Clinical Outcomes of Golimumab as First, Second or Third Anti-TNF Agent in Patients with Moderate-to-Severe Ulcerative Colitis

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Background: Golimumab efficacy data in ulcerative colitis (UC) are limited to anti tumor necrosis factor α (TNF)-naive patients. The aim of this study was to assess the short-term and long-term efficacy of golimumab used as first, second, or third anti-TNF in UC in a real-life clinical setting.

Methods: This retrospective multicenter cohort study included patients with moderate-to-severe UC treated with golimumab. The primary efficacy endpoints were short-term partial Mayo score response, long-term golimumab failure-free survival, and colectomy-free survival.

Results: In 142 patients with UC, golimumab was administered as first (40%), second (23%), or third anti-TNF (37%). Ninety-two patients (65%, 95% confidence interval 56.6 73) achieved short-term clinical response. Forty-five patients (32%, 95% confidence interval 23.7 39.7) achieved clinical remission. Response rates for golimumab were 75% as first anti-TNF, 70% as second anti-TNF (ns versus first anti-TNF), and 50% as third anti-TNF ($P = 0.007$ versus first anti-TNF). After 12 months median follow-up (interquartile range 6 18), 60 patients (42%, 95% confidence interval 34 51) had golimumab failure, and 15 patients (11%) needed colectomy. Thirty-one patients (22%) needed golimumab dose escalation, and 71% of these regained response after escalation. Starting maintenance with 100 mg golimumab doses and short-term nonresponse were independent predictors of golimumab failure.

Conclusions: In this real-life cohort of patients with UC, golimumab therapy was effective for inducing and maintaining clinical response. Although anti-TNF naive patients had better outcomes, golimumab was also effective in anti-TNF experienced patients. Only the patients given golimumab after previous failure of 2 anti-TNF agents had significantly worse outcomes. Golimumab dose escalation was beneficial and safe.

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Key Words: ulcerative colitis, golimumab, adalimumab, infliximab, secondary loss of response, dose escalation, colectomy, anti-TNF

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Data were generated in routine clinical practice.

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Golimumab, a subcutaneously administered fully human antibody to tumor necrosis factor α (TNF), induces clinical response and remission in patients with moderately to severely active ulcerative colitis (UC).[1] In patients who responded to induction therapy, golimumab doses administered every 4 weeks (q4wk) as a maintenance regimen was effective in maintaining clinical response through 1 year[2] In these pivotal induction and maintenance trials (known as the PURSUIT trials), previous treatment with TNF antagonists was an exclusion criteria, and so golimumab efficacy data in UC were limited to anti-TNF–naive patients.

Over the past decade, the TNF antagonists infliximab and adalimumab have been shown to be effective in the treatment of patients with moderate-to-severe UC. Because infliximab was the first anti-TNF agent to be approved for treatment of UC, the initial trials were conducted in patients who were naive to anti-TNF therapy.[3] The adalimumab ULTRA 2 clinical trial, however, included 40% of patients with UC who had previously been exposed to infliximab. The absolute effect of adalimumab when administered after earlier anti-TNF therapy was smaller than the effect observed in anti-TNF–naive patients.[4] Although the outcomes of a second anti-TNF drug in patients with UC given adalimumab after infliximab has been studied in a clinical setting,[5 8] the effectiveness of a third anti-TNF agent in UC is not well known.[9]

With the approval of golimumab for UC, clinicians now have 3 anti-TNF agents at their disposal.[10] Given that choosing between one and another is optional, it is of particular interest to assess the effectiveness of golimumab as a first, second, or third anti-TNF agent to enable patients and clinicians to make an informed decision. In addition, other important outcomes such as the benefit of golimumab dose escalation in case of inadequate response or secondary loss of response or the need for colectomy have not been well addressed.

The aim of this study was to assess the short-term and long-term clinical efficacy and safety of golimumab in UC used as first, second, or third anti-TNF agent. As secondary objectives, we evaluated predictors of response to induction, predictors of long-term outcomes, and the need for dose escalation and its efficacy and safety.

MATERIALS AND METHODS

Study Design and Patients

The study was a multicenter, open-label, uncontrolled, retrospective cohort study of patients with UC treated with golimumab. Eligible patients included men or women of at least 18 years of age with an established diagnosis of UC. The study population comprised all consecutive patients with moderate-to-severe UC who received golimumab induction doses and had at least 10 weeks of follow-up. Golimumab was administered with the posology approved for UC in the summary of product characteristics by the European Medicines Agency (EMA).[11] Golimumab was given as an initial dose of 200 mg, followed by 100 mg at week 2. Thereafter, patients with body weight less than 80 kg or patients with body weight greater than or equal to 80 kg received golimumab maintenance doses of 50 or 100 mg q4wk, respectively. The extent of disease was categorized using the Montreal classification.[12] Demographic and clinical characteristics as well as concomitant medications were recorded in most centers in prospectively maintained databases. The study was approved by the ethics committees of the participating centers. The Strengthening the Reporting of Observational Studies in Epidemiology (STROBE) guidelines were used in the design of the study and the preparation of the manuscript.[13]

Outcomes Measures and Efficacy Endpoints

The short-term primary endpoint was clinical response evaluated using the partial Mayo score at baseline and at week 8. Clinical response was defined as a 3-point decrease in the partial Mayo score or a decrease of ≥50% in the partial Mayo score and a final partial Mayo score of ≤2. We also evaluated clinical remission, defined as a partial Mayo score of 0 or 1. We assessed changes from baseline in partial Mayo score and C-reactive protein at week 8.

The long-term primary efficacy endpoints were the cumulative probabilities of golimumab failure-free survival and colectomy-free survival during follow-up. Golimumab failure was defined as discontinuation of the drug due to intolerance or absence or loss of response (primary nonresponse or secondary loss of response or tertiary loss of response despite golimumab dose escalation), as judged by the attending gastroenterologist. Patients who had secondary loss of response but regained response after escalation of golimumab dosing were not considered as failures. We defined sustained clinical benefit as the absence of golimumab failure. A last observation carried forward approach was used to evaluate sustained clinical benefit at weeks 12, 30, and 52. Corticosteroid-free clinical response and remission were evaluated at the last follow-up using the partial Mayo score. For patients who discontinued golimumab, the last follow-up visit was defined as the discontinuation visit (although patients continued to be assessed for the need for colectomy). For patients who continued on golimumab, the last visit corresponded to the last available visit. During follow-up, we assessed the proportion of patients who experienced secondary loss of response and the proportion of patients who were dose-escalated. We calculated the cumulative probability of golimumab failure-free survival and colectomy-free survival after dose escalation.

The rate of adverse events leading to golimumab withdrawal was also analyzed. All patients who received at least 1 dose of golimumab were included in the safety analysis.

Predictors of Response

We analyzed predictors of short-term response including age, sex, duration of disease, extent of disease, use of steroids or immunosuppressant at baseline, reason for discontinuation of last anti-TNF, and use of golimumab as first, second, or third anti-TNF.

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In the long-term, we analyzed the factors predictive of golimumab failure and colectomy. The following variables were included: age, sex, duration of disease, extent of disease, concomitant immunosuppressant therapy, short-term response, 50 or 100 mg golimumab maintenance doses, and use of golimumab as first, second, or third anti-TNF.

Statistical Analysis

Efficacy endpoints were analyzed after stratification by use of golimumab as first, second, or third anti-TNF agent. Proportions were expressed as percentages and 95% confidence intervals (CIs). Parametric or nonparametric tests were used to compare continuous variables, expressed as the mean and SD or median and interquartile range (IQR) (P25–P75), whereas categorical variables were compared using the chi-squared or Fisher's tests. Logistic regression was performed for predictors of short-term response. Adjusted odds ratios and their 95% CIs were calculated. In the long-term, 2 events—golimumab failure-free survival and colectomy-free survival rates—were estimated using survival analysis. The cumulative probability of the event-free survival was calculated by the Kaplan–Meier method. The time-to-event variables were analyzed from the date of the first golimumab induction dose until the date of occurrence of the event or last follow-up. Adjusted hazard ratios were calculated using Cox proportional hazard survival regression analysis.

RESULTS

Patient Characteristics

From January 2013 to September 2015, 142 consecutive patients with UC were identified in 24 inflammatory bowel disease referral centers. The mean age of our population was 46 years (SD ± 14, range 18–84), and the median disease duration was 7 years (IQR 3–13). Seventy-two patients were men (50.7%), 82 patients (57.7%) had extensive colitis, 53 (37.3%) left-sided colitis, and 7 (4.9%) proctitis. Sixty-three patients (44.4%) were receiving steroids at baseline, whereas 66 (46.5%) were receiving an immunosuppressant (64 patients azathioprine or mercaptopurine, and 2 methotrexate). Fifty-seven patients (40.1%) were naive

TABLE 1. Baseline Characteristics of Patients Stratified According to Whether Golimumab Was Administered as First, Second, or Third Line Anti-TNF Agent

	Golimumab as First Anti-TNF	Golimumab as Second Anti-TNF	Golimumab as Third Anti-TNF	*P*
n (%)	57 (40.1)	33 (23.2)	52 (36.6)	
Male, n (%)	28 (49.1)	17 (51.5)	27 (51.9)	0.95
Age, mean (SD), yr	44 (17)	47 (11)	48 (14)	0.46
Disease duration, median (IQR), yr, n (%)	3 (2 12)	6 (4 11)	8 (6 14)	0.04
>6	21 (36.8)	16 (48.5)	35 (67.3)	
3 6	6 (10.5)	9 (27.3)	15 (28.8)	<0.001
<3	30 (52.6)	8 (24.2)	2 (3.8)	
Disease location, n (%)				
Proctitis	3 (5.3)	1 (3.0)	3 (5.8)	
Left-sided	19 (33.3)	15 (45.5)	19 (36.5)	0.78
Extensive	35 (61.4)	17 (51.5)	30 (57.7)	
Partial Mayo score, median (IQR)	6 (5 7)	6 (5 7)	6.5 (6 8)	0.27
C-reactive protein, median (IQR), mg/L	7.8 (2.2 26.7)	6 (2.8 27.0)	8.1 (2.4 24.7)	0.60
Concomitant medication, n (%)				
Corticosteroids	29 (50.9)	10 (30.3)	24 (46.2)	0.16
Immunosuppressants	29 (50.9)	17 (51.5)	20 (38.5)	0.35
Previous anti-TNF agents, n (%)				
Infliximab		28 (84.8)		
Adalimumab		5 (15.2)		
Infliximab → Adalimumab			46 (88.5)	
Adalimumab → Infliximab			6 (11.5)	
Reason for discontinuation of the last anti-TNF, n (%)				
Primary failure		4 (12.1)	3 (5.8)	0.006
Secondary failure		18 (54.4)	45 (86.5)	
Adverse event		8 (24.2)	4 (7.7)	
Other		3 (9.1)	0 (0)	

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to anti-TNF agents, and 85 (59.9%) were anti-TNF–experienced (33 [23.2% overall] as second anti-TNF and 52 patients [36.6%] as third anti-TNF). Baseline characteristics of the 3 cohorts are summarized in Table 1.

The interval between the last anti-TNF dose and the first golimumab induction dose ranged from 2 to 337 weeks (median 5, IQR 3–22). All patients received a 200 mg golimumab dose at week 0 followed by a 100 mg dose at week 2. Subsequently, 100 patients (70.4%) and 40 patients (28.2%) started maintenance with q4wk 50 or 100 mg golimumab doses, respectively. Two patients (1.4%) were discontinued before week 6. All patients received the first induction dose at hospital and were instructed by trained personal about the administration of golimumab-prefilled SmartJect autoinjectors. The vast majority of patients self-administered golimumab maintenance doses at home. Golimumab q4wk maintenance doses were administered in the hospital by trained nurses in 3 patients (2.1%) because of blindness, obsessive-compulsive disorder with contamination/cleaning symptoms, and advanced age in 1 patient each. No variable analyzed in the study has more than 10% of missing data. With respect to the main outcomes, missing data accounted for less than 5% of the overall data. The flowchart of golimumab outcomes in the total population is shown in Figure 1.

Short-term Outcomes

Ninety-two of 142 patients (64.8%, 95% CI 56.6–73) achieved short-term clinical response. Forty-five patients (31.7%, 95% CI 23.7–39.7) achieved clinical remission. Corticosteroid-free response and remission rates were 56.9% (95% CI 48.3–65.6) and 29.9% (95% CI 21.9–38), respectively. Patients who received golimumab as third anti-TNF had significantly lower clinical response ($P = 0.007$) and remission ($P = 0.004$) rates when compared with anti-TNF–naive patients (Fig. 2). The mean partial Mayo score was 6 (SD ±1, range 4–9) at baseline and 3 (SD ±3, range 0–9) at week 8 ($P < 0.001$). Median C-reactive protein was 7.5 mg/L (IQR 1.8–22.4) at baseline and 5.5 mg/L (IQR 1.3–12.7) after induction ($P = 0.02$).

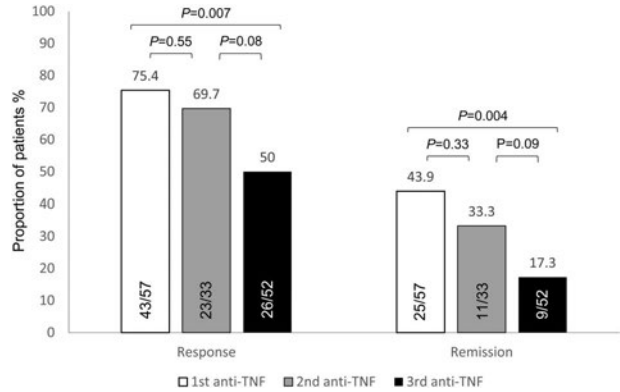

FIGURE 2. Proportion of patients with clinical response or remission at week 8: differences between patients treated with golimumab as first, second, or third anti-TNF agent.

Long-term Outcomes

After a median follow-up of 12 months (IQR 6–18), 82 of 142 patients (57.7%, 95% CI 49.3–66.2) maintained sustained clinical benefit (Fig. 3A). Sixty patients (42.2%, 95% CI 33.8–50.7) had golimumab failure. The reasons for golimumab failure in the overall population were primary nonresponse in 28 of 142 patients (19.7%), secondary loss of response in 19 patients (13.4%), tertiary loss of response after golimumab dose escalation in 9 patients (6.3%), and adverse events in 4 patients (2.8%) (Fig. 1). Median

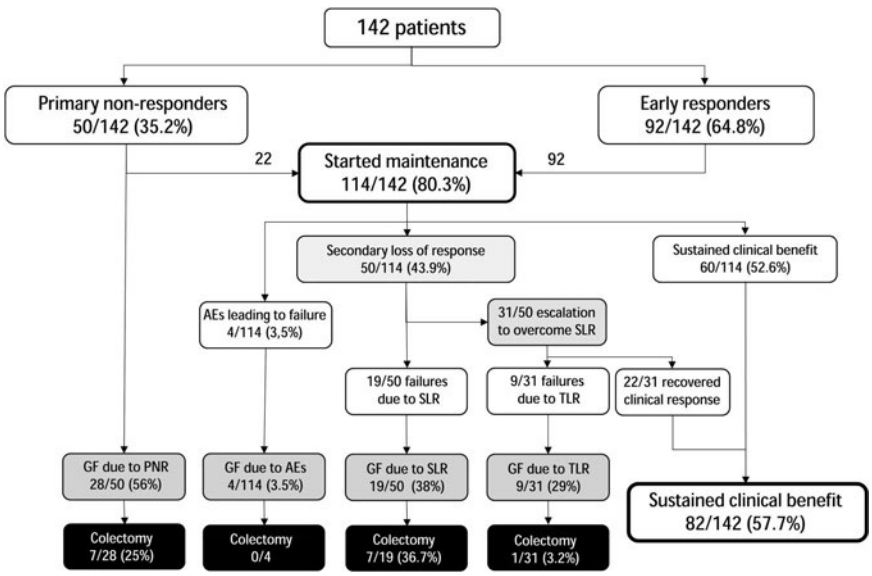

FIGURE 1. Flowchart of golimumab efficacy in the whole cohort. AE, adverse event; GF, golimumab failure; PNR, primary nonresponse; SLR, secondary loss of response; TLR, tertiary loss of response.

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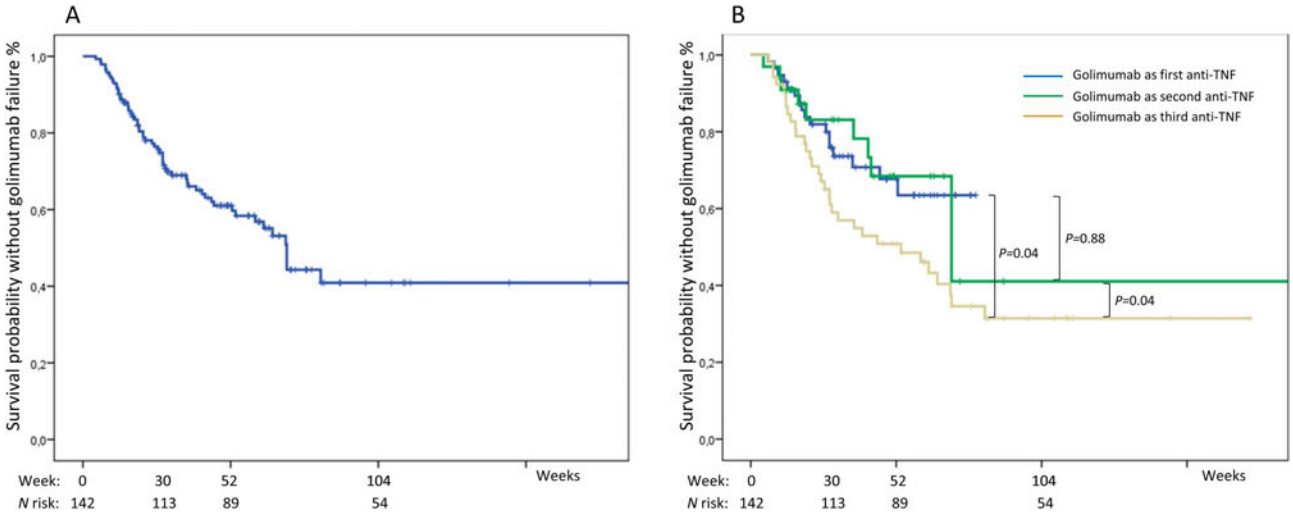

FIGURE 3. A, Cumulative probability of avoiding golimumab failure: overall population. B, Cumulative probability of avoiding golimumab failure: differences in the survival curves between patients treated with golimumab as first, second, or third anti-TNF agent. (Kaplan–Meier method).

time to golimumab discontinuation was 4.7 months (IQR 3–8). The probability of avoiding golimumab failure was 80%, 63%, and 44% at weeks 12, 30, and 52, respectively. Seventy-one of 113 patients (62.8%) and 41 of 89 patients (46.1%) maintained clinical benefit at weeks 30 and 52, respectively. Survival curves showed that only patients treated with golimumab as third anti-TNF had an increased probability of golimumab failure when compared with anti-TNF–naive patients ($P = 0.04$) (Fig. 3B).

At the last follow-up, 66 patients (46.5%, 95% CI 37.9–55.0) had partial Mayo response, and 50 (35.2%, 95% CI 27.0–43.4) were in clinical remission. Fifty-nine (41.5%, 95% CI 33.1–50) and 48 (33.8%, 95% CI 27.0–43.4) patients had corticosteroid-free clinical response and remission, respectively. The mean partial Mayo score was 6 (SD ± 1, range 4–9) at baseline and 3 (SD ± 3, range 0–9) at the last follow-up ($P < 0.001$). Median C-reactive protein at the last follow-up was 3.6 mg/L (IQR 1–13.1).

After a median time of 4 months (IQR 2–9), 15 of 142 patients (10.6%) needed colectomy (Fig. 4A). Probability of avoiding colectomy was 97%, 93%, and 85% at 12, 30, and 52 weeks, respectively. One of 57 anti-TNF–naive patients (1.7%) versus 4 of 33 patients (12.1%) given golimumab as second anti-TNF needed colectomy ($P = 0.05$). Ten of 52 patients (19.2%) given golimumab as third anti-TNF needed colectomy ($P = 0.03$ versus golimumab as first anti-TNF) (Fig. 4B).

Secondary Loss of Response and Need for Dose Escalation

During follow-up, 50 of 114 patients (43.8%) who started maintenance therapy experienced secondary loss of response (Fig.

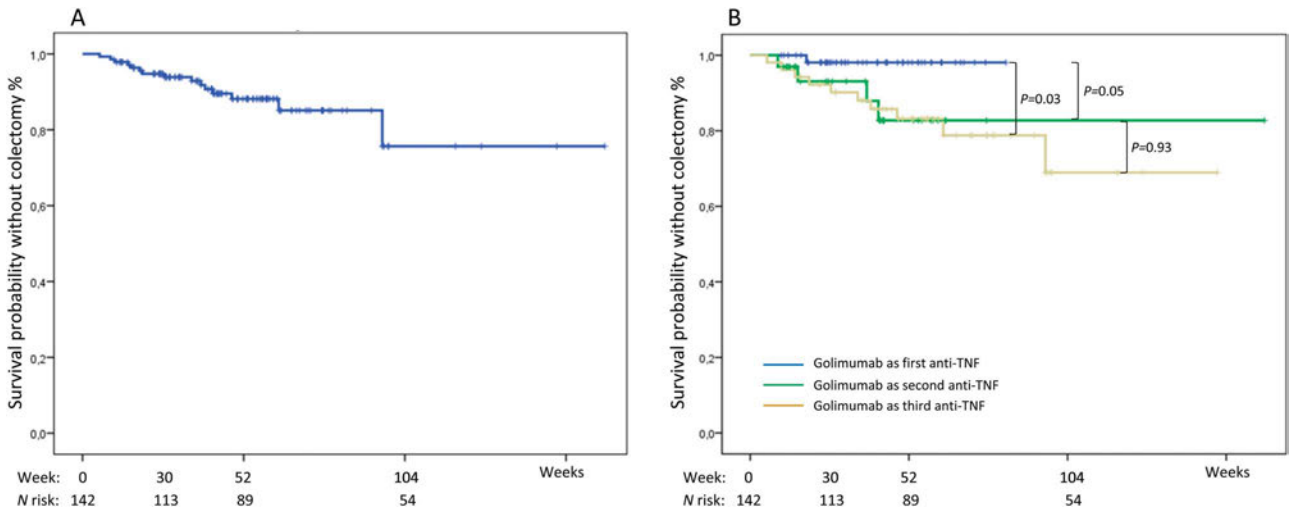

FIGURE 4. A, Cumulative probability of avoiding colectomy: overall population. B, Cumulative probability of avoiding colectomy: differences in the survival curves between patients treated with golimumab as first, second, or third anti-TNF agent. (Kaplan–Meier method).

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3). In 19 of 50 patients (38%), secondary loss of response led to golimumab discontinuation. In the remaining 31 patients (62%), golimumab dose was escalated to overcome secondary loss of response. Median time to escalation was 5 months (IQR 3–9). In 28 of 31 patients (90.3%), golimumab dose was escalated from 50 mg q4wk to 100 mg q4wk. Golimumab dose was escalated from 100 to 200 mg q4wk in 1 patient (3.2%) and to 100 mg every 2 weeks in 2 patients (6.4%). Golimumab was de-escalated from 100 to 50 mg q4wk in only 1 patient. Secondary loss of response and escalation rates did not differ significantly between patients treated with golimumab as first, second, or third anti-TNF agent. Thirty-seven of 50 secondary nonresponders (74%) were receiving 50 mg golimumab maintenance doses. In 75.7% of these patients, golimumab dose was escalated, and in the remaining ones, golimumab was discontinued. Conversely, among the 13 secondary nonresponders receiving 100 mg golimumab maintenance doses, golimumab dose was escalated in only 23.1%, and in the remaining patients, golimumab was discontinued ($P = 0.001$). Twenty-two of 31 patients (71%) regained response after golimumab dose escalation and avoided golimumab failure at the last follow-up (Fig. 3). Nine patients (29%) had golimumab failure because of tertiary loss of response. After dose escalation, only 1 patient (3.2%) required colectomy during the follow-up.

Predictive Factors

In the univariate analysis, patients receiving golimumab as third anti-TNF had a lower rate of short-term response (adjusted by duration of disease), when compared with anti-TNF–naive patients (hazard ratio 0.33, 95% CI 0.14–0.73; $P = 0.007$). In the univariate analysis, golimumab failure was associated with use of golimumab as third anti-TNF, starting maintenance with 100 mg golimumab doses and short-term nonresponse after induction. Multivariate analysis retained maintenance with 100 mg golimumab doses and short-term nonresponse as predictors of golimumab failure (Table 2). In the multivariate analysis, short-term nonresponse and maintenance without concomitant immunosuppressant therapy were identified as independent predictors of colectomy (Table 3).

TABLE 2. Multivariate Analysis of Factors Associated with Golimumab Failure

	Adjusted Hazard Ratio	95% CI	P
Short-term response			
No	1		
Yes	0.21	0.12 0.37	<0.001
Golimumab maintenance, mg q4wk			
50	1		
100	1.83	1.08 3.11	0.02

Candidate variables: sex, disease duration, golimumab as first, second, or third anti-TNF, maintenance doses, short-term response.

TABLE 3. Multivariate Analysis of Factors Associated with Colectomy

	Adjusted Hazard Ratio	95% CI	P
Short-term response			
No	1		
Yes	0.21	0.07 0.68	0.009
Concomitant IM			
No	1		
Yes	0.28	0.08 0.89	0.03

IM, immunosuppressant.
Candidate variables: disease duration, golimumab as first, second, or third anti-TNF, concomitant immunosuppressant, short-term response.

Safety

The safety analysis included 142 patients exposed to golimumab for a total of 1824 months (217 months of which were with escalated doses). Four patients (2.8%) experienced adverse events (paresthesia in one patient, cutaneous infection in one patient, pneumonitis in one patient, and recurrence of cervical neoplasia in one patient) leading to golimumab withdrawal. Rates of adverse events leading to discontinuation were similar for patients receiving standard doses or escalated doses.

DISCUSSION

This study reports the real-life outcomes of golimumab administered as first, second, or third anti-TNF agent in patients with UC. Importantly, we assessed for the first time the effectiveness of golimumab in patients with a history of failure of 1 or 2 anti-TNF agents. In our difficult-to-treat cohort of patients with UC, golimumab led to sustained benefits in a high proportion of cases, even in anti-TNF–experienced patients.

The efficacy of golimumab to induce and maintain remission in anti-TNF–naive patients with UC is well established from controlled clinical trials.[1,2] However, golimumab's real-life effectiveness remains largely unexplored, with only 3 published studies that included a small number of patients.[14 16] In our unselected population, which included anti-TNF–naive and experienced patients with UC, golimumab achieved higher short-term response and remission rates than in the controlled studies.[1] In real-world studies, outcomes with anti-TNF therapy have often been better than expected based on the results of randomized clinical trials. This may be the result of differences in outcome measures such as partial Mayo score versus full Mayo score including endoscopy. Furthermore, we evaluated response at week 8 (after receiving weeks 0, 2, and 6 golimumab doses), whereas in the PURSUIT trial, outcomes were evaluated at week 6.[1] In our study, the proportion of anti-TNF–naive patients was higher than the rates of anti-TNF–naive patients reported in clinical practice for adalimumab in UC.[5,6,18] This seems surprising, given that both infliximab and adalimumab were already

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approved for UC at the time of study. A possible explanation is the fact that golimumab efficacy data in UC were limited to anti-TNF–naive patients.

We evaluated long-term treatment with golimumab. The leading cause of golimumab discontinuation was no response to induction therapy (primary failure), but some early nonresponders started golimumab maintenance despite lack of response to induction doses. Of these, 27% had delayed response and avoided golimumab failure at the last follow-up (data not shown). Thus, in our study, starting golimumab maintenance therapy seems beneficial for a significant proportion of early nonresponders. This is in agreement with post hoc analyses from the PURSUIT studies, in which 28% of induction nonresponders treated with 2 additional 100 mg golimumab doses achieved response at week 14.[17] In these patients with delayed response, 100 mg golimumab maintenance resulted in sustained clinical benefit comparable with that seen in patients with early response to induction.[18]

Short-term response and remission rates were highest in anti-TNF–naive patients, and decreased with increasing exposure to previous anti-TNF (i.e., golimumab as first, then second anti-TNF agent), although golimumab remained effective for anti-TNF–experienced patients. In particular, response rates were not significantly different between patients who received golimumab as first or as second anti-TNF. Likewise, the probability of sustained benefit with golimumab at the last follow-up was not different in patients treated with golimumab as first or as second anti-TNF. We believe the findings of our study provide the best available evidence to support golimumab therapy in patients with UC who have failed one anti-TNF. By contrast, in the ULTRA 2 study, short-term and long-term outcomes with adalimumab after failing infliximab were considerably smaller than the efficacy observed in naive patients.[4] These results from the pivotal adalimumab trial were also reflected in 2 recent observational studies.[19,20]

To the best of our knowledge, no study has specifically evaluated the efficacy of a third anti-TNF agent in UC.[21] In this study, patients given golimumab after previous failure of 2 anti-TNFs had significantly worse short-term and long-term outcomes than naive patients. These data should be taken into account when comparing studies assessing outcomes of different anti-TNF agents in UC; that is, we should consider not only whether or not a patient has been exposed to an anti-TNF but also the number of previous anti-TNFs failed. Our study, with 36.6% of patients who received golimumab as a third anti-TNF agent, had a more difficult-to-treat population than any previous study assessing outcomes of anti-TNF agents in UC.

Regarding persistence, 72% of patients who initiated golimumab maintenance therapy remained on golimumab and had clinical benefit at the last follow-up (data not shown). The probability of maintaining golimumab was lower in patients treated with golimumab as a third anti-TNF compared with naive patients. We consider the observed colectomy rate very acceptable given the complexity of the treated population. Only 1.7% of anti-TNF–naive patients needed colectomy. Conversely, patients on golimumab as second or third anti-TNF were 7- and 11-times more likely, respectively, to undergo colectomy. We believe that these large differences in colectomy rates were not only the result of lower response to golimumab but also of general failure of medical treatments, which particularly affects patients who have previously failed the other 2 anti-TNF agents.

Our study evaluated for the first time the benefit of golimumab dose escalation in clinical practice. This issue is extremely important because, in the PURSUIT maintenance study, a subgroup analysis comparing patients who had secondary loss of response on golimumab 50 mg q4wk and escalated to 100 mg q4wk with those who continued receiving 50 mg q4wk did not reveal any difference in terms of clinical response at week 54.[2] Dose optimization was clearly beneficial in our study because 71% of patients with dose escalation regained response and could continue with golimumab at the last follow-up. Conversely, secondary nonresponders who discontinued golimumab without attempting dose escalation had the worst results regarding the need for colectomy.

Achieving short-term response is crucial to improve long-term outcomes with golimumab in UC. Patients who achieved short-term clinical response had an 80% reduction in the relative risk of golimumab failure. The association between golimumab as third anti-TNF and golimumab failure depended on the effect of short-term response and was not retained in the final multivariable model. Therefore, in early responders, the influence of previous anti-TNF use on the persistence with golimumab was marginal. Early responders also had an 84% reduction in the relative risk of colectomy. These data highlight the importance of achieving response to induction and, if necessary, through early dose optimization.

Patients weighing more than 80 kg who started golimumab maintenance at a dose of 100 mg q4wk had a lower probability of persisting with golimumab. This negative effect has not been reported previously and can perhaps be explained by the fact that golimumab escalation occurred in only 23% of secondary nonresponders receiving q4wk 100 mg doses (escalation occurred in 77% of patients on golimumab 50 mg q4wk). It seems that clinicians feel confident optimizing the drug in secondary nonresponders on maintenance doses of 50 mg but, probably due to lack of studies of dose escalation from 100 mg doses, they are more predisposed to discontinue golimumab in patients on these doses. Such studies evaluating dose escalation strategies in patients receiving 100 mg doses might help reduce the clinicians' concerns about dose escalation to further improve persistence. In our study, time between diagnosis and the first anti-TNF agent was not associated with golimumab failure or colectomy (data not shown). Accordingly, a recent study reported that early anti-TNF therapy was not predictive of hospitalization, colectomy, or secondary loss of response in UC.[22]

In our study, golimumab doses were generally well tolerated, with a safety profile consistent with that of large controlled studies.[1,2] After being instructed by trained personal, the vast majority of patients were able to self-administer golimumab at home. In certain patients with severe disability

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maintenance, doses were administered in the hospital by trained nurses. Golimumab seems to be appropriate for these disabled patients, given its subcutaneous administration every 4 weeks, even after dose escalation.

The main limitation of our study was the retrospective design, which does not allow for prespecified examinations, including endoscopy, outside those performed in routine clinical practice. Thus the definition of remission used in our study is weak because no endoscopic evaluation was carried out. Another limitation was that the decision to escalate or to withdraw golimumab was not standardized and was left to the criterion of the attending gastroenterologist. The retrospective design also meant that neither the golimumab trough levels nor the antibodies to golimumab were measured. Drug levels and antidrug antibodies are very relevant to our understanding of the mechanisms of the secondary loss of response to anti-TNF agents, and can help guide therapeutic decisions.[23 25]

In conclusion, in this difficult-to-treat real-life cohort of patients with moderate-to-severe UC, golimumab therapy was effective in inducing and maintaining clinical response. Although anti-TNF–naive patients had better outcomes, golimumab was also effective for anti-TNF–experienced patients. Only the patients given golimumab after previous failure of 2 anti-TNF agents had significantly worse short-term and long-term outcomes. Golimumab dose escalation to manage secondary loss of response was beneficial and safe, and this strategy was partly responsible for the high persistence with golimumab in patients who started maintenance therapy.

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