Original Article

Comparison of long-term outcomes of infliximab and adalimumab therapy in biologic-naive patients with ulcerative colitis

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Abstract

Background: To compare the long-term safety and efficacy of Adalimumab (ADA) and Infliximab (IFX) agents in biologic-naive patients with Ulcerative colitis (UC).

Methods: The key focus was on specific outcomes such as the requirement of hospitalization due to UC, colectomy, steroid administration, and severe infections that led to the discontinuation of therapy.

Results: Anti-TNF treatment was initiated in 208 of the 475 patients with ulcerative colitis. The final study population consisted of 86 biologic-naive patients with UC, including 41 treated with IFX and 45 treated with ADA. No significant differences in treatment details, baseline Mayo scores, risk factors, or demographic features were observed. The ADA group displayed a significantly increased need for steroids (44.4%) compared to the IFX group (14.6%). The UC-associated hospitalization, colectomy, and serious infections were similar between the ADA and IFX groups. Similar outcomes were observed with IFX or ADA as monotherapy or in combination with immunomodulators. The survival analysis revealed IFX had a longer time to secondary loss of response compared to ADA, however, without statistical significance (72.5% versus 46.7%, $P = 0.057$).

Conclusion: Our results hint at the likelihood of IFX and ADA presenting similar clinical outcomes as first-time agents in UC. Nonetheless, the need for steroids with ADA should be taken into consideration.

Keywords: Adalimumab, colectomy, infliximab, ulcerative colitis

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INTRODUCTION

Persistent inflammation of the colon and rectum signifies the chronic condition known as ulcerative colitis (UC). Therapeutic agents like infliximab (IFX) and adalimumab (ADA) have shown significant efficacy by blocking tumor necrosis factor (TNF)-α receptors for moderate to severe UC.[1,2] Despite ADA not typically being applied for inducing remission in steroid-resistant acute severe UC patients, IFX is often used for this application.[3,4] Previous studies suggest that anti-TNF medications may enhance remission induction, and decrease the need for disease-related hospitalization, surgery, and steroid use in UC.[1,2,5,6] However, there are concerns about their potential adverse effects, such as serious opportunistic infections and malignancy.[7-9]

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A limited number of investigations have directly compared IFX and ADA in terms of their long-term safety and effectiveness among UC patients, who haven't previously received biological treatment, and the findings from these studies have been somewhat inconclusive.[10,11] This study aimed to assess the long-term efficacy and safety of IFX compared to ADA in biologic-naive patients with UC.

PATIENTS AND METHODS

Study population

This study was an observational retrospective research at a single-center high-level referral hospital. It involved adult participants suffering from moderate to severe UC who hadn't previously received biologic treatment and were administered either IFX or ADA. These patients were observed between June 2007 and February 2021. The severity of UC in these patients was determined via the total MAYO score and MAYO endoscopic scores.[12,13] The inclusion criteria for the study are outlined in Figure 1. Patients were excluded if they had drug intolerance, primary loss of response, underwent anti-TNF therapy for pouchitis or rheumatologic conditions, or could not complete 12 weeks of follow-up for any reason. Patients with acute severe colitis were not included in the study as only infliximab is recommended for acute severe UC. Patient-related data such as hemoglobin levels, C-reactive protein (CRP) levels, Mayo score at diagnosis, duration of UC and anti-TNF treatment, location of UC, presence of extra-intestinal symptoms, and prior and concurrent medications were sourced from medical records. Ethics committee approval was received from Ankara Bilkent City Hospital Ethics Committee No. 1 on 02.07.2020 with approval number E1-20-862.

Definitions and outcomes

UC was defined following the Montreal classification guidelines.[14] Patients were classified as receiving anti-TNF-based combination immunomodulatory therapy if they received at least one year of immunomodulatory therapy within 30 days before and/or six months after the initiation of anti-TNF treatment. Immunomodulatory therapy refers to either azathioprine or methotrexate. Azathiopurine 2-2.5 mg/kg/day and methotrexate were administered as 25 mg/week for the first 3 months, and then 15 mg/week subcutaneously for 9 months. Therapeutic options were made based on the European Crohn and Colitis Organization (ECCO) guidelines.[15,16] In

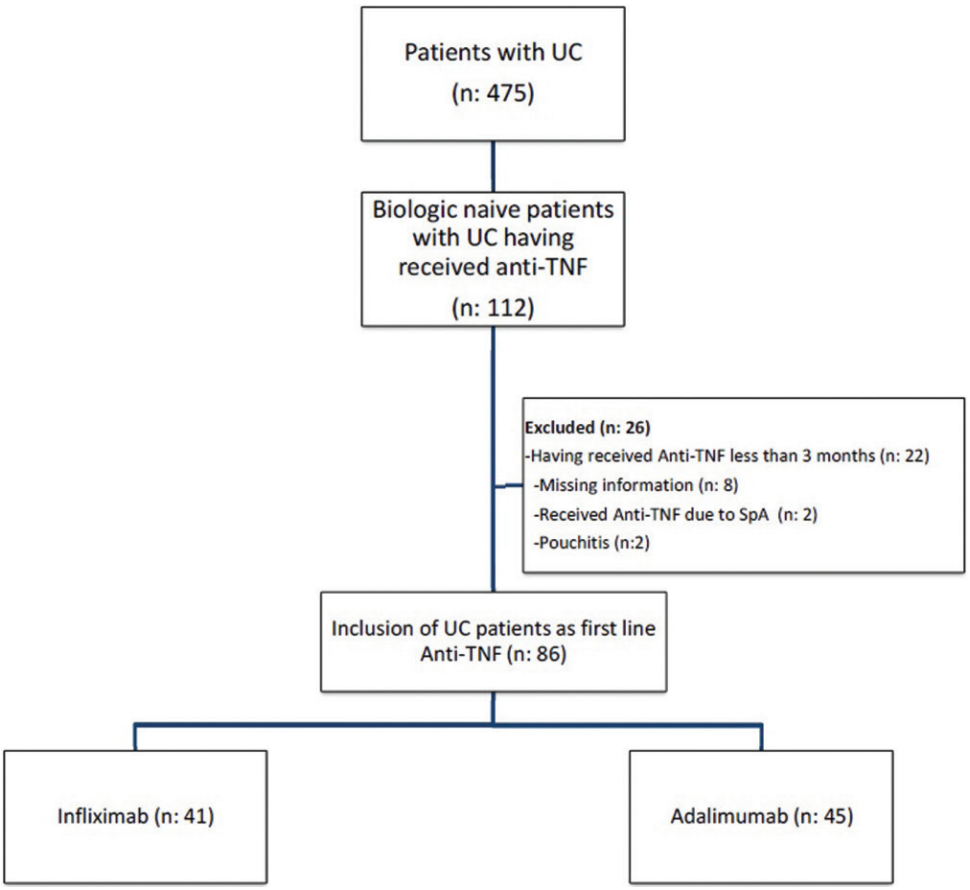

Figure 1: Inclusion criteria for the study

this study, long-term outcomes were evaluated in patients who were followed up for more than three months under first-line IFX or ADA therapy. The long-term treatment efficacy was evaluated through the need for steroids, UC-related hospitalization, and colectomy. The safety was evaluated through the occurrence of serious infections that led to treatment cessation or hospitalization.

Patient management

Our routine procedures dictated that patients under IFX maintenance therapy receive a dose of 5 mg/kg intravenously every eight weeks, while those under ADA maintenance therapy were given a dose of 40 mg subcutaneously every two weeks. In case of secondary loss of response under anti-TNF treatment, if the patient had a history of steroid resistance in previous treatment experience, steroids were not started, and anti-TNF dose escalation or switch to another anti-TNF or other biological treatment option were evaluated. If dose escalation was required, the IFX dose was escalated to once monthly and ADA was escalated once weekly. Treatment failure was classified as primary or secondary loss of response (LOR). Primary LOR was identified by the absence of improvement in clinical, endoscopic, and laboratory parameters within the first three months of treatment initiation. Secondary LOR, on the other hand, was characterized by initial improvement in these parameters followed by treatment failure after the third month. Secondary LOR was assessed based on the need for steroids, hospitalization, and colectomy. The long-term safety of these medications was assessed through the occurrence of serious opportunistic infections.

Statistical analysis

To ascertain the normality of the distribution of continuous variables in the study, the Kolmogorov-Smirnov test was used. Continuous variables were presented as median and interquartile range, while categorical variables' were depicted as frequency and percentage. The Mann-Whitney U test was used for continuous variables analysis and the Chi-Square test or Fisher's Exact test for categorical variables. Kaplan-Meier survival tables were created to evaluate the times until loss of response, and the log-rank test was employed to compare curves across groups. SPSS (version 25.0, IBM) was used, and a $P < 0.05$ was considered as statistically significanct.

RESULTS

During the study period, 475 patients with UC were followed over 7 years. Anti-TNF treatment with either IFX or ADA was initiated in 208 of these patients, 122 of whom were excluded from the study (75 due to biological experience, 35 due to primary loss of response or adverse events, 8 due to missing data, 2 due to spondyloarthritis, and 2 due to pouchitis) [Figure 2]. The final study population consisted of 86 biologic-naive patients with UC, including 41 treated with IFX and 45 treated with ADA. The median disease duration was 7.2 years (IQR: 8.0) for the IFX group and 8.1 years (IQR: 7.2) for the ADA group ($P = 0.16$). In IFX and ADA groups, active smoking was present in 12.2% and 11.1% ($P = 0.40$), family history of inflammatory bowel disease (IBD) was present in 17.1% and 11.1% ($P = 0.45$), and extra-intestinal manifestations were present in 48.8% and 53.3% of patients respectively ($P = 0.62$). The duration of TNF antagonist treatment was 4.9 years (IQR: 7.1) for the IFX group and 6.9 years (IQR: 7.9) for the ADA group ($P = 0.04$). Both groups had similar disease extent, steroid dependence, and previous medical therapy, including mesalazine, sulfapyridine, thiopurines, or steroids.

Prior experience with anti-TNF treatment and steroids was proportionately higher in the ADA group than in the IFX group (95.6% vs. 82.9%, respectively; $P = 0.06$), but there was no statistically significant difference between the two groups. Steroid-dependent patients had equal distributions across both groups. There were no significant differences in the proportion of steroid-dependent patients in the ADA and IFX groups (82.2% vs. 73.2% respectively, $P = 0.31$). A total of 71 patients (82.6%) had prior experience with at least one immunomodulator (thiopurine or methotrexate) before starting anti-TNF agents. The rates of combined therapy with thiopurines were closely matched in the IFX and ADA groups (36.6% vs. 35.6%, $P = 0.92$). At the study's outset, the IFX group had lower hemoglobin and albumin levels but higher C-reactive protein levels compared to the ADA group. However, the baseline Mayo score was similar across both groups ($P > 0.05$) [Table 1].

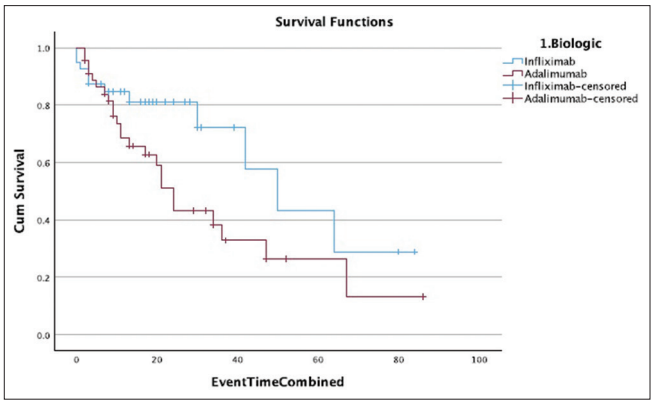

Figure 2: Duration of drug use based on overall outcomes in both groups

Table 1: Demographic characteristics, disease location, and behavior of patients with UC

	Total (*n*=86)	IFX group (*n*=41)	ADA group (*n*=45)	*P*
Age at onset of UC (years), Mean±SD	32.9±13.6	34.4±13.5	31.4±13.8	0.32
Disease duration (years), median (IQR)	7.7 (6.5)	7.2 (8.0)	8.1 (7.2)	0.16
Age at onset of TNF antagonist (years), Mean±SD	39.9±13.8	40.5±13.8	39.3±14.0	0.70
Duration of TNF antagonist (years), median (IQR)	5.7 (8.0)	4.9 (7.1)	6.9 (7.9)	0.04
Sex (male), *n* (%)	52 (60.5)	25 (61.0)	27 (60.0)	0.93
Smokers (Current/Ex)[1], *n* (%)	10 (11.6)/29 (33.7)	5 (12.2)/15 (36.6)	5 (11.1)/14 (31.1)	0.40
Family history of IBD[2], *n* (%)	12 (14.0)	7 (17.1)	5 (11.1)	0.45
Disease location, *n* (%)				0.23
Proctitis	1 (1.2)	0 (0.0)	1 (2.2)	
Left side	27 (31.4)	10 (24.4)	17 (37.8)	
Extensive	58 (67.4)	31 (75.6)	27 (60)	
Extra-intestinal manifestations[3], *n* (%)	44 (51.2)	20 (48.8)	24 (53.3)	0.62
Prior medical experience, *n* (%)				
Thiopurine	68 (79.1)	32 (78.0)	36 (80)	0.82
Methotrexate	3 (3.5)	2 (4.9)	1 (2.2)	0.60
Mesalazine	83 (96.5)	38 (92.7)	45 (100.0)	0.07
Sulphapyridine	9 (10.5)	4 (9.8)	5 (11.1)	0.56
Budesonide	2 (2.3)	1 (2.4)	1 (2.2)	0.73
Steroids	77 (89.5)	34 (82.9)	43 (95.6)	0.06
Steroid Resistance, *n* (%)	9 (10.5)	7 (17.1)	2 (4.4)	0.08
Steroid Dependence, *n* (%)	67 (77.9)	30 (73.2)	37 (82.2)	0.31
TNF antagonist outcomes, (long-term therapy effectiveness and safety)				
Steroid needed	26 (30.2)	6 (14.6)	20 (44.4)	0.003
UC-related hospitalization	10 (11.6)	4 (9.8)	6 (13.3)	0.74
Colectomy	3 (3.5)	2 (4.9)	1 (2.2)	0.60
Serious infection	3 (3.5)	1 (2.4)	2 (4.4)	0.54

HCT, HB, and categorical variables are summarized by mean±sd and frequency (%), respectively. Other variables are reported as median (1st quartile-3rd quartile), [1]*n*=94 for IFX and *n*=121 for ADA. [2]*n*=92 for IFX and *n*=114 for ADA. [3]*n*=95 for IFX and *n*=117 for ADA. [4]*n*=75 for IFC and *n*=89 for ADA. [5]*n*=74 for IFC and *n*=88 for ADA. [6]*n*=101 for IFC and *n*=121 for ADA

Patients were using ADA for a longer time (6.9 years) when compared to IFX (4.9 years, $P = 0.04$). ADA group required more steroid treatments (44.4%) than the IFX group (14.6%, $P = 0.003$). The instances of UC-related hospitalizations were 9.8% in IFX whereas it was 13.3% for ADA ($P = 0.74$). Colectomy was also not significantly different between the groups (IFX 4.9% vs ADA 2.2%, $P = 0.60$). Serious infections leading to treatment cessation were not significantly different between the two treatment groups (IFX 2.4% vs ADA 4.4%, $P = 0.54$) [Table 1]. Serious infections occurred in three patients. Two patients had colitis (cytomegalovirus and *entamoeba histolitica* colitis), and the other patient had pneumonitis (klebsiella pneumonia). No significant statistical differences were found when comparing the monotherapies and combination treatments in terms of halting treatment due to steroid requirement, hospitalization, colectomy, and infections, ($P > 0.05$ for all parameters) [Table 2].

In the Kaplan-Meier analysis, the time until secondary LOR was longer in the IFX group, without reaching statistical significance (72.5% versus 46.7%, $P = 0.057$) [Figure 2]. When the monotherapies ($P = 0.173$) and combinations with immunomodulators ($P = 0.201$) of both groups were compared, no statistically significant difference was observed time until secondary LOR [Figures 3 and 4]. In the log-rank test, the ADA group had a statistically higher need for steroids in both monotherapy and combination therapy groups ($P = 0.012$), whereas hospitalization and colectomy rates were statistically similar.

DISCUSSION

Both IFX and ADA serve as effective interventions for those with moderate to severe UC, unresponsive to aminosalicylates, immunomodulators, or corticosteroids.

Table 2: Subgroup analyses of the treatment outcomes based on the combination (concomitant or addition) of IM within each group

	IFX Group			ADA Group		
	Without IM (*n*=20)	With IM (*n*=21)	*P*	Without IM (*n*=28)	With IM (*n*=17)	*P*
TNF antagonist outcomes, *n* (%)						
Steroid needed	1 (5.0)	5 (23.8)	0.18	12 (42.9)	8 (47.1)	0.78
UC-related hospitalization	2 (10.0)	2 (9.5)	0.68	2 (7.1)	4 (23.5)	0.18
Colectomy	1 (5.0)	1 (4.8)	0.74	0 (0.0)	1 (5.9)	0.38
Serious infection	1 (5.0)	0 (0.0)	0.49			
Follow-up time from starting TNF to TNF outcome	1.00 (1.5)	1.0 (1.0)	0.47	1.0 (1.3)	2.0 (2.0)	0.05

Duration is reported as median (1st quartile-3rd quartile), while others are summarized by frequency (%). IM: Immunomodulator (Azathioprine, Mercaptopurine or Methotrexate)

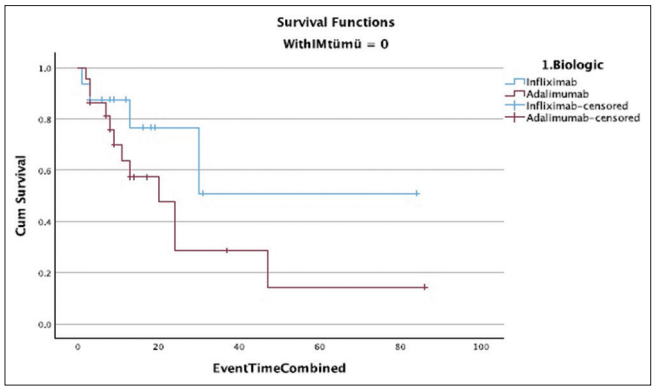

Figure 3: The duration of drug use based on the overall outcomes of monotherapies of both drugs

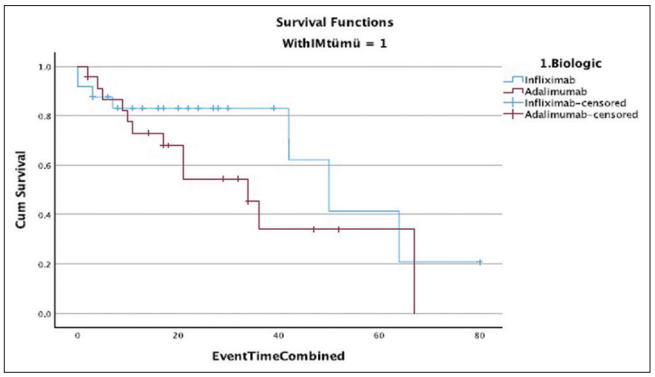

Figure 4: Drug survivals based on overall outcomes of combinations of both drugs with immunomodulators

Still, studies comparing their lasting efficacy and safety remain scarce. In our study, both patient groups had similar rates of prior steroid dependency. Our findings indicate no significant difference in UC-related hospitalization, colectomy, or serious infection between the two treatments. We observed that patients treated with IFX may have a lower need for corticosteroids compared to patients in the ADA group. These findings are consistent with the limited number of studies that have compared the long-term efficacy and safety of different TNF antagonists.[2,17,18]

Previous studies have also shown that patients using ADA are more likely to experience primary non-response compared to those using IFX, while both TNF antagonists have similar long-term efficacy and safety profiles in primary response settings.[8,10] The choice between different anti-TNF agents in UC remains unclear given the absence of clinical evidence. While some studies have shown that IFX is more efficacious and tolerable, others have not found any differences between the two groups in UC.[11,19,20] In our Kaplan-Meier analysis secondary loss of response was statistically similar in both groups, but longer in the IFX group. This could imply that IFX is more efficient and safe. Targovnik and colleagues[21] reported IFX cessation rates of 66.0% in one year and 41.3% in five years for UC patients, but without ADA data. In our study, the rates of treatment cessation after 5 years were 44% for IFX users and 26% for ADA users.

We compared the monotherapy of each TNF antagonist and their combination with an immunomodulator without any statistically significant differences in clinical outcomes. This contrasted with the SUCCESS study's data, suggesting that combination therapy of IFX with thiopurines was tied to a higher probability of steroid-free remission than monotherapy.[22] Pouillon and colleagues also found that the use of concomitant immunomodulators did not affect clinical outcomes, similar to our study. This may partly be explained by the fact that the majority of patients in both groups were also receiving concomitant mesalazine, which may contribute to drug compliance.[17,20] In our practice, we continued the combined immunomodulatory treatment with a TNF antagonist for at least 1 year in responding patients. However, our cohort database did not contain sufficient data on the duration of immunomodulator use.

In the current study, serum CRP levels were statistically high, while serum albumin and hemoglobin levels were low in the IFX group. The explanation for this may be the initiation of IFX as salvage therapy in steroid-resistant patients presenting with severe ulcerative colitis attacks. Patients presenting with a severe UC attack are more likely to have lower serum albumin, lower Hgb levels and higher CRP.

One strength of this study was the extended duration of TNF antagonist use, which allowed for a thorough evaluation of long-term outcomes. Additionally, the homogeneity of demographic characteristics such as smoking status, disease location, disease behavior, baseline Mayo score, and prior treatment history helped to control for potential confounders that could affect clinical outcomes. However, the study also had some limitations, including its retrospective and observational design, which may have introduced bias. Additionally, the sample size was relatively small, which may limit the generalizability of the results. Another potential limitation is that we preferred the use of IFX in patients presenting with severe UC attacks who did not respond to steroids, which may have influenced the results. Overall, while this study provides valuable insights into the long-term effectiveness and safety of IFX and ADA in the treatment of UC, additional research with larger sample sizes and prospective designs is needed to further clarify the comparative efficacy of these TNF antagonists.

In summary, the findings from this study suggest that both IFX and ADA might exhibit comparable performance in clinical outcomes such as the risk of UC-related

hospitalization, colectomy, and serious infections in UC. Yet, it was noted that the ADA group demonstrated a significantly increased need for steroids compared to the group treated with infliximab. Comparison of TNF antagonist monotherapy and combinations with immunomodulators revealed no differences in clinical outcomes. These observations suggest that both IFX and ADA might present comparable long-term effectiveness and safety when administered as monotherapy or in tandem with immunomodulators in the management of UC.

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Conflicts of interest

There are no conflicts of interest.

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