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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 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 study[2] 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,[3,4] 5 years later than in Crohn's disease did. Because usually there is a discrepancy between clinical trials and practice,[5] and there is an expert opinion that the regular dose of ADA might have been underpowered in UC,[6] there is a great need of data from real life. Although more than 2 years have gone by since the licensing, few real clinical experiences have been published to date[7,8,9,10,11,12,13] and some of them are retrospective analysis with relatively low numbers of patients. Therefore our goal was to prospectively collect data of every ADA-treated UC patient from each Hungarian biological centre after 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 [eMayo]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 per-protocol analysis was performed to evaluate primary efficacy. Paired samples t-testing was used to evaluate the change in eMayo scores. Statistical tests were performed using R statistical software [R version 3.1.2]; values of $p < 0.05$ were considered significant.

3. Results

A total of 73 active UC patients with a mean age at diagnosis of 30.8 years [range: 5–56 years] were prospectively enrolled in this multicentre study; 49 patients [67.1%] had received previous IFX therapy. The main reasons for IFX discontinuation and switch to ADA were: primary non-response in 10 patients [20.4%]; loss of response in 18 patients [36.7%]; acute or delayed infusion reaction in 18 patients [36.7%]; and other reasons in 3 patients [6.1%]. Of the total, 32.9% were on steroids and 52% on immunosuppressants at inclusion. The patients' demographic and clinical data are summarised in Table 1; 95.9% of patients received an induction dose of ADA 160 mg at Week 0 and then 80 mg at Week 2, and 3 did not.

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

Gender [male/female]	Number of patients [n=73]
	40/33
Mean age at the diagnosis [years]	30.8 [5–56]
Mean disease duration of adalimumab therapy [years]	10.8 [1–43]
Disease extent	
-Proctitis	13
-Left-sided colitis	14
-Extent colitis	46
Previous infliximab	49
Steroid-refractory UC	15
Steroid dependency	54
Concomitant medications	
-5-ASA	59
-Corticosteroid	24
-Azathioprine	38
Dose intensification of adalimumab	13
Side effect	3
Colectomy	5
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 15.7mg/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
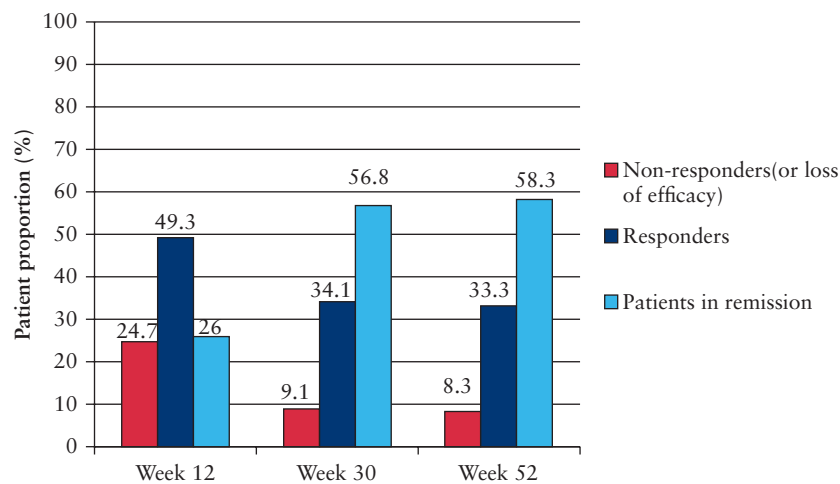

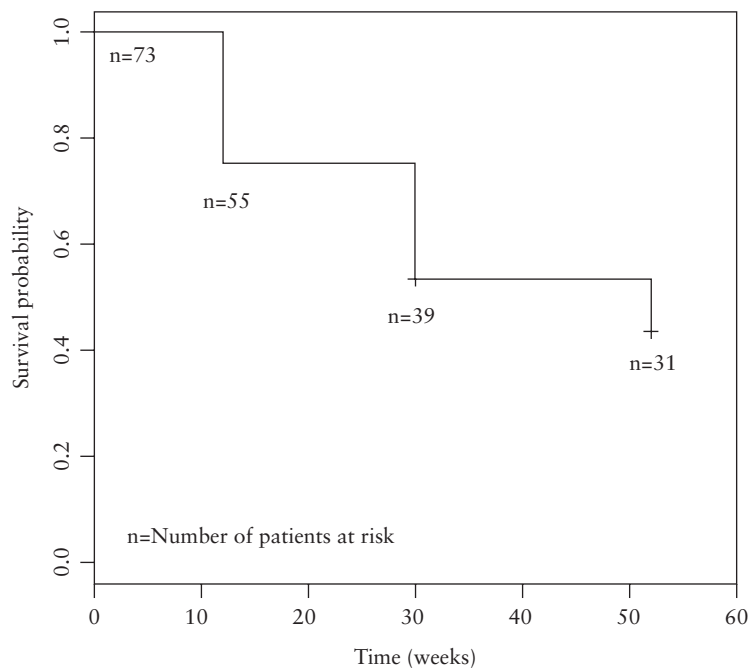**Figure 1.** Rates of non-responders, responders and patients with remission at Weeks 12, 30, and 52.

Figure 2. Kaplan-Meier curve showing a relapse-free survival of patients treated with ADA [adalimumab].
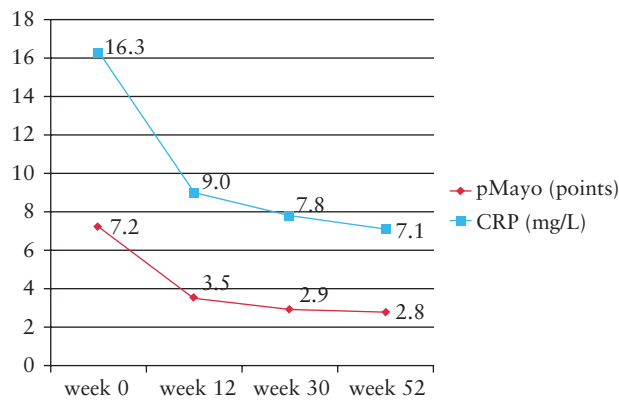
Figure 3. Changes in partial Mayo [pMayo] subscores and C-reactive protein [CRP] levels at Weeks 12, 30, and 52.

receiving ADA and 48.1% of the patients achieved mucosal healing at Week 52. Mean value of endoscopic Mayo subscore decreased significantly at Week 52 [*p* < 0.001]. Deep remission was shown in 55.6% of the patients at Week 52.

4. Discussion

This prospective multicentre study describes the efficacy and safety of ADA therapy in patients with active UC refractory to conventional medications, from real-life clinical practice with the collaboration of all IBD centres in Hungary. Two-thirds of the enrolled patients received IFX previously—the main indication of ADA therapy in these patients was loss of response—and 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 shown to have been achieved in almost 50% of the patients at Week 52. Escalation of ADA was performed in 17.8%, and minor side effects developed in 4.1% of the patients. Of all the patients, 5.4% underwent colectomy 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 ,160 mg/80 mg/40 mg 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 regimens of ADA, clinical response was seen at Week 52 in 30.2% and 18.3% of patients in the treatment and placebo arms, respectively.[3,4] 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 discrepancies between clinical trials and practice.

A 52-week, randomised, placebo-controlled, double-blind Japanese study evaluated the efficacy of ADA for induction and maintenance treatment in UC patients refractory to corticosteroid and/or immunomodulator therapy.[9] At Week 8, ADA induction therapy at 160/80 mg was superior to placebo in achievement of early response and mucosal healing compared with an induction dose of 80/40 mg. At Week 52, ADA 40 mg had achieved significantly higher rates of remission, response, and mucosal healing compared with

placebo. In this study, clinical remission [23%] and response [31%] rates after 52 weeks of ADA therapy were similar to those observed in large, pivotal clinical trials.

Gies *et al*. examined the response rates and long-term outcomes of IFX and ADA treatment among 53 outpatients with UC during a median follow-up time of 1.3 years.[10] According to their results, ADA proved to be as effective as IFX in real-life out patient treatment. Induction response rates also proved to be higher for ADA [80%] compared with the ULTRA trials.[3,4] This was probably due to the physician's global response assessment used for the evaluation of clinical response rather than the use of a defined full Mayo score and because response was assessed at Week 14 of induction therapy rather than at Week 8, as used in the clinical trials. In a study by Tursi *et al*.[11] clinical remission was obtained in 73.3% and 100% of UC outpatients on ADA therapy previously treated with IFX at Weeks 24 and 54, respectively. Our results also confirm a moderately higher efficacy of ADA both short termand long term than was seen in the large clinical trials. More than one-third of our patients showed clinical response at Week 12 and 45% at Week 52 and more than 90% of the patients who did not lose response atWweek 52 showed continuous clinical response at the end of the 1-year treatment period. Notably, no further significant improvement was statistically seen in the clinical activity at Week 30 or Week 52 compared with Week 12, which may be related to a rapid response to the ADA induction doses. Armuzzi *et al*. reported data on the effectiveness of ADA in UC patients treated in 22 Italian centres. Clinical remission rates proved to be 28.4%, 36.4%, and 43.2% at 12, 24 and 54 weeks, respectively ,showing lower rates than in our study. However, 49.1% of the patients who underwent colonoscopy after a median time of 11 months achieved endoscopic remission and among them 26.3% achieved complete mucosal healing, and this was nearly similar to our results.[14]

Although the development of antibodies to the drug can not be totally avoided, ADA is thought to be less immunogenic than IFX because of its fully human structure. Therefore, studies examining the efficacy of ADA in patients who previously responded to IFX and then lost response or became intolerant have high importance. The study of Taxonera *et al*.[12] was one of the first that evaluated the outcomes of ADA in UC patients previously treated with IFX. Clinical response and remission at Week 12 was achieved in 60% and 27% of the patients who were treated with ADA after failure of IFX, respectively. All patients who achieved clinical response at Week 12 were colectomy free in the long term. In our cohort, more than two-thirds of the patients were switched from IFX to ADA mainly because loss of response. Loss of response or intolerance to IFX is highly a significant problem in patients with UC. Our results, in accordance with those of Taxonera *et al*., confirm that patients with UC who lost response to or became intolerant of IFX may benefit from switching to ADA. In our cohort, 42% of the patients treated with previous IFX showed continuous clinical response after switching to ADA. It is also important to mention that previous IFX therapy did not influence disease activity, the need of dose intensification, or the frequencies of side effects in our 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*.[12] 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*,[14] ADA dose escalation was necessary in 35.2% of the patients and 25% underwent colectomy because of primary failure or secondary 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*.[8]. 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.[13]

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.

Funding

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, KF, TM; patient selection, data collection, and patient follow-up: AB, KF, KP, 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 KF are joint first authors.

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