Effectiveness and safety of adalimumab to treat outpatient ulcerative colitis

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

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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.[1,2] It is characterized by a relapsing and remitting course, sometimes requiring an aggressive therapeutic approach in order to prevent complications.[3] 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, 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-TNFa naive UC patients. Long-term clinical remission rates after 52 weeks were comparable (22%). However, we know that patients entering controlled clinical trials are not necessarily representative of those in real life. Some data about the efficacy and safety of ADA in real life are now becoming available.

ADA reimbursement for UC was approved in Italy in 2014, 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. Disease extension was assessed according to the Montreal classification, and severity was graded according to the Mayo score. All patients had to have active disease, defined as a Mayo score ≥ 3 points 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. 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 topical); 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. Parameters with a P value < 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
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.

### 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 topical steroids were given to the remaining 13 (38.2%).

Dose escalation of ADA was adopted in 9 (16.1%) patients requiring discontinuation of treatment. 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 naive 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.

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### Table 1

Demographics, disease characteristics, and concomitant medications.

|               | Number | Male sex | Mean (95% CI) age at diagnosis, y | Median (95% CI) disease duration prior to adalimumab infusion, y | Median (95% CI) BMI, kg/m² | Current smokers | Comorbidities | Appendectomy | Concomitant medications |
|---------------|--------|----------|---------------------------------|-----------------------------------------------------------------|---------------------------|------------------|---------------|--------------|------------------------|
| Number of patients | 107    | 61 (57.0)| 46.5 (43.6–49.5)                | 9.0 (6.8–10.0)                                                   | 22.3 (21.2–23.2)          | 10 (9.3)        | 34 (31.8)    | 13 (12.1)    | Steroid dependency |

### Table 2

Predictors of clinical remission induction.

| Predictor                        | Remission (56 patients) | No remission (46 patients) | P | Odd ratio (95% CI) logistic regression | P |
|----------------------------------|-------------------------|----------------------------|---|----------------------------------------|---|
| Sex, male                        | 20 (35.6)               | 28 (60.9)                  | 0.589 | —                                      | — |
| Age ≥ 40 y                       | 32 (67.1)               | 33 (71.7)                  | 0.187 | —                                      | — |
| Disease duration ≥ 5 y           | 38 (67.8)               | 35 (76.1)                  | 0.486 | —                                      | — |
| BMI ≥ 25 kg/m²                   | 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                        | 2 (1.9)                 |                            |     |                                        |    |
| Distal colitis                   | 36 (63.6)               |                            |     |                                        |    |
| pancolitis                       | 69 (46.3)               |                            |     |                                        |    |
| Median (95% CI) Mayo partial score at entry | 2 (2–3)               |                            |     |                                        |    |
| Median (95% CI) Mayo endoscopy subscore at entry | 7 (6–7)               |                            |     |                                        |    |
| 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) |                            |     |                                        |    |

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

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Odd radio (95% CI) logistic regression: 2.286 (0.941–5.553) 0.068

Chi-square test with 2 degrees of freedom was used for disease extension comparison.
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
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%, 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. This result is not easy to explain,

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**Figure 2.** Median C-reactive protein (A) and fecal calprotectin (B) values during follow-up. Error bars represent 95% confidence interval. Friedman test.
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 after approval of ADA by the Italian regulatory authorities for real-life UC management, shows that ADA is effective and safe in

### Table 3

| 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/m² | 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 | 0.795 |

#### Predictors of clinical remission persistence during follow-up. Univariate analysis

| Hazard ratio | 95% CI | P |
|--------------|--------|---|
| Naive-anti-TNFα | —  | 0.577–1.935 | 0.846 |
| 200 mcg/g | 1.673  | 0.732–3.822 | 0.374 |
| Fecal calprotectin > 200 mcg/g | 0.773  | 0.422–1.417 | 0.883 |
| Mayo score at entry = 3 | 1.043  | 0.568–1.913 | 0.483 |
| Mayo partial score at entry > 7 | 0.819  | 0.446–1.505 | 0.752 |
| Pancolitis | 1.207  | 0.629–2.317 | 0.846 |
| C-reactive protein ≥ 10 mg/dL | 0.773  | 0.422–1.417 | 0.483 |

Author contributions

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