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CLINICAL REVIEW

Golimumab in inflammatory bowel diseases: present and future scenarios

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Abstract

Golimumab is the third anti-TNF agent approved for the treatment of ulcerative colitis. Despite initial success demonstrated by PURSUIT trials, only few real-life studies have been published evaluating its efficacy and safety in clinical practice. Its subcutaneous route and monthly administration represent an advantage in patient compliance, respectively, vs infliximab (intravenous) and adalimumab (two doses per month). The most important weakness of the molecule which often leads clinicians to choose another anti-TNF is the impossibility to dose escalate or reduce the frequency of administrations in case of secondary failure; ongoing studies are trying to solve this problem by monitoring drug levels and the eventual presence of neutralizing anti-drug antibodies. No advantage has still been demonstrated for combination therapy of golimumab with immunosuppressants and further studies are necessary to evaluate this aspect. Preliminary data also report golimumab efficacy in Crohn's disease with higher doses than in ulcerative colitis with an acceptable safety profile. Additional studies are needed in this field to confirm the initial findings.

Keywords Anti-drug antibodies · Anti-TNF · Biologics · Drug monitoring

Abbreviations

AA	Anti-drug antibodies
ADA	Adalimumab
AEs	Adverse events
BE	Biologics experienced
BN	Biologics naïve
CCR	Continuous clinical response
CD	Crohn's disease
EMA	European Medicines Agency
FDA	Food and Drug Administration
GLM	Golimumab
IBD	Inflammatory bowel diseases
IFX	Infliximab
PGA	Physician Global Assessment
PURSUIT	Program of Ulcerative Colitis Research Studies Utilizing an Investigational Treatment
SC	Subcutaneous
TDM	Therapeutic drug monitoring
TNF	Tumour necrosis factor
UC	Ulcerative colitis

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Introduction

Ulcerative colitis (UC) is a lifelong inflammatory disease of the colon characterized by a relapsing and remitting course [1] and by a continuous localization of lesions from the rectum to various lengths of the colon. It is known to depend on interactions between environmental and genetic factors which result in gut immune system dysfunction [2]. Since it has no definite aetiology and the only curative treatment is proctocolectomy, all the medical therapies are focused on immunomodulation.

Current available immunotherapies depend on disease extent and severity including corticosteroids, thiopurines (azathioprine and 6-mercaptopurine), calcineurin inhibitors (cyclosporine in rescue therapy only) and biologics such as anti-tumour necrosis factor (TNF) and the new anti-integrins drugs. Anti-TNF agents are widely used for the treatment of steroid-dependent disease and for patients with steroid/thiopurines-resistant UC. Their mechanism of blocking soluble and membrane TNF on activated lymphocytes leads to apoptosis of these inflammatory cells [3].

Infliximab (IFX) and adalimumab (ADA) have been the first two released anti-TNF agents to show clinical efficacy and safety profile in patients with UC, but a relative number of patients initially treated with one of these two molecules have shown primary (up to 40%) or secondary (up to 60%) failure [4, 5]. Thus, considering that certolizumab is not approved in Europe for IBD, there was the need of a third biologic of the same class to help recover some unresponsive patients.

Golimumab (GLM) is a transgenic fully human monoclonal antibody, with a demonstrated efficacy for rheumatoid arthritis [6], ankylosing spondylitis [7] and psoriatic arthritis [8].

Apart from the application on rheumatological diseases, two randomized controlled trials [9, 10] confirmed its efficacy, sustained response and safety profile in UC, and the drug was approved by the Food and Drug Administration (FDA) in May 2013 and by the European Medicines Agency (EMA) in October 2013.

Review of the literature

A comprehensive review of the English-language literature on the use of GLM in humans for the treatment of UC or Crohn's disease was performed using the MEDLINE (Via PubMed) and Web of Science databases up to March 2018, using the key words "Golimumab", "Inflammatory bowel disease", "Ulcerative colitis" and "Crohn disease". A specific data extraction form was independently developed a priori by two authors (G. D. and M. LG.) to avoid missing articles. The focus of the research was to select and separate into subgroups all major themes of GLM (registration trials, real-life experience in UC, initial data in CD, pharmacokinetics and laboratory monitoring, combo therapy, safety profile, comparison with other anti-TNFs), with the intent of summarizing the current knowledge about this drug.

Studies not related to the topic of this review (animal studies, previous reviews or guidelines, letters to the editors) were excluded.

Molecule presentation and clinical practice

GLM has a molecular weight of approximately 150 kDa and was originally isolated from transgenic mice, immunized with human TNF. Similar to other anti-TNF agents, due to its gastric degradation and hydrophilicity, gut absorption is precluded and it is administered via the subcutaneous (SC) route. It crosses the placenta from week 22 of gestation via active transport, facilitated by the development of specific immunoglobulin receptors on the placenta [11].

It blocks both the membranous and the soluble TNF, preventing TNF binding to its specific receptor. Data from an in vitro study comparing GLM with IFX and ADA showed greater affinity for TNF (respectively, 18 pM vs 44 pM and 127 pM) and around threefold less concentration needed to neutralize TNF-induced E-selectin expression [12].

GLM indications in UC are similar to those of IFX and ADA in treating active ulcerative colitis. No trial has been conducted to recommend GLM for "rescue therapy" in patients with acute severe UC, where only IFX and cyclosporine take place.

Screening laboratory and instrumental practices to detect latent tuberculosis or other infections, as well as its contraindications, are the same as those for the other anti-TNFs, [13]. GLM is administered at a dose of 200 mg at week 0 and 100 mg at week 2 for induction of remission. The indications for maintenance are different for FDA (USA) and EMA (Europe). FDA recommends 100 mg every 4 weeks for all patients, while EMA recommends 100 mg every 4 weeks only for patients above 80 kg and 50 mg every 4 weeks for patients below 80 kg.

Pursuit studies

The Program of Ulcerative Colitis Research Studies Utilizing an Investigational Treatment (PURSUIT) includes a series of trials evaluating the efficacy and overall safety of GLM compared to placebo, in biologics naïve (BN) patients with moderate-to-severe UC. The most relevant results are shown in Table 1.

PURSUIT-SC study [9] was a multicenter, randomized, double-blind, placebo-controlled trial conducted between 2007 and 2010 and was the first phase 2 and 3 trial evaluating GLM induction therapy via the SC route. Data showed significantly higher clinical response rate and mucosal healing for both GLM induction regimens selected (400/200 mg and 200/100 mg) when compared to placebo in the 6-week time of observation, with no difference in the two GLM schemes.

PURSUIT-IV [14] was a trial with the same characteristics and eligibility criteria, conducted between 2007 and 2009 evaluating the efficacy of a single IV induction dose of GLM. This route of administration did not reach primary clinical end points at week 6 and the study enrollment was stopped due to insufficient results.

Analysis [9] of serum GLM exposure across PURSUIT-SC and PURSUIT-IV studies showed that the SC induction regimen was associated with more constant serum drug concentration during the 6-week induction regimen and that the higher peak concentration of the IV route was not that relevant for the long-period efficacy.

Table 1 Summary of PURSUIT studies

Study	All randomized patients groups	Naïve/experienced to anti-TNF	Duration of follow-up (weeks)	Clinical response	Clinical remission	Mucosal healing	Total AEs	Serious AEs (≥ 1)	Infections (≥ 1)
PURSUIT-SC [9]	331 placebo, 734 all GOL groups	All naïve	6	30.3% placebo, 51.0% GOL 200/100 mg ($p < 0.0001$), 54.9% GOL 400/200 mg ($p < 0.0001$)	6.4% placebo, 17.8% GOL 200/100 mg ($p < 0.0001$), 17.9% GOL 400/200 mg ($p < 0.0001$)	28.7% placebo, 42.3% GOL 200/100 mg ($p = 0.0014$), 45.1% GOL 400/200 mg ($p < 0.0001$)	38.2% placebo, 39.1% all GOL patients	6.1% placebo, 3.0% all GOL patients	12.1% placebo, 12.0% all GOL patients
PURSUIT-IV [14]	77 placebo, 214 all GOL groups	All naïve	6	30.1% placebo, 36.1% GOL 1 mg/kg ($p = 0.467$), 44.0% GOL 2 mg/kg ($p = 0.081$), 41.6% GOL 4 mg/kg ($p = 0.145$)	11.0% placebo, 9.8% GOL 1 mg/kg ($p = 0.832$), 16.0% GOL 2 mg/kg ($p = 0.370$), 13.0% GOL 4 mg/kg ($p = 0.702$)	32.9% placebo, 27.9% GOL 1 mg/kg ($p = 0.531$), 34.7% GOL 2 mg/kg ($p = 0.818$), 37.7% GOL 4 mg/kg ($p = 0.540$)	31.2% placebo, 36.6% all GOL patients	2.6% placebo, 3.8% all GOL patients	6.5% placebo, 10.8% all GOL patients
PURSUIT-M [10]	156 placebo, 464 all GOL groups	All naïve	54	31.2% placebo, 47.0% GOL 50 mg ($p = 0.10$), 49.7% GOL 100 mg ($p < 0.001$)	22.1% placebo, 33.1% GOL 50 mg ($p = 0.068$), 33.8% GOL 100 mg ($p = 0.011$)	26.6% placebo, 41.7% GOL 50 mg ($p = 0.011$), 42.4% GOL 100 mg ($p = 0.002$)	66.0% placebo, 74.2% all GOL patients	7.7% placebo, 12.5% all GOL patients	28.2% placebo, 39.8% all GOL patients
PURSUIT-J [17]	31 placebo, 32 GOL	All naïve	54	19.4% placebo, 56.3% GOL	6.5% placebo, 50.0% GOL	16.1% placebo, 59.4% GOL	71.0% placebo, 96.9% GOL	12.9% placebo, 3.1% GOL	35.5% placebo, 65.6% GOL

All 1064 patients of PURSUIT-SC and 164 patients of PURSUIT-IV participated in the subsequent 54-week GLM maintenance study (PURSUIT-M) [10] conducted between 2007 and 2011. GLM responders to induction regimens were randomized (1:1:1) to receive GLM 50 mg or 100 mg or placebo via the SC route every 4 weeks. Placebo responders were continued on placebo throughout the all observation period. Non-responders from both groups received GLM 100 mg SC every 4 weeks and left the study if there was persistent no response at week 16. Data showed a significantly higher proportion of clinical response maintenance than placebo for patients in the GLM 100 mg group (50% vs 31%) and the GLM 50 mg group (47% vs 31%). Similar trends were seen for deep remission and mucosal healing (42% for both GLM groups vs 27% for placebo, $p = 0.002$ using 2-sided Chi square test). In patients on 50 mg monthly dose partially losing response, dose increase to 100 mg resulted in no recovery.

PURSUIT-M has also been the first trial to introduce the concept of continuous clinical response (CCR) as a primary end point. This tool is independent of endoscopic assessment and physician's evaluation, defining a new concept of self-monitoring of disease course that not only makes patients responsible for their well-being, but also is a fundamental instrument to early identification of treatment failure and reduces the expense of health-care resources [15].

A prolonged observation of PURSUIT-M data until week 104 [16] was conducted in those patients who had completed PURSUIT-M and could benefit from continued treatment in investigators opinion. Specifically, patients on placebo and GLM 50 mg groups with symptoms relapse were switched to monthly GLM 100 mg, and if no response was achieved by week 16 after the optimization they were withdrawn from the study. Efficacy was assessed by physician global assessment (PGA) sub-score of the Mayo score. The study showed a sustained clinical response for GLM, with 53.8–58.5% maintaining inactive disease (PGA 0) and 80.5%–91.8% remaining with a stable inactive/mild disease (PGA 0–1). Corticosteroid-free patients at week 54 did not need corticosteroids in the following 50 weeks in 88.5% of cases.

In 2017, Japanese authors published similar results in long-term efficacy (56.3% vs 49.7% of PURSUIT-M) and safety at week 52 in a Japanese cohort of UC BN patients [17]. This study, the PURSUIT-J, is currently the last double-blind randomized placebo-controlled trial available for GLM.

Real-life results in ulcerative colitis

Data for the use of GLM in patients previously exposed to anti-TNF is limited in UC and only a systematic narrative review was possible. In fact, all PURSUIT trials have been conducted in BN patients and only few real-life studies [18–22] support its efficacy in biologics experienced (BE) patients. Summary of these data is resumed in Table 2.

A Spanish study involving nine centres in Andalusia was published in 2016 concerning 23 patients, 16 (70%) of whom were BE [18]. After a median treatment time of 14.3 weeks, clinical response was observed in 78% patients, 85.5% in the BN group and 75% in the BE group, without a statistically significant difference between them. Only 9% had endoscopic evaluation, so mucosal healing was not considered among the outcomes.

In a real-life observational study, Detrez et al. enrolled 21 patients, 11 (52%) of which BN and 10 (48%) BE [19]. At week 14, partial or complete clinical response was observed in 7 (64%) patients among BNs and in 3 (30%) among BEs for a total of 10 (48%). Among these last patients, mucosal healing was achieved in 4 out of 10 (19% of total cohort).

Table 2 Published real-life studies of GLM therapy in UC

Study	Patients (*n*)	Naïve/experienced to anti-TNF (%)	Duration of follow-up (weeks)	Clinical response	Clinical remission	Laboratory improvements	Endoscopic remission	Total AEs
Castro-Laria et al. [18]	23	30.4% BN vs 69.6% BE	From 4 to 36	85.5% BN, 75% BE, 78% BN + BE	Not available	Not available	Not available	0%
Detrez et al. [19]	21	52% BN vs 48% BE	14	BN + BE 48%	BN + BE 14%	Not available	19%	Not available
Bosca-Watts et al. [20]	33	27.3% BN vs 72.7% BE	14	BN + BE 69.7%	BN + BE 51.5%	Present	Not available	9%
Tursi et al. [21]	94	88.8% BN vs 11.2% BE	25	77.4% at 3 mo., 64.5% at 6 mo	44.1% at 3 mo., 36.5% at 6 mo	Present	19.3%	4.3%
Taxonera et al. [22]	142	40% BN vs 60% BE	52 (median)	BN + BE 65%	32% at 3 mo., 57.7% at 12 mo	Present	Not available	2.8%

In 2016, Bosca-Watts et al. published the results of 33 patients treated with GLM for 14 weeks [20]. At the beginning, 9 (27.3%) patients were BNs and 24 (72.7%) BEs, with 66.7% of this last group having experienced two anti-TNF. At 14 weeks evaluation, 6 (66.7%) among BNs and 17 (70.8%) among BEs were in clinical response, for a total of 23 (69.7%). 51.5% of patients were in clinical remission. Both mean faecal calprotectin and C-reactive protein values at baseline decreased during the follow-up.

Tursi et al. recently published a real-life study using GLM in 93 patients, with 9 (11.2%) BE [21]. At 3 months, remission was achieved in 41 (44.1%) patients, while it was obtained in 34 (36.5%) patients at 6 months. Shorter duration of disease (3.5 years in the remission group vs 8.0 years in the failure group) was the only predictor factor of remission with statistical significance ($p = 0.018$ with Mann–Whitney test) at the 6-month follow-up. Clinical response was reached in 77.4% and in 64.5% of patients at the 3- and 6-month follow-up, respectively. Laboratory parameters considered (C-reactive protein and faecal calprotectin) were significantly and progressively reduced in patients in remission. Mucosal healing was defined as Mayo endoscopic subscore of 0–1 and was reached in 18 (19.3%) patients, being significantly related with faecal calprotectin reduction ($p < 0.001$). On the other hand, among all patients still on GLM at 6 months, only 53% were in steroid-free remission. Discontinuation of treatment was necessary in 32.2% of patients (17.5% for primary failure, 10.7% for secondary failure, 3.2% for AEs).

A retrospective multicentre study by Taxonera et al. evaluated GLM in 142 consecutive patients with moderate to severe UC [22]. 40% of patients were BN, 23% had previously tried one anti-TNF and 37% two other anti-TNFs. 92 patients (65%) reached short-term clinical response. 45 patients (32%) achieved short-term clinical remission. Response rates were 75% for BN patients, 70% with second anti-TNF (with no statistical difference vs BN) and 50% with third anti-TNF ($p = 0.007$ vs first anti-TNF). Even remission rates were significantly better in BN patients and in patients who received GLM as second anti-TNF than patients receiving GLM as third anti-TNF ($p = 0.004$). At a median follow-up of 12 months, 57.7% of patients maintained sustained clinical remission. Dose escalation doubling the quantity per kg or halving the interval of administration was tried to overcome secondary loss of response with reported success.

The real-life data mentioned above show good response profile both in BN and BE patients with approximately no significant statistical difference. Nevertheless, these studies have low evidence level in consideration of the small number of enrolled patients and the heterogeneity of data, which do not permit a meta-analytic approach.

Conversely, the evidence for the efficacy of GLM in BE patients is more robust in rheumatology where 461 experienced patients with rheumatoid arthritis were randomized for the GO-AFTER study [23]; the results showed a significantly higher clinical response in patients taking GLM 50 mg or 100 mg as compared to placebo (35%, 38% and 18%, respectively), concluding that this drug has some benefit and it is worth trying also in patients with other anti-TNF exposures.

Pharmacokinetic, therapeutic drug monitoring and anti-drug antibodies

Experience gained with anti-TNFs allowed us to understand the importance of their pharmacokinetic, with particular focus on cases of drug failure/loss of response.

Therapeutic drug monitoring (TDM) thus gained a central role in biologics clinical management through dose adjustments to improve the outcomes, both in case of remission and failure/loss of response, but few data are available regarding its relevance in GLM management.

PURSUIT studies showed lower rates of clinical response, clinical remission and mucosal healing, in patients that presented lower serum GLM concentration, both in induction phase and maintenance phase at different weeks, suggesting a relevant role of serum drug concentration to obtain a good outcome. The authors also suggested possible thresholds of serum GLM concentration for the induction and maintenance phases that could be hopefully validated in further randomized trials [24], but no official cutoff is yet clinically available to optimize golimumab therapy.Anti-drug antibodies (AA) represent a real concern in management of biologics therapies because of their involvement in loss of response and hypersensitivity reactions. GLM AA could have a neutralizing action, while it is not clear if they are transient or persistent. Their development is more frequent in case of the presence of AA to other anti-TNFs previously managed [25].

The clinical impact of AA in case of GLM therapy, however, is yet to be defined. The rates of AA positivity are highly variable, but their presence is related to low or undetectable GLM levels in contrast to AA-negative patients [26]. On the other hand, there are no validated methods for AA monitoring at the moment. Enzyme-linked immunosorbent assay is characterized by low cost and high throughput, but also by drug interference leading to false negatives, and by inability to detect IgG4 AA, which may have an important role in drug neutralization. Radioimmunoassay and homogeneous mobility shift assay could exceed the mentioned limits, but they are expensive and less widespread. The same can be said about reporter gene assay, a bioassay that evaluates AA functional activity.

Combo therapy

There is nowadays no evidence for the efficacy and safety of combination therapy with GLM and immunosuppressants in UC. More specifically, no study has yet been proposed with concomitant use of thiopurines, except for a study on 6 patients where results were not conclusive [27]. The only data demonstrating the higher efficacy of combo-therapy with immunosuppressants are reported in the GO-FORWARD trial conducted in rheumatoid arthritis patients, where concomitant treatment of GLM with methotrexate resulted in improved physical function and reduction of signs and symptoms [28].

Findings from PURSUIT-M [10] trial showed lower positivity for GLM antibodies after 54 weeks in patients taking concomitant immunosuppressant (1.1% vs 3.8%, $p = 0.013$ with Chi square test), but this was not in correlation with better clinical outcome.

Subsequent analysis [24] of PURSUIT data showed that during the induction phase, median steady-state GLM levels were similar between the two groups of monotherapy and combo therapy with an immunomodulator among the 100 mg GLM group, while median serum GLM levels were only slightly higher in patients receiving combo therapy with GLM 50 mg compared to the group without immunomodulators. This finding may suggest that GLM is less immunogenic than IFX and combination therapy has disputable utility in avoiding the development of drug antibodies.

Safety profile

In all PURSUIT studies, similar proportion of adverse events (AEs) were reported between the GLM groups and the placebo group.

The most common AEs in PURSUIT-SC [9] were headache and nasopharyngitis, with low incidence of serious AEs (3.0% GLM vs 6.0% placebo) and severe infectious events (0.5% GLM vs 1.8% placebo); only mild to moderate injection site reactions were reported. PURSUIT-IV [14] did not show any additional safety finding.

In the PURSUIT-M trial [10], the incidences of infections and serious infections were, respectively, 39% and 3.2% in the two GLM groups and 28% and 1.9% in the placebo group. Incidence of injection site reactions was higher in the 100 mg GLM group (7.1%) than in the 50 mg GLM and placebo group (1.9% in both). Three deaths have been reported, all in the 100 mg GLM group: one for malnutrition and sepsis, one for disseminated tuberculosis, one for cardiac failure. An extension of data collection till week 104 showed similar safety profile [16].

Castro et al. reported no adverse event in their observational period in 23 patients [18]. Tursi et al. showed a low percentage (4.3%) of AEs in a series of 93 patients: 1 severe urticaria, 1 alopecia and 1 erythema nodosum resulting in discontinuation of treatment and 1 transient fever with no other consequence [21]. Bosca-Watts et al. reported AEs only in 3 out of 33 patients (2 urinary infections and 1 nausea), without the need of interrupting the medication [20]. In Taxonera study, 4 (2.8%) patients experienced AEs leading to GLM withdrawal (one paraesthesia, one cutaneous infection, one pneumonia and one recurrence of cervical neoplasia) [22].

The overall reported AEs of GLM were comparable to the well-known safety profile of the other two anti-TNFs [4, 29]. No additional data were available concerning elderly patients.

GLM safety in pregnancy is extractable from some studies where anti-TNFs were considered as a single group. In the prenatally anti-TNFs exposed infants, it has been shown a moderate risk of major birth defects (5% vs. 1.5% non-exposed patients, OR: 2.2) and preterm birth (17.6% vs 9.0%, OR: 1.69), but risk of malformations or spontaneous abortion is not increased [30]. A Scandinavian study showed only a slightly higher risk of birth defects in anti-TNFs exposed children, with no significantly statistical difference [31]; in addition, in this study only 4 women were specifically taking GLM and reported no adverse events during pregnancy. Consequently, specific information on its safety during pregnancy is still not available, and data are also lacking about its presence in breast milk.

It is recommended to perform a risk–benefit assessment for the use of GLM during pregnancy, especially if we consider that pregnancy is not responsible for IBD flares but is able to worsen the course of disease during the active phase [32].

In paediatrics, GLM has shown consistent safety profile across weight, concomitant medications and age, similar to adult results and the other anti-TNF paediatric studies [33].

Preliminary data in Crohn's disease

No formal trial has been performed to assess the efficacy of GLM in Crohn's disease (CD). A retrospective observational study conducted in 45 CD BE patients (97.7% had experienced two other anti-TNF) demonstrated optimal clinical response (71.1% at 6 months, 70.9% at 12 months) [34]. GLM dispensation in CD had been allowed in Canada for compassionate use, when other conventional therapies were not feasible or had been unsuccessfully tried. Most patients received higher GLM doses for induction and maintenance with the most prevalent regimen being 200 mg every 2 weeks. In the subset of patients with endoscopic evaluation

at 12 months, 82.3% achieved a score improvement and 64.7% reached mucosal healing. Severe AEs were recorded in 2 patients, both with serious infections requiring hospital admission. Only 3 (6.6%) patients had to withdraw GLM because of AE: one for infection and two for drug-induced lupus reactions. Infections had been observed in 20% of patients, resulting in the most frequent AE. Patients receiving combination therapy had a statistically significant higher prevalence of infection.

Another real-life retrospective study evaluated GLM efficacy in 115 CD patients, where GLM was the median third biologic administered [35]. Clinical response was achieved in 55.8% of cases after 4 months of treatment. The probability of maintaining the therapy without escalation at 6 and 12 months was 54.6% and 34.9%, respectively. The scheme maintenance dose was the same as that of UC for almost all the patients (only 1.9% received > 100 mg/4 weeks) and no serious AEs were reported. Limitations of this study were the lack of endoscopic data and the presence of C-reactive protein only for 80% of patients.

Randomized prospective trials with higher number of patients are needed to confirm these data. Initial conclusions based on the two studies reported above demonstrate GLM efficacy in anti-TNF-resistant CD patients and a satisfying safety profile even with higher serum drug levels.

Comparison with the other anti-TNF agents

There is no head-to-head trial comparing the efficacy of the three available anti-TNF agents for UC. Nevertheless, various network meta-analyses have been published in recent years with indirect comparison in terms of clinical and endoscopic remission, with different results.

A network meta-analysis by Danese et al. evaluating the efficacy of IFX, GLM, ADA and vedolizumab in moderate to severe UC concluded that all agents were equally effective in maintaining remission [36]. The same findings of equivalence in induction and maintenance of remission for the three anti-TNF agents have been demonstrated in two other network meta-analyses [37, 38].

On the other hand, some comparative studies showed better results for IFX and GLM than ADA. Specifically, Thorlund et al. concluded that IFX was the best molecule for induction and both IFX and GLM are equally superior to ADA for maintenance of remission [39]. Same evidence was reported by another study by Qun Mei et al. where IFX showed a higher rate of clinical response, clinical remission and mucosal healing than ADA during the induction phase and GLM was better than ADA in clinical response induction and endoscopic outcomes [40].

A cost-effectiveness analysis considering IFX, ADA and GLM has been conducted by Toor et al. [41] suggesting that the lowest additional cost of 1 full year of remission (compared to conventional therapy) was reached with GLM 100 mg ($935) and GLM 50 mg ($1048); IFX followed with $1975 and ADA produced the highest cost per additional remission ($7430). The authors concluded that especially GLM appeared cost efficient if balanced with the low rate of response and long-term remission of conventional therapies.

Only one evaluation by the Spanish group of Trigo-Vicente et al. has found ADA to be the most cost-effective biologic between the three anti-TNF and vedolizumab [42].

Future scenarios

Head-to-head trials are necessary to exactly compare the clinical efficacy and deep endoscopic remission of all the three anti-TNF agents in the management of active UC, both in short-term and long-term series. The first findings seem to confirm the superiority of IFX over GLM and ADA and that of GLM over ADA, demonstrating that the higher affinity of GLM for TNF does not translate to better outcomes.

The impossibility to dose escalate or reduce the frequency of dosing in case of secondary failure is the most important limitation of the GLM schedule regimen that abruptly leads to drug withdrawal. For this reason, a new protocol of GLM dose Optimisation to Adequate Levels to Achieve Response in Colitis (GOAL-ARC) has been recently approved [43]. Its aim is to evaluate the impact of dose escalation of GLM early after induction and during the subsequent maintenance phase in response to suboptimal drugs levels or persisting raised faecal calprotectin, which correlates with endoscopic activity. The results of this multicentred randomized controlled trial will be soon available with the intent to guide clinical practice.

Therefore, routine measurement via blood samples will eventually been proposed in the near future as an effective method to escalate GLM dose to achieve and maintain clinical response through the course of disease and avoid primary and secondary failure.

Conclusion

The exact place of GLM in UC treatment is yet to be defined; nowadays, it represents an alternative to the two other most used anti-TNF agents and additional real-life data are needed to confirm the speculation that BE patients with longer-time disease have less possibilities than BN patients to reach clinical remission. This suggests that patients with aggressive disease despite anti-TNF use would benefit swap therapy to other molecular targets, such as the currently available α4β7-integrin inhibitor vedolizumab.

In conclusion, the decision of drug prescription has to be based on the summation of drug safety and efficacy, physician's experience, personal compliance of the patient, drug cost and reimbursement. The findings here reported show that GLM is as well tolerated as the other anti-TNF, has a better compliance profile (SC administration and monthly schedule) and a lower cost per additional remission of the other brand products. It is mandatory to repeat these cost-analysis evaluations with IFX biosimilars and the impending release of ADA biosimilars in the near future.

Nowadays, GLM has no role in the treatment of CD. Few retrospective results show the clinical efficacy with higher doses than the routinely administered scheme in UC with acceptable tolerability profile. Randomized studies are needed in this field to confirm these findings.

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Compliance with ethical standards

Conflict of interest Gabriele Dragoni, Marco Le Grazie, Beatrice Orlandini and Francesca Rogai declare that they have no conflict of interest.

Human/animal rights All procedures followed have been performed in accordance with the ethical standards laid dowm in the 1964 Declaration of Helsinki and its later amendments.

Informed consent Informed consent was obtained from all patients for being included in the study.

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