

Original Article

Real World Effectiveness of Golimumab Therapy in Ulcerative Colitis Regardless of Prior TNF Exposure

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Abstract

Background: The efficacy of golimumab to induce and maintain remission in biologic-naïve patients with ulcerative colitis (UC) is established from placebo-controlled trials. However, golimumab's real-world effectiveness, important to physicians and payers, remains unexplored.

Aim: The goal of this study was to describe real-world use and rate of persistence among UC patients with golimumab therapy and to assess factors that predict discontinuation during golimumab maintenance treatment.

Methods: A retrospective study of UC patients receiving golimumab maintenance therapy (August 2012–August 2015) was conducted on dosing data from a national case management program. Treatment persistence, defined as time from index prescription to the last dose (gap in dose >60 days), was assessed using Kaplan-Meier survival analysis. Predictors of treatment persistence were explored with Cox proportional hazards regression.

Results: One hundred thirty-six patients (50.7% male) with a mean (SD) age of 44.4 (15.6) years were included. At golimumab initiation, 72.1% were naïve to anti-TNFs; 77.2% received 200 mg, while 4.4% and 18.4% received 50 mg and 100 mg, respectively, every 4 weeks (induction therapy). The median time to discontinuation was 530 days, with a cumulative probability of 63% to remain on therapy at one year. Age, gender, golimumab induction, golimumab maintenance dose and prior anti-TNF exposure were not significantly associated with treatment persistence. Dose adjustment occurred in 7.4% of patients during maintenance treatment.

Conclusions: Overall, the persistence rate of golimumab observed in the current real-world study is similar to that described in previous single-centre UC cohorts and consistent with that seen in controlled clinical trials.

Keywords: *Biologics; Compliance/adherence; Inflammatory bowel disease; Ulcerative colitis*

The current guidelines for clinical management of ulcerative colitis (UC) recommend anti-TNF therapy for immunosuppressant-refractory, steroid-refractory or steroid-dependent patients (1–3). To date, three anti-TNF agents have been licensed for the treatment of UC: infliximab, adalimumab and golimumab. The efficacy of infliximab and adalimumab has been

demonstrated in previous clinical trials (4–8). The efficacy of golimumab to induce and maintain remission in biologic-naïve patients with moderate to severe UC has been demonstrated in recently published, large, randomized controlled trials (5, 9–11). Although the efficacy of golimumab has been assessed in controlled settings and restricted patient populations

(12), its effectiveness across diverse patient populations seen in routine clinical practice remains largely unexplored. This real-world effectiveness—important to patients, physicians and payers—can be efficiently and effectively be described using observational methods (13).

UC is characterized as a lifelong disease, with periods of quiescence. Increased persistence and a well-established measure of drug effectiveness encompassing factors such as drug tolerability, treatment compliance and clinical efficacy have been shown to improve the health benefits of approved treatments (14) and reduce health care expenditure (15, 16). To date, few single-centre studies have explored the rate of drug persistence with golimumab (17).

The current study aimed to examine the persistence with golimumab of UC patients within the nationwide case management program BioAdvance[®] and to explore patient factors associated with time to golimumab discontinuation.

MATERIALS AND METHODS

Study design and population

This was a retrospective analysis of data collected through a nationwide Canadian case management program (CMP; BioAdvance[®]) from August 2012 to August 2015 on golimumab-treated patients with UC. Data collection from physician and patient questionnaires includes patient demographics, prior biologic use and prescription data. Eligible patients for the analysis included adults (18–80 years) enrolled in the CMP that consented to have their data analyzed anonymously in aggregate, had a physician-confirmed diagnosis of UC and had received at least one dose of golimumab. Patients with incomplete data were excluded. A sample size of 130 patients would provide 80% power to detect a hazard ratio above 1.85 for a predictive factor for golimumab discontinuation with an alpha of 0.05.

Statistical analysis

The main objective of the study was to provide an estimate of discontinuation-free survival (persistence) of golimumab for UC. Time to discontinuation, defined as the time from the index prescription to the last dose before a gap in dose >60 days, was assessed with the Kaplan-Meier survival method (right-censoring patients still on continuous treatment at their last assessment). The secondary objective was to assess factors that predict golimumab discontinuation during golimumab maintenance treatment. Both univariate- and multivariate-adjusted logistic regression analyses were used to assess potential risk factors, which included prior treatment with anti-TNF therapy, gender, age and golimumab induction and maintenance doses. Dose optimization was defined as any golimumab maintenance dose that differed (increased or decreased) from the first maintenance dose. Statistical analyses were carried out using SPSS 21.0 (SPSS Inc., Chicago, IL) and SAS 9.4 (SAS Institute, Cary, NC).

RESULTS

A total of 136 eligible patients were included in the analysis. The mean duration of follow-up was 188 days (median, 126 days). As of August 31, 2015, patients had been followed for a total of 70 patient-years.

Table 1 summarizes the patient population's baseline characteristics. The mean (SD) age was 44.4 (15.6) years, approximately half (50.7%) the patients were male, and the majority of patients (72.1%) were anti-TNF naïve.

Based on survival analysis, patients persisted on golimumab for a median of 530 days, and the cumulative probability to remain on therapy after one year was 63% (Figure 1). Figures 2 and 3 describe persistence on golimumab by prior anti-TNF experience ($P=0.71$) and by gender ($P=0.59$), respectively, showing no significant association of either parameter with the outcome. In multivariate analysis, no statistical association between time to golimumab discontinuation and age ($HR=1.01$, $P=0.34$), gender ($HR=1.20$, $P=0.59$), golimumab induction dose ($HR=1.33$, $P=0.46$), golimumab maintenance dose ($HR=1.56$, $P=0.99$), or prior anti-TNF exposure ($HR=1.14$, $P=0.71$) was detected (Table 2).

Table 3 summarizes golimumab dose by prior biologic experience. The majority of patients (77.2%) received 200 mg of golimumab at induction, regardless of prior anti-TNF experience (naïve: 77.6%, experienced: 76.3%). Among anti-TNF-naïve patients, 71.6% of patients received a maintenance dose of 100 mg every four weeks. During the maintenance period, at a median time of 126.5 days, 10 (7.4%) patients underwent dose adjustment, corresponding to 8.2% of anti-TNF naïve patients and 5.3% of those previously treated with an anti-TNF.

Table 1. Overall patient and treatment characteristics

Variable	Level	Total N=136
Gender		
Female	n (%)	67 (49.3)
Male	n (%)	69 (50.7)
Age	Mean (SD)	44.4 (15.7)
Region*		
Western Canada	n (%)	45 (33.1)
Maritimes	n (%)	13 (9.6)
Ontario	n (%)	44 (32.4)
Quebec	n (%)	34 (25.0)
Biologic Naive	n (%)	
No	n (%)	38 (27.9)
Yes	n (%)	98 (72.1)

*Maritimes includes these provinces: Nova Scotia and New Brunswick. Western Canada includes these provinces: Alberta, British Columbia, Manitoba and Saskatchewan.

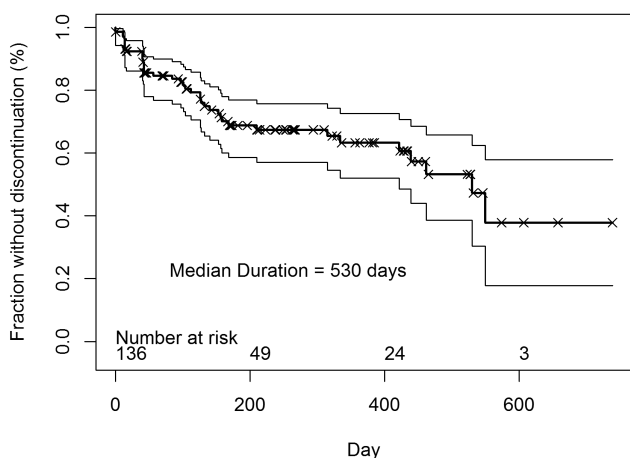


Figure 1. Persistence on golimumab therapy (nonpersistence >60 days gap)—overall. Median persistence was 530 days.

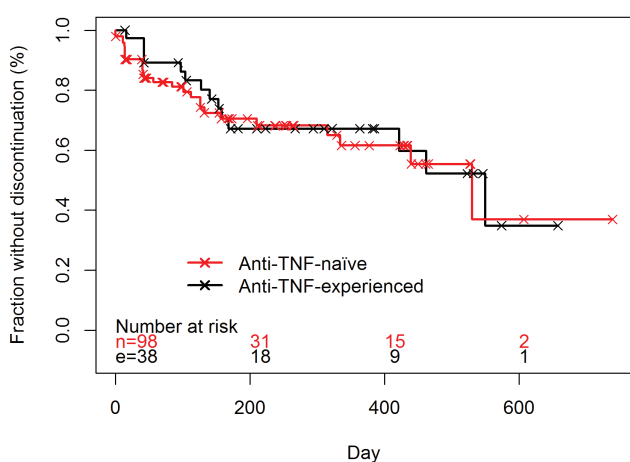


Figure 2. Persistence on golimumab therapy (nonpersistence >60 days gap) by prior anti-TNF experience.

Of these, seven patients had their golimumab dose increased, and three received a dose reduction.

DISCUSSION

The efficacy of golimumab in refractory moderate to severe UC has been shown in restricted populations of patients across several controlled clinical trials (7, 9, 11). In this study, we evaluated the persistence of golimumab therapy across a diverse patient population seen in routine clinical practice using dosing data from a comprehensive case management program. Persistence with therapy, defined as the amount of time that a patient remains on drug therapy, is an established surrogate measure of drug effectiveness in long-term observational and real-world studies, which incorporates several domains including drug tolerability, treatment compliance and clinical efficacy (18). Regarding the latter, previous studies have reported that persistence with anti-TNF therapy is associated with maintained clinical response (9, 11, 19). In the present study, 63%

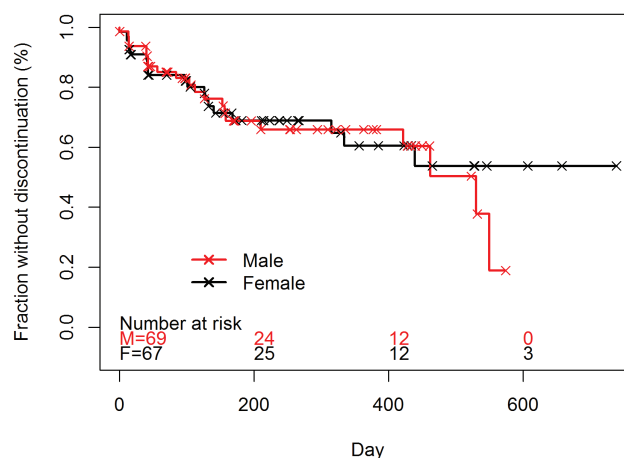


Figure 3. Persistence on golimumab therapy (nonpersistence >60 days gap) by gender.

of patients remained on therapy after one year (median persistence of 530 days). In comparison, the clinical response rate at week 60 that was observed in the placebo-controlled, phase 3 PURSUIT trial, which included anti-TNF-naïve patients only, was 50% (9, 11, 20). Thus, the outcomes appear similar—if not better—in this cohort, which includes TNF-naïve and TNF-failure patients. This observation suggests that results of the PURSUIT randomized controlled trials could be generalized to the diverse patient populations seen in clinical practice.

To our knowledge, no prior studies have assessed persistence with golimumab treatment in UC patients in Canada. Furthermore, even though previous publications have reported data on persistence with anti-TNF agents, none have restricted the patient population to UC patients (21, 22), thus not allowing an indirect comparison with our study.

UC is a lifelong disease with an unpredictable pathogenesis marked by potentially long periods of inactivity. Uninterrupted maintenance treatment is recommended, even during periods of asymptomatic remission (14, 23). This is particularly important in chronic conditions where patients are at high risk for non-adherence (14, 24, 25). To date, this represents the first study aiming to identify significant predictors of discontinuation of golimumab maintenance treatment of UC. We did not identify significant predictive factors of golimumab persistence including, among others, previous biologic experience and gender. The study by Renna et al. evaluating the real-world effectiveness of golimumab and adalimumab identified no significant predictors of golimumab response and observed no differences between groups, based on previous biologic experience (anti-TNF naïve versus experienced) among patients who persisted on golimumab for eight weeks. However, these results should be compared to the present study findings with caution, due to the differing outcomes (response versus discontinuation) and follow-up periods (26).

Although to our knowledge no studies have directly evaluated persistence and potential predictive factors of golimumab

Table 2. Predictors of time to golimumab discontinuation- multivariate analysis

Parameter	N	Hazard Ratio	95 % Confidence interval	P-value
Anti-TNF naïve	136	1.14	0.56–2.21	0.71
Female gender	136	1.20	0.63–2.27	0.59
Age (years)	136	1.01	0.99–1.03	0.34
Induction dose (200 mg vs. 100 mg)	136	1.33	0.63–2.83	0.46
Maintenance dose (50 mg vs. 100 mg)	136	1.56	0.65–3.76	0.99

Table 3. Golimumab dose by prior anti-TNF experience

Variable	Level	Anti-TNF Naïve N=98	Anti-TNF Experienced N=38	Total N=136
Golimumab Induction				
50 mg	n (%)	4 (4.1)	2 (5.3)	6 (4.4)
100 mg	n (%)	18 (18.4)	7 (18.4)	25 (18.4)
200 mg	n (%)	76 (77.6)	29 (76.3)	105 (77.2)
Golimumab Maintenance				
50 mg	n (%)	16 (16.3)	5 (13.2)	21 (15.4)
100 mg	n (%)	53 (54.1)	30 (78.9)	83 (61.0)
200 mg	n (%)	5 (5.1)	0 (0.0)	5 (3.7)
Missing	n (%)	24 (24.5)	3 (7.9)	27 (19.9)
Dose Adjustment				
Unchanged	n (%)	90 (91.8)	36 (94.7)	126 (92.6)
Optimized	n (%)	8 (8.2)	2 (5.3)	10 (7.4)

discontinuation in UC, similar studies have aimed to identify predictors of medication adherence (16, 23, 27–29). For instance, Lachaine et al. assessed medication adherence to any of the mesalamine-delayed/extended-release tablets using Canadian prescription claims. This study identified male gender (odds ratio [OR]=1.3; 95% confidence interval [CI], 1.1–1.6), older age (>60 years; OR=1.6; 95% CI, 1.3–2.0) and current use of corticosteroids (OR=1.4; 95% CI, 1.1–1.8) as predictors of high medication adherence (28). A study by Kane et al. assessing adherence with maintenance mesalamine in quiescent UC showed that males were twice as likely as females to be non-adherent with their UC treatment (24). However, our study did not assess medication adherence, but rather, persistence with golimumab treatment, which may explain the different findings. In rheumatoid arthritis, adherence to biologic therapies has been linked to lower health care resource utilization and the need for concomitant therapies such as corticosteroids (30). A study in rheumatoid arthritis (31) suggested that golimumab's every four-week dosing schedule may account for some increased persistence compared to other subcutaneous therapies.

A minority of patients underwent dose adjustment (~7%) during a median follow-up time of 126.5 days. Our results concur with Detrez et al., who reported that adequate exposure to golimumab serum concentrations drives clinical response. Similar to our study, both study populations included anti-TNF-naïve

and anti-TNF-experienced patients (17). Specifically, Detrez et al. reported 61.9% of patients maintaining a stable dose during follow-up without a significant difference between the anti-TNF-naïve and anti-TNF-experienced groups.

This study has several limitations. Persistence was used as a surrogate measure for efficacy (i.e., we assumed that a patient staying on golimumab is, in fact, continuing to have a response worthy of ongoing therapy). Due to the nature of the database, disease activity was not possible to be assessed. The fact that the majority of patients in this cohort were anti-TNF-naïve in an era where two other biologics are available for treatment of UC suggests that both the patient and treating physician felt ongoing use of golimumab was appropriate based on the clinical benefit. The assumption that patients who experience positive outcomes are more likely to persist treatment further solidifies this premise. Another limitation is that information on smoking and concomitant immunosuppressant use, which might influence drug persistence, was not available. While immunosuppressant use was not associated with golimumab response in the PURSUIT trial (9), combination therapy is generally thought to improve outcomes, especially in bio-naïve, immunosuppressant-naïve UC (33). Patient selection for treatment with golimumab was based on the judgement of the treating physicians, which may have resulted in selection bias; however, this is in line with the observational nature of the current study, and one would argue that the study population is reflective of

the real-world. In addition, the database design, which is similar to claims data but with richer patient-level information, does not include some disease-related or patient-specific information such as biomarkers and concomitant medications that may be included in patient charts. Nonetheless, the present study design was selected due to statistical power afforded by such an approach, allowing us to examine the effectiveness of this product in a multi-centre real world setting. Furthermore, the study was powered to detect a hazard ratio above 1.75; therefore, any weaker effects would not be able to be detected as statistically significant in our study. Finally, time to golimumab discontinuation due to any reason was evaluated, and nonpersistence with golimumab could not be attributed to lack of efficacy or tolerability issues.

The major strength of the study is that it includes a large number of patients seen in real-world by both academic- and community-based gastroenterologists. This enhances the generalization of the findings to the UC population and broadens the possible use of golimumab into a TNF-exposed patient population.

In summary, the results of the current study have shown that the majority of patients persisted with golimumab therapy after one year, with a median of persistence of 530 days. A minority of patients underwent dose adjustment (~7%) during the follow-up period. These real-world data demonstrate the effectiveness of subcutaneous golimumab in the treatment of UC patients and suggest comparable or higher effectiveness compared with clinical trials across a broader patient population than those included in registration trials.

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Conflicts of Interest

BB and AHS have served as consultants and have received honoraria and grants. MW and BS are employees of Janssen Inc. FC has served as a consultant of Janssen Inc. This study was funded in part

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