Adalimumab for ulcerative colitis: results of a Brazilian multicenter observational study

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Introduction

Ulcerative colitis (UC) is an inflammatory disease of the large bowel with variable degree of activity, extent and disease course1,2,9,10,18,28,29. Up to 15% of patients can present with severe disease at diagnosis9,30 and in up to 28% it can progress proximally in 10 years16,30. Most patients have a recurrent and remitting disease course with periodic flares, in which intravenous corticosteroids and eventually colectomy can be necessary3,6. Treatment with tumor necrosis factor (TNF) inhibitor agents can be used in moderate-to-severe UC, refractory to conventional treatment with aminosalicylates and immunomodulators and/or in steroid-dependent patients6,17. The most commonly used anti-TNF agents are infliximab (IFX) and adalimumab (ADA). IFX, a chimeric monoclonal antibody, has proven efficacy in UC in pivotal trials ACT 1 and 2, in induction and maintenance of remission in moderate-to-severe UC, as well as reducing the need for colectomy21,22,26. As all biological agents, IFX can be immunogenic, thus infusion reactions and secondary loss of response, related to antibodies to the drug may be a relevant problem15. ADA is a fully human monoclonal antibody and recombinant immunoglobulin G1 (IgG1)25. This drug was approved by regulatory agencies after proven efficacy in ULTRA I and II trials19,26,27,29,30.

The rate of colectomy in ULTRA II trial was less than 5%, without stratification regarding the previous use of another anti-TNF agent4. The drug was approved by Food and Drug Administration (FDA) and National Sanitary Surveillance Agency (ANVISA), in 2012 and 2014, respectively14.

Despite the results of the clinical trials, there is a discrepancy between those and real world data in UC25, similar to what was observed in terms of efficacy of ADA in Crohn’s disease (CD)13. Retrospective studies of case series tend to have higher effectiveness rates than randomized trials, which have a more strict analysis. Furthermore, it is enquired what the ideal dose of ADA in the management of UC would be needed12, showing the need of data from real life studies to better define the drug’s role in treatment algorithms. There is scarce real world data on the use of ADA in UC reported in Brazil and Latin America, which motivated the present study4,2,9,10,18,28,29.

The primary aim of this study was to analyze clinical remission rates in ADA induction and maintenance in UC treatment. Secondary objectives were to analyze clinical response, endoscopic remission, colectomy rates, adverse events, and secondary loss of response, besides dose optimization or drug switching during the follow-up period.

ABSTRACT – Background – Adalimumab is a monoclonal antibody, tumor necrosis factor-alpha (TNFα) inhibitor that has efficacy for inducing and maintaining remission in moderate-to-severe ulcerative colitis. Real world studies with adalimumab in Latin American ulcerative colitis patients are scarce. Objective – To assess the clinical remission rates in induction and maintenance with adalimumab therapy in ulcerative colitis. Methods – Observational, multicenter and retrospective study on a case series of patients with moderate-to-severe ulcerative colitis under adalimumab therapy. The variables analyzed were: demographic data, previous infliximab status, concomitant drugs, the Montreal Classification, disease activity (Mayo score) at weeks 0, 8, 26 and 52, or until the last follow-up. Clinical remission was defined as a partial Mayo score ≤2 and Last observation carried forward (LOCF) and Non responder imputation (NRI) analysis were used. Results – Thirty-six patients were included in the study. With LOCF analysis, remission rates at weeks 8, 26 and 52 were of 41.7%, 47.2% and 47.2%, respectively. With NRI analysis, remission rates at weeks 8, 26 and 52 were of 41.7%, 41.7% and 27.8%, respectively. Conclusion – Adalimumab was effective in the treatment of moderate-to-severe ulcerative colitis. Clinical remission was observed in approximately 40% of the patients at weeks 8 and 26, and in almost a quarter of the patients after 1 year of follow up.

HEADINGS – Proctocolitis. Ulcerative colitis. Adalimumab. Inflammatory bowel diseases.

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METHODS

Study design

This was a longitudinal, analytical, observational and retrospective study of a case series of patients with moderate-to-severe UC under ADA therapy. All patients were treated in seven referral centers for inflammatory bowel disease (IBD) from south/southeast Brazil, and were analyzed from August 2014 to October 2016.

Inclusion and exclusion criteria

The inclusion criteria were: patients with moderate-to-severe UC (Mayo score >6) that used subcutaneous ADA in regular doses (160 mg at week 0 and 80 mg at week 2 as induction, followed by 40 mg every 2 weeks for maintenance therapy, with dose optimization to weekly after induction, if necessary according to physicians’ individual perception). All individuals included were treated as outpatients, were between 18 and 80 years of age, and were refractory to conventional therapy. The exclusion criteria were: patients with undetermined inflammatory bowel disease (UIBD) or with diagnosis of Crohn’s disease (CD), besides patients with severe UC admitted to the hospital. Patients under 18 and over 80 years old, patients who underwent colorectal surgery previously or those in use of other biologic agents were also excluded.

Variables analyzed

The variables analyzed were: gender, age at UC diagnosis, extent of disease according to the Montreal Classification(27), disease duration from diagnosis to the beginning of biological therapy, smoking status, use of corticosteroids at the beginning of ADA, concomitant use of immunomodulators and previous use of IFX. In addition, the degree of disease activity, as defined by the Mayo score, was evaluated at weeks 0, 8, 26 and 52, or until the latest follow-up visit. The Mayo score is a classification used to determine disease severity, as detailed in Figure 1(29). Mild disease is defined as Mayo score between 2 and 6, moderate-to-severe disease between 6 and 12 points. Mucosal healing was evaluated according to the endoscopic Mayo sub-score. The need for colectomy during follow-up, secondary loss of response (with dose optimization rates or drug switching for other biological agents) and presence and type of adverse events were also analyzed.

Definitions

Clinical remission was defined as a partial Mayo score ≤2. Clinical response was defined as a reduction of partial Mayo score by 2 or more points between the beginning of treatment and certain periods of follow-up. Endoscopic remission or mucosal healing was defined as Mayo endoscopic sub-score ≤1. Primary loss of response was defined as lack of clinical improvement after the induction period. Secondary loss of response was defined as the need for one of the following outcomes during treatment: colectomy, dose optimization for weekly ADA or drug switching.

Statistical methods

A shared database was used to collect demographic and clinical characteristics with the use of Excel spreadsheets, Microsoft Office software package, 2013. The results of the variables of the study were described with the mean, median, minimum, maximum value and standard deviation (quantitative variables) or as frequency and percentage (categorical variables). The Wilcoxon non-parametric test was used to compare the initial and last assessments of the Mayo endoscopic sub-score. The colectomy free time and the need for switch of medication were described with the use of Kaplan-Meier curves. The clinical remission and clinical response rates were analyzed with the NRI (non-responder imputation) and LOCF methods (last observation carried forward). In the NRI method, patients with a shorter follow-up time were considered to be failures in the later periods of analysis. On the other hand, in the LOCF evaluation, the lastly evaluated information was carried forward, and it served as a value for the subsequent periods. P values <0.05 were considered as statistical significant. Data were analyzed by using the SPSS Statistics v.20 software package.

Ethical considerations

This study was approved by the Research Ethics Committee of the Catholic University of Paraná (PUCPR) and the other institutions involved, with reference report number 009181/2016, via the Ministry of Health’s website Plataforma Brasil.

RESULTS

A total of 36 patients who used ADA for treatment of UC were included in this analysis. The baseline characteristics of all analyzed patients are described in detail in Table 1. As observed, the mean age at diagnosis was 40.7 years (17-77). The majority of patients had extensive colitis and long-term disease (average disease duration of 80 months). Approximately one third of the patients (n=14) had received IFX therapy previously. Of the total number of cases, 91.7% had used corticosteroids at the initiation of ADA therapy and two-thirds were using concomitant azathioprine (AZA) during ADA treatment. The mean baseline partial Mayo score was 6.6 (±2.2) and the mean endoscopic baseline sub-score was 2.5 (±0.7).

![FIGURE 1. Mayo scoring System for Assessment of UC Activity. *Each patient served as his or her own control to establish the degree of abnormality of the stool frequency. †The daily bleeding score represented the most severe bleeding of the day. ‡ The physician’s global assessment acknowledged the three other criteria, the patient’s daily record of abdominal discomfort and general sense of well-being, and other observations, such as physical findings and the patient’s performance status. Adapted from Schroeder et al.(29).]
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Primary outcome

Clinical remission (partial Mayo score ≤2) was observed in 41.7% of the cases at week 8 and in 47.2% at weeks 26 and 52, according to the LOCF analysis. In the NRI analysis, clinical remission was observed in 41.7% of the patients at weeks 8 and 26 and in 27.8% at week 52. These data are demonstrated in detail in Figure 2.

Secondary outcomes

- **Clinical response**
  
  More than half of the patients had clinical response (partial Mayo score drop ≥2 points) at week 8, after ADA induction treatment (55.6% by LOCF and NRI analyses). There was a gradual increase in the response rate at weeks 26 and 52 by LOCF and a decrease by the NRI methods. These data are illustrated in detail in Figure 3. At the end of the 52 weeks, 47.2% of the patients maintained clinical response, according to the NRI analysis.

- **Endoscopic remission**
  
  One third of the patients (12/36) had endoscopic remission, defined as Mayo endoscopic sub-score ≤1, in follow-up colonoscopy after the beginning of treatment. The mean time to perform the first colonoscopy was 8.4 months (±3.5). One of the patients in endoscopic remission had a flexible sigmoidoscopy after total colectomy with ileorectal anastomosis due to therapeutic failure.

- **Secondary loss of response**
  
  The secondary loss of response to ADA was observed in half of the patients (18/36) during follow-up (7/14 patients with previous use of IFX and 11/22 naïve patients). These patients required ADA dose optimization or drug switching. Optimization of ADA therapy for a weekly dosing was required in 8 patients among which three switched to other therapies later on. Thus, switching to another biological agent was observed in 11 cases and that usually took place in the first semester of treatment (Figure 4). Five of them switched to IFX, 4 to vedolizumab and 2 to etrolizumab.

### Table 1. Baseline characteristics of the 36 patients included in the analysis

| Characteristic                                      | Total (n = 36) |
|-----------------------------------------------------|----------------|
| Age at diagnosis (years ± SD)                       | 40.7 ± 16.6    |
| Disease duration at ADA therapy initiation (months; mean, min-max) | 80.3 (12-192) |
| Gender (n/%)                                        |                |
| Female                                              | 17 (47.2)      |
| Male                                                | 19 (52.8)      |
| Montreal (n/%)                                      |                |
| E1                                                  | 2 (5.6)        |
| E2                                                  | 7 (19.4)       |
| E3                                                  | 27 (75)        |
| Smoking (n/%)                                       |                |
| 2 (5.6)                                             |
| Steroids at initiation of ADA (n/%)                 | 33 (91.7)      |
| Concomitant azathioprine (n/%)                      | 24 (66.7)      |
| Previous IFX (n/%)                                  | 14 (38.9)      |
| Follow-up period with ADA (months; mean, min-max.)  | 12.6 (2-26)    |

SD: standard deviation; Min: minimum; Max: maximum; IFX: infliximab; ADA: adalimumab.
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**DISCUSSION**

This retrospective multicenter study described the efficacy and safety of ADA in patients with moderate-to-severe UC, refractory to conventional therapy, from seven referral centers in IBD from south/southeast Brazil. It is the first Latin American study to demonstrate the effectiveness and safety profile of ADA in UC to date. Most of the evaluated patients had long-term disease, extensive colitis and used corticosteroids in the initiation of ADA treatment. One-third of the patients had previously taken IFX. These characteristics emphasize a population of patients with extensive and refractory disease.

In this analysis, the clinical remission rates were 41.7% at week 8 (LOCF and NRI methods); and 47.2% (LOCF) and 27.8% (NRI) at week 52. The drop in the clinical remission rates with the NRI analysis was expected, as patients with a shorter follow-up were considered to be failures in the later periods of our study. This is a more conservative analysis, which tends to minimize the results. In pivotal trials, clinical remission rates were lower as compared to our results, 18.5% at week 8 (ULTRA I) and 16.5% and 17.3% at week 8 and 52, respectively (ULTRA II). This variation of 10 points between these studies and ours could be explained by the differences in clinical remission definition, which considered the cases with Mayo score ≤2 at the present study and was restricted to the cases with Mayo score ≤2 without any subscore >1, in the pivotal trials. Therefore, having a less strict definition of remission may have been the cause of the higher rate in the present study as compared to the randomized trials. Real-life studies often show better results than pivotal studies, as they tend not to be so strict as compared to prospective trials.

In a case series, Tursi et al. reported high rates of clinical remission in patients with moderate-to-severe UC, refractory to IFX. At week 52, all patients (15 cases) were in remission, unlike the rates described in the literature and in the present study. It was expected that clinical remission rates in this study could be lower as most of the sample comprised patients with previous IFX exposure and with extensive disease (pancolitis). However, the score used to define clinical remission in this Italian study was the Crohn’s disease activity index (CDAI). This made it difficult to compare it with the partial Mayo score that is used in most of the studies in UC. This was an important limitation of the study mentioned above.

A second Italian multicenter study with a larger sample of patients reported lower rates of clinical remission, lower than the rates at week 8 in our study, which was 41.7%. The induction dose in the Italian group was heterogeneous, 160/80 mg of ADA in 17 patients and 80/40 mg of ADA in 11 patients. That may have been the reason for lower remission rates in the short term. In this study, the long-term remission rate was 43.2% at week 52, which was similar to those 47.2% (LOCF) demonstrated in our study, at week 52. Similarly, patients included in this multicenter Italian study had extensive (pancolitis) and long disease duration. However, most of the patients (78.4%) had previous use of IFX, unlike our study, in which only 38.9% had previous exposure to this agent.

Regarding clinical response, our study reported a rate of 55.6% at week 8, similar to pivotal trials, 54.6% (ULTRA I) and 50.4% (ULTRA II). At week 52, clinical response was observed in 61.1% of the cases, with the LOCF method. On the other hand, with the NRI method, it decreased to 47.2%, a less expressive drop.

**Colectomy rates**

Six patients from the total sample underwent colectomy during follow-up due to therapeutic failure (16.7%). Half of the surgical patients had previously used IFX (3/6). Figure 5 demonstrates the analysis of colectomy rates according to the follow-up time (Kaplan-Meier curve). As seen, all patients had their surgical procedures during the first semester of treatment.

![Figure 5. Cumulative probability of colectomy-free time under adalimumab therapy.](image)

**Safety**

The main adverse events described in the study are detailed in Table 2. Most of the adverse events were related to infections. There was no mortality in the present study, and only one patient presented malignancy (a basal cell skin carcinoma), which was locally excised without significant clinical consequences.

**TABLE 2. Summary of adverse events during adalimumab treatment**

| Adverse events                  | Overall (n=36) |
|--------------------------------|---------------|
| Most common infections (n/%)    | 17 (47.2%)    |
| Urinary tract infection         | 6 (16.7%)     |
| Sinusitis                       | 5 (13.9%)     |
| Pneumonia                       | 4 (11.1%)     |
| Other infections (n/%)           | 5 (13.9%)     |
| Herpes zoster                   | 1 (2.8%)      |
| Perianal abscess                | 1 (2.8%)      |
| Gastroenteritis                 | 1 (2.8%)      |
| Tonsillitis                     | 1 (2.8%)      |
| Parotitis                       | 1 (2.8%)      |
| Local injection reaction (n/%)   | 2 (3.6%)      |
| Skin reaction (n/%)             | 3 (8.3%)      |
| Other (basal cell carcinoma)    | 1 (2.8%)      |
than the findings of ULTRA II (30.2%)\textsuperscript{25}. García et al., in a Spanish multicenter study, obtained higher rates of clinical response (70.8%), which may have been justified by the later assessment of induction, at week 12. However, the rate decreased to 35% (LOCF) at week 54, in disagreement with the findings of our study with the same method (61.1%) at week 52\textsuperscript{30}.

In an American study, Afif et al. demonstrated less than half of the clinical response rate found at our study, at week 8. This might be due to stricter definition of response, which included a decrease in rectal bleeding ≥1. Despite of this, the rate increased at week 24 (50%), similarly to the data from our analysis\textsuperscript{11}. An indirect comparison between the present study and the main real world studies from the international literature regarding clinical remission and response, as well as colectomy rates, is shown in detail in Table 3.

The endoscopic remission rate at the present study was 33.3%, with colonoscopy performed in the mean time of 8.4 months (week 33) after the initiation of ADA treatment, which was similar to the literature. In the ULTRA II study, the rates reported at week 8 were higher (41.1%), which decreased to 25%, at week 52\textsuperscript{30}. Afif et al. observed the highest endoscopic remission rates, 49.1% after an average of 44 weeks with use of ADA\textsuperscript{11}.

In our study, half of the patients lost clinical response during follow-up, with dose optimization to ADA weekly being required in eight cases. On the other hand, Bálint et al. observed lower loss of response rates, 9.1% at week 30\textsuperscript{18}. Among those who remained in response (34.1%), 8.3% lost response at week 52. The drug was optimized in 17.8% of the cases\textsuperscript{39}. In the Spanish study, dose optimization was observed in 37.5% of the cases, among which 14.3% did not respond even after ADA weekly intake\textsuperscript{9}.

From the patients included in our analysis, 16.6% (6/36) underwent colectomy during ADA treatment, similarly to the findings from a Canadian study, which observed colectomy rates in 12% of the cases\textsuperscript{38}. The small number of colectomies in ULTRA II trial did not allow adequate comparison to our data in terms of surgical outcomes\textsuperscript{25}. Colectomy rates were heterogeneous in the international literature (12 to 46.2%)\textsuperscript{23,25,10,28}. A French study revealed the highest colectomy rates (46.2%)\textsuperscript{39}. In this sample, most of the patients had extensive colitis and long-term disease, similarly to the findings of our study. However, the entire sample was composed of patients that had used IFX before\textsuperscript{30}. Therefore, higher colectomy rates may be explained by the fact that the sample was composed of refractory patients. Taxonera et al. reported lower colectomy rates (20%) in a study with similar baseline characteristics to the French study\textsuperscript{28}. This demonstrates the heterogeneity of findings in the literature.

In regards to the variables associated with an increase in colectomy rates, Armuzzi et al. observed that only the exposure to immunomodulators was a significant risk factor. The previous exposure to IFX also increased colectomy rates as compared to naive patients (29% vs 10.5%), although no significant statistical difference was demonstrated\textsuperscript{25}.

There are many adverse events related to anti-TNF agents, from mild to severe, and in certain cases the drug must be discontinued or switched. At the present study the overall adverse events rate was 67.9%, mainly due to infections. There was a predominance of respiratory infections in our sample of patients. Only one patient developed a non-melanoma skin cancer. None of these patients stopped treatment due to adverse events. In ULTRA I, II and III trials, the rate of serious adverse events remained constant at 19%, 12% and 17.7%, respectively\textsuperscript{5,19,25}. ADA therapy discontinuation occurred in only 10.7% in the ULTRA III trial\textsuperscript{18}. On the other hand, Afif et al. obtained the highest serious adverse events rates (30%), leading nine patients to stop ADA treatment (45%). However, there was no mortality and none of the adverse events was considered to be drug-related\textsuperscript{11}.

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TABLE 3. Indirect comparison of remission, response and colectomy rates between the main retrospective studies from different countries with the present sample of patients

| Author                  | Reference | Country | Patients with ADA (n) | Clinical remission (%) | Clinical response (%) | Colectomy (%) |
|-------------------------|-----------|---------|----------------------|------------------------|-----------------------|--------------|
|                         |           |         |                      | Short-term             | Long-term             |              |
|                         |           |         |                      | Short-term             | Long-term             |              |
| Afif et al.             | 1         | USA     | 20                   | 5% week 8              | 25% week 24           | 25% 50% 0%   |
| Armuzzi et al.          | 2         | Italy   | 88                   | 28.4% week 12*         | 43.2% week 54         | 49.3% week 52 33.3% week 52 5.4% 25% |
| Bálint et al.           | 3         | Hungary | 73                   | 26% week 12            | 58.3% week 52         | 70.8% week 54 35% week 54 22.9% |
| García-Bosch et al.     | 9         | Spain   | 48                   | 50% week 12            | 30% week 54           | 70.8% week 54 35% week 54 22.9% |
| Gies et al.             | 10        | Canada  | 25                   | -                      | -                     | 80% week 14 70% week 54 12% |
| Oussalah et al.         | 19        | France  | 13                   | -                      | -                     | - 46.2% |
| Taxonera et al.         | 28        | Spain   | 30                   | 10% week 4             | 26.7% week 12         | 53.3% week 4 60% week 12 20% |
| Tursi et al.            | 29        | Italy   | 15                   | 73.3% week 24          | 100% week 54          | - - 0% |
| Present study           | -         | Brazil  | 36                   | 41.7% (LOCF and NRI)   | 47.2% (LOCF) and 27.8% (NRI) | 55.6% (LOCF and NRI) 61.1% (LOCF and NRI) 16.7% |

ADA: adalimumab; LOCF: last observation carried forward; NRI: non-responder imputation.

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This study had clear limitations that must be considered during the interpretation of its results. It was a retrospective study with limited number of cases, from IBD referral centers, with more severe and refractory patients. Moreover, many patients did not complete the 52-week period needed for a full evaluation. In these cases, the use of the NRI and LOCF methods, may have contributed to the estimated results.

In summary, ADA demonstrated efficacy and safety in the treatment of moderate-to-severe UC. Clinical remission was observed in approximately 40% of the patients at week 8 and at week 26, and in nearly a quarter of the patients after one year of follow-up. Clinical response was observed in approximately 50% of the cases. One-third of the patients had reached endoscopic remission. There were significant rates of secondary loss of response to ADA, followed by dose optimization or drug switching. Colectomy was required in 16.6% of all patients. The safety profile observed was similar to that described in the literature. This was the first Latin American study performed on patients with ADA in UC.

**Authors’ contributions**

Kotze PG, Zacharias P and Facchin L designed the study. All authors except for Olandoski M did data collection and were involved in patient care. Olandoski M did the statistical analysis. Zacharias P and Kotze PG drafted the article and all authors gave final revision and permission for publication.

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