Journal of Enterocolitis

Original Article

Outcomes of Anti-TNF Treatment in Crohn's Disease: A Real-Life, Tertiary Center Experience

İlkay Ergenç[1], Haluk Tarık Kani[1], Cağlayan Keklikkıran[1], Hazal Salva[2], Yasin İzgi[2], Simge Saydam[2], Sevde Berce Karakaya[3], Yeşim Özen Alahdab[1], Özlen Atuğ[1]

[1]Department of Gastroenterology, Marmara University, Faculty of Medicine, Istanbul, Turkey
[2]Department of Internal Medicine, Marmara University, Faculty of Medicine, Istanbul, Turkey
[3]Marmara University, Faculty of Medicine, Istanbul, Turkey

Cite this article as: Ergenç İ, Kani HT, Keklikkıran C, et al. Outcomes of anti-TNF treatment in crohn's disease: A real-life, tertiary center experience. *J Enterocolitis.* 2022;1(1):17-22.

Corresponding author: İlkay Ergenç, e-mail: ergencilkay@gmail.com

Received: March 2, 2022 **Accepted:** April 6, 2022

DOI: 10.5152/Jenterocolitis.2022.220810

Abstract

Objective: The main treatment option for Crohn's Disease is anti-tumor necrosis factor agents. In this study, we assess the real-life experience of anti-tumor necrosis factor treatment in a tertiary center.

Methods: We enrolled the patients retrospectively who were followed up at our Inflammatory bowel disease-specific gastroenterology outpatient clinic between October 2006 and April 2019. We collected demographic and clinical data from the electronic hospital database and hardcopy of patient files. The primary outcomes of this study are short-term and long-term efficacy. Secondary outcomes are the safety of treatments and indications of anti-tumor necrosis factor initiation.

Results: A total of 870 Crohn's disease patients were screened, 236 were exposed to anti-tumor necrosis factor, and 200 patients were included for the final analysis. The median follow-up period of anti-tumor necrosis factor treatment was 55 months (range: 4-168). A total of 133 patients received infliximab, 97 received adalimumab, and 11 received certolizumab as first-, second-, or third-line treatment. In total, 6 patients (4.2%) were primary unresponsive and 15 (10.6%) patients were secondary unresponsive to infliximab; 3 patients (2.8%) were primary unresponsive and 14 patients (13.3%) were secondary unresponsive to adalimumab; and 2 (18%) patients were primary unresponsive and 1 (9%) patient was secondary unresponsive to certolizumab. The most common indication of anti-tumor necrosis factor treatment was fistula formation (47.7%, n=87). However, 63 (50.0%) fistulizing patients had no response to anti-tumor necrosis factor treatment.

Conclusion: Two-thirds of the patients had treatment response, and no significant difference was seen between agents. Half of the patients has fistulizing disease and 50% of them were non-responders.

Keywords: Adalimumab, anti-TNF, certolizumab, Crohn's disease, infliximab, real-life

INTRODUCTION

Crohn's disease (CD) is a complex, immune-mediated inflammatory disease that involves all gastrointestinal tract with accompanying extra-intestinal findings.[1] It has a wide clinical spectrum from isolated inflammatory ileal disease to widespread ileocolonic involvement with fistulizing or stenosing behavior.[2] Perianal fistulizing CD is also the most challenging form of the disease. Up to half of the patients could be complicated by a fistula in the disease course.[3] The presence of fistulae is often associated with severe disease, diminished life quality, and decreased treatment response.[4]

Biologic agents including anti-TNF agents are one of the treatment options for CD with an increasing frequency of use in recent decades. Anti-tumor necrosis factor (anti-TNF) agents are widely used to both remission induction and maintain mild to severe intestinal and extra-intestinal involvements.[5] The effectiveness and safety of these agents were evaluated in previous studies also including Turkish patients as well.[6-8] The data from the clinical trials may not reflect the real-life conditions because of their strict design, particularly including criteria and follow-up conditions. For this reason, real-life experience provides additional information about the treatment in the context of daily patient care.[9]

The aim of this study was to assess the treatment choices, short- and long-term response, treatment duration, and the safety of anti-TNF agents in patients with CD.

METHODS

Patients

We enrolled the patients retrospectively who were followed up at our Inflammatory bowel disease (IBD)-specific gastroenterology out-patient clinic between October 2006 and April 2019. Inflammatory bowel disease diagnosis was established with clinical, biochemical, endoscopic, and histologic findings. Patients who completed induction doses of at least 1 anti-TNF treatment were included in the study. Induction was described as 5 mg/kg of intravenous infusion at weeks 0, 2, and 6 for infliximab; as 160 mg of subcutaneous injection at week 0, 80 mg at week 2, 40 mg at

week 4 for adalimumab; and as 400 mg of subcutaneous injections at weeks 0, 2, and 4 for certolizumab.

Inclusion criteria were patients at least 18 years old or older at the time of the last visit and treated with at least 1 anti-TNF agent, and exclusion criteria were insufficient data for statistical evaluation and lost to follow-up. All procedures followed were in accordance with the ethical standards of the responsible committee on human experimentation and with the Helsinki Declaration of 1975, as revised in 2008. Marmara University School of Medicine Research Ethics Committee has approved this study protocol. (Date: September 06, 2019, Desicion no: 09.2019.186).

Data Collection

We collected demographic and clinical data from the electronic hospital database and hardcopy of patient files. Information on age, gender, date of diagnosis, Montreal classification, smoking habits, IBD-related surgical history, previous and current medical treatment, anti-TNF start, stop and switch dates, anti-TNF treatment schedule and reasons for anti-TNF discontinuation, Crohn's disease activity index (CDAI) scores before and every 3 months after anti-TNF treatment, ileocolonoscopy and Magnetic Resonance (MR) enterography results, viral serology, Purified Protein Derivative (PPD)/Tuberculin Skin Test results, history of cytomegalovirus (CMV) colitis, hepatitis, and tuberculosis was collected for each patient. Laboratory test records, the intensity of abdominal complaints, and physical examination findings of the patients for each visit were completely recorded.

All disease severity status and treatment responses decided by the same IBD specialized gastroenterologist according to the number of daily liquid stool, laboratory results, physical examination findings, radiologic, endoscopic, and histological data were collected if exist.

Primary unresponsiveness (PU) in patients was defined as those who failed to achieve complete or partial remission after induction doses of biologic therapy. Secondary unresponsiveness (SU) was defined as loss of response in patients who achieved complete or partial remission after induction doses of biologic therapy. Short-term efficacy (STE) was defined as complete or partial remission at week 12, and long-term efficacy (LTE) was defined as complete or partial remission at week 52 since the initiation of the biologic agent.

Study Outcomes

Primary outcomes of this study are short-term and long-term efficacy and safety of treatments. Secondary outcomes are the predictors of anti-TNF initiation and treatment response and time to cessation of Anti-TNF agents.

MAIN POINTS

- Anti-tumor necrosis factor (anti-TNF) treatment had a good response rate with a sufficient safety profile.
- Fistulizing disease was the most common indication of anti-TNF treatment.
- Complete and partial response rates were similar between the anti-TNF agents.

Statistical Analysis

Categorical variables were presented as percentages and continuous variables as mean ± standard deviation. Baseline characteristics were compared with non-parametric *t*-test, analysis of variance, and chi-square tests. A *P* of <.05 was considered statistically significant. Statistical Package for the Social Sciences version 22.0. (IBM SPSS Corp.; Armonk, NY, USA).

RESULTS

Baseline Characteristics

A total of 870 CD patients were screened and 236 were exposed to anti-TNF. Thirty-six patients were excluded due to incomplete data and were lost to follow-up and 200 patients were included for the final analysis.

Mean age was 40 ± 13 years and 46% were female. Median time from the CD diagnosis to the onset of anti-TNF was 2 years (range: 0-34). Median follow-up period under anti-TNF treatment was 55 months (range: 4-168). Fistulizing disease was seen in 119 (59.5%) patients, stricturing disease was seen in 24 (12.0%) patients, coexisting fistulizing and stricturing disease was seen in 7 (3.5%) patients, and no fistula or stricture was seen in 50 (25.0%) CD patients (Table 1).

Treatment Choice and Maintenance of the Therapy

A total of 161 (81.5%) patients were exposed to only 1 anti-TNF agent. The treatment was stopped after a long-term remission in 11 patients with a patient request in 7, due to side effects in 7 patients and secondary unresponsiveness in 2 patients.

As a first agent, continuation rates without any change were found to be 55.3%, 67.5%, and 80% for infliximab, adalimumab, and certolizumab, respectively. Median follow-up time for certolizumab, infliximab, and adalimumab was 20, 49, and 50 weeks, respectively.

Thirty-nine patients received 2 different types of anti-TNF agents and 2 patients received 3 different types of anti-TNF agents consecutively (Figure 1). Median follow-up time was 19 months (range: 1-120) after the initiation of a second anti-TNF agent (n=39) and 7 months (range: 7-7) after the initiation of a third anti-TNF agent (n=2).

Vedolizumab was used as anti-integrin agent in 14 patients as a second (n=11) or third-line (n=3) treatment. Treatment choices, switches, continuation, and cessation diagrams of each agent were summarized in Figure 2 and 3.

Response to Anti-TNF Therapy

A total of 133 patients received infliximab, 97 received adalimumab, and 11 received certolizumab as first-, second-, or third-line treatment. Among patients who were treated with infliximab, 6 (4.2%) were PU and 15 (10.6%) were SU. Among patients who were treated with adalimumab, 3 (2.8%) were PU and 14 (13.3%) were SU. In patients who were treated with certolizumab, 2 (18%) were PU and 1 (9%) was SU (Table 3). No statistically significant difference was seen in response rates between agents (*P* =.12).

Within 241 reviewed anti-TNF treatment exposures, 166 of those had CDAI scores noted before treatment, at 12th week, and 1st year of the treatment. The median CDAI score at the beginning of the treatment was 115, and no significant difference was seen between anti-TNF

Table 1. Demographic and Clinical Characteristics of Patients

Characteristic	N=200
Age	40.5 ± 13.09
Gender, %	
Male	54
Female	46
Smoking, %	
Active smoker	27.5
Lifetime smoker	29
Never smoked	45.5
Mean age at diagnosis	32.4 ± 12.6
Mean duration of disease (years)	8.1 ± 4.8
Montreal classification	
Age at diagnosis, %	
A1 (<16)	4.5
A2 (17-40)	61.6
A3 (>40)	33.8
Localisation of disease, %	
L1 (ileum)	32.7
L2 (colon)	11.1
L3 (ileocolon)	55.8
L4 (upper GI)	5
Perianal disease, %	
Abscess	4, n=8
Fistula	28, n=56
Abscess+fistula	19.5, n=39
Behavior, %	
B1 (inflammatory)	29, n=58
B2 (structuring)	15.5, n=31
B3 (penetrating)	55.5, n=111
Anti-TNF treatment experience, %	
Second line	21.5, n=43
Third line	3.5, n=7
Median duration of disease at start of anti-TNF (year)	2 (min: 0, max: 34)
Median duration of anti-TNF therapy (months)	
First line	31 (min: 1, max: 168)
Second line	19 (min: 1, max: 120)
Third line	7 (min:7, max: 7)
Anti-TNF treatment indication, %	
Flare	25, (n=44)
Fistula	47.7, (n=87)
Stenosis	1.7, (n=3)
Prophylaxis	0.6, (n=1)
Extra-digestive involvement	4, (n=7)
Steroid dependent disease	2.3, (n=5)
Steroid refractory disease	2.3, (n=5)
Immunomodulatory therapy failure	8, (n=14)
Side effects of immunomodulatory therapy	8.5, (n=15)
Concomitant 5-ASA, %	64.5 (n=100)
Concomitant azathioprine, %	72.9 (n=113)
Tuberculosis prophylaxis, %	51 (n=102)
CMV colitis history, %	0.6 (n=1)
Extra-intestinal involvement, %	
Peripheral arthritis	22.4 (n=33)
Sacroiliitis	8.2 (n=12)
Erythema nodosum	16.3 (n=24)

TNF, tumor necrosis factor; GI, gastrointestine.

groups (P=.076). In infliximab exposure group (n=133), CDAI scores at the beginning of treatment, 12th week, and 1st year were 115, 83, and 65, respectively. For adalimumab-exposed group (n=97), CDAI scores at the beginning of treatment, 12th week, and 1 year were 114, 81, and 78, respectively.

Short-Term Efficacy

According to clinical, endoscopic, biochemical, and radiologic data, complete response and partial response rates were respectively seen as 51.3% and 43.3% for infliximab users, 59.7% and 36,1% for adalimumab users, 36.4% and 45.5% for certolizumab users. There was no difference was seen between 3 agents in complete and partial response rates (P=.281) (Table 2).

Long-Term Efficacy

Remaining on the same anti-TNF agent for infliximab and adalimumab at the end of the first year was 64.5% and 87.3%, respectively. Patients who were treated with adalimumab were seen to continue on the same agent more commonly in the first year when compared to infliximab (P=.000). Complete and partial response rates in the first year were 56.7% and 36.5% respectively for infliximab and 70.8% and 25% respectively for adalimumab, no difference was seen between 2 agents (P=.192). In certolizumab group, 3 of 11 patients had complete responses whereas 5 of 8 had a partial response in the first year (Table 3).

Healing of Fistula with Anti-TNF Agents

The most common indication of anti-TNF treatment was fistula formation (47.7%, n=87). Complete healing was seen in 20 (15.9 %) patients and partial healing was seen in 43 (34.1%) patients. However, 63 (50.0%) patients had no response to anti-TNF treatment (Table 5).

Perianal Disease

Perianal disease was seen in 103 (51.5%) patients. In patients with perianal disease, 5 (4.9%) had perianal abscess, 56 (54.4%) had perianal fistula, and 42 (40.8%) had both abscess and fistula formation. A seton was placed on 52 (50.5%) patients along with biological treatment. In 87 (47.7%) patients, anti-TNF treatment was started based on a new diagnosis of fistulizing disease, and in 44 (25%) patients, anti-TNF treatment was started based on a disease flare without a new fistula. Of the 98 fistulizing CD patients, total healing was seen in 16 (15.5%) patients, partial healing (decrease or absence of discharge with a persistent fistula) was seen in 33 (32.0%), and no response was seen in 42 (40.8%) patients.

Safety

Severe allergic reaction was seen in 8 patients with infliximab and in 4 patients with adalimumab exposure. Treatment cessation due to serious adverse reactions was seen in 21 patients who were exposed to infliximab and in 11 patients who were exposed to adalimumab. No serious side effect was seen in patients who were exposed to certolizumab (Table 4).

DISCUSSION

This is a retrospective real-life data of a single experience in patients with CD who were treated with anti-TNF agents. The study, supply valuable information with a sufficient number of patients, second- and third-line treatment data, long median follow-up time of nearly 5 years, and reflection of real-life from the field.

Certainly, anti-TNF therapies became a mainstay of treatment in CD in the last decades but still, questions remain about their efficacy and durability.[8] Complete response rates for both adalimumab and infliximab were not more than half even in clinical trials.[10,11] In our study, complete remission rate was consistent with the literature. The primary and the secondary unresponsiveness rates were very low if we accept the partial response as treatment success. These rates were slightly below compared to the previous studies.[8,12] In a real-life setting, sub-optimal

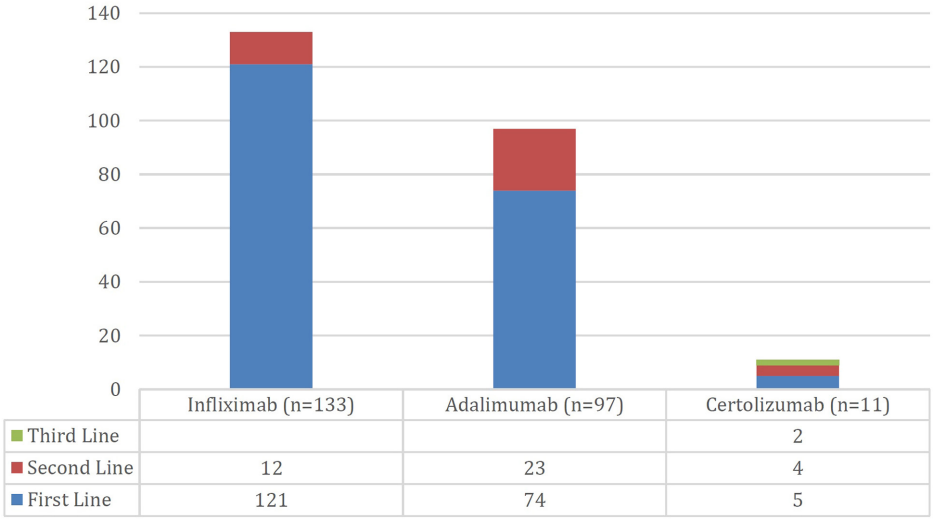

Figure 1. Distribution of anti-TNF agents. TNF, tumor necrosis factor.

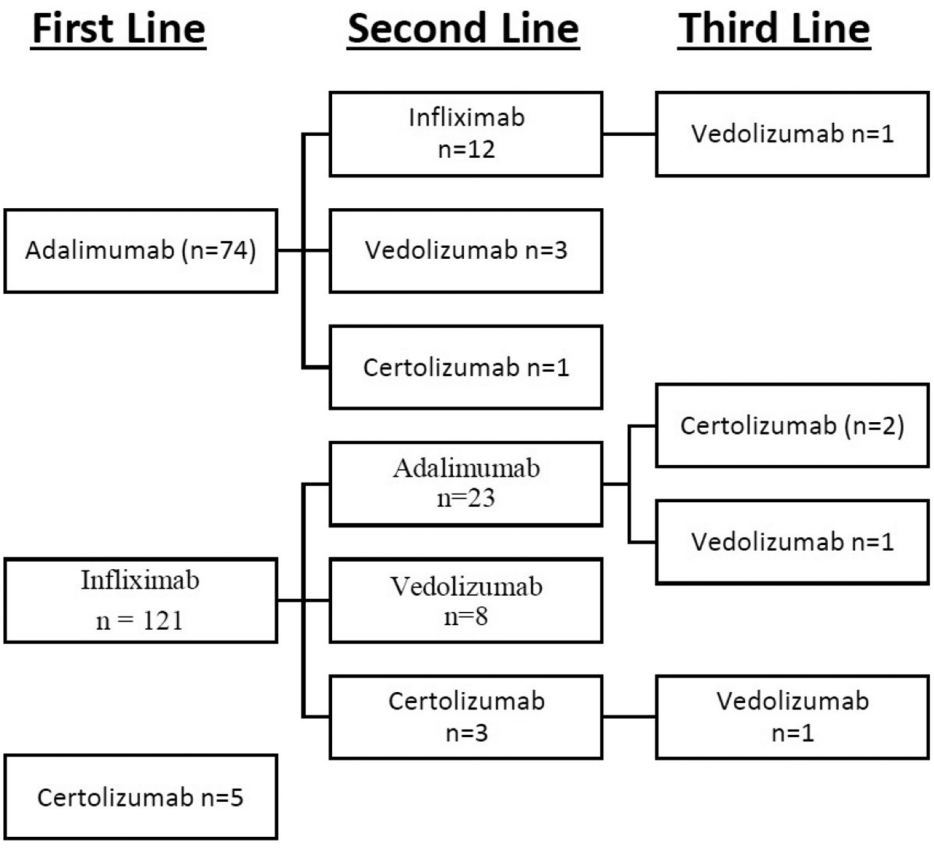

Figure 2. Anti-TNF and anti-integrin agent alterations as first-, second-, and third-line treatment. TNF, tumor necrosis factor.

response is also acceptable in some cases due to limited treatment alternatives at the time of the study. This approach may change with the implantation of newly anti-cytokine treatments like ustekinumab in the disease management.[13]

Complete and partial response rates were similar between adalimumab and infliximab, but the duration of treatment rate was higher in adalimumab. This may be explained by the selection of subcutaneous drug in mild to moderate disease by the clinician or patient. Controversy, in severe form of disease, especially complicated fistulizing CD, clinicians are more prone to choose the infliximab. The different ratio of fistulizing disease between the treatments agent is another heterogeneity that restricts the comparative analysis.

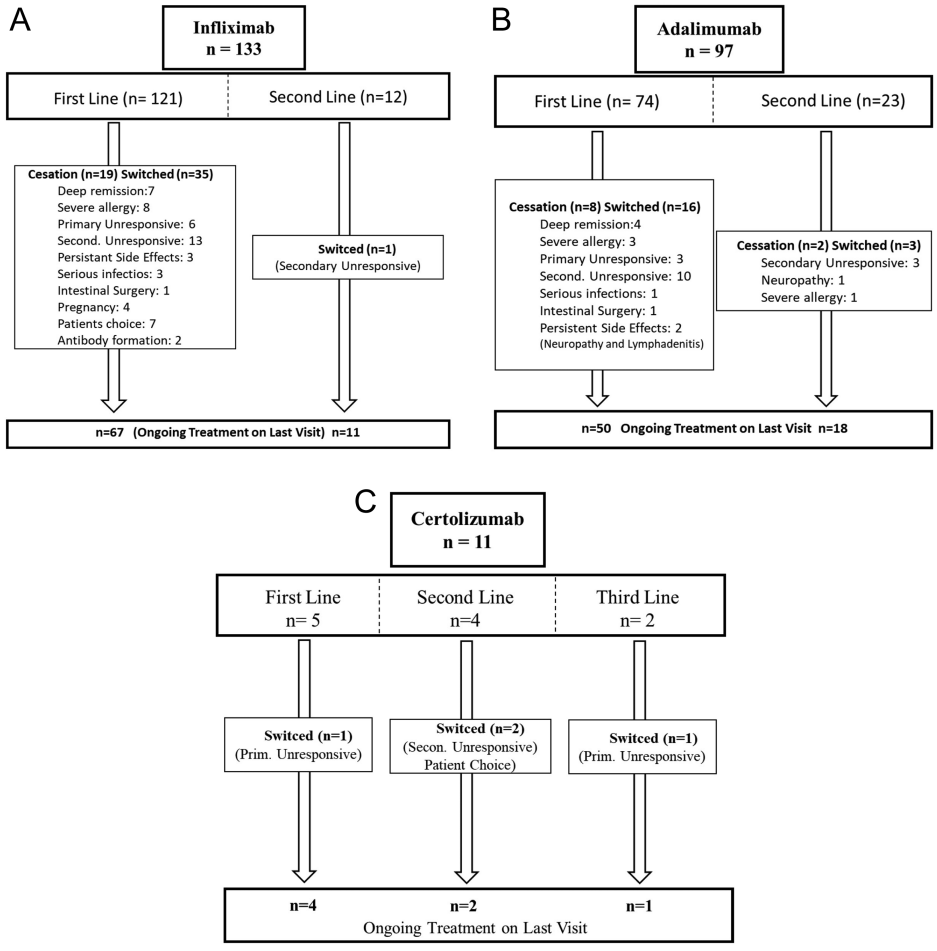

Figure 3. (a) Treatment agent changes on the course of the disease in patients who received infliximab as first-line anti-TNF agent. TNF, tumor necrosis factor. (b) Treatment agent changes on the course of the disease in patients who received adalimumab as first-line anti-TNF agent. (c) Treatment agent changes on the course of the disease in patients who received certolizumab as first-line anti-TNF agent. .

Table 2. Short-Term Efficacy Rates of Anti-TNF Agents

		Infliximab, %, n=133	Adalimumab,%, n=97	Certolizumab n=11
First line	Complete response	52.8, n=64	59.4, n=44	-
	Partial response	42.1, n=51	36.4, n=27	4/5
Second line	Complete response	41.6, n=5	60.8, n=14	3/4
	Partial response	58.3, n=7	39.1, n=9	1/4
Third line	Complete response	--	--	1/2
	Partial response	--	--	--
Total	Complete response	**51.8, n=69**	**59.7, n=58**	**36.4% n=4**
	Partial response	**43.6, n=58**	**37.1, n=36**	**45.5% n=5**

TNF, tumor necrosis factor.

Table 3. Unresponsiveness Rates of Anti-TNF Agents

		Infliximab	Adalimumab	Certolizumab
First line	Primary unresponsive	6/121	3/74	1/5
	Secondary unresponsive	12/121	11/74	-
Second line	Primary unresponsive	-	-	-
	Secondary unresponsive	1/12	2/23	1/4
Third line	Primary unresponsive	-	-	1/2
	Secondary unresponsive	-	-	-
Total	Primary unresponsive	**6/133**	**3/97**	**2/11**
	Secondary unresponsive	**13/133**	**13/97**	**1/11**

TNF, tumor necrosis factor.

Table 4. Frequencies of Severe Adverse Reactions on Anti-TNF Agents

	Infliximab (n=133)	Adalimumab (n=97)
Severe allergic reactions	8	4
Neuropathy	-	2
Thrombocytopenia	1	1
Serious infections	4	1
Pruritus	1	--
Rash	3	3
Alopecia	1	--
Syncope	1	--
Haemoptysis	1	--
Gingivitis	1	--

TNF, tumor necrosis factor.

Table 5. Fistula Response According to Anti-TNF Agents

	Infliximab, % (n=43)	Adalimumab, % (n=29)	Certolizumab, % (n=4)
Complete closure	27.9, n=12	6.9, n=2	--
Partial closure	23.3, n=10	6.9, n=2	25, n=1
Improvement in fistula drainage	20.9, n=9	10.3, n=3	--
No response	27.9, n=12	72.4, n=21	75, n=3

Fisher's Exact Test value:19.39; *P*=. 004

TNF, tumor necrosis factor.

The most common indication of anti-TNF was fistula formation. Perianal fistulizing disease impairs the quality of life in CD and it is also a well-known poor prognostic factor of disease.[14-16] Half of our patients had fistulizing disease and nearly all were perianal. Half of the patients with fistula were unresponsive. Two-thirds of the perianal fistulizing CD patients were treated with infliximab, whereas one-third with adalimumab. No clinical improvement rates of perianal fistula were less than 30% in infliximab but more than 70% in adalimumab treatment arm. Despite a large number of data, it is not possible to imply the preferred anti-TNF in the fistulizing disease.[17]

The CDAI scores of our cohort were lower than the accepted disease activity thresholds even before the treatment. Although these patients had active disease according to objective clinical, radiological, and endoscopic findings, the scores were mildly elevated. Crohn's disease activity index is a historical activity score based on symptoms mainly and does not correlate well, especially in fistulizing patients. In the radiological and non-invasive era of CD, there is a need to reconsider the parameters of CD disease activity scores.

It is not possible to evaluate the effectiveness of certolizumab owing to the fact the small number of patients and short treatment period. Serious adverse effect rate was very low. Most common serious side effects were allergic reactions and rash. Allergic reactions rate was similar between agents.

In conclusion, this retrospective analysis of single-center, real-life experience of anti-TNF treatment in CD shows that anti-TNF treatment has a good response with acceptable safety and duration rate. The effectiveness and safety were similar between agents.

Ethics Committee Approval: Ethics committee approval was received for this study from the ethics committee of Marmara University School of Medicine Research Ethics Committee, (Date: September 6, 2019, Desicion no: 09.2019.186).

Informed Consent: Informed consent was not obtained since the protocol designed as retrospectively.

Peer-review: Externally peer-reviewed.

Author Contributions: Concept – H.T.K., I.E., O.A., Y.O.A.; Design - I.E., H.T.K.; Supervision – Y.O.A., O.A.; Resources – Ç.K.; Materials – I.E., H.T.K., H.S.; Data Collection and/or Processing – C.K., H.S., Y.I., S.S., B.K.; Analysis and interpretation – I.E., H.T.K., O.A.; Literature Search – I.E., H.T.K.; Writing Manuscript – I.E.; Critical review – Y.O.A., O.A.; Other – I.E., H.T.K., C.K., H.S., Y.I., S.S., B.K., Y.O.A., O.A.

Declaration of Interests: The authors declared no financial conflicts of interest.

Funding: The authors declared that this study has received no financial support.

REFERENCES

1. Atuğ Ö, Kani HT, Banzragch M, İmeryüz N, Akın H. Incidence rate of anemia in inflammatory bowel diseases. *Turk J Gastroenterol*. 2016;27(2):143-148. [CrossRef]
2. Bengi G, Keyvan H, Durmaz SB, Akpınar H. Frequency, types, and treatment of anemia in Turkish patients with inflammatory bowel disease. *World J Gastroenterol*. 2018;24(36):4186-4196. [CrossRef]
3. Seyfried S, Herold A. Management of perianal fistulas in Crohn's disease. *Visc Med*. 2019;35(6):338-343. [CrossRef]
4. Kanı HT, Ergenç İ, Arıkan H, et al. Validation and reliability of the Turkish version of the inflammatory bowel disease questionnaire for ulcerative colitis and Crohn's disease. *Turk J Gastroenterol*. 2020;31(8):566-572. [CrossRef]
5. Lima CCG, Queiroz NSF, Sobrado CW, Silva GLR, Nahas SC. Critical analysis of anti-TNF use in the era of new biological agents in inflammatory bowel disease. *Arq Gastroenterol*. 2020;57(3):323-332. [CrossRef]
6. Rutgeerts P, Van Assche G, Sandborn WJ, et al. Adalimumab induces and maintains mucosal healing in patients with Crohn's disease: data from the EXTEND trial. *Gastroenterology*. 2012;142(5):1102-1111.e2. [CrossRef]
7. Sandborn WJ, Abreu MT, D'Haens G, et al. Certolizumab pegol in patients with moderate to severe Crohn's disease and secondary failure to infliximab. *Clin Gastroenterol Hepatol*. 2010;8(8):688-695.e2. [CrossRef]
8. Adegbola SO, Sahnan K, Warusavitarne J, Hart A, Tozer P. Anti-TNF therapy in Crohn's disease. *Int J Mol Sci*. 2018;19(8):2244. [CrossRef]
9. Kirchgesner J, Lemaitre M, Rudnichi A, et al. Therapeutic management of inflammatory bowel disease in real-life practice in the current era of anti-TNF agents: analysis of the French administrative health databases 2009-2014. *Aliment Pharmacol Ther*. 2017;45(1):37-49. [CrossRef]
10. Papamichael K, et al. Infliximab in inflammatory bowel disease. *Ther Adv Chronic Dis*. 2019;10:2040622319838443. [CrossRef]
11. D'Haens GR, van Deventer S. 25 years of anti-TNF treatment for inflammatory bowel disease: lessons from the past and a look to the future. *Gut*. 2021;70(7):1396-1405. [CrossRef]
12. Ford AC, Sandborn WJ, Khan KJ, Hanauer SB, Talley NJ, Moayyedi P. Efficacy of biological therapies in inflammatory bowel disease: systematic review and meta-analysis. *Am J Gastroenterol*. 2011;106(4):644-660. [CrossRef]
13. Attauabi M, Burisch J, Seidelin JB. Efficacy of ustekinumab for active perianal fistulizing Crohn's disease: a systematic review and meta-analysis of the current literature. *Scand J Gastroenterol*. 2021;56(1):53-58. [CrossRef]
14. Plevris N, Jenkinson PW, Arnott ID, Jones GR, Lees CW. Higher anti-tumor necrosis factor levels are associated with perianal fistula healing and fistula closure in Crohn's disease. *Eur J Gastroenterol Hepatol*. 2020;32(1):32-37. [CrossRef]
15. Kotze PG, Shen B, Lightner A, et al. Modern management of perianal fistulas in Crohn's disease: future directions. *Gut*. 2018;67(6):1181-1194. [CrossRef]
16. Panes J, Reinisch W, Rupniewska E, et al. Burden and outcomes for complex perianal fistulas in Crohn's disease: systematic review. *World J Gastroenterol*. 2018;24(42):4821-4834. [CrossRef]
17. de Groof EJ, Sahami S, Lucas C, Ponsioen CY, Bemelman WA, Buskens CJ. Treatment of perianal fistula in Crohn's disease: a systematic review and meta-analysis comparing seton drainage and anti-tumour necrosis factor treatment. *Colorectal Dis*. 2016;18(7):667-675. [CrossRef]