Golimumab pharmacokinetics in ulcerative colitis: a literature review

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Ther Adv Gastroenterol

2017, Vol. 10(1) 89–100

DOI: 10.1177/
1756283X16676194

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Abstract: Golimumab (GLM) is the latest anti-tumor necrosis factor (TNF) that gained its marketing license. Thanks to the PURSUIT induction and maintenance trials, it was approved for the treatment of ulcerative colitis (UC) in 2013. The other anti-TNF drugs available are infliximab and adalimumab. These two drugs have validated algorithms concerning prescription and therapeutic drug monitoring (TDM) but little is known about GLM.

The available data on GLM's exposure–response relationship in UC are from the PURSUIT trials and are recently published. The data reveal all the factors that may impact the pharmacokinetic (PK) parameters: dosage, body weight (BW), concomitant drugs, the presence of anti-drug antibodies (ADABs), sex and age. In addition, the GLM trough level at steady-state appears to be correlated with the patient's improvement which may make it a precious indicator to predict the clinical response.

There is, however, no consensus on a possible therapeutic level or cutoff associated with clinical response, remission, or any other outcome measure such as endoscopic healing in UC. This lack of a threshold value, and its validation with different assay techniques, makes it difficult to use GLM TDM in clinical practice. As with other anti-TNF agents, GLM is associated with development of ADABs, of which the prevalence and effects are still insufficiently described. The objective of this review is to describe current data and understanding of the PK of GLM including serum concentrations of GLM and ADABs in UC patients. Better understanding of these parameters could lead to improved patient care with GLM.

Keywords: antibody to golimumab, golimumab, trough levels, UC

Introduction

The use of monoclonal antibody against tumor necrosis factor (TNF)- α has changed clinical practice in patients with inflammatory bowel diseases (IBD). Infliximab and adalimumab are extensively studied and have demonstrated their effectiveness in patients with active IBD. Despite a significant cost, anti-TNF biologics can reduce the need for surgery, the number of hospitalizations and allow withdrawal of corticosteroids. However, resistance to these treatments, through anti-drug antibody (ADAB) development is a real concern [Nanda *et al.* 2013; Paul *et al.* 2014; Moore *et al.* 2016]. Therapeutic drug monitoring (TDM), including measurement of antibodies against anti-TNF and drug trough levels are increasingly used to improve disease outcomes in IBD [Colombel *et al.* 2012; Roblin *et al.* 2014a; Ben-Horin and Chowers, 2014]. This monitoring

can lead to optimization of drug dose in case of a loss of response. Treatment algorithms including TDM have been proposed to improve the outcome of anti-TNF therapy in IBD [Ben-Horin and Chowers, 2014]. Still, some patients with a therapeutic drug level may relapse while others can remain in clinical remission despite low serum trough levels of anti-TNF [Steenholdt *et al.* 2014a; Vande Casteele *et al.* 2015]. Concomitant use of an immunomodulator can reduce ADAB development and is associated with higher drug trough levels [O'Meara *et al.* 2014]. Patients with a loss of clinical response to a first anti-TNF may regain response after a switch to another anti-TNF because ADABs may not be crossreactive but are prone to develop *de novo* ADABs [Frederiksen *et al.* 2014]. Golimumab (GLM) is a human immunoglobulin (Ig)G1 κ monoclonal antibody that received a French marketing license

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Table 1. Recommended GLM dosage and schedule according to the US FDA and EMA.

Indication	FDA recommendation	EMA recommendation
RA, PsA and AS	50 mg once a month	50 mg every 4 weeks if BW < 100 kg 100 mg every 4 weeks if BW > 100 kg and no clinical response after three 50-mg administration.
UC	200 mg week 0 100 mg week 2 100 mg every 4 weeks	200 mg week 0 100 mg week 2 50 mg every 4 weeks if BW < 80 kg 100 mg every 4 weeks if BW > 80 kg
pJIA		50 mg every 4 weeks

AS, ankylosing spondylitis; BW, body weight; GLM, golimumab; EMA, European Medicines Agency; pJIA, polyarticular juvenile idiopathic arthritis; PsA, psoriatic arthritis; RA, rheumatoid arthritis; UC, ulcerative colitis; US FDA, United States Food and Drug Administration.

in 2009. This monoclonal antibody binds to both the soluble and transmembrane bioactive forms of human TNF- α , and thereby prevents the binding of TNF- α to its receptors, inhibiting TNF bioactivity [Shealy *et al.* 2010]. GLM is indicated for rheumatoid arthritis (RA), psoriatic arthritis (PsA), ankylosing spondylitis (AS), and ulcerative colitis (UC) [Sandborn *et al.* 2014a]. Limited pharmacokinetic (PK) information is available in UC patients treated with GLM. Most PK data on GLM exposure-response relationship in UC are from the PURSUIT induction and maintenance trials and recently published [Sandborn *et al.* 2014a, 2014b; Rutgeerts *et al.* 2015; Hyams *et al.* 2016]. In PURSUIT trials, higher rates of clinical response and remission are reported in patients with GLM serum levels within the third and fourth quartile of distribution. There is, however, no consensus on a possible therapeutic level or cutoff associated with clinical response, remission, or any other outcome measure such as endoscopic healing in UC. This lack of a threshold value, and its validation with different assay techniques, makes it difficult to use GLM TDM in clinical practice. As with other anti-TNF agents, GLM is associated with development of ADABs, of which the prevalence and effects are still insufficiently described. Antibodies to anti-TNF may be transient [Vande Casteele *et al.* 2013] and can have adverse effects (AEs) such as injection site reaction and loss of efficacy [Bingham *et al.* 2015]. ADABs influence the PK of GLM by increasing its clearance [Adedokun *et al.* 2016b]. The objective of this review is to describe current data and understanding of the PK of GLM including serum concentrations of GLM and ADABs in UC patients. Better understanding of

these parameters could lead to improved patient care with GLM in UC.

Review methodology

We performed a literature review of all papers in English published in PubMed, Cochrane, Embase and in main learned society websites prior to August 2016. The term 'GLM' was matched with the terms 'UC', 'biologics', 'PK', 'trough level' and 'ADAB'. Reports of congresses presentations and randomized controlled trials were also included.

Mechanisms and schedule

GLM is a humanized anti-TNF monoclonal antibody, administered through subcutaneous (SC) injections. GLM blocks soluble and transmembrane TNF- α , inhibiting TNF- α receptor binding. However, compared with infliximab and adalimumab, GLM preclinical studies showed greater conformational stability and higher binding affinity for soluble and transmembrane TNF- α [Shealy *et al.* 2010]. GLM has been approved by the US Food and Drug Administration (FDA) and the European Medicines Agency (EMA) for RA, PsA, AS and UC (Table 1). In addition, the EMA adopted a new indication for GLM in polyarticular juvenile idiopathic arthritis (pJIA) in May 2016.

In PsA and AS studies with 50 and 100 mg GLM doses administered through SC injection every 4 weeks, no significant difference of efficacy and safety was reported between the two doses [Kavanaugh *et al.* 2009; Braun *et al.* 2012]. The lower dosage is recommended by the US FDA and EMA. Data from the PURSUIT-M study

showed that administration of GLM 100 mg every 4 weeks in UC patients, who lost response to initial treatment with 50 mg, did not result in significantly higher response rates [34.6% *versus* 28.0%] compared with patients who continued the 50 mg dose [Sandborn *et al.* 2014b]. The US FDA recommends a 100 mg maintenance dose in UC patients while the EMA adapts the maintenance dose in relation to body weight (BW) as shown in the (Table 1).

GLM efficacy in UC

The PURSUIT-SC induction study [Sandborn *et al.* 2014a], evaluating two dosages of GLM (200 mg at week 0 followed by 100 mg at week 2 and 400/200 mg) *versus* placebo in anti-TNF naïve patients with moderate-to-severe UC showed that rates of clinical response at week 6 (51.0%, and 54.9%, respectively) were higher compared with those given placebo (30.3%; $p < 0.0001$ for both comparisons).

Rates of clinical remission (17.8% and 17.9% respectively) and mucosal healing (42.3 and 45.1% respectively) and mean changes in IBDQ (Inflammatory Bowel Disease Questionnaire (Quality of Life)) scores (27.0 ± 33.72 and 26.9 ± 34.28 respectively) were significantly higher compared with placebo treatment at week 6.

Induction nonresponders (at week 6) were dose-optimized to 100 mg; of these 32% were in response by week 18 (after 2 additional 100 mg doses), indication that 'delayed' response may occur after dose increase to 100 mg. Delayed responders were not distinguished by baseline characteristics GLM levels, or ADA status from those who did not achieve delayed response [Colombel *et al.* 2016]. Continued therapy is not useful in patients who show no evidence of therapeutic benefit within 12–14 weeks of the start of GLM treatment [Rutgeerts *et al.* 2014].

Similar patterns of response were observed among patients randomized in other study phases. Patients who presented a clinical response at week 54 maintained it through week 104 and up to 4 years [Gibson *et al.* 2016; Reinisch *et al.* 2016].

PK

Studies on the GLM PK have been conducted on the SC and intravenous (IV) induction studies of

PURSUIT [Sandborn *et al.* 2014a; Rutgeerts *et al.* 2015]. The comparison of the IV and SC injections shows more favorable PK of GLM when administered in a SC route, probably related to a more sustained serum concentrations over the 6-week induction period, compared with one single IV infusion [Rutgeerts *et al.* 2015]. Currently, only the SC GLM formulation is approved and available.

GLM PK is summarized in Table 2.

Concomitant drug effects on PK

Concomitant use of immunomodulators [Adedokun *et al.* 2016b], nonsteroidal anti-inflammatory drugs, oral corticosteroids, or sulfasalazine did not influence the apparent clearance of GLM.

Immunomodulators can increase the serum concentration of TNF antagonists by either reducing the formation of ADAbs or by reducing the reticuloendothelial system-mediated drug clearance.

Analysis of the PURSUIT data showed that during induction, median serum GLM levels were similar between combination therapy (addition of an immunomodulator) and monotherapy in the 100 mg GLM group while median steady-state GLM concentration were slightly higher among patients receiving GLM 50 mg in combination with immunomodulators *versus* without immunomodulators [Adedokun *et al.* 2016c].

In addition, there was a positive exposure-response relationship between serum GLM concentration and efficacy regardless of immunomodulator use [Adedokun *et al.* 2013]. Combination therapy *versus* GLM monotherapy in UC patients showed clinical response in 44% *versus* 50% [Dulai *et al.* 2014]. This result may indicate that GLM is less immunogenic than infliximab and therefore combination therapy may be less essential to avoid development of ADAbs.

GLM levels are positively correlated with methotrexate (MTX) dosages supporting the PK finding that MTX treatment increases drug levels by approximately 0.6 µg/ml [Zhou *et al.* 2007; Chen *et al.* 2015] and could reduce GLM clearance by 17.1% [Zhou *et al.* 2007; Xu *et al.* 2010].

Table 2. GLM main PK parameters.

Absorption	Tmax	2–6 days
	Cmax (SC injection of 50 mg)	3.2 ± 1.4 µg/ml
	Absolute bioavailability	53%
Distribution	Mean volume distribution (a single IV administration over the dose range of 0.1–10.0 mg/kg)	58–126 ml/kg distributed primarily in the circulatory system with limited extravascular distribution
Elimination	Mean systemic clearance	4.9–6.7 ml/day/kg
	Mean half-life	approximately 2 weeks
	Mean steady-state trough serum concentration	0.4–0.6 mcg/ml (active RA) 0.5 mcg/ml (active PsA) 0.8 mcg/ml (active AS)
	Mean steady-state trough serum concentration (100 mg GLM SC every 4 weeks)	1.8 ± 1.1 µg/ml
AS, ankylosing spondylitis; GLM, golimumab; IV, intravenous; PK, pharmacokinetics; PsA, psoriatic arthritis; RA, rheumatoid arthritis; SC, subcutaneous.		

BW effect on PK

The BW effect on PK is controversial. Treatment with the US FDA-recommended maintenance dose regimen of GLM 100 mg in UC patients did not result in meaningful differences in clinical efficacy among different weight groups. Across the PsA and AS populations, also, no meaningful differences in clinical efficacy were observed among the subgroups by weight quartile. The RA trial did show evidence of a reduction in clinical efficacy with increasing BW, but this effect was observed for both tested doses of GLM (50 mg and 100 mg). Conversely, the PK of the PURSUIT trial showed that BW was significant on all PK parameters [Adedokun *et al.* 2016b]. The GO-KIDS pediatric RA (JIA) study [Leu *et al.* 2014] revealed that an adjustment of the dosage with 30 mg/m² SC GLM during the maintenance phase in addition to MTX resulted in sustained steady-state trough serum GLM mean concentrations over time (1.14, 1.13, 1.19, and 1.08 mg/ml at week 12, 16, 24 and 48 respectively). The exposure-response relationship demonstrated that the body surface area-adjusted dosing regimen of 30 mg/m² SC GLM every 4 weeks provided adequate drug exposure for the desired efficacy. The steady-state trough GLM levels obtained in this study were similar across different age groups (at week 12 1.49, 0.95 and 1.21 mg/ml for the 2–6 years, 6–12 years and ≥12 years groups respectively) and were also similar to those seen in adult RA patients who received 50 mg SC every 4 weeks.

At week 8 and week 54, adult UC patients with BW > 80 kg showed lower GLM concentration compared with patients with BW < 80 kg when

receiving the same 50 mg GLM dose. Prescription of 100 mg dose for UC maintenance is supported by the EMA in patients with BW > 80 kg.

A high BW could be related to an altered bioavailability of anti-TNF agents or a higher TNF level especially in obese patients [Body Mass Index (BMI) > 30]. The potential interactions between PK, TNF level, BMI, and clinical outcomes have not been investigated adequately. However, Ordás and colleagues suggest that patients with a higher BMI (obese patients) may have an increased production of proinflammatory cytokines, such as TNF, resulting in a higher inflammatory burden, therefore requiring higher doses of TNF antagonists to neutralize these excess of TNF (the ‘sink’ hypothesis) resulting in a higher apparent clearance of GLM [Ordás *et al.* 2012].

GLM immunogenicity effect on PK

Only a few study results of GLM ADAbs are available, and different studies show different results. The presence of ADAbs can have an impact on the PK [Adedokun *et al.* 2016b] or not [Zhuang *et al.* 2013] depending on the study. This point needs more investigation. The fact that only few reliable assays to measure GLM and ADAbs are available has thus far limited research interest and application of GLM TDM in clinical practice (see below).

Sex effect on PK

Population PK analyses suggested no PK differences between male and female patients after BW adjustment in the RA, PsA and UC trials.

There is no recommendation for dosage adjustment based on sex.

Age effect on PK

Population PK analyses indicated that PK parameters of GLM were not influenced by age in adult patients. Patients with age ≥ 65 years had apparent clearance of GLM similar to patients with age < 65 years. No ethnicity-related PK differences were observed between Whites and Asians, and there were too few patients of other races to assess for PK differences.

Results of the pediatric PK parameters studied in a pediatric UC patient population were comparable with those reported in adult UC patients [Hyams *et al.* 2016; Adedokun *et al.* 2016a].

GLM lab monitoring

Methods available for GLM measuring

TDM with serum level measurement and ADA_b detection can be a useful tool leading to the optimization of anti-TNF treatment. There are many techniques developed for anti-TNF drug and ADA_b level determination. Some techniques are adapted for GLM and ADA_b measuring in daily practice.

Because of the low cost and high throughput, the ELISA (enzyme-linked immunosorbent assay) technique is often the preferred analysis method. However, ELISA-based detection methods suffer from two major disadvantages: interference with drugs (so-called drug sensitive), and the inability to detect IgG4 ADA_bs, which may have a greater potential for neutralization [Aalberse *et al.* 2009; Sethu *et al.* 2012]. For measurement of GLM serum concentrations, both a TNF-coated ELISA and a sandwich-type ELISA were developed [Detrez *et al.* 2016]. The study set a cutoff number for both techniques (0.5 and 0.1 $\mu\text{g/ml}$ respectively). They also measured ADA_bs using a bridging ELISA and a newly-developed drug-tolerant immunoassay that enables the measurement of ADA_bs in the presence of GLM [Martín *et al.* 2015b]. Radioimmunoassay (RIA) can detect IgG4 antibodies and is less affected by drug/rheumatoid factor interference; however, this method remains less widespread mainly because of its higher costs and the need to use radioisotopes. A third newly-developed technique

is Homogeneous Mobility Shift Assay. It is based on chromatography and allows ADA_b detection even if the drug is present at high levels [Colombel *et al.* 2012]. This technique is more expensive than ELISA and is currently not available in Europe. Finally, Reporter Gene Assay is a bioassay that evaluates the functional activity of the ADA_b. The advantage of this technique is that it detects only the ADA_b that neutralizes the anti-TNF activity. Bioassays are recommended by the US FDA and the EMA considering that they are more reflective (than competitive ligand-binding assays) of the *in vivo* situation.

Methods comparison

There are two studies [Martín *et al.* 2015a; Jurado *et al.* 2015] that compared the marketed Promonitor-GLM with the Sanquin laboratory assay method. Both techniques are based on ELISA technology, the main difference is that the Promonitor method uses a horseradish peroxidase-conjugated anti-GLM human monoclonal antibody specifically designed to bind GLM while the Sanquin detection reagent is a biotinylated rabbit polyclonal Ig directed to GLM, and therefore requires a third incubation step with streptavidin to develop the capture reaction. The two papers found an excellent correlation and agreement between GLM levels obtained with each technique. Only one sample was reported [Martín *et al.* 2015a] by Promonitor-GLM as negative while a positive result (10 ng/ml) was reported with the Sanquin ELISA.

Another study revealed an excellent correlation between anti-TNF-coated ELISA and sandwich ELISA [Detrez *et al.* 2016] with a preference for the second technique that showed a higher sensitivity and specificity in addition to an accuracy and imprecision calculated to be 100% and 5%, respectively.

The main problem with ADA_b detection is that the presence of the drug in the sample can result in a false-negative result in so-called drug-sensitive assay formats like ELISA. Using a drug-tolerant immunoassay, GLM ADA_bs started being detectable within 14 weeks of therapy while they were undetectable with a drug-sensitive assay [Detrez *et al.* 2016]. Therefore, drug-tolerant assays should be used in further studies to assess the exact prevalence of GLM ADA_bs. A study comparing two methods of ADA_b detection

proved that sensitivity for the detection of ADABs of RIA and ELISA are comparable even though RIA is known to be a less drug-sensitive assay [Martín *et al.* 2015a].

The comparison data from large 'real world' experience practice between GLM and ADAB assay techniques currently available are few but largely indicates that current methods are reliable. A large study aiming to compare four ELISA assays for GLM measurement in UC is ongoing [anti-IgG detection antibody (Theradiag) or an antibody directed against the idiotype of GLM (Sanquin and KU Leuven, Janssen R&D)]. Its results might allow further expansion of GLM PK research and development of therapeutic algorithms including TDM in clinical practice, especially in UC.

GLM trough level and the clinical response

Serum GLM levels were significantly associated with efficacy outcome in RA, PsA [Kneepkens *et al.* 2014; Chen *et al.* 2015] and UC [Sandborn *et al.* 2014a] patients. In adult UC patients, a steady-state is obtained at approximately week 8 after two induction doses of 200 mg and 100 mg administered at week 0 and 2 of induction, respectively [Sandborn *et al.* 2014a]. Week 8 could therefore be a good time for dose optimization based on the GLM serum level, if needed. More studies are necessary, however, to demonstrate if GLM level can predict the long-term clinical response.

In the PURSUIT-SC (induction) trial, an exposure-response relationship was observed, with UC patients in the highest serum GLM concentration quartiles having greater rates of clinical response when compared with those in the lower quartiles at week 6. Patients with GLM levels in the lowest quartile consistently showed lower rates of clinical response, clinical remission, and mucosal healing, with rates of success sometimes approaching those observed in patients assigned to placebo, during both induction and maintenance. As expected, patients in this category were more likely to have factors known to contribute to a higher clearance of GLM, including a higher incidence of immunogenicity, higher BW, higher inflammatory burden [Sandborn *et al.* 2014a, 2014b; Adedokun *et al.* 2016a]. In addition, the comparison of GLM levels in patients receiving 100/50 mg; 200/100 mg or 400/200 mg GLM reveals a positive relationship between GLM dose

and its concentration through week 6 [Adedokun *et al.* 2016c].

These findings are consistent with those from Detrez and colleagues, aiming to investigate whether a low GLM serum concentration reduces the efficacy of this drug in patients with UC, and demonstrating that 80% of the partial clinical responders had a serum GLM concentration located in the highest quartiles at week 6 [Detrez *et al.* 2016]. This same study showed that median serum GLM concentration was significantly higher in partial clinical responders than in nonresponders: 10.0 (7.8–10.5) µg/ml *versus* 7.4 (4.8–8.3) µg/ml at week 2 ($p = 0.035$) and 5.1 (4.0–7.9) µg/ml *versus* 2.1 (1.8–4.2) µg/ml at week 6 ($p = 0.037$). In addition, it was suggested that the GLM concentration at week 6 may be predictive of the clinical response at week 14. The Receiver Operating Characteristic (ROC) curve analysis revealed a cutoff of 2.6 µg/ml at week 6 [90% specificity, 56% sensitivity, Area Under Receiver Operating Characteristic (AUROC) 0.79 (95% CI); $p = 0.034$] for the association of week 6 serum GLM level with partial clinical response at week 14 [Detrez *et al.* 2016]. Adedokun and colleagues also looked for an optimal serum GLM concentration threshold and ROC estimates for key efficacy endpoints revealed that a serum GLM concentrations of 2.5 µg/ml at week 6 during induction and 1.4 µg/ml at week 44 (steady-state trough) during maintenance are estimated to be desirable concentration targets for attainment of optimal clinical outcomes [Adedokun *et al.* 2016a].

At weeks 30 and 54 of the PURSUIT-M study [Sandborn *et al.* 2014b], median serum GLM concentrations were 1.73 µg/ml and 1.81 µg/ml, respectively, in the GLM 50 mg group, and 3.81 µg/ml and 3.52 µg/ml, respectively, in the GLM 100 mg group. The patients follow up revealed that higher serum GLM concentrations at week 54 were associated with greater proportions of patients who maintained clinical response through week 54 (continuous clinical response through week 54 was the primary endpoint of this study) or who were in clinical remission at both weeks 30 and 54, further supporting the efficacy of GLM in the maintenance of clinical benefit in patients with UC, and supported by the exposure-response relationship with GLM in UC.

The clinical improvement has also been observed in pediatric UC patients. The serum GLM levels in the pediatric UC population were generally

comparable with or numerically higher than in the adult studies. In fact, at weeks 2, 4, 6 and 14, mean pediatric serum GLM concentrations were 6.5, 6.5, 2.6 and 2.1 µg/ml, respectively, which were similar to those observed in adults who received 200/100 mg induction (6.4, 5.6, 2.1, 1.8 µg/ml) [Hyams *et al.* 2016; Adedokun *et al.* 2016a].

The exposure-response relationship indicates that TDM may be useful to establish a personalized therapy strategy for individual patients. Prospective studies including GLM TDM are needed to investigate whether establishing an individualized therapeutic level is useful and when such level should be achieved (e.g. as early as week 2, or 6–10 for UC patients treated with GLM).

GLM immunogenicity

As mentioned above, GLM ADAAb can only be accurately assessed with drug-tolerant assays. GLM ADAAb is neutralizing but it is not clear whether some are transient while others may be persistent.

Rates of ADAAb positivity vary between studies, ranging from 2.1–8.1% up to 15.2–19% [Kay *et al.* 2008; Keystone *et al.* 2009; Sandborn *et al.* 2014a, b; Rosas *et al.* 2014; Kneepkens *et al.* 2014; Martín *et al.* 2015a; Chen *et al.* 2015; Detrez *et al.* 2016]. Overall, GLM is less immunogenic compared with infliximab. The wide range of ADAAb positivity among different studies may be explained by the number of patients recruited and also the presence or absence of MTX in the rheumatology patient population studied. In fact, the presence of MTX decreased anti-GLM antibody incidence from 7% to 2%. Another explanation could be the use of drug-tolerant immunoassays in the recent studies.

The PURSUIT-SC long-term extension revealed that the GLM dose might have an impact on ADAAb development. The proportion of patients positive for antibodies to GLM was numerically higher in the 50 mg *versus* 100 mg dose regimen in the PURSUIT trial (4.4% *versus* 3.7%) [Reinisch *et al.* 2016].

Presence of ADAAb reaction to a previous anti-TNF biological therapy can raise the risk of developing ADAAbs to the next anti-TNF. In fact, 20% of patients with rheumatic disease who developed

ADAAbs under adalimumab therapy, subsequently developed ADAAbs to GLM after the switch [Rosas *et al.* 2014].

Patients treated with concomitant immunomodulators (Azathioprine, 6-MP and MTX) have lower levels of ADAAbs than patients receiving GLM without immunomodulators [Adedokun *et al.* 2013; Sandborn *et al.* 2014b].

There is no evidence yet that GLM ADAAbs can be transient like infliximab ADAAbs. Though, one study does report that, and ADAAbs have been overcome in one patient through a drug dose escalation [Detrez *et al.* 2016].

GLM immunogenicity in pediatric patients was comparable with that in an adults study (6.3% *versus* 4.3%) [Hyams *et al.* 2016; Adedokun *et al.* 2016a].

Impact of ADAAbs on GLM level and clinical response

To date, little is known about GLM ADAAb development and its relation to clinical response. Many studies came to the conclusion that ADAAb-positive patients had low or undetectable GLM levels in contrast with patients who were ADAAb negative [Garcès *et al.* 2013; Kneepkens *et al.* 2014; Chen *et al.* 2015].

In the PURSUIT trial, while there was no apparent impact of GLM ADAAbs on efficacy during induction, a numerically lower proportion of patients who were ADAAb-positive to GLM achieved maintenance efficacy outcomes compared with those who tested negative for antibodies [Adedokun *et al.* 2016c]. The same has been found in ADAAb-positive rheumatic patients that were reported to have significantly lower clinical response rates or persistent active disease compared with ADAAb-negative patients [Chen *et al.* 2015]. On the other hand, the follow up of ADAAb-positive IBD patients (using a drug-tolerant immunoassay) revealed that a partial clinical response can be obtained even in the presence of ADAAb [Detrez *et al.* 2016]. Out of four patients, only one patient had to be switched to another anti-TNF agent while three others maintained clinical response through week 14. In conclusion, the ADAAb positivity cannot predict the patient clinical outcome and does not result in a systematic therapeutic failure.

GLM level and AEs

Patients with AS, receiving higher doses of GLM, had a greater risk of serious infections compared with patients receiving lower doses [Braun *et al.* 2012]. This is consistent with the PURSUIT-M results showing that 8.4% of patients treated with GLM 50 mg and 14.3% of GLM 100 mg reported at least one AE. An indirect comparison revealed that serious AEs were significantly more frequent among patients treated with a maintenance dose of 100 mg of GLM compared with those treated with infliximab [Kawalec and Pilc, 2016].

On the opposite, Adedokun *et al.* [2014] exploratory analysis of the PURSUIT data reveals that the distribution of serum area under the curve in patients who experienced one or more safety events were comparable to that in patients with no safety event and concludes to the absence of correlation between serum GLM exposure and the occurrence of infections, serious infections, or serious AEs in UC patients treated with 50 mg or 100 mg every 4 weeks through 1 year.

GLM in UC algorithm

Even though there are still no direct studies comparing GLM efficacy with infliximab and adalimumab, this drug is part of the 'ménage à trois' in treatment algorithms such as the one presented by Danese for UC (Figure 1) [Danese, 2013]. In fact, an indirect comparison did not observe any significant differences in clinical response between infliximab and GLM either during the induction or the maintenance phase of UC treatment. There were also no differences established in the frequency of clinical remission between these two drugs at the end of the maintenance phase [Kawalec and Pilc, 2016]. These comparison results need to be taken with caution since the analysis criteria and the compared populations were different and without any prospective randomization effort.

French [Peyrin-Biroulet *et al.* 2016] and Canadian [Bressler *et al.* 2015] guidelines recommend the patients TDM in UC patients in case of loss of response. On the other hand, anti-TNF trough concentration measurement did not demonstrate any clinical interest in IBD patients during remission. In fact, three studies [Steenholdt *et al.* 2014b; Vande Casteele *et al.* 2015; DHaens *et al.* 2016] aimed to determine whether patients follow up based on TDM is superior to real life for

Figure 1. GLM indication in UC [Danese, 2013]. GLM, golimumab; UC, ulcerative colitis.

maintaining remission in IBD patients. Though these studies had different designs, all of them concluded that the maintenance phase did not show superiority for continued level-based drug adjustment over clinically-based adjustment. These studies had some limitations decreasing their conclusion impact and TDM might be not indicated during maintenance phase.

The proposed GLM concentration thresholds [Adedokun *et al.* 2016a; Detrez *et al.* 2016] have not been prospectively validated but can be the first tool of TDM. Just like adalimumab [Roblin *et al.* 2014b], GLM should have its own algorithm based on TDM.

We suggest here an algorithm (Figure 2) based on GLM PK and following the scheme of the previously published algorithms for infliximab and adalimumab. In recent studies, GLM appears to be less immunogenic which may lead to a different TDM algorithm compared with other anti-TNFs. Many questions remain unanswered regarding the patients with low GLM levels. This algorithm shall be validated in future practice with large association studies and randomized clinical trials using drug-tolerant assays.

Conclusion

An advantage of GLM in comparison with infliximab is that it can be administered by a SC injection. Patients administering GLM at home may

Figure 2. Therapeutic algorithm for GLM in patients with UC clinical relapse.
ADAb, anti-drug antibody; GLM, golimumab; TNF, tumor necrosis factor; UC, ulcerative colitis.

be less compliant compared with IV administration in clinic; the latter, however, requires time-consuming hospital visits and an overall added expense. An advantage of GLM over adalimumab is the 4-week dosing schedule for maintenance treatment compared with the 2-week dosing interval that is being used for adalimumab [Löwenberg *et al.* 2014].

With time, long-term clinical efficacy and AEs of the different anti-TNF agents will help to determine which drug will be most suitable for long-term care in UC patients.

When a treatment is prescribed to a patient, it is usually a balance between the efficacy, the safety profile, the physician personal's experience, the compliance of the patient, drug pricing and reimbursement. It is a step-by-step approach in order to achieve a clinical improvement and remission using more powerful and potentially less-well-tolerated therapies. Anti-TNF agents are the last step of this approach. The GLM overall benefit-to-risk ratio is comparable with that of other anti-TNF biologics as reflected in the GLM summary characteristics. Correct positioning of GLM in the UC treatment algorithm needs further study. Such algorithms may include TDM to further improve patient-reported, biological, clinical, and endoscopic outcomes. TDM is an emerging tool to address the unmet clinical need of treatment optimization and individualized patient treatment in chronic inflammatory diseases.

Acknowledgements

Ines Harzallah and Josselin Rigaiil contributed equally to this work.

Funding

This research received no specific grant from any funding agency in the public, commercial, or not-for-profit sectors.

Conflict of interest statement

Xavier Roblin declares an interest in MSD (France), Abbvie (France), Hospira (France), Takefa (France), Theradiag (France) and Janssen (France). The conflict of interest is based on consulting fees.

References

- Aalberse, R., Stapel, S., Schuurman, J. and Rispens, T. (2009) Immunoglobulin G4: an odd antibody. *Clin Exp Allergy* 39: 469–477.
- Adedokun, O., Chan, D., Padgett, L., Xu, Y., Hyams, J., Turner, D. *et al.* (2016a) Pharmacokinetics and exposure-response relationships of golimumab in pediatric patients with moderate to severe ulcerative colitis: results from a multicenter open label study. *Gastroenterology* 150: S590.
- Adedokun, O., Xu, Z., Liao, S., Marano, C., Strauss, R., Zhang, H. *et al.* (2016b) Population pharmacokinetic modeling analysis of golimumab in adult patients with moderately to severely active ulcerative colitis. *Gastroenterology* 150: S408.

- Adedokun, O., Xu, Z., Marano, C., Strauss, R., Zhang, H., Davis, H. *et al.* (2013) Effects of immunomodulators on the pharmacokinetics and efficacy of golimumab in patients with moderately to severely active ulcerative colitis : results from phase 2/3 PURSUIT-SC induction and maintenance studies. *United Eur Gastroenterol J* 1: A80.
- Adedokun, O., Xu, Z., Marano, C., Strauss, R., Zhang, H., Johanns, J. *et al.* (2014) Serum golimumab exposure and the incidence of selected safety events in patients with ulcerative colitis following treatment with golimumab: an exploratory analysis of the PURSUIT study data. *Gastroenterology* 146: S-588.
- Adedokun, O., Xu, Z., Marano, C., Strauss, R., Zhang, H., Johanns, J. *et al.* (2016c) Pharmacokinetics and exposure-response relationship of golimumab in patients with moderately-to-severely active ulcerative colitis: results from Phase 2/3 PURSUIT Induction and Maintenance Studies. *J Crohns Colitis* pii: jjw133. 20 July 2016 [Epub ahead of print].
- Ben-Horin, S. and Chowers, Y. (2014) Tailoring anti-TNF therapy in IBD: drug levels and disease activity. *Nat Rev Gastroenterol Hepatol* 11: 243–255.
- Bingham, C., Mendelsohn, A., Kim, L., Xu, Z., Leu, J., Han, C. *et al.* (2015) Maintenance of clinical and radiographic benefit with intravenous golimumab therapy in patients with active rheumatoid arthritis despite methotrexate therapy: week-112 efficacy and safety results of the open-label long-term extension of a phase III, double-blind, randomized, placebo-controlled trial. *Arthritis Care Res* 67: 1627–1636.
- Braun, J., Deodhar, A., Inman, R., van der Heijde, D., Mack, M., Xu, S. *et al.* (2012) Golimumab administered subcutaneously every 4 weeks in ankylosing spondylitis: 104-week results of the GO-RAISE study. *Ann Rheum Dis* 71: 661–667.
- Bressler, B., Marshall, J., Bernstein, C., Bitton, A., Jones, J., Leontiadis, G. *et al.* (2015) Clinical practice guidelines for the medical management of nonhospitalized ulcerative colitis: the Toronto consensus. *Gastroenterology* 148: 1035e3–1058e3.
- Chen, D., Chen, Y., Hung, W., Chen, H., Hsieh, C., Chen, Y. *et al.* (2015) Immunogenicity, drug trough levels and therapeutic response in patients with rheumatoid arthritis or ankylosing spondylitis after 24-week golimumab treatment. *Ann Rheum Dis* 74: 2261–2264.
- Colombel, J., Feagan, B., Sandborn, W., Van Assche, G. and Robinson, A. (2012) Therapeutic drug monitoring of biologics for inflammatory bowel disease. *Inflamm Bowel Dis* 18: 349–358.
- Colombel, J., Reinisch, W., Gibson, P., Sandborn, W., Feagan, B., Xu, S. *et al.* (2016) Delayed response to golimumab therapy: UC patient characteristics and long-term clinical outcome: post hoc analyses from the PURSUIT program. *Gastroenterology* 150: S778.
- Danese, S. (2013) IBD: Golimumab in ulcerative colitis: a ‘ménage à trois’ of drugs. *Nat Rev Gastroenterol Hepatol* 10: 511–512.
- Detrez, I., Dreesen, E., van Stappen, T., de Vries, A., Brouwers, E., van Assche, G. *et al.* (2016) Variability in golimumab exposure: a ‘real-life’ observational study in active ulcerative colitis. *J Crohns Colitis* 10: 575–581.
- DHaens, G., Vermeire, S., Baert, F., Bossuyt, P., Buisson, A., Bouhnik, Y. *et al.* (2016) Drug-concentration *versus* symptom-driven dose adaptation of Infliximab in patients with active Crohn’s disease: a prospective, randomised, multicentre trial (Tailorix). *J Crohns Colitis* 10: S24–S24.
- Dulai, P., Siegel, C. and Peyrin-Biroulet, L. (2014) Anti-tumor necrosis factor- α monotherapy *versus* combination therapy with an immunomodulator in IBD. *Gastroenterol Clin North Am* 43: 441–456.
- Frederiksen, M., Ainsworth, M., Brynskov, J., Thomsen, O., Bendtzen, K. and Steenholdt, C. (2014) Antibodies against infliximab are associated with de novo development of antibodies to adalimumab and therapeutic failure in infliximab-to-adalimumab switchers with IBD. *Inflamm Bowel Dis* 20: 1714–1721.
- Garcés, S., Demengeot, J. and Benito-Garcia, E. (2013) The immunogenicity of anti-TNF therapy in immune-mediated inflammatory diseases: a systematic review of the literature with a meta-analysis. *Ann Rheum Dis* 72: 1947–1955.
- Gibson, P., Feagan, B., Sandborn, W., Marano, C., Strauss, R., Johanns, J. *et al.* (2016) Maintenance of efficacy and continuing safety of golimumab for active ulcerative colitis: PURSUIT-SC maintenance study extension through 1 Year. *Clin Transl Gastroenterol* 7: e168.
- Hyams, J., Griffiths, A., Veereman, G., Turner, D., Chan, D., Adedokun, O. *et al.* (2016) A multi-center open-label study assessing pharmacokinetics, efficacy, and safety of subcutaneous golimumab in pediatric patients with moderately-severely active ulcerative colitis. *Gastroenterology* 150: S132.
- Jurado, T., Plasencia, C., Martin, S., Navarro, R., Bonilla, G., Villalba, A. *et al.* (2015) Comparison of golimumab levels detected by two different enzyme-linked immunosorbent assays: promonitor vs sanquin. *Ann Rheum Dis* 74: 471–471.
- Kavanaugh, A., McInnes, I., Mease, P., Krueger, G., Gladman, D., Gomez-Reino, J. *et al.* (2009) Golimumab, a new human tumor necrosis factor α antibody, administered every four weeks as a subcutaneous injection in psoriatic arthritis: twenty-four-week efficacy and safety results of a randomized, placebo-controlled study. *Arthritis Rheum* 60: 976–986.

- Kawalec, P. and Pilc, A. (2016) An indirect comparison of infliximab *versus* adalimumab or golimumab for active ulcerative colitis. *Arch Med Sci* 12: 1097–1109.
- Kay, J., Matteson, E., Dasgupta, B., Nash, P., Durez, P., Hall, S. *et al.* (2008) Golimumab in patients with active rheumatoid arthritis despite treatment with methotrexate: a randomized, double-blind, placebo-controlled, dose-ranging study. *Arthritis Rheum* 58: 964–975.
- Keystone, E., Genovese, M., Klareskog, L., Hsia, E., Hall, S., Miranda, P. *et al.* (2009) Golimumab, a human antibody to tumour necrosis factor α given by monthly subcutaneous injections, in active rheumatoid arthritis despite methotrexate therapy: the GO-FORWARD Study. *Ann Rheum Dis* 68: 789–796.
- Kneepkens, E., Plasencia, C., Krieckaert, C., Pascual-Salcedo, D., van der Kleij, D., Nurmohamed, M. *et al.* (2014) Golimumab trough levels, antidrug antibodies and clinical response in patients with rheumatoid arthritis treated in daily clinical practice. *Ann Rheum Dis* 73: 2217–2219.
- Leu, J., Mendelsohn, A., Ford, J., Davis, H., Zhou, H. and Xu, Z. (2014) Long-term pharmacokinetics of body surface area-adjusted doses of golimumab following repeated subcutaneous administrations in pediatric patients with polyarticular juvenile idiopathic arthritis. *Arthritis Rheumatol* 66: S55–S56.
- Löwenberg, M., de Boer, N. and Hoentjen, F. (2014) Golimumab for the treatment of ulcerative colitis. *Clin Exp Gastroenterol* 7: 53–59.
- Martín, S., del Agua, A., Torres, N., Pascual-Salcedo, D., Plasencia, C., Ruiz-Argüello, B. *et al.* (2015a) Comparison study of two commercially available methods for the determination of golimumab and anti-golimumab antibody levels in patients with rheumatic diseases. *Clin Chem Lab Med CCLM* 53: e297–e299.
- Martín, S., Ruiz del Agua, A., Torres, N., Pascual-Salcedo, D., Plasencia, C., Jurado, T. *et al.* (2015b) Validation of a homogenous mobility shift assay (HSMA) for the measurement of golimumab (GLM) and antibodies-to-golimumab (ATG) in inflammatory bowel disease (IBD) patient serum. *ACR/ARHP Annual Meeting*. Abstract 2734. 29 September 2015 [Epub ahead of print].
- Moore, C., Corbett, G. and Moss, A. (2016) Systematic review and meta-analysis: serum infliximab levels during maintenance therapy and outcomes in inflammatory bowel disease. *J Crohns Colitis* 10: 619–625.
- Nanda, K., Cheifetz, A. and Moss, A. (2013) Impact of antibodies to infliximab on clinical outcomes and serum infliximab levels in patients with inflammatory bowel disease. *Am J Gastroenterol* 108: 40–47.
- O'Meara, S., Nanda, K. and Moss, A. (2014) Antibodies to infliximab and risk of infusion reactions in patients with inflammatory bowel disease: a systematic review and meta-analysis. *Inflamm Bowel Dis* 20: 1–6.
- Ordás, I., Feagan, B. and Sandborn, W. (2012) Therapeutic drug monitoring of tumor necrosis factor antagonists in inflammatory bowel disease. *Clin Gastroenterol Hepatol* 10: 1079–1087; quiz e85–e86.
- Paul, S., Moreau, A., Del Tedesco, E., Rinaudo, M., Phelip, J., Genin, C. *et al.* (2014) Pharmacokinetics of adalimumab in inflammatory bowel diseases: a systematic review and meta-analysis. *Inflamm. Bowel Dis* 20: 1288–1295.
- Peyrin-Biroulet, L., Bouhnik, Y., Roblin, X., Bonnaud, G., Hagège, H. and Hébuterne, X. (2016) French national consensus clinical guidelines for the management of ulcerative colitis. *Dig Liver Dis* 48: 726–733.
- Reinisch, W., Gibson, P., Sandborn, W., Feagan, B., Marano, C., Strauss, R. *et al.* (2016) Safety, Efficacy, and pharmacokinetics of golimumab in patients with moderately to severely active ulcerative colitis: PURSUIT-SC Long term extension. *Gastroenterology* 150: S776–S777.
- Roblin, X., Rinaudo, M., Del Tedesco, E., Phelip, J., Genin, C., Peyrin-Biroulet, L. *et al.* (2014b) Development of an algorithm incorporating pharmacokinetics of adalimumab in inflammatory bowel diseases. *Am J Gastroenterol* 109: 1250–1256.
- Roblin, X., Rinaudo, M., Sparrow, M., Moreau, A., Phelip, J., Genin, C. *et al.* (2014a) Pharmacokinetics in IBD: ready for prime time? *Curr Drug Targets* 15: 1049–1055.
- Rosas, J., Llinares-Tello, F., Martín, S., Senabre, J., Salas, E., Oliver, S. *et al.* (2014) Evaluation of serum level of golimumab and antibodies anti-golimumab in patients with rheumatic diseases: results from a local registry. *Ann Rheum Dis* 73: Abstract 935.
- Rutgeerts, P., Feagan, B., Marano, C., Padgett, L., Strauss, R., Johanns, J. *et al.* (2015) Randomised clinical trial: a placebo-controlled study of intravenous golimumab induction therapy for ulcerative colitis. *Aliment Pharmacol Ther* 42: 504–514.
- Rutgeerts, P., Reinisch, W., Feagan, B., Sandborn, W., Tarabar, D., Hebzda, Z. *et al.* (2014) How long should golimumab treatment be continued in patients with ulcerative colitis who do not respond to initial induction therapy? *United Eur Gastroenterol J* 2: A67.
- Sandborn, W., Feagan, B., Marano, C., Zhang, H., Strauss, R., Johanns, J. *et al.* (2014a) PURSUIT-SC Subcutaneous golimumab induces clinical response

and remission in patients with moderate-to-severe ulcerative colitis. *Gastroenterology* 146: 85–95.

Sandborn, W., Feagan, B., Marano, C., Zhang, H., Strauss, R., Johanns, J. *et al.* (2014b) PURSUIT-M Subcutaneous golimumab maintains clinical response in patients with moderate-to-severe ulcerative colitis. *Gastroenterology* 146: 96e1–109e1.

Sethu, S., Govindappa, K., Alhaidari, M., Pirmohamed, M., Park, K. and Sathish, J. (2012) Immunogenicity to biologics: Mechanisms, prediction and reduction. *Arch Immunol Ther Exp (Warsz.)* 60: 331–344.

Shealy, D., Cai, A., Staquet, K., Baker, A., Lacy, E., Johns, L. *et al.* (2010) Characterization of golimumab, a human monoclonal antibody specific for human tumor necrosis factor α . *MAbs* 2: 428–439.

Steenholdt, C., Bendtzen, K., Brynskov, J., Thomsen, O. and Ainsworth, M. (2014a) Clinical implications of measuring drug and anti-drug antibodies by different assays when optimizing infliximab treatment failure in Crohn's disease: post hoc analysis of a randomized controlled trial. *Am J Gastroenterol* 109: 1055–1064.

Steenholdt, C., Brynskov, J., Thomsen, O., Munck, L., Fallingborg, J., Christensen, L. *et al.* (2014b) Individualised therapy is more cost-effective than dose intensification in patients with Crohn's disease who

lose response to anti-TNF treatment: a randomised, controlled trial. *Gut* 63: 919–927.

Vande Casteele, N., Ferrante, M., van Assche, G., Ballet, V., Compernelle, G., van Steen, K. *et al.* (2015) Trough concentrations of infliximab guide dosing for patients with inflammatory bowel disease. *Gastroenterology* 148: 1320e3–1329e3.

Vande Casteele, N., Gils, A., Singh, S., Ohrmund, L., Hauenstein, S., Rutgeerts, P. *et al.* (2013) Antibody response to infliximab and its impact on pharmacokinetics can be transient. *Am J Gastroenterol* 108: 962–971.

Xu, Z., Lee, H., Vu, T., Hu, C., Yan, H., Baker, D. *et al.* (2010) Population pharmacokinetics of golimumab in patients with ankylosing spondylitis: impact of body weight and immunogenicity. *Int J Clin Pharmacol Ther* 48: 596–607.

Zhou, H., Jang, H., Fleischmann, R., Bouman-Thio, E., Xu, Z., Marini, J. *et al.* (2007) Pharmacokinetics and safety of golimumab, a fully human anti-TNF- α monoclonal antibody, in subjects with rheumatoid arthritis. *J Clin Pharmacol* 47: 383–396.

Zhuang, Y., Lyn, S., Lv, Y., Xu, Z., Bouman-Thio, E., Masterson, T. *et al.* (2013) Pharmacokinetics and safety of golimumab in healthy Chinese subjects following a single subcutaneous administration in a randomized phase I trial. *Clin Drug Investig* 33: 795–800.