

Golimumab in the treatment of ulcerative colitis

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Abstract: Golimumab was approved by the US Food and Drug Administration and the European Medicines Agency for the treatment of moderate-to-severe ulcerative colitis in 2013 and was the third antitumour-necrosis-factor therapy after adalimumab and infliximab licensed for this indication. However, given it is the most recent of these drugs to become available, evidence regarding its optimal use and its positioning in relation to other biological therapies is only now emerging. In this article, we review the efficacy, effectiveness and safety of golimumab both in the setting of clinical trials and in 'real world' observational studies. We also explore the limited data available regarding the possible role of therapeutic-drug monitoring and dose flexibility.

Keywords: ulcerative colitis, golimumab, Simponi

Received: 22 September 2018; revised manuscript accepted: 14 November 2018.

Introduction

The US Food and Drug Administration (FDA) and the European Medicines Agency (EMA) approved golimumab for the treatment of moderate-to-severe ulcerative colitis (UC) in 2013. It stands beside infliximab and adalimumab to complete the group of antitumour-necrosis-factor (anti-TNF) therapies available to induce and maintain remission in this patient group. However, given it is the most recent of these drugs to become available, evidence regarding its optimal use and its position in relation to other biological therapies is only now becoming available.

Golimumab is a fully human monoclonal antibody that binds to both membrane-bound and soluble anti-TNF. It has superior binding affinity compared with other anti-TNF therapies and early *in vitro* and *in vivo* studies suggested that it would result in more potent neutralization of anti-TNF as a result.¹ Golimumab is administered by subcutaneous (SC) injection allowing for self-administration, patient independence and subsequent reduced healthcare utilization and cost. This is due to golimumab's protein stability profile allowing it to be prepared as a high-concentration liquid formulation.¹

Although no head-to-head trials have been performed, a network meta-analysis comparing the efficacy of biologic agents in patients with UC suggested that golimumab is approximately equivalent to adalimumab. However, golimumab has the potential advantage of only needing to be administered monthly as opposed to weekly or every other week for adalimumab.² Unlike infliximab, golimumab is not used as a rescue therapy for the treatment of hospitalized patients with acute severe UC. Furthermore, the recent network meta-analysis by Singh *et al.* that found that golimumab was less likely to achieve mucosal healing than infliximab after induction in biologic-naïve patients, odds ratio (OR) 0.52 [95% confidence interval (CI) 0.33–0.83]³ but not adalimumab, OR 1.10 (95% CI 0.71–1.71). Despite this, clinical remission rates were not statistically different when comparing golimumab with adalimumab or infliximab.

Golimumab as induction treatment

The initial induction doses of golimumab (200 mg then 100 mg) are given 2 weeks apart, and subsequent maintenance doses (either 50 mg or 100 mg) are given at 4-weekly intervals.

Ther Adv Gastroenterol

2019, Vol. 12: 1–8

DOI: 10.1177/
1756284818821266

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Golimumab was shown to be effective in the integrated phase II and III PURSUIT (Programme of Ulcerative colitis Research Studies Utilizing an Investigational Treatment) trials.⁴ Initially, both SC and intravenous (IV) trials ran concurrently, but on interim analysis, superior clinical efficacy and pharmacokinetic profiles in the SC trial led to the discontinuation of the IV arm.⁵

In terms of optimal dosing, the induction regimen was initially evaluated in a phase II trial (PURSUIT-SC)⁴. Induction doses of 100/50 mg, 200/100 mg and 400/200 mg were compared and the change in Mayo scores from baseline to week 6 were -3.0, -2.0 and -3.0, respectively. Subsequently, induction doses of 200/100 mg and 400/200 mg were evaluated in the phase III induction study in which 774 patients, never previously exposed to anti-TNF, were enrolled with endpoints being assessed over a 6-week period. The primary endpoint was 'clinical response' defined by a decrease in the Mayo score by at least three points and by 30% or more, in association with a bleeding subscore of 0 or 1, or a decrease ≥ 1 . The primary endpoint was achieved significantly more frequently in the 400/200 mg (55%, $p < 0.0001$) and 200/100 mg (51%, $p < 0.0001$) groups compared with placebo (30%). Secondary endpoints included 'clinical remission' (Mayo score ≤ 2 with no subscore > 1), mucosal healing (endoscopic Mayo subscore of 0 or 1 at week 6), and impact on quality of life. Mucosal healing was achieved by 28.7%, 42.3% ($p = 0.0014$) and 45.1% ($p \leq 0.0001$) of patients in the placebo, 200/100 mg and 400/200 mg groups respectively.

Golimumab as maintenance treatment

The maintenance regimens for golimumab differ between Europe and the United States. In Europe, there is a weight-based regimen in which patients who are less than 80 kg receive 50 mg every 4 weeks, whereas those who are 80 kg or more receive 100 mg.

Maintenance of remission in UC with golimumab was assessed in the PURSUIT-Maintenance (PURSUIT-M) study.⁶ This included 464 responders in the initial PURSUIT-SC study who were re-randomized to receive placebo, 50 mg or 100 mg golimumab every 4 weeks. The primary endpoint was stringent compared with the other registration trials for anti-TNF in patients with UC; maintenance of response was

assessed by the Partial Mayo Score at 4-weekly intervals with a full Mayo score (including endoscopic assessment) being performed at weeks 30 and 54, with no allowance for loss of response at any point. The endpoint was reached in significantly more patients who received 50 mg (47%, $p = 0.010$) and 100 mg (50%, $p < 0.001$) of golimumab compared with placebo (31%). Mucosal healing was achieved at weeks 30 and 54 by 26.6%, 41.7% ($p = 0.011$) and 42.4% ($p = 0.002$) of patients in the placebo, 50 mg and 100 mg groups, respectively. Interestingly, in a *post hoc* analysis of this trial reported by Colombel and colleagues,⁷ significant mucosal healing rates were also reported in the nonresponders to induction who then went on to receive 100 mg 4-weekly golimumab as part of the PURSUIT trial protocol. Mucosal healing rates in this group were 52.7% at week 30 and 42.9% at week 54, indicating that a delayed response may occur. However, aside from C-reactive protein levels at end of induction, baseline characteristics were unable to predict who these patients would be.

More recently, the long-term extension (LTE) of the PURSUIT-M trial⁸ has been published. The LTE included 666 patients who were responders and completed treatment through to week 52 who were then followed to assess safety and efficacy for an additional 3 years. Efficacy analyses were performed on 195 of these patients, that is, those that were randomized to golimumab maintenance at baseline and continued to take the drug during the LTE. Of these patients, 134 remained on golimumab until week 216 and 77.6% of these patients had a Physicians Global Assessment score of 0 at that time point equating to 53.3% if an intention-to-treat analysis was used.

Real-world observational effectiveness studies

As with all new drugs, real-world data publications allow an assessment of the use of the drug in everyday practice and, therefore, complement the data derived from clinical trials. While the quality of the data is unarguably poorer, the patients who are included in such observational studies are more representative of 'real world' practice than patients who participate in clinical trials who are, by definition, a well-defined subsection of the overall patient cohort. A summary of the published real-world cohorts is presented in Table 1.

Table 1. Summary of real-world observation of golimumab in UC.

Study	Year	Number patients	Anti-TNF exposed	Follow-up period	Clinical response	Clinical remission	Mucosal healing
Detrez <i>et al.</i> ⁹	2016	21	52%	14 weeks	14%	–	19%
Bosca-Watts <i>et al.</i> ¹⁰	2016	33	73%	14 weeks	70%	52%	–
Taxonera <i>et al.</i> ¹¹	2017	142	60%	8 weeks	65%	32%	–
Tursi <i>et al.</i> ¹²	2017	93	11%	24 weeks	65%	37%	19%
Samaan <i>et al.</i> ¹³	2017	44	30%	12 weeks	52%	34%	–
Samaan <i>et al.</i> ¹³	2017	23	–	–	–	–	35%
Bossuyt <i>et al.</i> ¹⁴	2018	87	13%	14 weeks	–	–	40%
Probert <i>et al.</i> ¹⁵	2018	205	0%	6 weeks	69%	39%	–
Probert <i>et al.</i> ¹⁵	2018	205	0%	54 weeks	25%	18%	–
O'Connell <i>et al.</i> ¹⁶	2018	72	36%	12 weeks	55%	–	–

TNF, tumour necrosis factor; UC, ulcerative colitis.

Detrez and colleagues⁹ reported a cohort of 21 patients from Belgium treated with golimumab for moderate-to-severe UC. Just under half of the patients (48%) achieved partial clinical response at week 14, defined as marked clinical improvement. Complete clinical response was only achieved in 14% of patients, while only 19% patients achieved mucosal healing. However, in contrast to the PURSUIT trials, in which all participants were anti-TNF naïve, 52% were previously exposed to anti-TNF in this cohort.

Bosca-Watts and colleagues¹⁰ prospectively followed 33 patients with moderate-to-severe UC commenced on golimumab across several centres in Spain. The majority of these patients (73%) were anti-TNF exposed. Despite this, clinical response (defined by a decrease in the partial Mayo score of at least three points) was achieved by 70% of patients at week 14, and 51.5% achieved clinical remission. Mucosal healing data were not reported, but the mean faecal calprotectin value fell from 300 µg/g to 170.5 µg/g.

Taxonera and colleagues¹¹ performed a retrospective analysis on 142 patients with UC treated with golimumab across several Spanish centres. Again, the majority of these patients (60%) had been previously exposed to anti-TNF. Short-term clinical response, defined as a 3-point decrease in the Partial Mayo Score or a decrease of $\geq 50\%$ in the

Partial Mayo Score and a final Partial Mayo Score of ≤ 2 at 8 weeks, was seen in 64.8%. Short-term clinical remission rate was 31.7% and both clinical response and remission rates were lower if golimumab was given as the third anti-TNF agent. However, after a median follow up of 12 months, 42% patients had golimumab failure, the majority of which was due to primary nonresponse.

Tursi and colleagues¹² prospectively observed 93 patients over a 6-month period, the majority of whom were anti-TNF naïve (88.8%). At 6 months, clinical remission, defined as a Mayo score ≤ 2 , was achieved by 36.5% patients, and 64.5% achieved clinical response. However, only 19% had steroid-free remission at week 26, with the same number achieving mucosal healing.

Samaan and colleagues¹³ performed a retrospective cohort study of 57 patients. Simple Clinical Colitis Activity Index (SCCAI) scores were collected before and after treatment; clinical response being defined as a reduction in SCCAI ≥ 3 and clinical remission being defined as a score < 3 . Paired pre- and postinduction scores were only available for 31 patients, but in this group, the median SCCAI score fell from 7 (range 2–19) to 3 (range 0–11) after a median time of 12 weeks ($p < 0.0001$). Forty-four patients were included in the response and remission analysis, as an additional 13 (23%) patients discontinued treatment

due to documented nonresponse despite not having SCCAI scores recorded. Of these, 23 patients (52%) had a clinical response and 15 (34%) achieved clinical remission. Only 23 patients had postinduction endoscopies, and mucosal healing (endoscopic Mayo score 0–1) was seen in 35%.

Bossuyt and colleagues¹⁴ retrospectively analysed 91 patients who were previously included in the SMART study (an open-label observational study that explored patient preference for either pen or syringe to deliver golimumab in Belgium). The majority of these patients (87%) were anti-TNF naïve, and all received standard induction and maintenance regimens with the option of dose optimization during the maintenance phase. The primary endpoint was golimumab continuation without steroids at week 26, which occurred in 41% of patients. At week 52, this reduced to 30%. A total of 34% patients had primary nonresponse and 23% had secondary loss of response within the first year. The mucosal healing rate at week 14 was 40%, and if this outcome was achieved it predicted steroid-free golimumab continuation at week 52 (OR 9.38, $p < 0.001$).

Probert and colleagues¹⁵ prospectively analysed 205 anti-TNF-naïve patients as a part of the UK-based GO-COLITIS trial. The primary endpoint was sustained clinical response through to week 54 as defined by a decrease in the Partial Mayo Score (PMS) ≥ 2 points and $\geq 30\%$ from baseline, plus either a decrease in the rectal bleeding subscore of ≥ 1 point or an absolute rectal bleeding subscore of 0 or 1. This was achieved in only 25% of patients. Interestingly, of the 52 patients that achieved clinical response at week 54, a significant proportion (60%) discontinued therapy but still maintained clinical response for a further 12 weeks.

Finally, O'Connell and colleagues¹⁶ evaluated 72 UC patients receiving golimumab in Ireland. Clinical response was measured at 3 months and corticosteroid-free remission was measured at 6 months, the rates being 55 and 39%, respectively. Over a mean follow-up duration of 8.7 months (0.4–39.2), 44% patients discontinued the drug.

Safety of golimumab

The safety analyses from the initial PURSUIT trials were reassuring and this was confirmed by the recently published LTE of the PURSUIT-M

trial⁸ which is summarized in Table 2. Adverse events were more common in the golimumab 100 mg cohort and the most common adverse event was worsening of UC which occurred in 20.8%, 19.1% and 26.9% of patients in the placebo, 50 mg and 100 mg groups, respectively. It is interesting that disease worsening was more prevalent in the 100 mg group. However, this is a small percentage difference and exposure–response analysis (rather than dose response) is more telling in this regard.

Infections were also more common in the 100 mg cohort, of which nasopharyngitis and upper-respiratory-tract infections were the most common.

There were nine deaths reported; one in the placebo group, one in the 50 mg golimumab group and seven in the 100 mg group. Two deaths had been previously reported; the other seven deaths included gallbladder cancer, rectal cancer, colon cancer, acute myocardial infarction, accidental overdose and aspiration following colectomy.

Perhaps unsurprisingly, given experience with other anti-TNF therapies, in the LTE programme there were four cases of tuberculosis (TB) in patients receiving golimumab 100 mg. However, none of these patients had a history of active or latent TB or of contact with TB; nor did they have positive screening tests at the time of commencement of the drug. Therefore, as with all anti-TNF therapies, pretreatment screening for TB and a low index of suspicion for TB infection remains imperative.

Taxonera and colleagues¹¹ confirmed that the promising safety profile seen in the PURSUIT programme was reflected in real life; over a period of 18–24 months, only four patients (2.8%) experienced adverse events. These included paraesthesia, cutaneous infection, pneumonitis and recurrence of cervical neoplasia. In addition, no cases of TB were reported in this study.

Therapeutic-drug monitoring

It is increasingly accepted that dose optimization with therapeutic-drug monitoring (TDM) improves outcomes with biological agents in patients with inflammatory bowel disease (IBD).^{17–19} Serum golimumab concentrations were taken periodically from patients in both the phase II and III PURSUIT-SC and PURSUIT-M

Table 2. Safety data from the long-term extension of PURSUIT-M trial.⁸

	Placebo	50 mg golimumab	100 mg golimumab
Adverse events per 100 patient-years	187.71 (CI: 162.47–215.76)	187.68 (CI: 170.83–205.74)	211.45 (CI: 203.78–219.32)
Infections per 100 patient-years	38.87 (CI: 27.89–52.73)	51.97 (CI: 43.29–61.88)	67.37 (CI: 63.07–71.88)
Malignancies	0 (CI: 0.00–2.84)	1.26 (CI: 0.26–3.27)	0.74 (CI: 0.35–1.36)
Tuberculosis	0 (CI: 0.00–2.84)	0 (CI: 0.00–1.24)	0.37 (CI: 0.12–0.86)

CI, confidence interval.

trials and an exposure–response relationship was established on *post hoc* analysis.²⁰

For the induction study, serum golimumab concentrations (SGCs) were correlated with clinical response, clinical remission and mucosal healing outcomes at week 6. In the patients receiving 200 mg/100 mg (the current accepted induction regimen) the median SGC peak was 6.27 µg/ml at week 2, and 1.78 µg/ml at week 6. However, at week 6, median SGCs in patients who achieved clinical response, clinical remission and mucosal healing were higher at 2.96 µg/ml, 3.14 µg/ml and 3.14 µg/ml, respectively, compared with patients who did not achieve those outcomes who had median SGCs of 1.55 µg/ml, 2.13 µg/ml, and 1.70 µg/ml, respectively. The authors concluded that a level of 2.5 µg/ml at week 6 is desirable to achieve optimal response and this would suggest that using the current induction regimen may result in many patients being underdosed.

For the maintenance study, trough SGCs were tested at weeks 30, 44 and 54 and were also found to correlate with clinical response, sustained clinical remission and mucosal healing. In the patients receiving 50 mg golimumab, median trough SGCs were 1.73 µg/ml and 1.81 µg/ml at week 30 and 54, respectively. For patients receiving 100 mg, levels were expectedly higher at 3.81 µg/ml and 5.52 µg/ml, respectively. Week 44 (steady-state trough) levels were correlated with clinical response at week 54, sustained clinical remission at week 30 and week 54 and mucosal healing at week 30 and week 54. The median SGCs in patients who achieved these outcomes were 1.17 µg/ml, 1.50 µg/ml and

1.22 µg/ml, respectively. The authors therefore conclude that a steady-state level of 1.4 should be targeted.

An exposure–response relationship was also validated in the aforementioned small, observational study by Detrez *et al.*⁹ Serum samples were collected during the first 14 weeks of therapy and golimumab and antigolimumab antibody concentrations were retrospectively analysed. When compared with nonresponders, patients who achieved partial response had drug levels that were higher at weeks 2 and 6; 10.0 (7.8–10.5) µg/ml versus 7.4 (4.8–8.3) µg/ml and 5.1 (4.0–7.9) µg/ml versus 2.1 (1.8–4.2) µg/ml, respectively. Interestingly, these levels were much higher than those in the PURSUIT-SC *post hoc* analysis.

There is probably insufficient evidence to say TDM for golimumab is ready for clinical use. However, drug-level monitoring became a routine part of clinical practice for adalimumab and infliximab with far less robust datasets than the PURSUIT *post hoc* analysis. The above thresholds need to be evaluated prospectively but could be used as a guide in clinical practice now. This is particularly important given there is a strong possibility that golimumab is being underdosed with the current dosing regimens in both Europe and the United States.

Loss of response and immunogenicity

Secondary loss of response (LOR) to anti-TNF therapy is a significant issue. With regards to infliximab and adalimumab, LOR can be due to the formation of antidrug antibodies, as the drugs evoke an immune response.²¹ The immunogenicity of golimumab is yet to be fully established. In the

aforementioned *post hoc* analysis of PURSUIT, antidrug antibodies were measured using a 'drug sensitive' assay. The incidence of antidrug antibodies at week 54 was low (3%), but, as with infliximab and adalimumab, concomitant immunomodulator use decreased immunogenicity (combination therapy 1.5% versus monotherapy 3.5%).²⁰ In the LTE arm of the PURSUIT-M trial, the rate of antibody formation, albeit using the same drug-sensitive assay, remained low (4.4% in the golimumab 50 mg group and 3.7% in the golimumab 100 mg group).⁸

In contrast, Detrez and colleagues⁹ used a drug-tolerant assay. In the four patients (19%) that developed antigolimumab antibodies, three of these had achieved partial clinical response at the time that antibodies were detected and, furthermore, the presence of antibodies was not associated with undetectable golimumab levels. However, the number of patients was small, and the duration of this study was short, and so the lack of association is difficult to interpret.

Dose escalation

One strategy to overcome LOR is dose escalation. This can either be empirical (without TDM) or optimization driven by TDM. However, unlike for infliximab and adalimumab, dose escalation is not within licence for golimumab. Given that there is a strong possibility that current golimumab dosing practices result in subtherapeutic levels and LOR may be attributable to pharmacokinetic, rather than pharmacodynamic failure, this is a concern.

In the aforementioned study by Taxonera *et al.*,¹¹ 28 patients were dose escalated either by increasing the dose from 50 to 100 mg 4 weekly (90.3%), from 100 to 200 mg 4 weekly (3.2%) or to 100 mg every 2 weeks (6.4%). A significant amount (71%) of patients were able to recapture response with this strategy.

Currently, in Ireland, authors of the randomized multicentred GOAL-ARC study aim to clarify whether dose optimization of golimumab based on faecal calprotectin and drug levels during induction and maintenance phases can improve clinical response and remission rates.²² In this study, patients in the intervention arm will be progressively dose escalated every 4 weeks up to 200 mg 4 weekly, although this dose can only be given three consecutive times. This will hopefully allow for more personalized dosing regimens and,

therefore, better clinical outcomes, and will clarify whether dose escalation addresses the significant LOR seen in the real-world cohorts.

Golimumab and Crohn's disease

Although currently only licensed for use in UC, there is recent evidence to suggest that golimumab is also effective in the treatment of Crohn's disease. A retrospective analysis of 115 patients observed a clinical response of 55.8% after a mean duration of 3.8 months although the majority of patients (80.7%) required dose escalation by 24 months.²³ Golimumab was used as the third anti-TNF agent in the majority (91.3%) of patients. A further retrospective observational study of 45 patients reported a clinical response rate of 77.7% at 3 months.²⁴ However, induction and maintenance regimens were higher than standard UC dosing in most cases and mucosal healing at 12 months was only achieved in 47% of patients.

Conclusion

Golimumab is a safe and effective treatment in moderate-to-severe UC, and is broadly comparable with other anti-TNF agents. However, there are still several questions in regard to its optimal use, including whether the current induction and maintenance regimens can be optimized, whether TDM might guide this process and, finally, what benefit (if any) might be gained by using the drug in combination with an immunomodulator.

Funding

Financial support for research: MSD, Takeda.

Conflict of interest statement


GC: none. MAS: advisory fees: Takeda, Janssen; lecture fees: Takeda, MSD, Janssen, Dr Falk Pharma. PMI: advisory fees: Abbvie, Warner Chilcott, Takeda, MSD, Vifor Pharma, Pharmacosmos, Topivert, Genentech, Hospira, Samsung Bioepis; lecture fees: Abbvie, Warner Chilcott, Ferring, Dr Falk Pharma, Takeda, MSD, Johnson and Johnson, Shire.

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