Effectiveness and safety of adalimumab to treat outpatient ulcerative colitis

A real-life multicenter, observational study in primary inflammatory bowel disease centers

Antonio Tursi, MD[a],*, Walter Elisei, MD[b], Roberto Faggiani, MD[c], Leonardo Allegretta, MD[d],
Nicola Della Valle, MD, PhD[e], Giacomo Forti, MD[f], Marilisa Franceschi, MD[g], Antonio Ferronato, MD[g],
Sara Gallina, MD[e], Tiziana Larussa, MD, PhD[h], Francesco Luzza, MD, PhD[h], Roberto Lorenzetti, MD[i],
Giammarco Mocci, MD[j], Antonio Penna, MD[k], Stefano Rodino', MD[l], Ladislava Sebkova, MD[l],
Antonio de Medici, MD[m], Giuseppe Pranzo, MD[n], Cristina Ricciardelli, MD[o], Giuseppina Grasso, MD[d],
Stefano Scorza, MD[e], Costantino Zampaletta, MD[c], Marcello Picchio, MD[p]

Abstract

Adalimumab (ADA) was approved in Italy for the treatment of ulcerative colitis (UC) unresponsive to standard treatments in 2014, but no data from real life are currently available. The aim of the present study was to assess the real-life efficacy and safety of ADA in managing UC outpatients in some Italian primary inflammatory bowel disease (IBD) centers after approval of ADA reimbursement.

Consecutive UC outpatients with at least 3-month follow-up were retrospectively evaluated. The primary end point was the induction and maintenance of remission in UC, defined as Mayo score ≤2.

One hundred seven patients were included. At 3-month follow-up, obtained in 102 (95.3%) patients, 56 (54.9%) patients achieved a clinical remission. At univariate analysis, both Mayo partial score >7 and Mayo subscore for endoscopy = 3 at entry showed to be significantly associated with the lack of remission induction.

During a median (95% confidence interval [CI]) follow-up of 18 (12–24) months, 56.6% of patients were under clinical remission; clinical response was achieved in 89.2% of cases. Mucosal healing was achieved in 66 (76.7%) patients, and colectomy occurred in 3 (2.8%) patients. Both C-reactive protein and fecal calprotectin values significantly decreased during follow-up. Steroids discontinuation occurred in 67 (66.7%) patients, and ADA dose escalation was adopted in 9 (16.1%) patients under remission. No factor was significantly related to the maintenance of clinical remission.

This first Italian experience found ADA safe and effective to induce and maintain remission in real-life UC outpatients.

Abbreviations: ADA = adalimumab, CRP = C-reactive protein, FC = fecal calprotectin, GOL = golimumab, IBD = inflammatory bowel diseases, IFX = infliximab, MH = mucosal healing, TNF = tumor necrosis factor, UC = ulcerative colitis.

Keywords: adalimumab, induction, remission, treatment, ulcerative colitis

1. 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 characterized by a relapsing and remitting course, sometimes requiring an aggressive therapeutic approach in order to prevent complications.[2] Tumor necrosis factor α (TNFα) plays an important role in the pathogenesis of the disease,[1] and the introduction of monoclonal anti-TNFα antibodies has greatly improved our treatment options in UC patients refractory or intolerant to standard treatments.[2,3]

Adalimumab (ADA) is a subcutaneously administered fully human anti-TNFα antibody,[1] worldwide approved for the treatment of moderate-to-severe UC in adults who have an inadequate response or are intolerant to conventional therapies (including steroids and thiopurines). In the 2 pivotal randomized controlled registered trials, ULTRA I and II, ADA significantly induced and maintained short-term clinical response (55%) and remission (19%) after 8 weeks in anti-TNF naive UC patients.[4] Long-term clinical remission rates after 52 weeks were comparable (22%).[5–7] However, we know that patients entering controlled clinical trials are not necessarily representative of those in real life.[8] Some data about the efficacy and safety of ADA in real life are now becoming available.[9–13]

ADA reimbursement for UC was approved in Italy in 2014,[14] but no large real-life Italian data are currently available. The aim of the present study was to assess the efficacy and safety of ADA to treat a large UC outpatient population in some Italian primary inflammatory bowel disease (IBD) centers after approval of ADA reimbursement for UC by Italian Regulatory Authorities.

2. Materials and methods

This retrospective, observational study analyzed a group of UC outpatients unresponsive to standard treatments and treated with ADA in 14 Italian primary IBD centers (namely centers identified by The Italian National and Regional Health Systems as able to manage uncomplicated IBD patients). We assessed patients enrolled from May 1, 2014 to December 31, 2017, who completed the induction treatment.

2.1. Clinical assessment

Eligible patients included adult men and women (≥18 years old) with an established diagnosis of UC according to standard endoscopic and histological criteria.[1] Disease extension was assessed according to the Montreal classification,[15] and severity was graded according to the Mayo score.[16] All patients had to have 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 sex, age at diagnosis, smoking status, disease extension, disease duration, previous immunosuppressive and anti-TNFα 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, after 2, 3, 6, and then every 6 months.

The study was conducted according to Good Clinical Practice and the Declaration of Helsinki for human studies and animal welfare regulations. All patients gave written informed consent before they underwent to endoscopy and ADA treatment. Since the present study was retrospective design, no Ethic Committee approval was requested by current law.

2.2. Study treatment

All patients were eligible for injection of ADA after exclusion of active hepatitis B virus, active cytomegalovirus and active or latent tuberculosis infection.

The induction dose of ADA was 160 mg at week 0, 80 mg at week 2, and then 40 mg every 2 weeks.

The need for treatment discontinuation was left to the investigators' judgment, as well as concomitant medications including oral and topical aminosalicylates, steroids, and immunosuppressants.

2.3. Endoscopy

Ileo-colonoscopy was performed in all the enrolled patients and classified according to Mayo subscore for endoscopy.[16] During follow-up it was scheduled at 6, 12, and 24 months.

2.4. End points

The primary end point was the induction of clinical remission in UC, defined as Mayo partial score ≤2, at 3 months, and maintenance of clinical remission, during the follow-up. Secondary end points were

- Clinical response, defined as reduction of at least 2 point in the Mayo partial score during follow-up (if blood in stool is present, it must be reduced of at least one point).
- Reaching of mucosal healing (MH), defined as Mayo subscore for endoscopy ≤1, during follow-up.
- Prevention of colectomy.

2.5. Clinical data

The following clinical data were assessed during follow-up:

- Reduction of steroid use and assessment of type of steroid used during the follow-up (systemic vs topic); Assessment of adverse event 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 dose escalation in order to maintain remission;
- Assessment of CRP and FC during follow-up.

2.6. Statistics

Continuous non-parametric variables were reported as median with 95% confidence interval (95% CI) and categorical variables as number (percentage) through the text and tables. Statistical analysis was performed by Fisher exact test and chi-square for categorical data. 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. Univariate analysis was performed to assess the possible influence of baseline demographic and clinical variables on induction of clinical remission at 2-month follow-up. Parameters with a P value < 0.05 using univariate analysis were entered into a multivariate logistic regression model to identify independent predictors for clinical remission at 2-month follow-up. To evaluate the role of the same predictive demographic and clinical variables on maintenance of clinical remission during follow-up, univariate analysis with log-rank test was used. Hazard ratio (HR) was calculated with 95% CI. All variables with a P value < 0.05 at log-rank test were entered into a Cox proportional hazards survival regression. Data were analyzed using MedCalc Release 14.8.1.

3. Results

One hundred seven patients were enrolled. The clinical characteristics of the study group and the indication for ADA treatment are showed in Table 1. Steroid dependency and refractory were the most common indication to ADA. Disease

Table 1

Demographics, disease characteristics, and concomitant medications.

Number	107
Male sex	61 (57.0)
Mean (95% CI) age at diagnosis, y	46.5 (43.6–49.5)
Median (95% CI) disease duration prior to adalimumab infusion, y	9.0 (6.8–10.0)
Median (95% CI) BMI, kg/m^2	22.3 (21.2–23.2)
Current smokers	10 (9.3)
Comorbidities	34 (31.8)
Appendectomy	13 (12.1)
Indications for adalimumab therapy	
Steroid dependency	71 (66.4)
Steroid refractory	15 (14.0)
Resistance to anti-TNFα	17 (15.9)
Extraintestinal localization	4 (3.7)
Disease extension	
Proctitis	2 (1.9)
Distal colitis	36 (33.6)
Pancolitis	69 (64.5)
Median (95% CI) Mayo partial score at entry	7 (6–7)
Median (95% CI) Mayo endoscopy subscore at entry	2 (2–3)
Median (95% CI) C-reactive protein, mg/L	11.0 (8.1–15.0)
Median (95% CI) fecal calprotectin, mcg/g	265.0 (209.6–418.6)
Concomitant medications	
Mesalazine	48 (44.9)
Mesalazine with corticosteroids	44 (41.1)
Immunomodulators	12 (11.2)
No medications	3 (2.8)
Naive to anti-TNFα	63 (58.9)

Values are expressed as number (percentage) of patients, unless otherwise specified. CI, confidence interval.

distribution was mostly pancolitic. More than half of patients were naive to anti-TNFα.

3.1. Induction of clinical remission

At 3-month follow-up, obtained in 102 (95.3%) patients, 56 (54.9%) patients achieved a clinical remission.

At univariate analysis both Mayo partial score at entry >7 and Mayo subscore for endoscopy at entry = 3 showed to be significantly associated with the lack of remission induction. However, no factor was significantly and independently related to failure of remission induction at multivariate logistic regression (Table 2).

3.2. Maintenance of remission

The median (95% CI) follow-up for all patients was 18 [12–24] months. Clinical remission maintenance during the follow-up is reported in Figure 1. Overall, 60 (56.6%) patients were under clinical remission. In particular, clinical remission was maintained in 85.1%, 76.2%, 66.2%, and 45.8% at 6, 12, and 24 months, respectively.

Colonoscopy was performed in 86 (80.4) patients during follow-up. MH was achieved in 66 (76.7%) patients.

Colectomy was performed in 3 (2.8) patients (2 due to primary failure, one of them previously treated with infliximab [IFX], and one due to secondary failure).

Both CRP and FC values decreased significantly during follow-up (Figure 2 A, B).

Steroids discontinuation occurred in 67 (65.7%) patients. In the remaining 35 (34.3%) patients, who assumed steroids during follow-up, systemic steroids were administered in 21 (61.8%) patients and topic steroids were given to the remaining 13 (38.2%).

Dose escalation of ADA was adopted in 9 (16.1%) patients under remission. Interruption of therapy occurred in 5 (4.9%) patients for primary failure and in 8 (7.8%) patients for secondary failure. Among them, 2 patients (both due to primary failure and naïve to anti-TNFα) were switched to infliximab, and 2 (both due to secondary failure, and already treated with infliximab) to vedolizumab.

One patient interrupted the therapy due to pregnancy.

No factor was significantly related to the maintenance of clinical remission (Table 3).

3.3. Safety

One case of leukopenia occurred at 24-month follow-up, requiring discontinuation of treatment.

Table 2

Predictors of clinical remission induction.

	Remission (56 patients)	No remission (46 patients)	P*	Odd radio (95% CI) logistic regression	P
Sex, male	30 (53.6)	28 (60.9)	0.589	—	—
Age ≥ 40 y	32 (57.1)	33 (71.7)	0.187	—	—
Disease duration ≥ 5 y	38 (67.8)	35 (76.1)	0.486	—	—
BMI ≥ 25 kg/m^2	18 (32.1)	15 (32.6)	0.871	—	—
Current smokers	3 (5.3)	7 (15.2)	0.051	—	—
Appendectomy	7 (12.5)	6 (13.0)	0.829	—	—
Previous treatment with immunomodulators	8 (14.3)	4 (8.7)	0.539	—	—
Disease extension					
Proctitis	—	1 (2.2)			
Left-sided colitis (distal colitis included)	19 (33.9)	14 (30.4)	0.517†	—	—
Pancolitis	37 (66.1)	31 (67.4)			
Mayo partial score at entry > 7	16 (28.6)	25 (54.3)	0.015	2.286 (0.941–5.553)	0.068
Mayo subscore for endoscopy at entry=3	17 (30.3)	25 (54.3)	0.025	2.000 (0.826–4.844)	0.125
C-reactive protein ≥ 10 mg/dL	23 (41.1)	28 (60.9)	0.073	—	—
Fecal calprotectin >200 mcg/g	26/40 (65.0)	13/27 (48.1)	0.263	—	—
Naive to anti-TNFα	37 (66.1)	21 (45.6)	0.061	—	—

Values are expressed as number (percentage) of patients. CI, confidence interval.

* Fisher exact test.

† Chi-square test with 2 degrees of freedom was used for disease extension comparison.
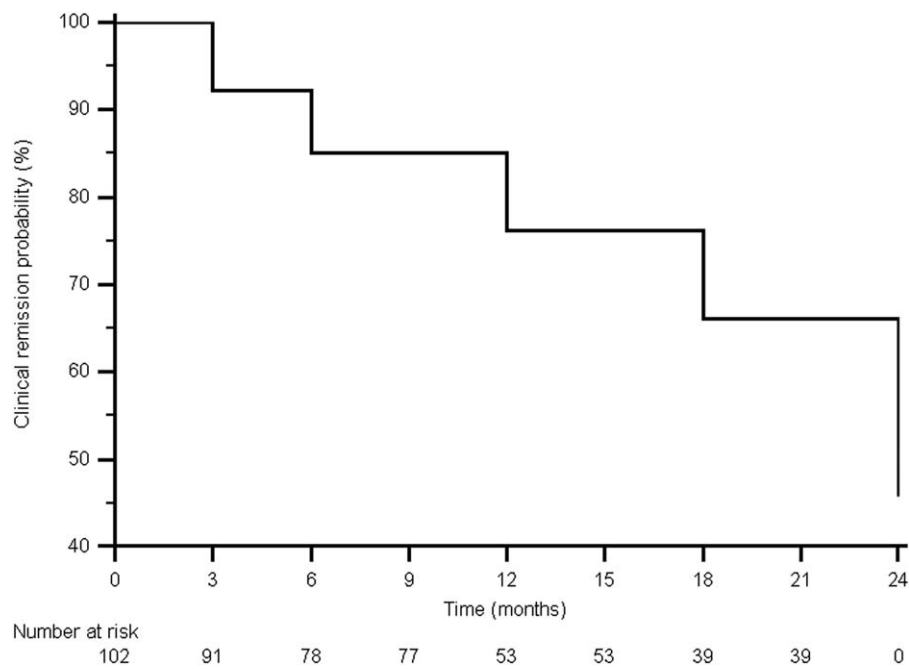
Figure 1. Kaplan–Meier curves of cumulative probability of clinical remission maintenance during follow-up.

4. Discussion

Two case series of active UC Italian patients treated with ADA, one in a tertiary and one in a referral center as compassionate use, has been published in the last years.[17,18] However, the present observational study is the first one conducted in a large series of active UC outpatients after ADA approval by the Italian Regulatory Authorities for real-life UC management, and managed in primary gastroenterology IBD centers.

Our results suggest that scheduled ADA is effective in UC population, both naïve and already treated with anti-TNFα, even if treated in primary gastroenterology care: almost 60% of patients entered clinical remission during a 18-month median follow-up, and the vast majority of them allowed steroid withdrawal and steroid-free remission during the same follow-up.

With respect to the primary end point, our results seem to be better than the ones reported both in pivotal and real life studies. The pivotal trials ULTRA I and ULTRA II show a remission rate of 29.5% and 30.9% at week 52, respectively,[5,7] while the real life studies reached a higher remission rate at 12 to 24 months of 35% to 51%.[9–13] Data from the recent transnational trial InspirADA,[19] as well as the Italian results extracted from this trial,[20] show a remission rate lower than ours. Moreover, these results were obtained in a real-life population, in which about half of patients were prior exposed to anti-TNFα. These significant results are not easy to explain. Apart from the incomparable time point evaluations, these results may be explained by different UC populations enrolled. The vast majority of the studies, both pivotal and real life, enrolled patients with moderate-to-severe disease, while the median Mayo score of our study group was 7, which implies a mild-to-moderate disease. Therefore, it is likely that our patients were affected by a milder disease, able to explain our excellent results. This fact seems to be confirmed by the predictors of remission induction. We found that both Mayo partial score at entry >7 and Mayo

subscore for endoscopy at entry = 3 showed to be significantly associated with the lack of remission induction, while no factor was significantly and independently related to lack of remission induction at multivariate analysis. This result is explained by the fact that these 2 parameters are not independent, since it is well known that MH influences the reaching of clinical remission.[21] Significantly, we found that previous exposure to anti-TNFα does not influence the reaching of remission. This result differs from the one reported in the literature.[5–7] A possible explanation is the occurrence of a type II error, linked to the real life type of enrolment. A more reliable hypothesis may be that patients with mild-to-moderate UC may have much more chances to reach remission when using ADA, irrespective of duration of disease and prior anti-TNFα exposure. This fact seems particularly important to obtain remission, while we did not find any other factor influencing remission maintenance. Therefore, reaching remission is the most important factor, because ADA seems to be able to preserve remission, when achieved.

The effect of ADA in treating UC in real life seems to be comparable to other anti-TNFα antibodies. A recent systematic review with network meta-analysis found no significant differences among the anti-TNFα therapies in induction and maintenance of remission in UC patients [22]; similar results are reported by a recent, pilot study comparing ADA vs Golimumab (GOL) in real life.[23] In our real-life experience, Infliximab (IFX) showed a similar clinical remission/response rate,[24] while GOL showed less favorable clinical remission/response rates.[25] Considering the rate of secondary failure, that seems to affect up to 59% of UC patients treated with anti-TNFα therapies,[26] we recorded a significant lower rate than the one reported using IFX or GOL in real life.[27,28] The chance to apply a dose escalation may probably explain why ADA seems to work better than GOL in those patients, even if dose escalation occurred in only 16% of case in our population. Any conclusion cannot be unfortunately drawn about this point, because the studied populations, as well as the length of the follow-up, were
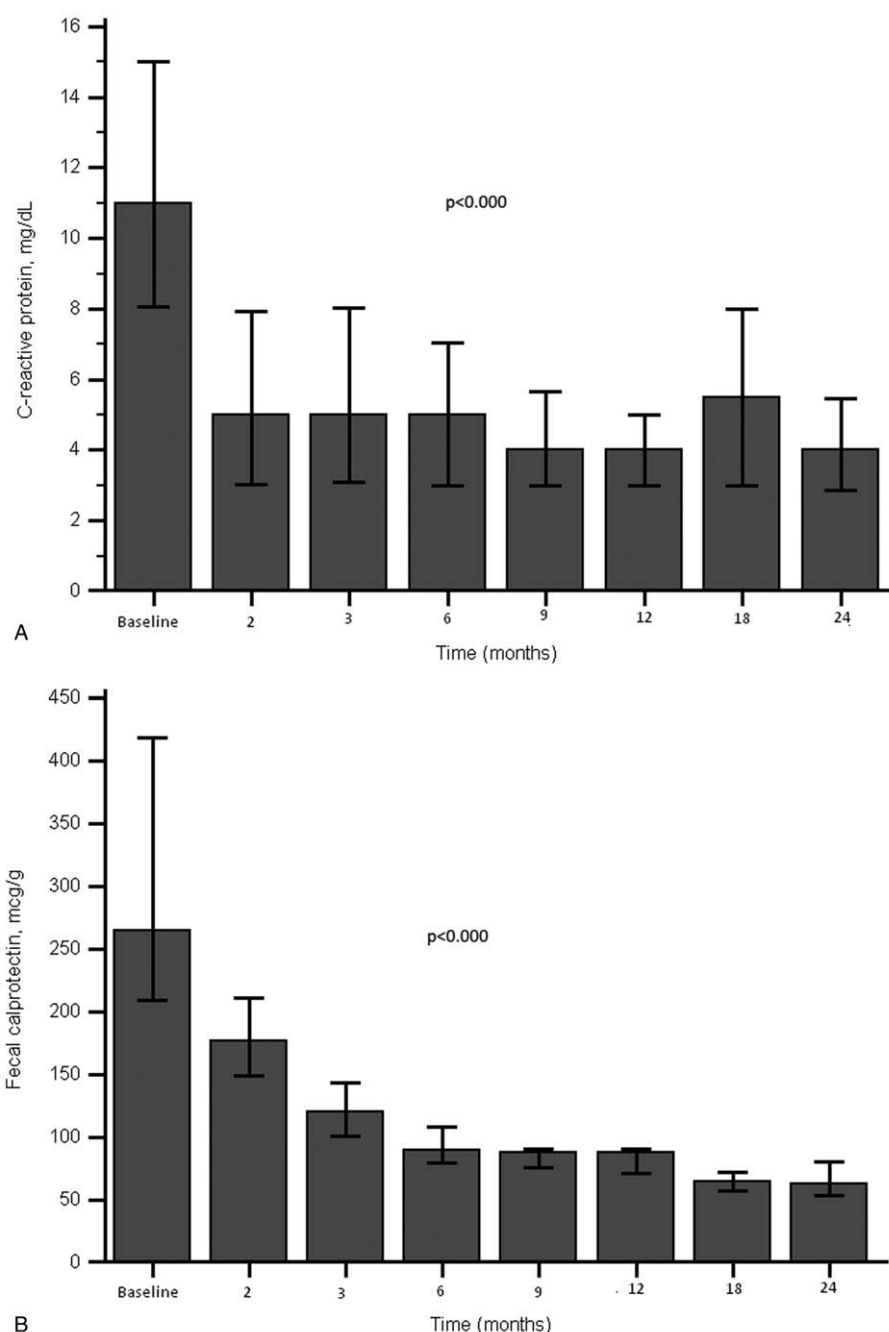
Figure 2. Median C-reactive protein (A) and fecal calprotectin (B) values during follow-up. Error bars represent 95% confidence interval. Friedman test.

different. However, we can state that ADA seems to be as effective as IFX and better than GOL in achieving clinical remission/clinical response in real-life UC population.

Our study also found that ADA is effective in reaching the secondary end points. The most important secondary end point was the impressive rate of MH. This rate was significantly higher than the one reported in both pivotal and real-life studies, which never overcomes 50%. It is likely that the milder endoscopic damage detected at entry (the median Mayo score at entry was 2) may explain our results. It is also likely that this high rate of MH may influence the significant dropping of CRP and FC during follow-up, as well as the very low rate of colectomy reported. In

fact, the colectomy rate in the real life studies ranges from 5.4% to 22%,[9–13,17] while we reported only a 2.5% rate of colectomy.

ADA effectiveness was also confirmed by the significant dropping in using steroids during follow-up. In fact, we reported that only a minority of patients continued to assume steroids to maintain remission. Hence, a good control of the disease, represented by high MH rate and high remission rate, permits also to avoid steroids and surgery.

Finally, ADA seems to be very safe in real life. We only reported one case of leukopenia occurring after 2 years of treatment, while literature reports a significant higher rate of adverse events under treatment with ADA.[5,7,9–13,17] This result is not easy to explain,

Table 3

Predictors of clinical remission persistence during follow-up.

	Univariate analysis		
	Hazard ratio	95% CI	P
Sex, male	1.247	0.681–2.284	0.441
Age ≥ 40 y	1.209	0.628–2.331	0.225
Disease duration ≥ 5 y	1.070	0.532–2.154	0.834
BMI ≥ 25 kg/m^2	2.152	0.761–6.087	0.243
Current smokers	1.172	0.391–3.515	0.774
Presence of comorbidities	1.044	0.528–2.063	0.894
Appendectomy	0.874	0.326–2.348	0.759
Disease extension			
Proctitis	—	—	—
Left-sided colitis (distal colitis included)	Reference	Reference	Reference
Pancolitis	1.207	0.629–2,317	0.752
Mayo partial score at entry > 7	0.819	0.446–1.505	0.483
Mayo subscore for endoscopy at entry=3	1.043	0.569–1.913	0.883
C-reactive protein ≥ 10 mg/dL	0.773	0.422–1.417	0.374
Fecal calprotectin >200 mcg/g	1.673	0.732–3.822	0.225
Naive–anti-TNFα	1.056	0.577–1.935	0.846

too. We can only speculate that a milder disease leads to its easier control, with lower risk to develop opportunistic infections or disease-related complication even under immunosuppressive treatment.

This study has limitations. The first one is the retrospective design that does not permit to enroll patients having the same timing through the follow-up (both as clinical and endoscopic follow-up). The second one is that only outpatients with mild-to-moderate disease were enrolled. This could be a bias of selection, and could therefore influence the final results.

In conclusion, this first Italian real-life cohort study, conducted after approval of ADA by the Italian regulatory authorities for real-life UC management, shows that ADA is effective and safe in UC outpatients in real life, including patients with prior exposure to anti-TNFα. As this is a retrospective study, prospective studies are needed to confirm these results.

Author contributions

Conceptualization: Antonio Tursi, Marcello Picchio.
Data curation: Antonio Tursi.
Formal analysis: Antonio Tursi, Walter Elisei, Marcello Picchio.
Funding acquisition: Antonio Tursi.
Investigation: Antonio Tursi, Roberto Faggiani, Leonardo Allegretta, Nicola Della Valle, Giacomo Forti, Marilisa Franceschi, Antonio Ferronato, Sara Gallina, Tiziana Larussa, Francesco Luzza, Roberto Lorenzetti, Giammarco Mocci, Antonio Penna, Stefano Rodinò, Ladislava Sebkova, Antonio De Medici, Giuseppe Pranzo, Cristina Ricciardelli, Giuseppina Grasso, Stefano Scorza, Costantino Zampaletta.
Methodology: Antonio Tursi, Walter Elisei, Marcello Picchio.
Project administration: Antonio Tursi, Walter Elisei.
Resources: Antonio Tursi, Marcello Picchio.
Software: Walter Elisei, Marcello Picchio.
Supervision: Antonio Tursi, Walter Elisei.
Validation: Antonio Tursi, Walter Elisei, Marcello Picchio.
Visualization: Antonio Tursi.
Writing – original draft: Antonio Tursi.
Writing – review & editing: Walter Elisei, Roberto Faggiani, Leonardo Allegretta, Nicola Della Valle, Giacomo Forti,

Marilisa Franceschi, Antonio Ferronato, Sara Gallina, Tiziana Larussa, Francesco Luzza, Roberto Lorenzetti, Giammarco Mocci, Antonio Penna, Stefano Rodinò, Ladislava Sebkova, Antonio De Medici, Giuseppe Pranzo, Cristina Ricciardelli, Giuseppina Grasso, Stefano Scorza, Costantino Zampaletta, Marcello Picchio.

References

[1] Dignass A, Eliakim R, Magro F, et al. Second European evidence-based consensus on the diagnosis and management of ulcerative colitis part 1: definitions and diagnosis. J Crohns Colitis 2012;6:965–90.

[2] Dignass A, Lindsay JO. Second European evidence-based consensus on the diagnosis and management of ulcerative colitis part 2: current management. J Crohns Colitis 2012;6:991–1030.

[3] Nielsen OH, Ainsworth MA. Tumor necrosis factor inhibitors for inflammatory bowel disease. N Engl J Med 2013;369:754–62.

[4] Reinisch W, Sandborn WJ, Hommes DW, et al. Adalimumab for induction of clinical remission in moderately to severely active ulcerative colitis: results of a randomised controlled trial. Gut 2011;60:780–7.

[5] Sandborn WJ, van Assche G, Reinisch W, et al. Adalimumab induces and maintains clinical remission in patients with moderate-to-severe ulcerative colitis. Gastroenterology 2012;142:257–65.

[6] Reinisch W, Sandborn WJ, Panaccione R, et al. 52-week efficacy of adalimumab in patients with moderately to severely active ulcerative colitis who failed corticosteroids and/or immunosuppressants. Inflamm Bowel Dis 2013;19:1700–9.

[7] Sandborn WJ, Colombel JF, D'Haens G, et al. One-year maintenance outcomes among patients with moderately-to-severely active ulcerative colitis who responded to induction therapy with adalimumab: subgroup analyses from ULTRA 2. Aliment Pharmacol Ther 2013;37:204–13.

[8] Ha C, Ullman TA, Siegel CA, et al. Patients enrolled in randomized controlled trials do not represent the inflammatory bowel disease patient population. Clin Gastroenterol Hepatol 2012;10:1002–7.

[9] Bálint A, Farkas K, Palatka K, et al. Efficacy and safety of adalimumab in ulcerative colitis refractory to conventional therapy in routine clinical practice. J Crohns Colitis 2016;10:26–30.

[10] Iborra M, Pérez-Gisbert J, Bosca-Watts MM, et al. Spanish Working Group on Crohn's Disease and Ulcerative Colitis (GETECCU). Effectiveness of adalimumab for the treatment of ulcerative colitis in clinical practice: comparison between anti-tumour necrosis factor-naïve and non-naïve patients. J Gastroenterol 2017;52:788–99.

[11] Sandborn WJ, Sakuraba A, Wang A, et al. Comparison of real-world outcomes of adalimumab and infliximab for patients with ulcerative colitis in the United States. Curr Med Res Opin 2016;32:1233–41.

[12] García-Bosch O, Gisbert JP, Cañas-Ventura A, et al. Observational study on the efficacy of adalimumab for the treatment of ulcerative colitis and predictors of outcome. J Crohns Colitis 2013;7:717–22.

[13] Taxonera C, Iglesias E, Muñoz F, et al. Adalimumab maintenance treatment in ulcerative colitis: outcomes by prior anti-TNF use and efficacy of dose escalation. Dig Dis Sci 2017;62:481–90.

[14] Regime di rimborsabilita' e prezzo a seguito di nuove indicazioni terapeutiche del medicinale per uso umano Humira (adalimumab). Gazzetta Ufficiale della Repubblica Italiana 2014; 98: 12-3.

[15] Satsangi J, Silverberg MS, Vermeire S, et al. The Montreal classification of inflammatory bowel disease: controversies, consensus, and implications. Gut 2006;55:749–53.

[16] Schroeder KW, Tremaine WJ, Ilstrup DM. Coated oral 5-aminosalcylic acid therapy for mildly to moderately active ulcerative colitis. N Eng J Med 1987;317:1625–9.

[17] Armuzzi A, Biancone L, Daperno M, et al. Adalimumab in active ulcerative colitis: a "real-life" observational study. Dig Liver Dis 2013;45:738–43.

[18] Tursi A, Elisei W, Picchio M, et al. Effectiveness of adalimumab for ambulatory ulcerative colitis patients after failure of infliximab treatment: a first "real-life" experience in primary gastroenterology centers in Italy. Ann Gastroenterol 2014;27:369–73.

[19] Travis S, Feagan BG, Peyrin-Biroulet L, et al. Effect of adalimumab on clinical outcomes and health-related quality of life among patients with ulcerative colitis in a clinical practice setting: results from InspirADA. J Crohns Colitis 2017;11:1317–25.

[20] Kohn A, Biancone L, Gionchetti P, et al. Effect of adalimumab on patients with moderate to severe ulcerative colitis in Italian clinical practice setting: results from INSPIRADA. United Eur Gastroenterol J 2016;4(Suppl. 5):A455–6.

[21] Cholapranee A, Hazlewood GS, Kaplan GG, et al. Systematic review with meta-analysis: comparative efficacy of biologics for induction and maintenance of mucosal healing in Crohn's disease and ulcerative colitis controlled trials. Aliment Pharmacol Ther 2017;45:1291–302.

[22] Vickers AD, Ainsworth C, Mody R, et al. Systematic review with network meta-analysis: comparative efficacy of biologics in the treatment of moderately to severely active ulcerative colitis. PLoS One 2016;11: e0165435.

[23] Renna S, Orlando E, Macaluso FS, et al. Letter: a prospective real life comparison of the efficacy of adalimumab vs. golimumab in moderate to severe ulcerative colitis. Aliment Pharmacol Ther 2016;44: 310–1.

[24] Tursi A, Elisei W, Picchio M, et al. Managing ambulatory ulcerative colitis patients with infliximab: a long term follow-up study in primary gastroenterology centers. Eur J Intern Med 2014;25:757–61.

[25] Tursi A, Allegretta L, Buccianti N, et al. Effectiveness and safety of golimumab in treating outpatient ulcerative colitis: a real-life prospective, multicentre, observational study in primary inflammatory bowel diseases centers. J Gastrointestin Liver Dis 2017;26:239–44.

[26] Ma C, Huang V, Fedorak DK, et al. Outpatient ulcerative colitis primary anti-TNF responders receiving adalimumab or infliximab maintenance therapy have similar rates of secondary loss of response. J Clin Gastroenterol 2015;49:675–82.

[27] Taxonera C, Rodríguez C, Bertoletti F, et al. clinical outcomes of golimumab as first, second or third anti-TNF agent in patients with moderate-to-severe ulcerative colitis. Inflamm Bowel Dis 2017; 23:1394–402.

[28] Baki E, Zwickel P, Zawierucha A, et al. Real-life outcome of anti-tumor necrosis factor (in the ambulatory treatment of ulcerative colitis. World J Gastroenterol 2015;21:3282–9.