Original Article

Efficacy and Safety of Adalimumab in Ulcerative Colitis Refractory to Conventional Therapy in Routine Clinical Practice

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Abstract

Background and Aim: Adalimumab [ADA] was approved for the treatment of ulcerative colitis [UC] refractory to conventional therapy in 2012 in Europe. Due to the observed discrepancies between clinical trials and practice, data on the outcome of ADA therapy are really needed from the real life. The aim of this study was to estimate the short- and long-term efficacy and safety of ADA in UC patients from each Hungarian biological centre.

Patients and Methods: This prospective study consisted of UC patients treated with ADA in 10 Hungarian inflammatory bowel disease centres. The primary endpoints of the study were rates of continuous clinical response, remission, non-response and loss of response at Weeks 12, 30, and 52. The secondary endpoints included mucosal healing at Week 52 and the comparison of the efficacy of ADA between biological naive and infliximab [IFX]-treated groups. Colonoscopy was performed before starting the therapy and at Week 52.

Results: In all, 73 active UC patients were enrolled in the study: 67.1% of the patients received previous IFX therapy; 75.3% of the patients showed short-term clinical response at Week 12. The probability of maintaining ADA was 48.6% at Week 52 with a continuous clinical response in 92% of these remaining patients. Mucosal healing was achieved in 48.1% of the patients at Week 52. Escalation of ADA was performed in 17.6%, and minor side effects developed in 5.4% of the patients; 5.4% of the patients underwent colectomy during the 1-year treatment period.
Conclusion: UC is a progressive disease that may need early aggressive therapy to prevent structural and functional complications. The results of our study demonstrated the favourable efficacy of short- and long-term ADA treatment for patients with UC.

Key Words: Ulcerative colitis; adalimumab; continuous clinical response; mucosal healing

1. Introduction
Ulcerative colitis [UC] is a chronic autoimmune condition characterised by various disease courses. It seems that almost half of the patients have severe, chronic continuous or chronic intermittent disease type.¹ These patients are frequently faced with severe relapses which require corticosteroid therapy with the possibility of hospitalisation or even colectomy. The risk of serious complications can be decreased by using immunosuppressive and/or biological agents. Infliximab [IFX], a chimeric monoclonal anti-tumour necrosis factor [anti-TNF] antibody proved its efficacy for inducing and maintaining remission in moderate-to-severe UC in the ACT study² and was approved by the Europe, Middle East and Africa [EMEA], among others, for the treatment of UC in 1997. Despite the favourable results came from trials or clinical observations, considerable unmet needs remain in addition to the chimeric nature and route of administration related to IFX. Recently—after the significantly positive results observed in two clinical studies—the fully human IgG1 anti-TNF antibody, the subcutaneously administered adalimumab [ADA], also gained approval by the EMEA in 2012,¹⁴ 5 years later than in Crohn’s disease did. Because usually there is a discrepancy between clinical trials and practice,¹ and there is an expert opinion that the regular dose of ADA might have been underpowered in UC,² there is a great need of data from the approval of drug for treatment of moderate to severe UC, and to estimate the short- and long-term efficacy and safety of this biological drug.

2. Patients and Methods
This prospective study consisted of UC patients treated with ADA in 10 Hungarian tertiary gastroenterology and inflammatory bowel disease [IBD] centres between 2013 and 2014. Eligible patients included males and females with an established diagnosis of UC and with clinically and endoscopically active disease defined by Mayo Scoring System. A shared common database was used to collect demographic and clinical data. Medical records as to gender, disease extension, disease duration, ADA induction and maintenance regimen, the need for dose escalation or discontinuation of ADA, concomitant medications, previous IFX therapy, response to ADA therapy at Weeks 12, 30, and 52, C-reactive protein [CRP] levels, side effects, the need for colectomy, and the assessment of mucosal healing at Week 52 were collected.

The primary endpoints of the study were rates of clinical remission, response and non-response at Week 12, rates of continuous clinical response, remission and loss of efficacy at Weeks 30 and 52, and proportion of patients remaining on ADA therapy at the end of the first year. The secondary endpoints included mucosal healing at Week 52 and comparison of the efficacy of ADA between biological naive and IFX-treated groups. Patients were clinically assessed at Weeks 0, 12, 30, and 52. Colonoscopy was performed before starting the therapy and at Week 52. Only patients with Mayo endoscopic subscore of at least 2 were enrolled in the study. Clinical remission was defined as complete steroid withdrawal, and as a partial Mayo subscore [pMayo score] ≤ 2, with no individual subscores >1; response to ADA was specified as decreasing in pMayo by 3 or more points. Continuous clinical response was defined as a maintained response through Week 52 without intermediate relapse. Mucosal healing was defined as Mayo endoscopic subscore ≥ Mayo[0]of 0 and 1.

Deep remission assessed at Week 52 was defined as clinical and endoscopic remission. Categorical data were analysed using Pearson’s chi-square test or Fisher’s exact test. The effects of drug therapy on the CRP and pMayo were examined with repeated measures analysis of variance [ANOVA]. A statistical protocol analysis was performed to evaluate primary efficacy. Paired samples t-testing was used to evaluate the change in pMayo scores. Statistical tests were performed using R statistical software [R version 3.1.2]; values of p < 0.05 were considered significant.

Table 1. Demographic and clinical features of the patients enrolled in the study.

<table>
<thead>
<tr>
<th>Gender [male/female]</th>
<th>Number of patients [n=73]</th>
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<tr>
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<td>Mean age at the diagnosis [years]</td>
<td>30.8 [5–56]</td>
</tr>
<tr>
<td>Mean disease duration of adalimumab therapy [years]</td>
<td>10.8 [1–43]</td>
</tr>
</tbody>
</table>

Disease extent
- Proctitis: 13
- Left-sided colitis: 14
- Extent colitis: 46

Previous infliximab
- Previous infliximab: 49

Steroid-refractory UC
- Steroid dependency: 54

Concomitant medications
- 5-ASA: 59
- Corticosteroid: 24
- Azathioprine: 38

Dose intensification of adalimumab
- Dose intensification of adalimumab: 13

Side effect
- Side effect: 3

Colectomy
- Colectomy: 5

Mucosal healing at Week 52 [%]
- Mucosal healing at Week 52 [%]: 48.1

UC, ulcerative colitis; 5-ASA, 5-aminosalicylic acid.
At baseline, mean pMayo score was 7.1, mean Mayo endoscopic subscore was 2.7 and mean CRP was 15.7 mg/l. At Week 12, 24.7% of the patients did not respond to induction therapy. Clinical response and remission were achieved in 49.3% and 26% of the patients, respectively. At Week 30, loss of response occurred in further 9.1% of the patients. Clinical response and remission were achieved in 34.1% and 56.8% of the remaining patients, respectively. At Week 52, loss of response developed in 8.3% of the remaining patients, whereas clinical response and remission were achieved in 33.3% and 58.3% of the patients, respectively. Of the patients originally enrolled, 45.2% showed continuous clinical response at Week 52.

Rates of non-responders, responders, and patients with remission at Weeks 12, 30, and 52 are summarised in Figure 1. Figure 2 includes a Kaplan-Meier curve showing the relapse-free survival of patients treated with ADA; pMayo and CRP levels decreased significantly at Week 12 \( p < 0.001, p < 0.001 \), Week 30 \( p < 0.001, p < 0.001 \), and Week 52 \( p < 0.001, p = 0.03 \) compared with the beginning of ADA therapy. However, no further significant improvement was statistically seen in the clinical activity and CRP levels at Week 30 or Week 52 compared with Week 12. Changes in pMayo scores and CRP levels during the treatment period are presented in Figure 3. Dose escalation with the increase of ADA dose to weekly administration was needed in 13 \( 17.8\% \) patients. ADA was stopped in 20 patients before the end of the first year \( 47.5\% \) primary non-response, 17.5% loss of response, 7.5% intolerance, 35% non-compliance, and others. Minor side effects developed in three patients [skin rash in two patients, fatigue and myalgia in one patient] during the whole therapy. No serious infection, tuberculosis [TB] or malignancy occurred during the treatment period. Colectomy was required in five \( 5.4\% \) patients during the 1-year treatment period.

Previous IFX therapy did not influence disease outcome, the need of dose intensification, or the frequencies of side effects in patients

![Figure 1](http://ecco-jcc.oxfordjournals.org/)

**Figure 1.** Rates of non-responders, responders and patients with remission at Weeks 12, 30, and 52.

![Figure 2](http://ecco-jcc.oxfordjournals.org/)

**Figure 2.** Kaplan-Meier curve showing a relapse-free survival of patients treated with ADA [adalimumab].
rates of remission, response, and mucosal healing compared with 80/40
apy at 160/80

mens of ADA, clinical response was seen at Week 52 in 30.2% and chronic active UC treated with induction and maintenance regi-

of patients on placebo. In the ULTRA 2 trial, of 494 patients with
maintenance treatment in UC patients refractory to corticosteroid
were approved for the treatment of active, refractory UC in 2012

duced clinical response at Week 12 and half of these patients
ience developed in 4.1% of the patients. Of all the patients, 5.4%
developed during the 1-year treatment period.

The subcutaneously administered fully human anti TNF-α ADA
was approved for the treatment of active, refractory UC in 2012
in Europe. ULTRA 1 and 2 were the first randomised controlled clinical trials that confirmed the efficacy of ADA in UC after the previous beneficial results in Crohn's disease. In the ULTRA 1 trial, 16.9% of patients achieved steroid-free remission at 8 weeks with ADA 160mg/80mg/40mg every other week, compared with 9% of patients on placebo. In the ULTRA 2 trial, of 494 patients with chronic active UC treated with induction and maintenance regi-

men of ADA, clinical response was seen at Week 52 in 30.2% and 18.3% of patients in the treatment and placebo arms, respectively. However, response rates for anti-TNF agents in real-life clinical practice are less well defined. Despite the time elapsed from the authorisation of ADA therapy in UC, only limited data have become available from everyday practice that might resolve the apparent discrep-

ancies between clinical trials and practice.

A 52-week, randomised, placebo-controlled, double-blind Japanese study evaluated the efficacy of ADA for induction and remission at Week 12 was achieved in 60% and 27% of the patients who were switched to ADA. ADA dose escalation was needed in 23% and colectomy was required in 20% of the patients in the study of Taxonera et al.

None of these patients undergoing colectomy showed clinical response to ADA at Week 12 and half of these patients needed colectomy within the first 12 weeks. In the study of Armuzzi et al., ADA dose escalation was necessary in 35.2% of the patients and 25% underwent colectomy because of primary failure or second-

ary loss of response to ADA therapy after a median of 5.5 months. Both studies revealed higher rates of dose escalation and colectomy than in our patient cohort, which may be explained by the more common use of concomitant immunosuppression at inclusion in our patients.
Similarly to our results, rates of clinical response, remission, and mucosal healing in ADA-treated patients who had lost response or developed intolerance to IFX were similar in IFX-naive and previously exposed patients in the study of Afif et al. Not only the fact of previous IFX therapy, but also the response to that, may be important to predict the outcome of ADA therapy. The study of Garcia-Bosch et al. revealed that response to prior treatment with IFX was the only predictive factor of response to ADA at Week 12.15

The main limitation of our study is that immunogenicity, ie occurrence of anti-ADA antibodies, was not evaluated. However, in clinical practice it is uncommon to determine serum trough levels and antibody formations at every visit, mainly due to financial reasons. The majority of the clinical studies from real life did not investigate the efficacy of ADA on mucosal inflammation, although endoscopy is the most objective measure of efficacy. Mucosal healing was achieved in 43% of the patients in the ULTRA 2 trial, 49% in the study of Armuzzi et al., and 48% of our cohort—showing highly identical results.

UC is still a progressive disease that may need an early aggressive therapy to prevent the structural and functional complications. Anti-TNF therapies are useful to achieve these goals. The results of our study and those detailed above demonstrated the favourable efficacy of short- and long-term ADA treatment for patients with UC. Our results revealed that patients responded well to long-term therapy, with stable remission and mucosal healing rates.

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Conflict of Interest
None.

Author Contributions
Study design, supervision of patient selection, data collection, and manuscript preparation: AB, K, TM; statistical analysis, figures, and manuscript preparation: MS, AB, KA, TM; patient selection, data collection, and patient follow-up: AB, KA, KA, LL, PM, I, H, ÁV, GH, AS, FN, ZS, ZG, FZ, ÁZ, J, ÁC, RB, ÁMMR, TM; supervision of the patient selection and manuscript preparation: TM. AB and KA are joint first authors.

References