Original Article

Comparison of Two Treatment Strategies in Inflammatory Bowel Disease: Biosimilar Adalimumab Monotherapy or in Combination with Azathioprine

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ABSTRACT

Background:
Tumor necrosis factor-alpha (TNF-alpha) inhibitors, such as adalimumab (ADA) and infliximab, are among the most effective biological drugs for inducing and maintaining remission in patients with moderate to severe inflammatory bowel disease (IBD). Studies have shown that the effectiveness of infliximab is increased with the concomitant use of immunosuppressive drugs. However, little is known about ADA. Our aim was to compare the efficacy of monotherapy with biosimilar ADA and combination therapy with ADA + azathioprine (AZA) in IBD patients.

Materials and Methods:
In this retrospective cohort study, the medical records of anti-TNF-naïve IBD patients referred to a tertiary hospital in Tehran during 2019-2020 who received biosimilar ADA (CinnoRA®) were reviewed. We compared the effectiveness of treatment, serum levels of ADA, anti-adalimumab antibodies, and laboratory data between the two monotherapy and combination therapy groups.

Results:
A total of 65 patients were enrolled. Fifty-six (86.2%) patients had ulcerative colitis, and the remaining had Crohn's disease. 50 patients (76.9%) received combination therapy, and 15 (23.1%) were in the monotherapy group. The rate of clinical remission in the combination therapy group (50%) did not differ significantly from the monotherapy group (40%). The drug levels were in the therapeutic range (≥7.5 µg/mL) in 57.5% of patients in the combination therapy group and 76.9% of those in the monotherapy group. The antibody test result was positive in 40% of patients taking AZA + ADA and 10% of patients in the ADA group, neither were significantly different.

Conclusion:
Adding AZA may not play a significant role in improving the therapeutic effectiveness of ADA in treating IBD.

Keywords: Adalimumab, Immunosuppressive drug, Combination therapy

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INTRODUCTION

Inflammatory bowel disease (IBD) is an autoimmune disease. The global prevalence of IBD is 0.3%, and its prevalence in Iran is 0.1%. Due to the industrialization of societies, the expansion of western lifestyles, and changing eating habits, the number of people suffering from this disease is increasing in developing countries such as Iran (1).

Ulcerative colitis (UC) and Crohn's disease (CD) are the main types of IBD, which differ based on the location of involvement in the gastrointestinal tract and the extent of involvement of the gastrointestinal wall. Given the autoimmune nature of IBD, immunomodulators are the treatment of choice for moderate to severe UC and CD (2).

Previously, conventional immunosuppressants such as azathioprine (AZA) and methotrexate (MTX) were mostly used to control the disease, but in recent years, biologic immunomodulators such as adalimumab (ADA) and infliximab (IFX) with more specific effects on the immune system, acting as anti-tumor necrosis factors (anti-TNFs), are being considered for the treatment of patients with IBD (3).

Recent studies show that up to 30% of patients with IBD do not respond well to anti-TNFs. Also, the therapeutic response in 40% of patients decreases during treatment and requires an increase in dosing or discontinuation or a change in the treatment regimen (4).

Lack of response to primary treatment or reduced secondary response is thought to be due to pharmacokinetic factors such as insufficient drug concentration, development of anti-drug antibodies, and increased drug clearance, as well as pharmacodynamics such as inflammation from a non-TNF-dependent pathway (4).

The results of studies comparing the efficacy of IFX treatment in monotherapy and in combination with conventional immunomodulators are conflicting (5). In the COMMIT study, no significant difference was observed in the proportion of patients achieving remission in the two groups of monotherapy with IFX and combination therapy with IFX+MTX (6). In contrast, in a randomized, double-blind trial, Colombel and colleagues showed that IFX in combination with AZA could lead to better treatment response in patients with CD (7).

ADA is more available in our region. Based on the report by Mohagheghi Darehranj and co-workers in 2020, ADA under the brand name of CinnoRa has an acceptable efficacy in the treatment of moderate to severe IBD in Iran (8). Based on our knowledge, little information is available about differences in monotherapy and combination therapy of ADA. We aimed to compare monotherapy with ADA and combination therapy with ADA+AZA in patients with IBD to determine whether adding AZA to ADA can increase the efficacy of this anti-TNF medication by lowering the amount of anti-ADA antibodies (AAAs). We also wanted to know if the blood concentrations of ADA had any effect on achieving remission in patients who were suffering from IBD.

MATERIALS AND METHODS

Study design

We conducted a retrospective cohort study to evaluate the efficacy of two treatment regimens; the combination therapy with ADA (CinnoRA®, CinnaGen, Iran)+AZA or monotherapy with ADA on patients with IBD who were referred to Imam Khomeini Hospital clinic (Tehran, Iran) between August 2019 and March 2020.

Study population

Eligible patients aged 16-65 years, had been diagnosed with IBD based on laboratory tests and clinical parameters, and were naïve to anti-TNFs. Those who were simultaneously using other immunosuppressants, steroids, or non-steroidal anti-inflammatory drugs (NSAIDs), and patients with malignancy or any other chronic hepatic, renal, or cardiac diseases were excluded. In the end, a total number of 65 patients were recruited for the study.

Study interventions

Patients were allocated to two groups of ADA+AZA and ADA monotherapy. All patients received ADA with an induction dose of 160 mg on day 1 and 80 mg on day 15, and a maintenance dose of 40 mg every other week beginning day 29 based on Mohagheghi Darehranj's study(8).

Patients in the combination therapy group, in addition to ADA, received 100 mg AZA daily.

Study outcomes

The main objective was to compare the efficacy of

combination therapy and monotherapy with proactive therapeutic concentration monitoring in patients with IBD. We used the Mayo score and Harvey-Bradshaw Index (HBI) to determine disease severity in patients with UC and CD, respectively. Laboratory tests including complete blood count (CBC), erythrocyte sedimentation rate (ESR), C-reactive protein (CRP), and stool exam were performed in the first and last visits. Moreover, we evaluated the blood concentration of ADA and antibodies against ADA in the last visit (after 6 months of starting treatment with ADA) and used Inflammatory Bowel Disease Questionnaire (IBDQ) to assess the patients' quality of life.

Statistical analysis

Demographic data and baseline characteristics were analyzed using descriptive statistics. Summary statistics included means and standard deviations for continuous variables and frequencies and percentages for categorical variables. The Shapiro-Wilk test was used to verify the normality assumption. If the normality assumption was met, parametric tests, including *t* test and paired *t* test, were performed for continuous variables; otherwise, non-parametric tests, including the Mann-Whitney U test and Wilcoxon signed-rank test, were applied. The Chi-square test or Fisher exact test was used to compare categorical variables. ROC analysis was performed for ADA level in order to examine its ability to predict remission status. For all statistical analyses, $P<0.05$ was considered statistically significant. All analyses were conducted using SPSS software, version 25 (SPSS Inc., Chicago, IL, USA).

RESULTS

65 anti-TNF-naïve IBD patients, including 9 (13.8%) patients with CD and 56 (86.2%) patients with UC, were enrolled in the study. 15 (23.1%) patients received ADA as monotherapy, and 50 (76.9%) patients were on combination therapy with ADA+AZA. Among the patients with CD, three (33.3%) were in the monotherapy group, and six (66.7%) received combination therapy. Among the patients with UC, 12 (21.4%) were in the monotherapy group, and 44 (78.6%) received combination therapy. Patients' baseline demographic and clinical data are shown in Table 1. The differences in demographic

Table 1. Demographic and clinical data of participants at baseline

		Value	*P* value
Age (years); mean±SD	CD	41.8±14.5	0.13
	UC	36.7±10.5	
	Monotherapy	37.6±9.1	0.67
	Combination therapy	36.2±11.8	
BMI; mean±SD	CD	24.7±3.6	0.31
	UC	23.3±3.8	
	Monotherapy	23.6±4.2	0.94
	Combination therapy	23.5±3.7	
Sex (male); n (%)	CD	6 (66.7)	0.48
	UC	28 (50.0)	
	Monotherapy	9 (60.0)	0.66
	Combination therapy	25 (50.0)	
Smokers; n (%)	CD	0 (0.0)	0.58
	UC	7 (12.5)	
	Monotherapy	1 (6.7)	>0.99
	Combination therapy	6 (12)	
HBI; median (range)	Monotherapy	6 (4-16)	0.90
	Combination therapy	7.5 (4-15)	
Mayo score; mean±SD	Monotherapy	5.4±2.7	0.86
	Combination therapy	5.3±2.5	
IBDQ; mean±SD	Monotherapy	37.0±13.2	0.67
	Combination therapy	35.5±11.6	

BMI, Body mass index; CD, Crohn's disease; HBI, Harvey-Bradshaw index; IBDQ, Inflammatory Bowel Disease Questionnaire; IQR, Interquartile range; SD, Standard deviation; UC, Ulcerative colitis.

characteristics between the patients in the two groups were not statistically significant.

In terms of efficacy evaluation, in patients who had UC, the changes in the mean Mayo score during the 6 months of study in both the combination therapy group and monotherapy group were significant compared with the baseline ($P<0.001$ and $P=0.004$, respectively) (Figure 1A).

In patients who were suffering from CD, although after 6 months of receiving ADA with or without AZA, the changes in median HBI were not statistically significant from the baseline ($P=0.14$ and $P=0.18$, respectively), the trends were declining (Figure 1B).

At the end of the study, the mean IBDQ score was significantly more than the baseline in both groups of combination therapy and monotherapy ($P<0.001$ and $P=0.02$, respectively) (Figure 2).

The number of patients with CD in each disease severity category at baseline and the end of the study is shown in Table 2.

Also, the number of patients with UC in each disease severity category before and after treatment in both groups is shown in Table 3.

In the post-treatment evaluation, 31 patients (47.7%) were in remission, and the rate of remission was not significantly different between the two treatment groups of combination therapy and monotherapy ($P=0.56$), and also between patients with CD and UC ($P=0.48$).

The median (IQR) levels of ADA (8.7 [7.2-10.6] µg/mL) in patients who were in remission were not significantly different from the median (IQR) levels of ADA (8.0 [4.4-10.0] µg/mL) in patients with active disease. Based on ROC curve analysis, we found no optimal cut-off for ADA concentration, which indicates remission and there was no significant association between ADA serum levels and remission (AUC=0.63, $P=0.11$) (Figure 3). A comparison of the two groups in terms of the level of

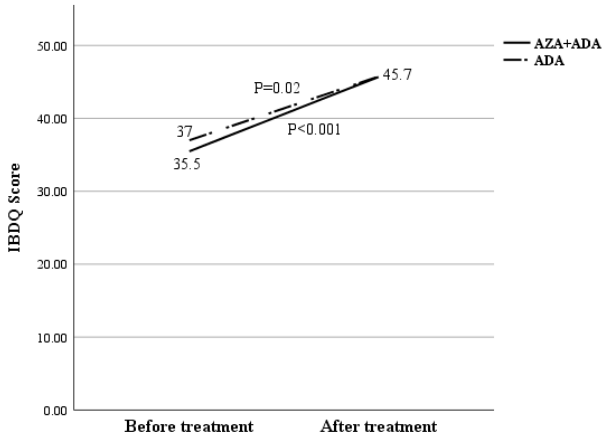

Figure 2. Mean of IBDQ score in two groups of monotherapy and combination therapy before and after treatment. ADA, addalimumab; AZA, azathioprine; IBDQ, Inflammatory Bowel Disease Questionnaire

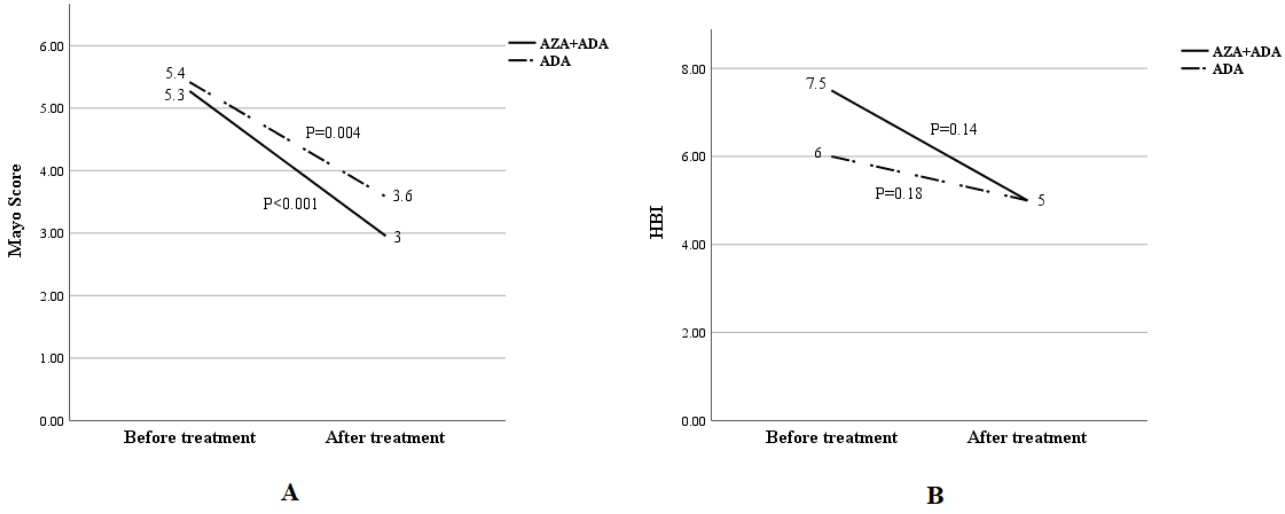

Figure 1. [A] mean of Mayo score and [B] median of HBI in two groups of monotherapy and combination therapy before and after treatment. ADA, addalimumab; AZA, azathioprine; HBI, Harvey-Bradshaw Index

Table 2. Distribution of patients based on the severity of CD in two groups of monotherapy and combination therapy

		Baseline		After treatment	
		Combination therapy	Monotherapy	Combination therapy	Monotherapy
Patients n (%)	Remission	1 (16.7)	1 (33.3)	2 (33.3)	1 (33.3)
	Mild	2 (33.3)	1 (33.3)	3 (50.0)	1 (33.3)
	Moderate	3 (50.0)	1 (33.3)	1 (16.7)	1 (33.3)
	Severe	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)

Table 3. Distribution of patients based on the severity of UC in two groups of monotherapy and combination therapy

		Baseline		After treatment	
		Combination therapy	Monotherapy	Combination therapy	Monotherapy
Patients n (%)	Remission	2 (4.5)	1 (8.3)	23 (52.3)	5 (41.7)
	Mild	16 (36.4)	3 (25.0)	12 (27.3)	2 (16.7)
	Moderate	9 (20.4)	4 (33.3)	4 (9.1)	4 (33.3)
	Severe	17 (38.6)	4 (33.3)	5 (11.4)	1 (8.3)

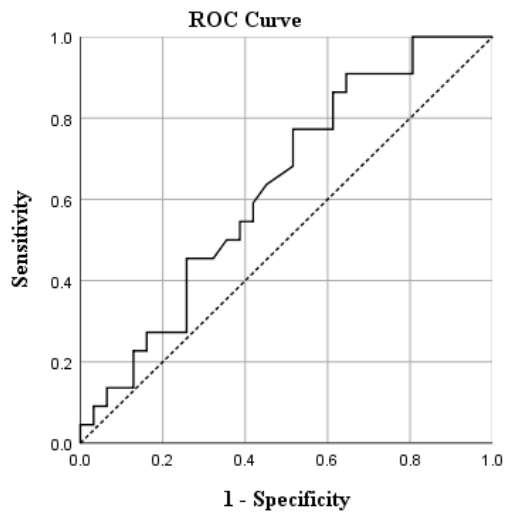

Figure 3. Association between ADA levels and remission status

laboratory parameters after treatment is shown in Table 4. There is no statistically significant difference based on laboratory data between the two groups ($P>0.05$). Also, the after-treatment amounts of HBI, Mayo score, and IBDQ score were not significantly different between the two groups of monotherapy and combination therapy.

ADA serum concentrations were measured in 53 (81.5%) patients after 6 months of starting treatment, and as shown in Table 4, the difference between the median ADA concentration in the two groups was not statistically significant ($P=0.23$). Also, the blood concentrations of ADA were in the therapeutic range (≥7.5µg/mL) in 23

Table 4. Laboratory data and efficacy parameters in the two groups after treatment

Variables	Combination therapy (ADA+AZA)	Monotherapy (ADA)	*P* value
Calprotectin; mean±SD	493±574.1	412.9±401.1	0.65
Calprotectin>200 n (%)	21 (55.3)	6 (50)	>0.99
WBC; mean±SD	9642.9±9920.8	9315.4±3114.2	0.91
ESR; mean±SD	25±22.3	31.6±27.7	0.37
PLT; mean±SD	283.4±81.3	329.2±126.3	0.15
CRP; median (IQR)	1 (0-3)	1 (0-2.25)	0.56
HBI; median (range)	5 (2-8)	5 (4-9)	0.69
Mayo score; mean±SD	3.0±2.2	3.6±2.2	0.39
IBDQ; mean±SD	45.7±11.2	45.7±9.8	0.99
ADA levels; median (IQR)	8.1 (4.4-9.7)	8.3 (7.1-11.5)	0.23

AAA, anti-adalimumab antibody; ADA, adalimumab; CRP, C-reactive protein; ESR, erythrocyte sedimentation rate; HBI, Harvey-Bradshaw index; IBDQ, Inflammatory Bowel Disease Questionnaire; PLT, platelet; WBC, white blood cell.

(57.5%) patients receiving combination therapy and 10 (76.9%) patients in the monotherapy group. Moreover, the serum levels of AAA were measured in 40 (61.5%) patients, and the difference between the median of AAA in the two groups was not statistically significant ($P>0.05$). The result of the AAA test was positive in 40% of patients in the combination therapy group and 10% of patients in the monotherapy group ($P=0.21$, Table 4).

DISCUSSION

Anti-TNF drugs, including ADA and IFX, have good efficacy in controlling many autoimmune diseases like IBD. However, the ineffectiveness or reduced efficacy of these medications over time is observed in some patients (9). AAA formation may lead to the reduction of serum ADA concentration, and it is proposed that the addition of conventional immunomodulators such as AZA to anti-TNFs can reduce the formation of anti-drug antibodies (10). Here, we evaluated and compared the effectiveness of two regimens of monotherapy (ADA) and combination therapy (ADA+AZA) in patients with IBD.

In our study, adding AZA to ADA provided no benefits in patients with IBD. We reported a remission rate of 47.7%, which varies in different studies (25% to 80%) based on study design and population (11-14). Also, we noticed that in both groups of patients (monotherapy and combination therapy), the quality of life and disease severity improved after treatment. It is worth noting that treatment efficacy, quality of life, remission rate, serum levels of ADA and AAA, and laboratory factors (WBC, CRP, ESR, calprotectin, and platelet) were not significantly different between the two groups after treatment. We believe that the high AAA concentration in both groups could be due to our patient selection, which was done from a tertiary and referral center. Consistent with the results of our study, in the CHARM trial in 2007, Colombel and colleagues reported that adding AZA to ADA cannot lead to better clinical response in patients with CD (15). Also, in 2012, Reenaers and colleagues in a retrospective study on 207 patients with CD, noticed that the rate of achieving remission is the same even when immunosuppressive drugs were added to ADA (16). Moreover, in a prospective observational study in 2016, Matsumoto and co-workers compared the efficacy of monotherapy and combination therapy in 176 patients with CD and reported that there was no significant difference in terms of treatment response between the two groups. Also, they observed no difference in ADA and AAA blood concentrations between the two groups of monotherapy and combination therapy (17). Contrary to the results of our study, Kiss and others in 2011 reported that adding AZA to ADA might help increase the rate of remission at 52 weeks of treatment and lead to ADA dose reduction (18). This discrepancy may result from a longer duration of follow-up in this study compared with our study.

We also examined the association between remission rate and ADA blood levels and observed that the serum levels of ADA in patients with therapeutic responses were not significantly different from those who had no clinical response. In 2017, Ward and colleagues conducted a retrospective study on 191 patients with CD of whom 95 were receiving ADA. In line with our findings, they did not find any association between remission rate and ADA blood concentrations (19). In contrast, based on studies by Roblin and colleagues in 2014 and Yarur and others in 2016, higher serum levels of ADA, specially >7.1 and >12.1 µg/mL , were associated with an increased chance of achieving remission and mucosal healing in patients with IBD (20,21). This difference may be partly due to the short length of our study compared with these studies. This may also indicate that although a therapeutic concentration of the drug is necessary to achieve remission, it is not enough, and not all patients with a sufficient amount of ADA in their blood experience remission. The results of our study are consistent with studies that have shown no association between ADA blood levels and remission rate. Due to the existence of contradictory results, more studies are required to clarify the association between ADA blood levels and clinical response.

Limitations

Small sample size, short duration of the study, and retrospective, non-randomized, monocentric design were the important limitations of this study. Moreover, because of cultural limitations, the evaluation of remission achievement was only clinical, and no endoscopic or histological evaluations were performed on enrolled

patients.

Therefore, we recommend randomized, multicenter clinical trials with a bigger sample size and longer follow-ups.

CONCLUSION

According to the results of this study, AZA did not increase the efficacy of ADA in patients with IBD. There was no significant difference in the ADA and AAA concentrations between patients receiving ADA monotherapy and combination therapy. Moreover, there was no association between ADA concentrations and the rate of remission in IBD patients. Hence, AZA does not affect the efficacy and pharmacokinetics of ADA in patients with IBD.

CONFLICT OF INTEREST

The authors declare no conflict of interest related to this work.

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