

Effectiveness and Safety of Golimumab in Treating Outpatient Ulcerative Colitis: A Real-Life Prospective, Multicentre, Observational Study in Primary Inflammatory Bowel Diseases Centers

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ABSTRACT

Background & Aims: Golimumab (GOL) has been recently approved in Italy for the treatment of ulcerative colitis (UC) unresponsive to standard treatments. Our aims were to assess the real-life efficacy and safety of GOL in managing UC outpatients in Italian primary Inflammatory Bowel Diseases (IBD) centres.

Methods: Consecutive UC outpatients with at least 3-months follow-up were enrolled. Primary end-point was the induction and maintenance of remission in UC, defined as Mayo score ≤ 2 , at 6-month follow-up.

Results: Ninety-three patients were enrolled. At 6-month follow-up, remission was obtained in 34 (36.5%) patients. Shorter duration of disease was the only significant predictive factor of remission. Clinical response was achieved in 60 (64.5%) patients, while mucosal healing (MH) was obtained in 18 (19.3%) patients. Sixteen (47.0%) patients under remission were still under therapy with steroids. C-reactive protein and fecal calprotectin significantly dropped during the follow-up ($p < 0.001$ for both proteins). Adverse events occurred in 4 (4.3%) patients and 3 of them stopped treatment. Colectomy was performed in only one patient (1.1%).

Conclusions: Golimumab seems to be safe and effective in inducing and maintaining remission in real life UC outpatients.

Key words: induction – golimumab – remission – treatment – ulcerative colitis.

Abbreviations: ADA: Adalimumab; CRP: C-reactive Protein; GOL: Golimumab; FC: Fecal calprotectin; IBD: Inflammatory Bowel Diseases; IFX: Infliximab; IQR: Interquartile range; MH: Mucosal Healing; SC: Subcutaneously; TBC: Tuberculosis; TNF α : Tumor necrosis factor α ; UC: Ulcerative Colitis.

INTRODUCTION

Ulcerative colitis (UC) is a lifelong disease arising from an interaction between genetic and environmental factors, observed predominantly in the developed countries of the world [1]. It is characterised by a relapsing and remitting course, sometimes requiring an aggressive therapeutic approach in order to prevent complications [2]. Tumor necrosis factor α (TNF α) plays an important role in the pathogenesis of the disease [1], and the introduction of monoclonal anti-TNF α antibodies infliximab (IFX) and adalimumab (ADA) has greatly improved our treatment options

in UC patients refractory or intolerant to standard treatments [2, 3].

Golimumab (GOL) is a subcutaneously (SC) administered fully human anti-TNF α antibody [4], already approved in rheumatic disorders [5-10]. Two recent double-blind randomised placebo-controlled studies found SC GOL effective in obtaining and maintaining remission in moderate-to-severe UC [11, 12], while no effectiveness was found when using the intravenous route [13]. While controlled studies are debating about the optimal route for drug administration, no consistent data are currently available about the use of SC GOL to manage UC in real life.

SC GOL reimbursement for UC has been recently approved in Italy [14]. Small prospective studies have found GOL effective and safe in inducing UC remission [15-17]. A more recent, retrospective large study found GOL effective and safe also in maintaining UC remission [18], but no prospective data are currently available about the effectiveness of SC GOL in maintaining remission in real life. The aim of the present study was to assess the efficacy and safety of GOL in treating a larger UC outpatient population treated in Italian primary Inflammatory Bowel Diseases (IBD) centres.

MATERIAL AND METHODS

This study is a prospective, cohort, observational study on UC outpatients unresponsive to standard treatments and treated with SC GOL in Italian primary IBD centres (namely centres identified by Italian National and Regional Health Systems as able to manage uncomplicated IBD patients) starting from 1st of May 2015, and having at least a 3-month follow-up.

Clinical assessment

Eligible patients included men and women at least 18 years of age with an established diagnosis of UC according to standard endoscopic and histological criteria [1]. The disease extension was assessed according to the Montreal classification [19], and severity according to the Mayo score [20]. All patients had to have an active disease, defined as a Mayo score ≥ 3 points [20] in spite of concomitant treatment.

A shared common database was used to collect demographic and clinical data. Data collected at baseline were gender, age at diagnosis, smoking status, disease extension, disease duration, previous immunosuppressive and infliximab therapies, concomitant medications at baseline, C-reactive protein (CRP) and fecal calprotectin (FC) levels, Mayo score and Mayo subscore for endoscopy. Patients were clinically assessed at entry and at month 3 and 6.

The study protocol conformed to the ethical guidelines of the 1975 Declaration of Helsinki as reflected in a priori approval by the institution's Human Research Committee. The study was conducted according to the clinical practice guidelines. All patients gave written informed consent before they underwent endoscopy and SC GOL treatment.

Study treatment

All patients were eligible for the injection of SC GOL after the exclusion of an active hepatitis B virus infection, active cytomegalovirus infection, and TBC infection.

Induction dose of GOL was 200 mg at week 0, 100 mg at week 2, and then 100 or 50 mg at week 6 and then every four weeks according to body weight. The need for treatment discontinuation was left to the investigators' judgement, as well as concomitant medications including oral and topical aminosalicylates, steroids and immunosuppressants.

Endoscopy

Ileo-colonoscopy was performed in all the enrolled patients and classified according to the Mayo subscore for endoscopy [15]. It was performed at entry, and after 24 weeks.

End-points

Primary end-point was the induction and maintenance of remission in UC, defined as Mayo score ≤ 2 , at 6-month follow-up.

Secondary end-points were:

- clinical response to SC GOL, defined as the reduction of at least 2 points in the Mayo score during follow-up (if blood in stool was present, it had to be reduced at least one point);
- reaching of mucosal healing (MH), defined as Mayo subscore for endoscopy ≤ 1 , at 6-month follow-up;

- reduction of steroid use during the study;
- prevention of colectomy;
- assessment of adverse events incidence during treatment;
- assessment of discontinuation of treatment, due to primary failure (defined as failure in reaching remission/clinical response at any time of treatment), or secondary failure (defined as loss of remission/clinical response after reaching it under treatment), or due to side effects;
- assessment of CRP and FC during the follow-up.

Statistical analysis

Data were analyzed using MedCalc® Release 14.8.1. The characteristics of the study group were analyzed as median with interquartile range (IQR) for continuous non-parametric variables and as a percentage for categorical variables. Statistical analysis was performed by Fisher's exact test and chi-square for categorical data. Mann-Whitney test was used for continuous non-parametric variables. The Friedman test was used to investigate any change of partial Mayo partial score, CRP and FC levels during follow-up. *p* values < 0.05 were considered statistically significant.

RESULTS

Ninety-three patients were enrolled. The clinical characteristics of the study group and the indication for SC GOL treatment are showed in Table I.

At 3-month follow-up, remission was obtained in 41 (44.1%) patients, while it was reached in 34 (36.5%) patients

Table I. Demographics, disease characteristics, and concomitant medications

Characteristics	
Male gender, n (%)	48 (51.6)
Median (IQR) age, years	44.0 (33.7-54.2)
Median (IQR) disease duration, years	4.0 (2.0-9.0)
Indication for therapy, n (%)	
Steroid-dependency	79 (84.9)
Steroid-resistance	7 (7.5)
Switch for failure	7 (7.5)
Extent of disease, n (%)	
Distal colitis	13 (14.0)
Left-sided colitis	34 (36.6)
Pancolitis	46 (49.5)
Median (IQR) Mayo score	8 (8-9)
Smoking, n (%)	14 (15.1)
Previous treatment with infliximab, n (%)	9 (11.2)
Patients receiving corticosteroids, n (%)	76 (81.7)
Patients receiving immunomodulatory drugs, n (%)	15 (16.1)
Median (IQR) Mayo subscore for endoscopy	2 (2-3)
Median (IQR) CRP (mg/L)	18.0 (7.0-37.0)
Median (IQR) calprotectin (mcg/g)	300.0 (220.0-650.0)

Data is given as number (percentage) of patients and as median (IQR): interquartile range). CRP: C-reactive protein.

Table II. Predictors of clinical remission at 6-month follow-up

Characteristics	Remission (34 patients)	No remission (59 patients)	p*
Male gender, n (%)	18 (52.9)	38 (64.4)	0.385
Median (IQR) age, years	47.5 (35.0-56.0)	45.0 (34.5-58.5)	0.933
Median (IQR) disease duration, years	3.5 (2.0-7.0)	8.0 (4.0-15.0)	0.018
Indication for therapy, n (%)			
Steroid-dependency	31 (91.2)	48 (81.3)	0.380
Steroid-resistance	2 (5.9)	5 (8.5)	
Switch for failure	1 (2.9)	6 (10.2)	
Extent of disease, n (%)			
Distal colitis	3 (8.9)	10 (16.9)	0.551
Left-sided colitis	13 (38.2)	21 (35.6)	
Pancolitis	18 (52.9)	28 (47.5)	
Median (IQR) Mayo score	8.0 (8.0-9.0)	8.0 (8.0-9.5)	0.407
Smoking, n (%)	6 (17.6)	8 (13.5)	0.764
Median (IQR) CRP (mg/L)	21.0 (12.0-40.0)	13.0 (7.0-40.0)	0.317
Median (IQR) FC (mcg/g)	300.0 (220.0-550.0)	350.0 (225.0-670.5)	0.389

Data is given as number (percentage) of patients and as median (IQR, interquartile range). CRP, C-reactive protein, FC, fecal calprotectin. * Chi-square test for categorical variables and Mann-Whitney test for continuous variables.

at 6-month follow-up. Predictors of remission at 6-month follow-up are analysed in Table II. Duration of disease was the only factor significantly related to remission.

Clinical response was achieved in 72 (77.4%) and in 60 (64.5%, $p < 0.00001$) patients at 3- and 6-month follow-up, respectively. Figure 1 describes the median (IQR) partial Mayo

score, CRP and FC levels during follow-up. These parameters were all significantly reduced. Mucosal healing at 6-month follow-up was obtained in 18 (19.3%) patients, and it showed significant relationship with FC reduction ($p < 0.001$).

At 6-month follow-up, 16 (47.0%) patients under remission were still under therapy with steroids. Thus, only 53% of

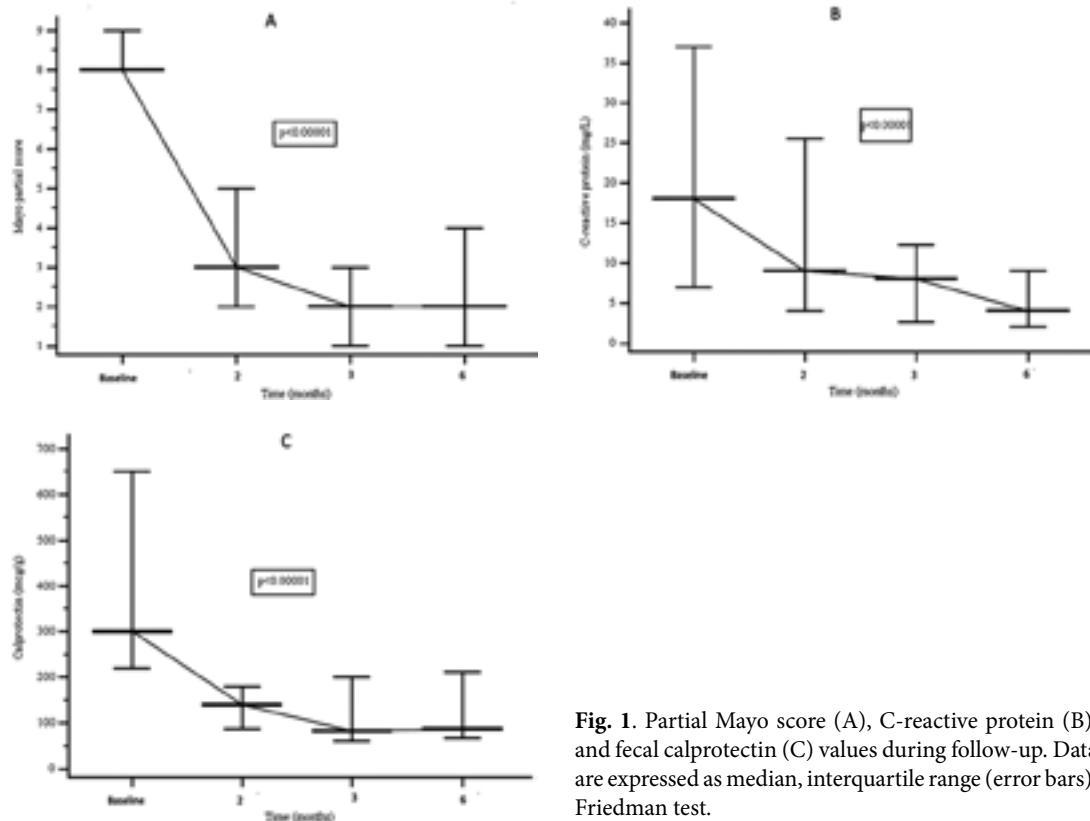


Fig. 1. Partial Mayo score (A), C-reactive protein (B), and fecal calprotectin (C) values during follow-up. Data are expressed as median, interquartile range (error bars). Friedman test.

patients (18 patients) under remission within 6 months of treatment reached steroid-free remission.

Discontinuation of treatment occurred in 30 patients (32.2%): in 17 patients (17.5%) due to primary failure, in 10 patients (10.7%) due to secondary failure, in 3 patients (3.2%) due to side effects. Five patients, priorly exposed to IFX, were dropouts due to ineffective treatment. Any differences in the use of immunosuppressants were recorded between patients with primary and secondary loss of response. Dropouts were therefore treated with IFX (15 patients), ADA (10 patients) or Vedolizumab (5 patients).

Side effects occurred in 4 patients (4.3%): 3 patients (3.2%) stopped treatment (1 due to severe urticaria, 1 due to alopecia, 1 due to the occurrence of erythema nodosum); 1 patient (1.1%) suffered from fever, which subsided with antipyretic therapy without suspension of SC GOL. Colectomy occurred in only one patient (1.1%).

DISCUSSION

This observational study is the first study conducted in a series of active UC outpatients in primary gastroenterology IBD centres.

These real life results show that SC GOL achieves a good percentage of clinical response and clinical remission after 24 weeks of treatment. In particular, we obtained remission in 44% of patients at the 3rd month, and only 8% of them lost the remission during the following three months. Percentage of clinical response seems to be similar to that reached in real life in referral centres [21], but lower to that obtained both in the controlled trials [11] and in a recent short-term real-life, Spanish experience [17]. It is not clear why this occurs. The patients enrolled in the pivotal studies, as well as the vast majority of our population, were naïve to anti-TNF α antibody, while the vast majority of patients enrolled by Bosca-Watts et al. were previously exposed to anti-TNF α [17]. Thus, prior exposure to IFX does not seem to explain these differences. However, we found that two-thirds of patients priorly exposed to IFX dropped out. Therefore, it seems that GOL works less in patients priorly exposed to anti-TNF α treatment, confirming that a second anti-TNF α in patients with IBD works better when the reason to withdraw the first anti-TNF α is intolerance, compared with secondary or primary failure [22]. Looking at the predictors of remission under treatment with SC GOL, we found that only a shorter duration of the disease was a significant predictor of successful response to the treatment. Our results are similar to the ones reported by Bosca-Watts et al., who identified duration of the disease less than 2 years as a significant predictor of successful response to SC GOL [17]. This means that patients treated with SC GOL at the beginning of their natural history may have much more chance to reach remission when using this drug. Other ways to improve SC GOL efficacy in reaching/maintaining remission may be by increasing the dose from 50 to 100 mg or by shortening the infusion to every four weeks. The GO-KINETIC trial showed that most of the patients who initially responded to induction therapy developed signs of secondary loss of response soon after completing the induction phase [23]. Thus, we can hypothesize that some patients may need more than the

standard dose of 50 mg or 100 mg GOL every four weeks during maintenance treatment. Unfortunately, this approach is currently not permitted by the Italian regulatory authorities. Finally, another possible explanation of the higher clinical response may be the definition of the clinical response. We used the same definition of PURSUIT trials, as requested by the Italian Regulatory Authority, when other studies defined it as 3 points decline in the Mayo score [17]. This conduct could falsely increase the clinical response on GOL in our cohort, so this controversial point will have to be evaluated more extensively in further studies.

Compared to other anti-TNF α antibodies, the effect of GOL in treating UC in real life seems to be comparable to other anti-TNF α . A recent systematic review with network meta-analysis found no significant differences among the anti-TNF α therapies in induction and maintenance of remission in UC patients [24], and similar results are reported by a recent, pilot study comparing ADA vs. GOL in real life [15]. In our real-life experience, IFX showed a higher clinical remission/response rate [25], while ADA in priorly exposed anti-TNF α population reached similar clinical remission/response rates [26]. Considering the rate of secondary failure, that seems to affect up to 59% of UC patients treated with anti-TNF α antibodies [27], we recorded a lower rate than that recorded by using IFX or ADA in real life [18, 28]. Any conclusion cannot be drawn regarding this aspect because the studied populations, as well as the length of the follow-up, were different. However, we can conclude that SC GOL seems to be as effective as other anti-TNF α therapies in clinical remission/clinical response in the UC population.

Concerning the secondary end-points, we found that SC GOL reaches MH in a low percentage of patients (<20%), but CRP and FC significantly dropped during the study period. Moreover, steroid-free remission was obtained in 53% of patients reaching remission. This data probably means that the treatment is effective in obtaining remission/clinical response, but patients still need steroids to maintain remission/clinical response. Unfortunately, we do not know whether those patients still took the same amount of steroids or a reduction was reached, and this topic should be analysed in the extension of the clinical observation. Conflicting results were found when we compared secondary end-point results with the current literature. We recorded a low percentage of MH at 6 months, significantly worse than that obtained in the pivotal PURSUIT study [11] and in the Bosca-Watts Spanish experience [17]. Looking at the populations enrolled, no difference can be found regarding the severity, extent and duration of the disease or current smokers. Other unidentified factors might explain these differences, which is worth being analysed in further studies.

With respect to safety, we found that GOL was safe, since <10% of our population showed adverse events. However, the vast majority of those patients had to stop treatment due to severe AEs, and this percentage is similar to the one reported in pivotal study and higher than the one reported in the Bosca-Watts real-life study [11, 17]. No clear explanation for these events can be provided. Alopecia and pruritus can be attributed to possible anaphylaxis or delayed hypersensitivity, while erythema nodosum can be attributed to paradoxical

exacerbation of inflammation, similarly to what occurs when using IFX [29]. Further, larger studies are required to assess GOL safety in real life.

The main limit of this study is that the duration of follow-up was short. Golimumab only became available in Italy two years ago and several centers started using SC GOL only several months after the Ministry of Health approval. Lastly we decided to analyze only patients having at least a 3-months follow-up, and this is the first large Italian experience in real-life use of SC GOL.

Another limit is the absence of serum GOL concentration assessment, able to identify correctly responders from non-responders. Sandborn et al. found that clinical response and clinical remission increased during the first 6 weeks of treatment according to serum GOL concentrations [11]. Detrez et al. recently found that serum GOL concentration was significantly higher in partial clinical responders than in non-responders, and that clinical non-responders had a significantly more severe colitis, indicated by a higher endoscopic Mayo score at baseline compared to partial clinical responders [21]. Ideally, we should measure drug levels to guide therapy and more effectively achieve the clinical response, and GOL should not escape the rule. Actually, experiences with IFX and ADA found that some patients appear to need much higher drug levels than others in order to have a beneficial effect [30, 31]. Unfortunately, we do not yet know the optimal serum level of anti-TNF α agents for all patients, and current assessment of serum level of anti-TNF α , as well as antibody anti-TNF α measurement, is not available in real life in Italy.

CONCLUSION

The present study demonstrates that SC GOL is effective and safe in UC outpatients in real life. Further studies with a longer follow-up are warranted in order to assess the effectiveness and safety of GOL therapy.

Conflicts of interest. The authors declare that they have no conflicts of interest concerning this study.

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