

# Effectiveness of adalimumab for ambulatory ulcerative colitis patients after failure of infliximab treatment: a first “real-life” experience in primary gastroenterology centers in Italy

Antonio Tursi<sup>a</sup>, Walter Elisei<sup>b</sup>, Marcello Picchio<sup>c</sup>, Antonio Penna<sup>d</sup>, Giacomo Forti<sup>e</sup>, Gian Marco Giorgetti<sup>f</sup>, Roberto Faggiani<sup>g</sup>, Costantino Zampaletta<sup>g</sup>, Giorgio Pelecca<sup>g</sup>, Giovanni Brandimarte<sup>h</sup>

ASL BAT, Andria; ASL Roma H, Albano Laziale; P. Colombo Hospital; Santa Maria Goretti Hospital; S. Eugenio Hospital; Belcolle Hospital; Cristo Re Hospital, Italy

## Abstract

**Background** Adalimumab (ADA) is the key treatment for ulcerative colitis (UC) unresponsive or intolerant to standard treatments. Our aim was to assess the efficacy and safety of ADA in treating ambulatory UC patients in primary gastroenterology centers.

**Methods** Fifteen patients (6 male, median age 29.9 years, range 22.8-39.9 years) were enrolled. All were previously treated with infliximab (IFX). Clinical activity and endoscopic severity were scored according to the Crohn's disease activity index (CDAI) score and Mayo subscore for endoscopy, respectively. Patients were clinically assessed at weeks 4, 8, and thereafter at weeks 16, 24, 32, 40, 48, and 54. Colonoscopy was performed before starting treatment, at weeks 24 and 54. The co-primary endpoints were clinical remission at 24 and 54 weeks. The secondary endpoints included: 1) sustained clinical remission; 2) steroid-sparing effect; 3) mucosal healing; 4) need for colectomy. Induction dose of ADA was 160 mg at week 0, and then 80 mg at week 2, while ADA maintenance treatment was 40 mg every two weeks.

**Results** Clinical remission was obtained in 11 (73.3%) and 15 (100%) patients at weeks 24 and 54 respectively. Ten patients (66.7%) were able to discontinue steroids and were under corticosteroid-free remission at week 54. No patients underwent to colectomy. Eight patients (53.33%) at week 24 and 9 patients (60%) at week 54 achieved complete mucosal healing (Mayo endoscopic score 0). Side effects were reported in 2 of 15 patients (13.3%); none of those patients stopped treatment.

**Conclusion** ADA seems to be effective and safe in UC outpatients affected by UC, and previously treated with IFX.

**Keywords** Adalimumab, clinical practice, clinical remission, mucosal healing, ulcerative colitis

*Ann Gastroenterol 2014; 27 (4): 369-373*

<sup>a</sup>Gastroenterology Service, ASL BAT, Andria, BT (Antonio Tursi);

<sup>b</sup>Division of Gastroenterology, ASL Roma H, Albano Laziale, Rome (Walter Elisei); <sup>c</sup>Division of Surgery, “P. Colombo” Hospital, Velletri, Rome (Marcello Picchio); <sup>d</sup>Division of Gastroenterology, “San Paolo” Hospital, Bari (Antonio Penna); <sup>e</sup>Digestive Endoscopy Unit, “Santa Maria Goretti” Hospital, Latina (Giacomo Forti); <sup>f</sup>Digestive Endoscopy and Nutrition Unit, “S. Eugenio” Hospital, Rome (Gian Marco Giorgetti); <sup>g</sup>Division of Gastroenterology, “Belcolle Hospital”, Viterbo (Roberto Faggiani, Costantino Zampaletta, Giorgio Pelecca); <sup>h</sup>Division of Gastroenterology, “Cristo Re” Hospital, Rome (Giovanni Brandimarte), Italy

Conflict of Interest: None

Correspondence to: Antonio Tursi, MD, 49 Via Torino, 76123 Andria (BT), Italy, Tel.: +39 0883 551094, Fax: +39 0883 1978210, e-mail: antotursi@tiscali.it

Received 16 June 2014; accepted 11 July 2014

## 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]. The introduction of infliximab (IFX), an anti-tumor necrosis factor (TNF)- $\alpha$  antibody, has greatly improved our treatment options in UC [2,3]. National and International Guidelines now recommend IFX as an effective and safe drug in inducing and maintaining remission in steroid-dependent or steroid-refractory UC, reducing complications significantly [2-6].

However, IFX is immunogenic and infusion reactions and loss of response related to antibodies to IFX may be a relevant

problem [7]. Adalimumab (ADA) is a fully human anti-TNF- $\alpha$  monoclonal antibody that does not share immunogenicity with IFX. ADA consists of human-derived heavy and light chain variable regions and a human IgG1 constant region: it binds specifically to TNF- $\alpha$  and blocks its interaction with the p55 and p75 cell surface TNF receptors [8]. ADA has been shown to be effective and safe for inducing and maintaining remission in patients with moderate to severe Crohn's disease (CD), either naïve to anti-TNF- $\alpha$  or with previous loss of response or intolerance to IFX [6,9-12]. Open-label and retrospective studies have shown that ADA can be an effective therapeutic option for inducing and maintaining remission in patients with active UC refractory or who are intolerant to standard therapy [13-19]. Two randomized controlled trials (RCTs) have shown that ADA is more effective than placebo for inducing and maintaining remission in patients with moderate-to-severe UC who did not have an adequate response to conventional therapy, including steroids and immunosuppressants [20,21]. However, the absolute benefit is not impressive and this has been a matter of some debate.

ADA reimbursement for UC has been recently approved in Italy too [22]. It has already been successfully used in referral centers, but no data are available from primary care gastroenterology centers. The present study reports data on the effectiveness and safety of ADA in the first cohort of UC patients treated in Italian primary care gastroenterology centers.

## Patients and methods

This study consisted of an uncontrolled, open-label retrospective case series of UC patients treated with ADA in different primary care gastroenterology centers.

Eligible patients included men and women at least 18 years of age with an established diagnosis of UC according to standard criteria [1]. All patients were classified according to the Crohn's disease activity index (CDAI) score [23] and had to have active disease, defined as a Mayo subscore for endoscopy  $\geq 2$  points [24], despite concomitant treatment. ADA induction and maintenance regimen, the need for dose escalation and timing of treatment discontinuation were left to the investigators' judgement, as well as concomitant medications including oral and topical aminosalicylates, steroids and immunosuppressants. A shared common database was used to collect demographic and clinical data.

Data collected at baseline were: gender, age at diagnosis, disease extension, disease duration, smoking habits, previous immunosuppressive and IFX therapies, concomitant medications at baseline, CRP levels, CDAI score and Mayo subscore for endoscopy. Patients were clinically assessed at weeks 4, 8 and thereafter at weeks 16, 24, 32, 40, 48, and 54. Colonoscopy was performed before starting treatment, at weeks 24 and 54.

The co-primary endpoints were clinical remission at 24 and 54 weeks. The secondary endpoints included: 1) sustained clinical remission; 2) steroid-sparing effect; 3) endoscopic

remission; 4) need for colectomy. Clinical remission was defined as CDAI score  $\leq 3$ ; sustained clinical remission was arbitrarily defined as clinical remission at week 24 maintained through week 54. Endoscopic remission was defined as a Mayo subscore for endoscopy  $\leq 1$ . A corticosteroid-sparing effect was defined as corticosteroid discontinuation without recurrence of symptoms, in patients receiving corticosteroids at baseline.

## Statistical analysis

Statistical analysis was performed using Fisher's exact test for categorical data and the Mann-Whitney test for continuous variables, and the level of significance was  $P=0.05$ . Statistical analyses were performed using MedCalc for Windows, version 7.3.0.1 (MedCalc Software, Mariakerke, Belgium).

## Results

From January 2013 to December 2013, 15 active UC patients (6 male), with a median age at diagnosis of 29.9 years (range 22.8-39.9) were enrolled. All patients were treated as outpatients in primary gastroenterology centers. Since ADA reimbursement for UC was approved only in April 2014 [22], ADA was administered in those patients for compassionate reasons.

Ten patients (66.7%) had pancolitis, and 5 (33.3%) had left-sided colitis. The median duration of disease was 7.8 years (range 4.5-18.2). Three patients were smokers. All were previously treated with IFX, and the median duration of IFX therapy was 19.2 months (range 2.7-28.0), with a median number of infusions per patient of 10.0 (range 3.7-14.3). The main reasons for IFX discontinuation were primary non-response in 5 patients (33.3%); loss of response (defined as symptoms or/and endoscopic picture despite an increase of IFX dosing 5 to 10 mg/Kg or a decrease in interval to 4 weeks) in 7 patients (46.66%); intolerance (namely hypersensitivity reactions) in 2 patients (13.3%); and infections plus loss of response in 1 patient (6.7%). The median time from the end of IFX to the start of ADA therapy was 4.15 months (range 2.0-10.1). All patients were previously treated with azathioprine.

At baseline, the median CDAI score was 8 (range 4-10), and the median Mayo endoscopic subscore was 2 (range 2-3). The median CRP serum level was 9.35 mg/L (range 3.85-23.7). Concomitant corticosteroid use at the beginning of ADA treatment was recorded in 9 patients (60%), and mesalazine in all patients. All patients received an induction dose of ADA 160 mg at week 0 and then 80 mg at week 2.

Patients who showed clinical benefit from the induction regimen received ADA maintenance treatment at dose of 40 mg every two weeks. The median duration of ADA therapy was 13 months (range 6-16). Only two patients (13.3%) had their ADA dose increased to a weekly dose after a median time of 8 months (range 4-11.5). The main baseline characteristics of the patients are summarized in Table 1.

Clinical remission, according to the above reported definition, was obtained in 11 (73.3%) and 15 (100%) patients

**Table 1** Characteristics of the study group (15 patients)

Male sex, percentage	15 (40)
Median (range) age at diagnosis, years	29 (28.8-39.9)
Median (range) disease duration prior to adalimumab infusion, years	7.8 (4.5-18.2)
Mesalazine users, percentage	15 (100)
Indications for therapy, percentage	
Primary non-response	5 (33.3)
Loss of response	7 (46.7)
Intolerance	2 (13.3)
Infections+loss of response	1 (6.7)
Extent of disease, percentage	
Left-sided colitis	5 (33.3)
Pancolitis	10 (66.7)
Current smokers	3 (20)

Values are expressed as number (percentage) of patients, unless otherwise specified

at weeks 24 and 54 respectively. Significantly, remission was achieved also in those patients who experienced previous IFX primary failure. Ten patients (66.7%) were able to discontinue steroids and were under corticosteroid-free remission at week 54. Two patients (13.3%) needed one oral course and three patients (20%) needed one topical course of beclomethasone dipropionate in order to maintain remission during follow up. No patients underwent colectomy.

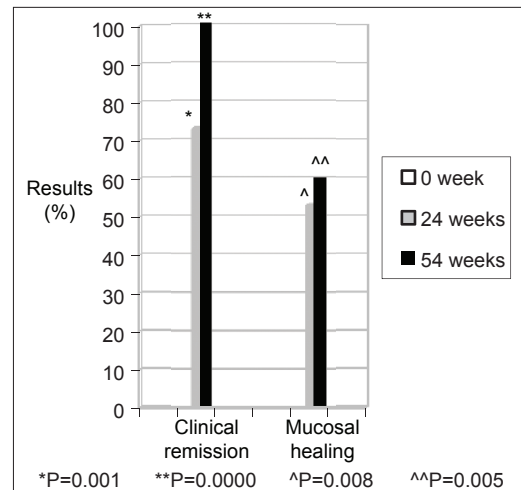
All patients completed colonoscopy at week 0, 24 and 54. Complete mucosal healing was achieved in eight patients (53.33%) at week 24 and nine patients (60%) at week 54 (Mayo endoscopic score=0). At week 54, six patients (40%) showed persistence of inflammation (four as Mayo 1 and two as Mayo 2). Results are summarized in Fig. 1.

Side effects, defined as loss of tolerance and/or alteration of laboratory data and/or occurrence of adverse event, were also assessed. Side effects were reported in 2 of 15 patients (13.3%): one developed community viral acquired pneumonia 6 days after ADA infusion, one developed skin reaction in the site of infusion controlled by antihistamines. None of those patients stopped treatment.

## Discussion

Although a larger case series of active UC treated with ADA in inflammatory bowel disease referral centers in Italy has been recently published [19], this observational study is to our knowledge the first study conducted in a series of active UC previously treated with IFX in primary gastroenterology centers in Italy.

Our results suggest that scheduled ADA is effective in UC populations already treated with IFX, even in primary gastroenterology care: almost all patients entered into clinical remission within three months, and the vast majority of them allowed steroid withdrawal and steroid-free remission within one year. This results seems to be better than those recently described by Armuzzi *et al* [19]. This study, conducted in referral



**Figure 1** Clinical remission and mucosa healing obtained during follow up

tertiary gastroenterology centers, found that approximately one third of patients entered into clinical remission within three months and this percentage increased to approximately 40% within one year. Moreover, steroid withdrawal was obtained in more than 50% of patients and induced steroid-free remission in 40% of them within one year [19].

Several other open-label or retrospective observational studies addressing the use of ADA in patients with UC have been published [13-18]. All these studies had a small sample size (13-50 patients) and the results are difficult to compare because of differences in patient populations, follow up, endpoints, and definitions of response/remission. In the short term (4-12 weeks), a response rate of 25-80% and a remission rate of 5-27% have been reported. In the long term (6-12 months), a response rate up to 50-70% has been reported [16-21]. The colectomy rate ranges across studies from 0% to 46% [16-21]. The comparison between our results and those of RCTs [20,21] deserves similar consideration. In the ULTRA 1 and ULTRA 2 trials, the percentages of patients achieving remission at 8 weeks were 18.5% and 16.5% respectively, and 29.5% and 30.9% at week 52 respectively [20,21]. These remission rates of short- and long-term remission were significantly lower than those observed in our study, and similar to those obtained by Armuzzi *et al* [19].

Apart from the different time point evaluations, differences can be explained by the different UC populations enrolled. Our population showed a median CDAI score 8, which describes a mild-to-moderate disease, while Armuzzi *et al* enrolled patients with severe disease [19]. It is therefore probable that the milder disease affecting our population, the cut-off for clinical remission of 3 instead of 2 and perhaps a geographical difference, such as those reported in the ULTRA-1 study [20], may explain our excellent results.

As far as mucosal healing is concerned, the retrospective design of the study did not allow firm conclusions to be reached. However, it is noteworthy that significant endoscopic improvement was obtained in almost all patients, and that complete mucosal healing (namely Mayo endoscopic score 0)

### Summary Box

#### What is already known:

- Resistance to standard treatment is the current indication to use anti-tumor necrosis factor- $\alpha$  monoclonal antibodies in ulcerative colitis (UC)
- Infliximab (IFX) and adalimumab (ADA) have been shown to be highly effective in those patients
- ADA has been shown to be highly effective in referral centers in Italy
- Effectiveness and safety of ADA in ambulatory UC managed in primary gastroenterology centers in Italy have not been showed yet

#### What the new findings are:

- ADA is able to obtain and maintain remission in UC ambulatory patients, even if already treated with IFX
- ADA is able to obtain and maintain mucosal healing in those patients
- No serious complication occurred during follow up using ADA

was obtained in more than 50% at week 24 and in 60% at week 54. Again, the milder endoscopic damage detected at entry (the median Mayo score at entry was 2) may explain our results.

A common findings in our and other experiences, RCTs included, is that both clinical and endoscopic response increase during the follow up under treatment with ADA. This suggests that the plateau of efficacy of ADA may have not yet been reached after 8 weeks; thus, longer exposure to ADA would probably be needed to observe a maximum response.

In conclusion, this first experience on a “real-life” cohort of ambulatory UC patients shows that ADA has been shown to be effective in patients already treated with IFX. Further, prospective studies are needed not only to confirm these results, but also to assess whether ADA may show the same effectiveness in UC anti-TNF- $\alpha$  naïve patients too.

### 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**:965-990.
2. Dignass A, Lindsay JO, Sturm A, et al. 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. Lichtenstein GR, Abreu MT, Cohen R, Tremaine W; American Gastroenterological Association. American Gastroenterological Association Institute technical review on corticosteroids, immunomodulators, and infliximab in inflammatory bowel disease. *Gastroenterology* 2006;**130**:940-987.
4. Travis S, Van Assche G, Dignass A, Cabré E, Gassull MA. On the second ECCO Consensus on Crohn's disease. *J Crohns Colitis* 2010;**4**:1-6.
5. D'Haens GR, Panaccione R, Higgins PD, et al. The London Position Statement of the World Congress of Gastroenterology on Biological Therapy for IBD with the European Crohn's and Colitis Organization: when to start, when to stop, which drug to choose, and how to predict response? *Am J Gastroenterol* 2011;**106**:199-212.
6. Orlando A, Armuzzi A, Papi C, et al. Italian Society of Gastroenterology; Italian Group for the study of Inflammatory Bowel Disease. The Italian Society of Gastroenterology (SIGE) and the Italian Group for the study of Inflammatory Bowel Disease (IG-IBD) Clinical Practice Guidelines: The use of tumor necrosis factor- $\alpha$  antagonist therapy in inflammatory bowel disease. *Dig Liver Dis* 2011;**43**:1-20.
7. Hanauer SB, Wagner CL, Bala M, et al. Incidence and importance of antibody responses to infliximab after maintenance or episodic treatment in Crohn's disease. *Clin Gastroenterol Hepatol* 2004;**2**:542-553.
8. HUMIRA® Product Monograph. Abbott.
9. Hanauer SB, Sandborn WJ, Rutgeerts P, et al. Human anti-tumor necrosis factor monoclonal antibody (adalimumab) in Crohn's disease: the CLASSIC-I trial. *Gastroenterology* 2006;**130**:323-333.
10. Colombel JF, Sandborn WJ, Rutgeerts P, et al. Adalimumab for maintenance of clinical response and remission in patients with Crohn's disease: the CHARM trial. *Gastroenterology* 2007;**132**:52-65.
11. Sandborn WJ, Rutgeerts P, Enns R, et al. Adalimumab induction therapy for Crohn disease previously treated with infliximab: a randomized trial. *Ann Int Med* 2007;**146**:829-838.
12. Panaccione R, Colombel JF, Sandborn WJ, et al. Adalimumab sustains clinical remission and overall clinical benefit after 2 years of therapy for Crohn's disease. *Aliment Pharmacol Ther* 2010;**31**:1296-1309.
13. Oussalah A, Laclotte C, Chevaux JB, et al. Long-term outcome of adalimumab therapy for ulcerative colitis with intolerance or lost response to infliximab: a single-centre experience. *Aliment Pharmacol Ther* 2008;**28**:966-972.
14. Afif W, Leighton JA, Hanauer SB, et al. Open-label study of adalimumab in patients with ulcerative colitis including those with prior loss of response or intolerance to infliximab. *Inflamm Bowel Dis* 2009;**15**:1302-1307.
15. Gies N, Kroeker KI, Wong K, et al. Treatment of ulcerative colitis with adalimumab or infliximab: long-term follow-up of a single-centre cohort. *Aliment Pharmacol Ther* 2010;**32**:522-528.
16. Taxonera C, Estellés J, Blanco I, et al. Adalimumab induction and maintenance therapy for patients with ulcerative colitis previously treated with infliximab. *Aliment Pharmacol Ther* 2011;**33**:340-348.
17. Ferrante M, Karmiris K, Compennolle G, et al. Efficacy of adalimumab in patients with ulcerative colitis: restoration of serum levels after dose escalation results in a better long-term outcome. *Gut* 2011;**60**(Suppl 3):A72.
18. McDermott E, Murphy S, Keegan D, et al. Efficacy of adalimumab as a long term maintenance therapy in ulcerative colitis. *J Crohns Colitis* 2013;**7**:150-153.
19. Armuzzi A, Biancone L, Daperno M, et al. Adalimumab in active ulcerative colitis: a “real-life” observational study. *Dig Liver Dis* 2013;**45**:738-743.
20. 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**:780-787.
21. 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**:257-265.
  22. Regime di rimborsabilità e prezzo a seguito di nuove indicazione terapeutiche del medicinale per uso umano Humira (adalimumab). *Gazzetta Ufficiale della Repubblica Italiana* 2014;**98**:12-13.
  23. Sutherland LR, Martin F, Greer S, et al. 5-aminosalicylic acid enema in the treatment of distal ulcerative colitis, proctosigmoiditis, and proctitis. *Gastroenterology* 1987;**92**:1894-1898.
  24. Schroeder KW, Tremaine WJ, Ilstrup DM. Coated oral 5-aminosalicylic acid therapy for mildly to moderately active ulcerative colitis. A randomized study. *N Engl J Med* 1987;**317**:1625-1629.