced within 24 h and maintained at week 8. Inflammatory markers in those receiving the iv. form showed a return to baseline at 24 weeks. Those receiving subcutaneous injections showed a sustained reduction in all markers except haptoglobin at 24 weeks.

Another study showed that golimumab plus methotrexate significantly reduced serum IL-18, CRP, SAA, E-selectin, TIMP-1 and MMP-9 levels compared with placebo through to week 16 [22]. Furthermore, a reduction in SAA, E-selectin and MMP-9 at week 4 correlated significantly with improvement in DAS28 at week 16.

Phase II study

The effect of subcutaneous golimumab alongside methotrexate was evaluated in a randomized double-blinded placebo-controlled trial involving 172 patients [20]. Patients were randomized to either receive placebo, 50 mg golimumab every 2 weeks, 50 mg every 4 weeks, 100 mg every 2 weeks or 100 mg every 4 weeks. At week 20, those receiving golimumab every 2 weeks were switched to injections every 4 weeks through to week 48. Those receiving placebo were switched to infliximab. Compared to the placebo plus methotrexate group, there was a significant improvement in ACR20 response in those receiving combined golimumab plus methotrexate (37.1 and 61%, respectively; $p = 0.010$). A significant difference was found in those receiving 100 mg golimumab every 2 weeks (79.4%; $p < 0.001$) at week 16. Although the other individual golimumab groups did not achieve statistical significance in ACR20, they did for ACR50 when compared with placebo. Those who were switched from injections every 2 weeks to every 4 weeks, did so without a significant effect on ACR20 responses.

In another randomized double-blinded placebo-control trialled involving 269 Japanese patients, patients were randomized to receive placebo, or subcutaneous golimumab 50 mg or 100 mg alongside a relatively lower dose of 6–8 mg methotrexate every 4 weeks [23]. At week 16, patients not reaching ACR20 could enter an early escape where those taking placebo received 50 mg golimumab and those receiving 50 mg had their dose increased to 100 mg. At 14 weeks, there was a significant improvement in patients receiving 50 mg golimumab (72.1%; $p < 0.0001$) and 100 mg (74.7%; $p < 0.0001$) versus placebo (27.3%) in terms of ACR20, ACR50 and ACR70. This was also the case at week 24. Furthermore, improvements in other markers such as DAS28 CRP, DAS28 ESR and health assessment questionnaire disability index (HAQ-DI) at weeks 14 and 24 was seen in patients taking golimumab compared with placebo. At week 24, significantly less radiographic progression was seen in those taking golimumab.

The GO-MONO study evaluated the efficacy and safety of subcutaneous golimumab 50 and 100 mg monotherapy in patients who had previously been exposed to nonbiological DMARDs [24]. A total of 316 patients were randomized to receive placebo (group 1), subcutaneous golimumab 50 mg (group 2) or golimumab 100 mg (group 3). At week 16, group 1 received golimumab 50 mg. At week 14, 50.5% of group 2 and 58.8% of group 3 achieved an ACR20 compared with 19% of group 1 ($p < 0.0001$). Similar significant improvements were also seen in ACR50, ACR70 and DAS28 response rates. *A priori* analysis of covariance (ANCOVA) demonstrated no significant difference in radiographic progression between groups, but *post hoc* analysis using normalized data did show significantly smaller changes in erosion and total van der Heijde/Sharp score (vdH–S) from baseline in group 3 compared with group 1. Table 1 provides a summary of the Phase II trials.

Phase III study

The safety and efficacy of golimumab was studied in a Phase III multicenter, randomized double-blinded, placebo-controlled trial involving 637 TNFα inhibitor-naive patients who had received less than 3 doses of methotrexate (Table 2) [25]. This GO-BEFORE study randomized patients to receive methotrexate plus placebo (group 1), 100 mg golimumab plus either placebo (group 2) or methotrexate (group 4), or 50 mg golimumab plus methotrexate (group 3). Golimumab was administered via subcutaneous injections every 4 weeks and methotrexate was titrated to 20 mg/week by week 8. Patients with <20% improvement in swollen and tender joint count at week 24 entered early escape: group 1 switched to 50 mg golimumab, group 2 had methotrexate added, group 3 increased the dose of golimumab to 100 mg and group 4 continued [26]. Patients with ≥1 swollen/tender joints in group 1 at week 52 were switched to golimumab 50 mg plus methotrexate if they were not entered into early escape. After 52 weeks, unblinding occurred and methotrexate, steroids and golimumab could be altered according to the investigator's discretion.

Its co-primary end points were improvement in ACR50 and inhibition of radiographic progression at week 24. Based on an intent-to-treat (ITT) analysis at week 24, there was no significant difference in ACR50 response between groups 3 and 4 combined when compared with group 1 (38.4 and 29.4%, respectively; $p = 0.053$). However, *post hoc* ITT analysis, which excluded three untreated patients, did show that the combined golimumab plus methotrexate groups were better than methotrexate alone (38.5 vs 29.4%; $p = 0.049$), and that golimumab alone was noninferior to methotrexate alone. These findings were maintained through weeks 52 and 104 [26]. At week 24, there was a significant improvement in ACR20 in group 3 (61.6%) and 4 (61.6%) when compared with group 1 (49.4%; $p = 0.028$) [25]. Improvement in HAQ at week 52 was seen in all groups. The 5-year follow-up demonstrated sustained improvements in ACR20, DAS28-CRP EULAR response and HAQ-DI ≥0.25 [27].

Radiographs taken at baseline, week 28 and week 52 demonstrated that golimumab in combination with methotrexate significantly inhibited radiographic progression (mean vdH–S change of 0.41) when compared with methotrexate alone (1.37; $p = 0.006$) at week 52 [28]. Golimumab monotherapy, however, showed no statistical difference compared with methotrexate monotherapy. At 5-year follow-up, 64% of patients randomized to

Table 1. Summary of Phase II trials.

Trial	Aims	Primary end points	Inclusion criteria	Methods	Results	Safety	Ref.
Kay *et al.* (2008)	To assess the efficacy, safety and pharmacology of subcutaneous GLM in patients with active RA despite MTX	ACR20 at week 16	Patients on stable does MTX ≥10 mg/week for ≥3 months and stable dose for ≥4 weeks Active RA defined by ≥6 swollen and ≥6 tender joints and 2 out of 3 of: CRP ≥1.5 mg/dl, ESR ≥28 mm/h, morning stiffness ≥30 min Oral corticosteroids at a dosage ≤10 mg of prednisone per day at stable dose ≥4 weeks prior to enrollment	172 patients on stable-dose MTX assigned to placebo, GLM 50 mg every 2 weeks, GLM 50 mg every 4 weeks, GLM 100 mg every 2 weeks and GLM every 4 weeks Patients at week 20 received open-label infliximab at week 20; those on injections every 2 weeks had their intervals increased to every 4 weeks	61% of patients in the combined GLM groups achieved an ACR20 response at week 16 compared with 37% placebo + MTX group ($p = 0.010$) 79% of the 100 mg GLM group every 2 weeks achieved an ACR20 response compared with placebo ($p < 0.001$) Significant difference in ACR50 in individual groups receiving GLM compared with placebo	3 serious infections in patients who received GLM No TB or lymphoma through to week 52 4 cases of cancer (1 lung cancer, 1 squamous cell cancer, 2 basal cell cancer skin) No deaths at week 52 No lupus-like symptoms described Nausea most-common side effect although no discontinuation from this	[20]
GO-FORTH	To assess the efficacy and safety of subcutaneous GLM + MTX in Japanese patients with active RA	ACR20 at week 14	Received ≥6 mg/week oral MTX for RA for ≥3 months before study agent initiation Stable MTX doses (6–8 mg/week) required for ≥4 weeks prior to the starting the study Active RA ≥3 months defined by: ≥4/66 swollen joints and ≥4/68 tender joints + ≥2 of the following: CRP >1.5 mg/dl or ESR >28 mm/h, morning stiffness ≥30 min, radiographic evidence of bone erosion, anti-CCP antibody-positive or rheumatoid factor-positive	269 patients on stable-dose MTX (6–8 mg) randomized to receive placbo (group 1), GLM 50 mg (group 2), GLM 100 mg (group 3) At week 14, patients with <20% improvement from baseline in tender and swollen joint counts could enter early escape: group 1 received GLM 50 mg, group 2 increased to GLM 100 mg and group 3 continued GLM 100 mg	Significant improvement in ACR20 in combined GLM groups (73.4%), group 2 (72.1%) and group 3 (74.7%) compared with group 1 (27.3%; $p < 0.0001$) At week 24, significant reduction in DAS28 response/remission, HAQ-DI and radiographic assessments compared with placebo	1 serious infection in group 3 at week 24 2 malignancies in group 2 at week 24 At week 16 1.1, 3.5 and 6.9% of patients in groups 1, 2 and 3, respectively, discontinued the study agent because of an AE	[23]

ACR20: American College of Rheumatology 20% improvement response; ACR50: American College of Rheumatology 50% improvement response; AE: Adverse event; ESR: Erythrocyte sedimentation rate; GLM: Golimumab; HAQ-DI: Health assessment questionnaire disability index; MTX: Methotrexate; RA: Rheumatoid arthritis; SAA: Serum amyloid A; TB: tuberculosis.

Table 1. Summary of Phase II trials (cont.).

Trial	Aims	Primary end points	Inclusion criteria	Methods	Results	Safety	Ref.
GO-MONO	To evaluate the efficacy and safety of Subcutaneous GLM 50 and 100 mg monotherapy in Japanese patients with RA despite previous DMARD treatment	ACR20 at week 14	Active RA ≥3 months, despite previous DMARD treatment Active defined as ≥6 swollen joints and ≥6 tender joints and ≥2 of the following: CRP ≥2.0 mg/dl or ESR ≥28 mm/h, morning stiffness ≥30 min, evidence of bone erosion on radiographs, anti-CCP antibodies or rheumatoid factor positive All DMARDs discontinued ≥4 weeks prior to trial Oral corticosteroids (stable dose ≤10 mg of prednisolone/day or equivalent) allowed	316 patients receive placebo (group 1), subcutaneous GLM 50 mg (group 2), GLM 100 mg (group 3) At week 16, group 1 received GLM 50 mg	Significantly greater ACR20 response rate in groups 2 (51/101; 50.5%) and 3 (60/102; 58.8%) than in group 1 (20/105; 19.0%; p < 0.0001)	1 serious infection in each group No deaths or TB reported 1 malignancy in group 3	[24]

ACR20: American College of Rheumatology 20% improvement response; ACR50: American College of Rheumatology 50% improvement response; AE: Adverse event; ESR: Erythrocyte sedimentation rate; GLM: Golimumab; HAQ-DI: Health assessment questionnaire disability index; MTX: Methotrexate; RA: Rheumatoid arthritis; SAA: Serum amyloid A; TB: tuberculosis.

golimumab and methotrexate had no radiographic progression [27]. In a further follow-up, patients with CRP >1 mg/dl patients treated with golimumab and methotrexate demonstrated significantly less radiographic disease progression compared with those on methotrexate alone [26]. This was consistent with findings at week 104 [26]. In an MRI substudy of 318 patients up to week 24, the combined golimumab and methotrexate group demonstrated significant improvement in synovitis, osteitis and bone erosion compared with placebo plus methotrexate as early as week 12 [29]. In patients treated with golimumab monotherapy, there was a significant improvement in wrist synovitis and bone osteitis, but not erosions, compared with placebo in combination with methotrexate at week 12. This difference was only observed for osteitis at week 24. This suggests that golimumab monotherapy produced a faster onset of action in reducing osteitis compared with methotrexate alone.

The GO-FORWARD trial assessed the efficacy and safety of subcutaneous golimumab every 4 weeks in patients with RA and not responsive to a stable dose of at least 15 mg methotrexate. In this multicenter, randomized, double-blinded, placebo-controlled trial, 444 patients were randomized to placebo and methotrexate (group 1), 100 mg golimumab and placebo (group 2), 50 mg golimumab and methotrexate (group 3) or 100 mg golimumab and methotrexate (group 4) [30]. At week 16, those with less than 20% improvement entered early escape in a double-blind fashion. Group 1 received 50 mg golimumab, group 2 received their usual stable dose of methotrexate and group 3 had their golimumab dose increased to 100 mg. At week 24, patients in group 1 had 50 mg golimumab plus methotrexate, irrespective of whether they were placed in the escape group or not.

The co-primary end points were improvements in ACR20 at week 14 and HAQ-DI at week 24. ACR20 response was significant in groups 3 (55.1%; p = 0.001) and 4 (56.2%; p < 0.001) but not group 2 (44.4%; p = 0.059). Similarly, significant median improvement in HAS-DI was seen in group 3 (0.38; p < 0.001) and 4 (0.50; p < 0.001), but not group 2 (0.13; p = 0.240). Furthermore, patients receiving golimumab plus methotrexate demonstrated a significant improvement in physical function, general health and fatigue when compared with placebo as demonstrated by the Study Short Form-36 questionnaire (SF-36) and the Functional Assessment of Chronic Illness Therapy-Fatigue (FACIT-Fatigue) questionnaire [31]. These results suggest that the addition of golimumab to methotrexate significantly improved the signs and symptoms of RA and physical function. Data at 52 weeks demonstrated that these response rates were sustained [31,32].

Radiographic changes, assessed as a secondary end point, demonstrated no significant differences in any of

the groups [28]. This may have been due to the majority of patients in the study having low levels of CRP, less disease activity at baseline and the limitations of the study design with regards to power for radiographic detection. A substudy of 240 patients in the GO-FORWARD trial evaluated the effectiveness of golimumab on MRI-detected synovitis, osteitis and bone erosions [33]. MRI of the dominant wrist and metacarpophalangeal joints were obtained at baseline and weeks 12 and 24. Patients receiving golimumab and methotrexate showed significant improvement in synovitis and osteitis compared with placebo at weeks 12 and 24. All treatment groups showed minimal erosive progression, therefore the effect of golimumab could not be analyzed.

The GO-AFTER trial assessed the efficacy of patients with RA who had previously been exposed to one or more TNFα inhibitors [34]. This international, multicenter, randomized, double-blind, placebo-controlled trial allocated 461 patients to receive subcutaneous injections of placebo, golimumab 50 mg or golimumab 100 mg every 4 weeks. These patients were permitted the concomitant use of methotrexate, sulfasalazine or hydroxychloroquine (alone or combined) if they were on a stable dose prior to enrolment. Its primary end point was achievement of ACR20 at week 14. Patients with less than 20% improvement in swollen and tender joint count received rescue therapy: placebo group were given 50 mg golimumab and the 50 mg group were given 100 mg golimumab. At week 14, an ACR20 was achieved in 18% of patients receiving placebo, 35% of patients receiving golimumab at 50 mg (odds ratio: 2.5 [95% CI: 1.5–4.2]; p = 0.0006), and 38% on 100 mg (odds ratio: 2.8 [1.6–4.7]; p = 0.0001). This difference was higher in the combined golimumab group for those taking concomitant DMARDs, compared with the placebo group. This difference was maintained at week 24.

Table 2. Summary of Phase III trials.

Study	Aim	Primary end points	Inclusion criteria
GO-BEFORE	To assess the efficacy and safety of subcutaneous GLM in MTX-naive patients with active RA	ACR50 response at week 24 Radiographic change from baseline in the modified Sharp/van der Heijde score at week 52	RA ≥3 months receiving ≤3 weekly doses of MTX ≥4 swollen and ≥ 4 tender joints and ≥2 of the following: CRP >1.5 mg/dl or ESR >28 mm/h, morning stiffness ≥30 min, radiographic/MRI evidence of bone erosion, anti-CCP antibody-positive or rheumatoid factor-positive Concurrent use of NSAIDs, other analgesics for RA, and oral corticosteroids (≤10 mg of prednisone/day or equivalent) was allowed if doses were stable for ≥2 weeks prior to trial Patients who had previously received adalimumab, infliximab, etanercept, natalizumab, rituximab or cytotoxic agents, including chlorambucil, cyclophosphamide or other alkylating agents, were excluded. Patients receiving anakinra, or alefacept or efalizumab, could participate 4 weeks and 3 months, respectively, after receiving the last dose

ACR20: American College of Rheumatology 20% improvement response; ACR50: American College of Rheumatology 50% improvement response; ACR70: American College of Rheumatology 70% improvement response; DAS28: Disease Activity Score in 28 joints; ESR: Erythrocyte sedimentation rate; EULAR: European League Against Rheumatism; GLM: Golimumab; HAQ: Health assessment questionnaire; HAQ-DI: Health assessment questionnaire disability index; iv.: Intravenous; MTX: Methotrexate; RA: Rheumatoid arthritis; SDAI: Simplified disease activity index.

In a long-term follow-up through to week 160, 236 patients continued the trial [35]. The remaining patients exited due to poor therapeutic response or adverse events. At week 160 ACR20 response was seen in 63% of group 1, 67% in group 2 and 57% in group 3. Those receiving rescue therapy from 50 to 100 mg showed improvements in ACR20, ACR50 and DAS28 12 weeks following escalation. The response rate in patients who received golimumab since week 0 was also seen in patients who had rescue therapy from placebo to 50 mg golimumab. Although difficult to draw firm conclusions from this long-term follow-up due to the lack of power and that dose escalation was due to the sole discretion of the investigator, this study helps to support the long-term efficacy of golimumab with prior TNFα inhibitor treatment. Furthermore, to the best of our knowledge, golimumab is the only TNFα inhibitor to have been shown in randomized control trials to have data supporting efficacy in patients who have failed previous anti-TNFα treatment. Although there have been previous studies investigating TNFα inhibitor switch, these have largely been small, nonrandomized studies or come from biologics registries [36]. In addition, 100 mg golimumab may be more efficacious than 50 mg, although further work needs to be done with regards to this.

The GO-FURTHER is a randomized, multicenter, double-blind, placebo-controlled trial assessing the efficacy of iv. golimumab 2 mg/kg plus methotrexate. A total of 592 patients on stable methotrexate were randomized to receive golimumab infusions at 2 mg/kg or placebo at weeks 0, 4 and every 8 weeks [37]. Its primary end point was ACR20 at 14 weeks. This was achieved in 58.5% of those receiving golimumab plus MTX compared with 24.9% in placebo plus MTX ($p < 0.001$). Furthermore, a significant difference was seen as early as week 2. DAS28-CRP moderate/good response, SDAI, CDAI and HAQ were also significantly improved in the golimumab plus MTX group at week 14.

Table 2. Summary of Phase III trials (cont.).

Methods	Results	Safety	Ref.
637 patients Group 1 (n = 160): placebo + MTX; group 2 (n = 159): GLM 100 mg + placebo; group 3 (n = 159): GLM 50 mg + MTX; group 4 (n = 159): GLM 100 mg + MTX Injections were every 4 weeks Early escape for patients with <20% improvement in both swollen and tender joint counts after week 24; group 1 switched from placebo to GLM 50 mg, group 2 switched from placebo to MTX capsules, group 3 increased GLM to 100 mg. Patients in group 4 continued to receive GLM 100 mg + MTX through week 48 At week 52, patients in group 1 with ≥1 tender or swollen joint received GLM 50 mg + MTX if they had not early escaped after week 24 Patients entered the open-label study extension at week 52. MTX and corticosteroids could be adjusted and the GLM escalated at the investigator's sole discretion	No significant difference in ACR50 at week 24 between combined GLM group and group 1 *Post hoc* modified intention-to-treat analysis did demonstrate statistical significant ACR50 response between combined GLM group and group 3 compared with group 1 Group 2 is not inferior to group 1 in ACR response at week 24 Improvement of GLM + MTX compared with placebo + MTX in ACR20, DAS28 response/remission and HAQ at week 24 At week 52 and 104, ACR20, ACR50 and DAS28 response/remission significantly improved in Combined groups 3 and 4 vs group 1. Clinical but not statistical improvement in HAQ score At week 52, GLM + MTX inhibited radiographic progression significantly better than MTX alone and in patients with CRP >1.0 mg/dl Com + MTX group demonstrated significant improvement in synovitis, osteitis and bone erosion compared with placebo + MTX as early as week 12	At week 104 incidences (95% CI) of serious infections in patient-years of follow-up: 2.58 (0.70–6.61) for group 1, 2.21 (0.72–5.15) for group 2, 4.28 (2.45–6.95) for group 3 and 6.21 (3.98–9.24) for group 4 Active TB in 11 patients receiving GLM at week 104 8 deaths at week 104: incidences (95% CIs) of death/100 patient-years were 0.00 (0.00–1.93) for group 1, 0.88 (0.11–3.19) for group 2, 1.07 (0.29–2.74) for group 3 and 0.52 (0.06–1.87) for group 4 14 malignacies: malignancy incidences (95% CIs)/100 patient years of follow-up were 1.93 (0.40–5.65) for group 1, 0.88 (0.11–3.19) for group 2, 1.61 (0.59–3.49) for group 3 and 0.78 (0.16–2.27) for group 4 No lupus-like syndrome in any patient at week 24 No patient in any treatment group had newly positive anti-dsDNA antibodies at week 24 More patients in groups 3 and 4 discontinued study agents compared with group 1 or group 2 at week 24. At week 52, 28 (7.6%) GLM + MTX patients discontinued subcutaneous study agent, compared with 6 (3.8%) placebo + MTX	[25–26,28–29]

ACR20: American College of Rheumatology 20% improvement response; ACR50: American College of Rheumatology 50% improvement response; ACR70: American College of Rheumatology 70% improvement response; DAS28: Disease Activity Score in 28 joints; ESR: Erythrocyte sedimentation rate; EULAR: European League Against Rheumatism; GLM: Golimumab; HAQ: Health assessment questionnaire; HAQ-DI: Health assessment questionnaire disability index; iv.: Intravenous; MTX: Methotrexate; RA: Rheumatoid arthritis; SDAI: Simplified disease activity index.

Table 2. Summary of Phase III trials (cont.).

Study	Aim	Primary end points	Inclusion criteria
GO-FORWARD	To assess the efficacy and safety of subcutaneous GLM on stable-dose MTX in patients with active RA	ACR20 at week 14 Change from baseline in HAQ-DI score at week 24	≥3 months RA Active defined as ≥4/66 swollen joints and ≥4/88 tender joints and ≥2 of the following: CRP >1.5 mg/dl or ESR >28 mm/h, morning stiffness ≥30 min, radiographic/MRI evidence of bone erosion, anti-CCP antibody-positive or rheumatoid factor-positive Concurrent use of NSAIDs, other analgesics for RA, and oral corticosteroids (≤10 mg of prednisone/day or equivalent) was allowed if doses were stable for ≥2 weeks prior to trial Stable-dose MTX 15–25 mg/week for ≥3 months Excluded if previous biologics or cytotoxic agents. Also if DMARDs except MTX or intramuscular, iv. or intra-articular corticosteroids used ≤4 weeks to commencing trial
GO AFTER	To assess the efficacy and safety of subcutaneous GLM in patients with active RA with previous exposure to TNFα inhibitor	ACR20 at week 14	Active RA: ≥3 months of ≥4 swollen and ≥4 tender joints Treated with ≥1 TNFα inhibitor Concomitant DMARD treatment with MTX, sulfasalazine and hydroxychloroquine ≥12 weeks at stable dose ≥4 weeks prior to study. Concurrent use of NSAIDs, other analgesics for RA, and oral corticosteroids (≤10 mg of prednisone/day or equivalent) was allowed if doses were stable for ≥2 weeks prior to trial

ACR20: American College of Rheumatology 20% improvement response; ACR50: American College of Rheumatology 50% improvement response; ACR70: American College of Rheumatology 70% improvement response; DAS28: Disease Activity Score in 28 joints; ESR: Erythrocyte sedimentation rate; EULAR: European League Against Rheumatism; GLM: Golimumab; HAQ: Health assessment questionnaire; HAQ-DI: Health assessment questionnaire disability index; iv.: Intravenous; MTX: Methotrexate; RA: Rheumatoid arthritis; SDAI: Simplified disease activity index.

Table 2. Summary of Phase III trials (cont.).

Methods	Results	Safety	Ref.
Patients needed to have tolerated MTX ≥3 months at dose 15–25 mg/week 444 patients randomized to placebo + MTX (group 1), GLM 100 mg + placebo (group 2), GLM 50 mg + MTX (group 3) or GLM 100 mg + MTX (group 4) Injections every 4 weeks Early escape at week 16 for groups 1, 2 or 3 with <20% improvement in tender and swollen joint counts. Group 1 received additional GLM 50 mg. Group 2 received active MTX at the same stable dose at screening. Group 3 had GLM increased to 100 mg At week 24, patients in group 1 not entering early escape crossed over to GLM 50 mg + MTX	ACR20 result reached statistical significance in patients with GLM + MTX compared with group 1 Median improvements from baseline in HAQ-DI scores in patients with GLM + MTX compared with group 1 at week 24 Significant improvement in ACR50, ACR70 and DAS28 remission in combined groups 3 and 4 at weeks 14 and 24 The response rates seen at week 24 in patients receiving GLM + MTX were sustained to week 52 Minimal radiographic progression in all treatment groups with no statistical difference between groups	Serious infection after in events/100 patient years (95% CI): 2 (0–10) for group 1, 8 (3–15) for group 2, 3 (1–8) for group 3, 10 (5–18) for group 4 2 deaths in group 2 7 malignancies: 1 patient with two malignancies in group 2 (basal cell carcinoma and squamous cell), two in group 1 after 24 weeks crossover (same patient with basal cell and squamous cell), one in group 3 and two in group 4 (one patient with basal cell cancer)	[28,30,32–33]
Eligible patients had to be treated with ≥1 TNFα inhibitor. They continued stable doses of MTX, sulfasalazine, hydroxychloroquine, oral corticosteroids or NSAIDs 461 patients randomized to injections of either placebo (group 1), 50 mg GLM (group 2) or 100 mg GLM (group 3) every 4 weeks At week 16, patients with <20% improvement from baseline in both tender and swollen entered early escape: the placebo group received 50 mg GLM, and those who were receiving GLM 50 mg received 100 mg GLM At week 24, group 1 crossed over to GLM 50 mg, group 2 continued GLM 50 or 100 mg per early escape protocol and group 3 unchanged	18% group 1, 35% group 2 (odds ratio 2.5 [95% CI: 1.5–4.2]; p = 0.0006), 38% group 3 (2.8 [1.6–4.7]; p = 0.0001) and 37% combined GLM group (2.6 [1.6–4.2]; p < 0.0001) achieved ACR20 at week 14 Patients with concomitant DMARDs reached ACR20 more than for those not receiving DMARDs GLM-treated patients achieved ACR50, ACR70, DAS28 remission, and DAS28 (EULAR) and HAQ-DI response at weeks 14 and 24 than those on placebo 236 patients continued through to week 160. ACR20 response maintained in 70–73% patients. At week 160, ACR20 group 1 was 63%, group 2 was 67% and group 3 was 57%	At week 160, serious infections incidences (95% CI) per 100 patient-years: group 1, 8.66 (2.81–20.22), group 2, 4.70 (2.63–7.75) and group 3, 8.07 (6.02–10.58) Adjusted for follow-up duration per 100 patient-years for GLM 50 mg and 100 mg were 4.70 (2.63–7.75) and 8.07 (6.02–10.58) for serious Infection, 0.95 (0.20–2.77) and 2.04 (1.09–3.49) for malignancy and 0.00 (0.00–0.94) and 0.62 (0.17–1.59) for death 1 case TB in group 3 1 death in group 1 while receiving placebo, 4 deaths in group 3. Incidences of death per 100 patient years (95% CI): group 1, 1.73 (0.04–9.65), group 2, 0.00 (0.00–0.94) and group 3, 0.62 (0.17–1.59) Malignancy risk per 100 patient years (CI 95%) group 1, 1.73 (0.04–9.66), group 2, 0.95 (0.20–2.77) and group 3, 2.04 (1.09–3.49) The incidence of all malignancies not significantly different from expected in the general US population but lymphoma risk may be increased with GLM 100 mg	[34,35]

ACR20: American College of Rheumatology 20% improvement response; ACR50: American College of Rheumatology 50% improvement response; ACR70: American College of Rheumatology 70% improvement response; DAS28: Disease Activity Score in 28 joints; ESR: Erythrocyte sedimentation rate; EULAR: European League Against Rheumatism; GLM: Golimumab; HAQ: Health assessment questionnaire; HAQ-DI: Health assessment questionnaire disability index; iv.: Intravenous; MTX: Methotrexate; RA: Rheumatoid arthritis; SDAI: Simplified disease activity index.

Table 2. Summary of Phase III trials (cont.).

Study	Aim	Primary end points	Inclusion criteria
GO FURTHER	Assess the efficacy of iv. GLM 2 mg/kg + MTX in patients with active RA receiving MTX	ACR20 at week 14	Active RA ≥3 months, defined by ≥6/66 swollen joints and ≥6/68 tender joints and RF/anti-CCP positive, CRP ≥1.0 mg/dl MTX regimen 15–25 mg/week for ≥4 weeks Concurrent use of NSAIDs, other analgesics for RA, and oral corticosteroids (≤10 mg of prednisone/day or equivalent) was allowed if doses were stable for ≥2 weeks prior to trial
Kremer *et al.* (2010)	To evaluate the efficacy and safety of iv. GLM in patients with RA	ACR50 at week 14	Active RA as defined by ≥4 swollen and ≥4 tender joints and ≥2 of the following: CRP >1.5 mg/dl or ESR >28 mm/h, morning stiffness ≥30 min, radiographic/MRI evidence of bone erosion, anti-CCP antibody-positive or rheumatoid factor-positive MTX for ≥3 months at stable dose 15–25 mg ≥4 weeks Concurrent treatment with NSAIDs or oral corticosteroids was allowed Previous TNF inhibitors within specified time frames allowed

ACR20: American College of Rheumatology 20% improvement response; ACR50: American College of Rheumatology 50% improvement response; ACR70: American College of Rheumatology 70% improvement response; DAS28: Disease Activity Score in 28 joints; ESR: Erythrocyte sedimentation rate; EULAR: European League Against Rheumatism; GLM: Golimumab; HAQ: Health assessment questionnaire; HAQ-DI: Health assessment questionnaire disability index; iv.: Intravenous; MTX: Methotrexate; RA: Rheumatoid arthritis; SDAI: Simplified disease activity index.

In an earlier study, patients with RA on a stable dose of MTX were randomized to receive placebo, iv. 2 mg/kg golimumab or iv. 4 mg/kg golimumab with or without methrotrexate every 12 weeks through to week 48 [19]. Its primary end point was ACR50 at week 14. Those with <20% improvement in swollen and tender joint count could enter early escape at week 16 or dose regimen adjustment at week 24. The primary end point of achieving ACR50 at week 14 was not reached. At week 24, patients receiving golimumab and methotrexate had a significant ACR50 response compared with placebo plus MTX (22 and 9%, respectively; p = 0.002). There was no significant difference in those receiving golimumab monotherapy. ACR20 improvement was significantly improved for the golimumab groups plus MTX. It may be that a different dosing strategy is required.

An extension of this study evaluated the efficacy and safety of golimumab when switched to open-label, 50-mg subcutaneous administration every 4 weeks, at week 48 [29]. Patients who were receiving methotrexate continued to receive the same dose, while those receiving placebo had their dose titrated according to the discretion of the investigator. It was shown that clinical improvements were sustained or improved in patients switched from the iv. to subcutaneous route.

Safety & tolerability

Phase III trials have demonstrated, as with other TNFα inhibitors, that there may possibly be an increased risk of serious infections in patients taking golimumab. Kremer *et al.* found that golimumab treatment may double the risk of infection [19]. In the GO-FORWARD and GO-BEFORE trials, more patients taking golimumab suffered from serious infections after 1 year [32] and 2 years [26], respectively, although confidence intervals were wide and did overlap. In the GO-AFTER trial, after adjusting for length of patient follow-up, golimumab 50 and 100 mg may present an increased risk of serious infection [35]. No difference was seen between treatment and placebo group in terms of infection in the GO-FURTHER trial, although there was a relatively short term follow-up of 24 weeks [37].

GO-AFTER was the only Phase III trial that may have shown an increased risk of lymphoma and malig-

Table 2. Summary of Phase III trials (cont.).

Methods	Results	Safety	Ref.
592 patients on stable 15–25-mg MTX received either iv. GLM 2 mg/kg or placebo at weeks 0, 4 and 8 At week 16, patients with <10% improvement in combined swollen/tender joint counts entered early escape to enter GLM arm	Significantly more GLM + MTX than placebo + MTX patients achieved ACR20 response (59 vs 25%; p < 0.001, respectively) Results in ACR20 response were observed as early as week 2 (33.2 vs 11.7; p < 0.001) Significant improvements in ACR50, ACR70, DAS28, HAQ and SDAI in the GLM arm at 24	Infections in 0.9% of GLM group compared with 0% in placebo No TB 1 death in placebo group (stroke secondary to hypertension) 1 cancer in placbo group and 1 cancer in treatment group; no lymphoma	[37]
643 patients on stable 15–25-mg MTX received either iv. placebo + MTX, GLM 2 mg/kg + MTX, GLM 4 mg/kg + MTX, GLM 2 mg/kg alone or GLM 4 mg/kg alone every 12 weeks Early escape for patients <20% improvement in the swollen and tender joint counts at week 16 or adjusted dose at week 24 After week 48, patients received open-label subcutaneous GLM 50 mg ± MTX (at investigator discretion) every 4 weeks for 24 weeks	Week 14: ACR50 response was 21% of the patients treated with GLM + MTX vs 13% of patients treated with placebo plus MTX; p = 0.051 ACR20 and ACR50 significantly improved in those treated with GLM + MTX compared with placebo at week 24 Week 48: ACR20 and ACR50 highest among those who had received GLM 4 mg/kg + MTX Switch from iv. to subcuatenous at 48 weeks demonstrated sustained or improved clinical response	Serious infections: 2 in placebo group, 23 in all GLM groups through to week 48; total 6% of serious infections reported in subcutaneous GLM group 2 cases of TB in GLM groups 6 deaths total in iv. GLM-treated group, although no association with any treatment arm was found; 2 patients died in subcutaneous GLM group 2 malignancies in placebo, 20 in GLM groups	[19,29]

ACR20: American College of Rheumatology 20% improvement response; ACR50: American College of Rheumatology 50% improvement response; ACR70: American College of Rheumatology 70% improvement response; DAS28: Disease Activity Score in 28 joints; ESR: Erythrocyte sedimentation rate; EULAR: European League Against Rheumatism; GLM: Golimumab; HAQ: Health assessment questionnaire; HAQ-DI: Health assessment questionnaire disability index; iv.: Intravenous; MTX: Methotrexate; RA: Rheumatoid arthritis; SDAI: Simplified disease activity index.

nancy in patients taking golimumab [35]. However, three out of the four patients with lymphoma were in the highest quartile of DAS28 and/or SDAI scores, with no change from baseline at time of diagnosis. The hypothesis that lymphoma may be associated with severity of RA rather than TNFα inhibition has been reported, although no definitive association has been established [38]. A study using registry data did not demonstrate any further increased association with lymphoma in patients with RA taking TNFα inhibitors [39]. A recent systematic review [40] and meta-analysis [41] also did not demonstrate a firm association with malignancy or nonmelanoma skin cancers.

There was no association between golimumab use and increased mortality. No lupus- like syndrome was demonstrated in any of the Phase III trials, although a recent case report has shown golimumab to be capable of exacerbating subacute cutaneous lupus erythematosus [42].

Long-term data suggest that golimumab is well tolerated. In the GO-BEFORE trial [26], 7.6 and 13.8% of patients on golimumab and 3.8 and 12% on placebo discontinued due to an adverse event and serious adverse event, respectively, at 2 years. Final 5-year data showed 215 out of 637 patients withdrew from the trial: 111 for adverse events, 23 for lack of efficacy, 20 lost to follow-up, 53 for other reasons and 8 deaths [27]. A total of 50% of patients discontinued treatment in the GO-AFTER study [35], but this may be a reflection of the study population itself, where patients have had previous TNFα inhibitors discontinued before.

Conclusion & expert opinion

Phase III trials have demonstrated that golimumab is an effective TNFα inhibitor for the treatment of patients with RA. It has been shown to significantly reduce inflammatory biomarkers and improve functional ability and swollen and tender joint counts within 3 months. Longer-term data have shown that these changes are sustained. Furthermore, golimumab inhibits radiographic progression and has been shown to improve synovitis and osteitis. It is interesting to note that one study failed to show benefit with radiographic progression in all treatment groups, with no statistical difference between the groups [28]. This may be due to the study design and

lack of power for adequate analysis, as well as the lower inflammation as evidenced by the low levels of CRP in these patients. Golimumab has also been shown to be a feasible alternative in patients who have already failed one or more previous TNFα inhibitor, although discontinuation of treatment among patients was higher than in other studies where patients were biologic naive.

The majority of these studies have evaluated golimumab in combination with methotrexate. In the GO-BEFORE study evaluating the effectiveness of golimumab in methotrexate-naive patients, combined golimumab with methotrexate group, but not golimumab monotherapy, had significant improvements in ACR20, DAS28 response/remission and HAQ. The GO-FORWARD study also did not show any difference in its primary end point of ACR20 between placebo on top of methotrexate and golimumab monotherapy. Short-term data from the GO-MONO study, however, have suggested that golimumab monotherapy is more effective than placebo alone when treating RA. The difference between these two trials may be a result of differences in disease severity between study populations in the trials, where patients with a lower disease activity may not respond to golimumab monotherapy compared with methotrexate. Patient characteristics, such as weight, have also been suggested to affect the pharmacokinetics of golimumab [24].

The tolerability and long- term safety profile of golimumab suggest that, overall, there is no evidence to suggest an increased risk of malignancy/lymphoma or death. Although there may be an increased risk of serious infection, these results need to be interpreted with caution as the confidence intervals were wide and overlapped.

Overall, there appears to be no significant differences in efficacy between 50 and 100 mg golimumab, although golimumab 100 mg every 2 weeks resulted in a significant improvement in ACR20 by week 16 [20] and long-term data suggest that in the GO-AFTER trial 100 mg golimumab may be more efficacious than 50 mg in patients who have previously failed a TNFα inhibitor [35].

Although golimumab has been shown to be an effective biological agent in treating RA, further research is required to determine the optimum dosing frequency. It remains to be seen if golimumab every 2 weeks is more efficacious, safe and tolerable compared with every 4 weeks. Furthermore, the role of iv. administration needs to be clarified, with the additional cost of iv. golimumab administration likely to be decisive. The administration of golimumab is currently only licensed for subcutaneous administration in the USA and EU. Finally, future studies are needed to evaluate the direct comparisons between anti-TNFα inhibitors to determine if golimumab should be the first line TNFα inhibitor.

Golimumab is a safe, well-tolerated and efficacious anti-TNFα agent that can be used in the treatment of RA in combination with methotrexate.

Financial & competing interests disclosure

P Emery has undertaken clinical trials and provided expert advice to Abbvie, BMS, Pfizer, UCB, MSD, Roche and Takeda. 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.

No writing assistance was utilized in the production of this manuscript.

Executive summary

Mechanism of action

- Fully humanized antibody directed against TNFα.

Pharmokinetics/pharmocodynamics

- Half-life of 100 mg subcutaneous administration was 10.9 days and 6.6–19.3 days in intravenous administration.
- Time to maximum concentration in subcutaneous route was 4 days.

Clinical efficacy/dosage/route of administration

- Can be administered at 50 or 100 mg subcutaneously, every 2 or 4 weeks.
- Increased efficacy when given with methotrexate.

Safety

- No increased risk of death or malignancy shown.
- Possible increased risk of serious infection, although confidence intervals were wide and did overlap.

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