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Comparison of infliximab with adalimumab in biologic-naïve patients with Crohn's disease: a single-center 13-year experience

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Abstract. – OBJECTIVE: Long-term comparison studies between infliximab (IFX) and adalimumab (ADA) with or without immunomodulator therapy are still needed in Crohn's disease (CD). In this study, we evaluated IFX and ADA for long-term clinical effectiveness and safety in CD patients who had not previously received a biologic treatment.

PATIENTS AND METHODS: The data of adult CD patients were collected retrospectively between December 2007 and February 2021. We compared CD-related hospitalization, CD-related abdominal surgery, steroid use, and serious infections.

RESULTS: Out of 224 CD patients, 101 started IFX first (median age: 38.12 years, 61.4% male), while 123 started ADA first (median age: 30.2 years, 64.2% male). The disease durations were 7.01 years and 6.91 years for IFX and ADA, respectively. There were no significant differences between the two groups with respect to age, gender, smoking, immunomodulator usage, and disease activity score at the onset of anti-TNF therapy ($p>0.05$). Overall, the median follow-up time was 2.36 and 1.86 years after starting anti-tumor necrosis factor-alpha (anti-TNF) therapy in the IFX and ADA groups, respectively. Steroid use (4.0% *vs.* 10.6%, $p=0.109$), hospitalization for CD (13.9% *vs.* 22.8%, $p=0.127$), abdominal surgery for CD (9.9% *vs.* 13.0%, $p=0.608$), and major infections (1.0% *vs.* 0.8%, $p>0.999$) did not differ significantly from one another. There were also no significant differences in the rates of these outcomes between concomitant immunomodulator therapy and monotherapy ($p>0.05$).

CONCLUSIONS: In this study, we observed no significant differences in the long-term effectiveness and safety of IFX and ADA in biologic-naïve patients with CD.

Key Words:
Crohn's disease, Infliximab, Adalimumab.

Introduction

Crohn's disease (CD) is a chronic, inflammatory, destructive disease that can affect the entire gastrointestinal tract[1]. Until the last decade, the medical options to treat CD were limited to corticosteroids, thiopurines (azathioprine or mercaptopurine), or methotrexate (MTX). Biologic treatments with anti-tumor necrosis factor-alpha (anti-TNF-α) agents, including infliximab (IFX) and adalimumab (ADA) alone or in combination with an immunomodulator (IM) for moderate to severe CD, brought significant changes to the management of CD, leading to improvements in disease control and quality of life.

Three anti-TNF agents are available for the treatment of CD; however, ADA and IFX are used more often for remission induction than certolizumab pegol[2]. The use of TNF-α inhibitors (IFX, ADA, and certolizumab pegol) for inducing remission in the treatment of moderate-to-severe CD that does not respond to conventional therapy is advised by the 2020 ECCO Guidelines on Therapeutics in Crohn's Disease Medical Treatment[3]. Additionally, for individuals with high-risk CD, the American Gastroenterology Association (AGA) and the American College of Gastroenterology (ACG) recommend biologic agents[4,5].

With a high level of specificity and affinity, IFX is a chimeric IgG 1 monoclonal antibody against TNF-α made up of 75% human and 25% murine sequences[6]. ADA is a recombinant monoclonal antibody that binds to human TNF-alpha, preventing it from connecting to TNF receptor sites, thus the inflammatory processes that are triggered by cytokines[7]. Involved tissues from patients with CD, ulcerative colitis, ankylosing spondylitis, rheumatoid arthritis, psoriatic arthritis, and psoriasis have

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been reported to have elevated TNF levels. IFX's primary function is to neutralize both soluble and transmembrane TNF. The downregulation of other proinflammatory cytokines and antibody-dependent cytotoxicity, apoptosis of T lymphocytes and monocytes, as well as the modulation of TNF-producing cells by complement fixation, are some of the other significant roles that IFX can play in addition to blocking TNF activity, according to research[6,8-10]. These actions can be shown in biopsy samples taken from individuals using this medication and in the decreased concentration of cytokines in their serum.

Biologic treatments have been shown to decrease the risk of hospitalization, as well as steroid and surgery need[11-13]. The introduction of the first two biologics (IFX, a chimeric monoclonal antibody approved in 1998, and ADA, a fully human monoclonal antibody approved in 2007) established a significant efficacy, up to double, in clinical and endoscopic remission, according to previously seen efficacy with conventional therapies, and decreased the need for corticosteroids[14].

In CD, the efficacy and safety of the two biological agents have been well established throughout numerous studies[15], most of which are randomized controlled trials, including short-term intervals and limited generalizability. Prior observational comparative studies[16] have shown variable results and were also limited by the potential misclassification of prior TNF-alpha antagonist exposure. Real-world, head-to-head, long-term comparisons between IFX and ADA combinations with or without immunomodulatory (IM) therapies are still needed and may provide valuable information regarding the management of CD.

This study aimed to compare the long-term clinical effectiveness and safety profiles of IFX and ADA in biologic-naïve patients with CD.

Patients and Methods

Patients

Data on all biologic-naïve patients with CD who started IFX or ADA treatment in our tertiary referral center were retrospectively collected between December 2007 and February 2021. Up until February 2019, data were collected at Ankara Numune Training and Research Hospital. The remaining data were collected by the same medical staff at Ankara City Hospital since Ankara Numune Training and Research Hospital was merged with it in February 2019.

Inclusion criteria were established diagnosis of CD with the Montreal classification, adult patients (aged ≥18 years), no prior exposure to biological therapy, and a history of having received either IFX or ADA first. Exclusion criteria included discontinuation of the first anti-TNF therapy before completion of induction therapy, an observation period of less than six months after drug initialization, a history of receiving IFX or ADA priorly for rheumatologic reasons, and patients with missing information.

All characteristics, findings and clinical courses of patients were obtained from the medical charts and hospital records. Data included patient demographics, duration of disease, follow-up time of anti-TNF therapy, location of disease according to the Montreal classification, smoking status, family history of inflammatory bowel disease (IBD), extraintestinal manifestations, prior major abdominal surgery, experienced medications, concomitant medication use, baseline C-reactive protein (CRP), hematocrit (HCT), hemoglobin (Hb), albumin and Crohn's disease activity index (CDAI) score. After starting anti-TNF therapy combined with an IM agent, if the patients experienced liver test abnormalities, intolerance to thiopurines or MTX within three months, had a planned pregnancy, or refused therapy, the corresponding patients were evaluated among the monotherapy group.

Administration of IFX or ADA

The first anti-TNF agent (IFX or ADA) was chosen according to the agreement between the patient and the physician. Since this was a retrospective study, the purpose for the selection of one therapy over the other was not known.

According to established guidelines, IFX was administered at a dose of 5 mg/kg at weeks 0 through 6 and then every eight weeks for maintenance therapy. ADA was used at standard doses, with subcutaneous doses of 160 mg at week 0, 80 mg at week 2, and 40 mg every two weeks for maintenance. Dose escalation was defined as either an increase in dose (10 mg/kg) or increased frequency of infusions (every four weeks) for IFX. For ADA, dose escalation was defined as shortening the intervals between subcutaneous injections of 40 mg every other week to weekly.

Outcomes of Interest

The outcomes of interest were effectiveness and safety consequences, which were described as any of the following events occurring after starting anti-TNF therapy.

Effectiveness included CD-related hospitalization (associated symptoms of abdominal pain, diarrhea, constipation, nausea, vomiting, gastrointestinal bleeding, and cessation of bowel movement), CD-related major abdominal surgery (intestinal resection or stricturoplasty), and steroid use for at least two months after the onset of anti-TNF therapy. Safety included serious infections leading to treatment cessation.

Effectiveness was evaluated until the occurrence of any events or the completion of the study (last follow-up date, February 2021).

Statistical Analysis

The distribution of continuous variables was assessed with the Shapiro-Wilk test, normality plots, coefficient of variation, and skewness/kurtosis statistics. Hb and HCT were presented as mean±standard deviation (mean±SD), while other numeric variables and categorical variables were reported as median [interquartile range (IQR): 1st-3rd quartile] and frequency (%), respectively.

The patient groups treated by IFX and ADA were compared using the independent samples *t*-test for Hb and HCT, and the Mann-Whitney U test for other quantitative variables. The Pearson's Chi-square test, Yates' Chi-square test, Fisher's exact test, and Fisher-Freeman-Halton test were performed to examine the qualitative variables between the two groups based on the size of the cross-table and the minimum expected frequency. Drug persistence was evaluated by Kaplan-Meier analysis with the log-rank test. Since the drug persistence rate was very close to 50.0% at the end of the follow-up period, the mean drug persistence duration was presented with its 95% confidence interval, instead of the median value. Subgroup analyses were performed considering the addition of IM therapies (thiopurines or MTX). A p-value <0.05 was considered statistically significant.

All statistical analyses and computations were performed *via* IBM SPSS Statistics for Windows Version 22.0 (IBM Corp., Armonk, NY, USA).

Results

Patients Characteristics

A total of 308 biologic-naïve adult patients with CD who received anti-TNF therapy were identified between December 2007 and February 2021. Forty-seven patients received anti-TNF therapy for less than six months, 34 patients had missing information, and three patients received anti-TNF therapy for rheumatologic reasons; therefore, 84 patients were excluded from the study. A total of 224 eligible patients were included, of whom 101 were treated with IFX and 123 were treated with ADA first (Figure 1).

Patient demographics, clinical features, and treatment characteristics stratified by IFX, and ADA are presented in Table I. Median disease durations were 7.01 years (IQR: 3.82-12.29) and 6.91 years (IQR: 3.94-10.95) for IFX and ADA, respectively.

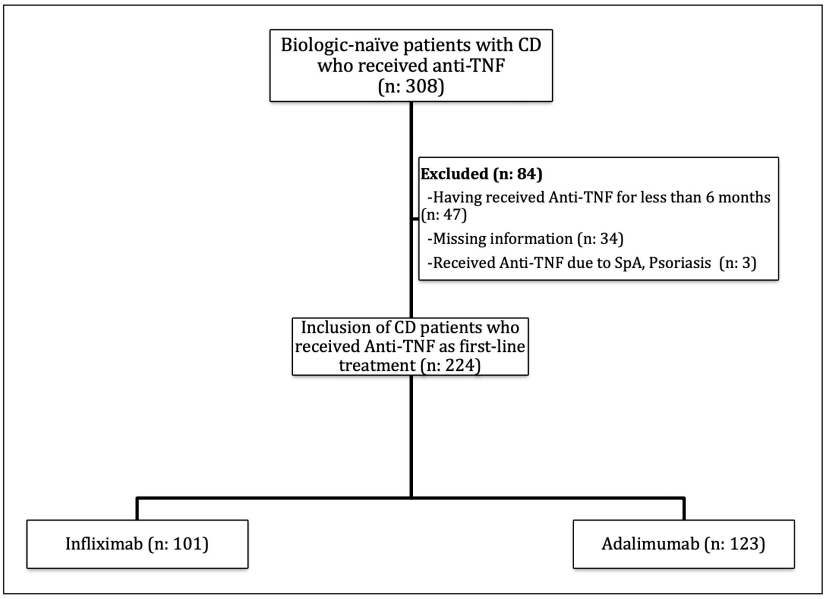

Figure 1. Flow chart for identification of biologic-naïve patients with Crohn's disease.

Table I. Demographic and clinical characteristics of patients with CD.

	Total (n=224)	IFX group (n=101)	ADA group (n=123)	*p*-value
Age at onset of CD (years)	31.41 (24.52-39.02)	32.18 (24.12-40.00)	30.02 (25.48-38.10)	0.631
Disease duration (years)	6.93 (3.85-11.49)	7.01 (3.82-12.29)	6.91 (3.94-10.95)	0.612
Age at onset of TNF antagonist (years)	37.23 (30.04-45.86)	37.66 (28.09-46.85)	35.81 (30.35-45.18)	0.583
Time interval between CD onset and the start of a TNF antagonist (years)	3.80 (1.37-8.82)	3.65 (1.20-9.85)	3.89 (1.47-8.08)	0.962
Follow-up time since starting TNF (years)	2.00 (1.21-3.41)	2.36 (1.29-3.35)	1.86 (1.10-3.44)	0.188
Female / Male	83/141 (37.1/62.9)	39/62 (38.6/61.4)	44/79 (35.8/64.2)	0.661
Smokers (Current/Ex)[1]	73/69 (34.0/32.1)	31/34 (33.0/36.2)	42/35 (37.4/28.9)	0.500
Family history of IBD[2]	25 (12.1)	10 (10.9)	15 (13.2)	0.775
Disease location				0.224
Ileal (L1)	85 (38.0)	41 (40.6)	44 (35.8)	
Colonic (L2)	33 (14.7)	19 (18.8)	14 (11.4)	
Ileo-colonic (L3)	103 (46.0)	40 (39.6)	63 (51.2)	
Upper GI disease (L4)	3 (1.3)	1 (1.0)	2 (1.6)	
Disease behavior				0.657
Inflammatory disease (B1)	153 (68.3)	69 (68.3)	84 (68.3)	
Stenosing (B2)	24 (10.7)	9 (8.9)	15 (12.2)	
Penetrating (B3)	47 (21.0)	23 (22.8)	24 (19.5)	
Perianal disease	81 (36.3)	33 (32.7)	48 (39.0)	0.325
Extra-intestinal manifestations[3]	108 (50.9)	50 (52.6)	58 (49.6)	0.658
Peripheral arthralgia	61 (28.8)	31 (32.6)	30 (25.6)	0.264
Peripheral arthritis	17 (8.0)	7 (7.4)	10 (8.5)	0.952
Ankylosing spondylitis	14 (6.6)	3 (3.2)	11 (9.4)	0.123
Sacroiliitis	12 (5.7)	6 (6.3)	6 (5.1)	0.942
Erythema nodosum	8 (3.8)	0 (0.0)	8 (6.8)	**0.009**
Pyoderma gangrenous	3 (1.4)	0 (0.0)	3 (2.6)	0.255
Aphthous ulcer	29 (13.7)	12 (12.6)	17 (14.5)	0.842
Uveitis	1 (0.5)	1 (1.1)	0 (0.0)	0.448
Episcleritis	1 (0.5)	0 (0.0)	1 (0.9)	>0.999
Primary sclerosing cholangitis	4 (1.9)	1 (1.1)	3 (2.6)	0.630
Prior major abdominal surgery	98 (43.8)	44 (43.6)	54 (43.9)	0.960
Prior IM exposure	212 (94.6)	95 (94.1)	117 (95.1)	0.958
Thiopurine	190 (84.8)	86 (85.1)	104 (84.6)	>0.999
Methotrexate	21 (9.4)	8 (7.9)	13 (10.6)	0.655
Concomitant medication (at baseline)	172 (76.8)	82 (81.2)	90 (73.2)	0.209
Thiopurine	56 (25.0)	33 (32.7)	23 (18.7)	**0.016**
Methotrexate	15 (6.7)	11 (10.9)	4 (3.3)	**0.045**
Mesalazine	79 (35.3)	34 (33.7)	45 (36.6)	0.649
Sulphapyridine	13 (5.8)	8 (7.9)	5 (4.1)	0.347
Budesonide	1 (0.4)	0 (0.0)	1 (0.8)	>0.999
Steroids	113 (50.4)	54 (53.5)	59 (48.0)	0.413
Baseline CRP4 (mg/L)	5.30 (1.92-14.15)	5.40 (2.10-19.60)	4.90 (1.90-11.95)	0.338
Hematocrit[4] **(%)**	40.74±5.14	39.90±5.52	41.45±4.72	0.054
Hemoglobin[4] **(mg/dL)**	13.24±1.92	12.96±1.99	13.47±1.83	0.089
Albumin[5] **(g/dL)**	4.20 (4.00-4.52)	4.20 (3.90-4.51)	4.30 (4.00-4.60)	0.355
Baseline CDAI score[6]	150 (100-252)	152 (100-266)	150 (100-240)	0.833

IFX: Infliximab, ADA: Adalimumab, CD: Crohn's Disease, TNF: Tumor Necrosis Factor, IBD: Inflammatory Bowel Disease, GI: Gastrointestinal, IM: Immunomodulator, CRP: C-reactive protein, CDAI: Crohn Disease Activity Index. Hemoglobin and hematocrit are presented as mean±sd. Categorical variables and other quantitative variables are reported in frequency (%) and median (1st quartile-3rd quartile), respectively. [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 IFX and n=89 for ADA. [5]n=74 for IFX and n=88 for ADA. [6]n=101 for IFX and n=121 for ADA.

The median ages at onset of CD and TNF antagonist were 32.18 years (IQR: 24.12-40.00) and 37.66 years (IQR: 28.09-46.85), respectively, in the IFX group and 30.02 years (IQR: 25.48-38.10) and 35.81 years (IQR: 30.35-45.18), respectively, in the ADA group. There were 39 (38.6%) females in the IFX group and 44 (35.8%) females in the ADA group. Among the IFX and ADA groups, active smoking was present in 33.0% (n=31) and 37.4% (n=42), family histories of IBD were present in 10.9% (n=10) and 13.2% (n=15), the perianal disease was present in 32.7% (n=33) and 39.0% (n=48), major abdominal surgery was present in 43.6% (n=44) and 43.9% (n=54), and at least one extraintestinal finding was present in 52.6% (n=50) and 49.6% (n=58), respectively. There were no significant differences between the two groups with respect to demographic and clinical characteristics, except for an erythema nodosum manifestation (p>0.05). Considering the extra-intestinal manifestations, erythema nodosum was seen in only eight (6.8%) patients in the ADA group, resulting in a significant difference compared to those in the IFX group (p=0.009).

Concomitant steroid use was found in 113 patients (50.4%) and there was no significant difference between the IFX (n=54, 53.5%) and ADA (n=59, 48.0%) groups (p=0.413). Overall, 71 (31.7%) patients had used concomitant IM agents at the time of starting anti-TNF. There were 27 (22.0%) therapeutic exposures to ADA initiated as an IM combination therapy and 44 (43.6%) to IFX combination therapy (Table I). Thiopurine or MTX as a combination therapy at baseline was more frequent in the IFX group, compared to those in the ADA group (p=0.016 and p=0.045, respectively) (Table I).

Comparative Effectiveness and Safety of IFX vs. ADA

The median follow-up duration from initiation of anti-TNF therapy was 2.36 years (IQR: 1.29-3.35) for the IFX group and 1.86 years (IQR: 1.10-3.44) for the ADA group (p=0.188), and the total median follow-up time was 2.00 years (IQR: 1.21-3.41). The mean drug persistence durations were 6.59 years (95% CI: 5.72-7.46) and 5.70 years (95% CI: 4.88-6.53) in the IFX and ADA groups, respectively, with a significant difference (p=0.047) (Figure 2). However, there were no significant differences between the IFX and ADA groups regarding the overall drug persistence rate (IFX *vs.* ADA: n=83, 82.2% *vs.* n=88, 91.5%, p=0.062). The two groups were also similar in terms of steroid use rate (IFX *vs.* ADA: 4.0% *vs.* 10.6%, p=0.109), CD-related hospitalization (IFX *vs.* ADA: 13.9% *vs.* 22.8%, p=0.127), and CD-related surgery (IFX *vs.* ADA: 9.9% *vs.* 13.0%, p=0.608) p=0.109 (IFX *vs.* ADA: 1.0% *vs.* 0.8%, p>0.999). All effectiveness and safety outcomes are displayed in Figure 3.

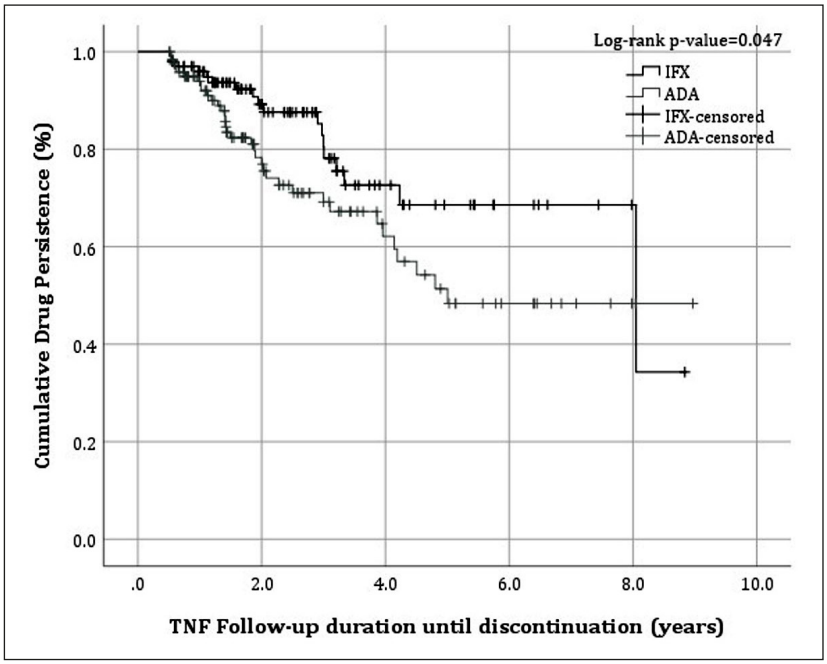

Figure 2. Kaplan-Meier curve for drug persistence in IFX and ADA groups.

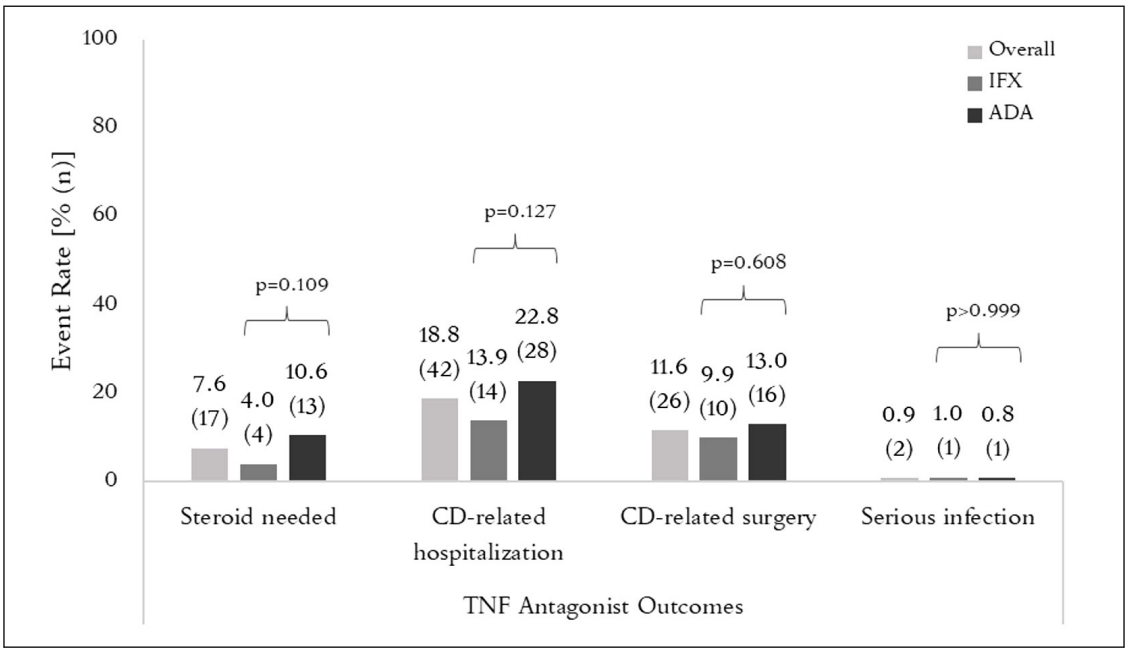

Figure 3. Distribution of TNF antagonist outcomes.

The analysis of each drug separately demonstrated that there were no significant differences in the rates of steroid use, CD-related hospitalization, and CD-related surgery between monotherapy and combination therapy with an IM agent (p>0.05) (Table II). There were also no significant differences between the combinations of IFX with an IM agent and ADA with an IM agent in terms of main outcomes (p>0.05) (Table II).

Discussion

CD is a chronic, inflammatory, and relapsing disease. Anti-TNF agents can be used in moderate and severe CD, both alone and in combination with IM treatments, in remission induction and maintenance therapy. However, long-term real-life data comparing ADA and IFX treatments head-to-head are lacking. In this single-center, large cohort study, we observed

Table II. Subgroup analyses of treatment outcomes of combination with IM agents or monotherapy within each group in CD.

	IFX (n=101)			ADA (n=123)			
	Mono (n=57)	With IM (n=44)	*p*-value	Mono (n=96)	With IM (n=27)	*p*-value	*p*-value[1]
TNF antagonist outcomes							
Steroid needed	1 (1.8)	3 (6.8)	0.315	11 (11.5)	2 (7.4)	0.731	>0.999
CD-related hospitalization	8 (14.0)	6 (13.6)	>0.999	22 (22.9)	6 (22.2)	>0.999	0.515
CD-related surgery	6 (10.5)	4 (9.1)	>0.999	10 (10.4)	6 (22.2)	0.116	0.164
Infectious adverse event leading to treatment cessation	0 (0.0)	1 (2.3)	0.436	1 (1.0)	0 (0.0)	>0.999	>0.999
Follow-up time from starting TNF	2.04 (1.33-3.35)	2.47 (1.25-3.48)	0.775	1.86 (1.15-3.27)	1.70 (0.90-3.64)	0.886	0.477

Follow-up time is reported as median (1st quartile-3rd quartile), while others are summarized by frequency (%). IFX: Infliximab, ADA: Adalimumab, CD: Crohn Disease, IM: Immunomodulator (Azathioprine, Mercaptopurine, or Methotrexate). [1]IFX Group with IM vs. ADA Group with IM.

that IFX and ADA were similar in terms of steroid use, CD-related hospitalization, CD-related major abdominal surgery, and serious infections leading to treatment cessation in the biologic-naïve CD patients. Our patients' baseline demographics, clinical and laboratory features, and concurrent conventional treatment characteristics were similar between the IFX and ADA groups. The median follow-up time after starting TNF antagonist treatment was 2.00 years (IQR: 1.21-3.41). Additionally, Kaplan-Meier analysis revealed a significant difference between the IFX and ADA groups in the mean drug persistence duration, which was 6.59 years in the IFX group and 5.70 years in the ADA group. Nevertheless, the total drug persistence rate did not significantly differ between the two groups. The IFX patients received more combination therapy than the ADA patients. However, we did not detect any significant differences regarding the four main outcomes between monotherapy and combination therapy with an IM agent in our inter- or intragroup analyses.

Randomized controlled studies[16] comparing anti-TNF therapies have been reported in IBD; however, large, and long-term prospective studies comparing the effectiveness of different anti-TNF therapies have not been performed. Real-world experiences[16-28] were reported regarding the comparison of effectiveness and safety between IFX and ADA in patients with CD, and based on these results, IFX and ADA seem to be proportionately effective and safe in patients with CD. Comparative analyses of IFX and ADA were also performed among biologic-naïve patients with CD[17-19,21-23,25,27,28]. The majority of those were able to compare important outcomes, such as hospitalization, abdominal surgery, or serious infection[18,22,23,25,27], whereas some examined only steroid-free clinical remission[17,19,21,28]. In a study released in 2021, Macaluso et al[16] examined biological therapies for inflammatory bowel diseases with real-life data, and concluded that IFX and ADA are equally effective in treating CD. IFX and ADA were evaluated in 327 patients by Doecke et al[20], who reported that their response characteristics were comparable. To maintain a response as good as ADA monotherapy, IFX needs to be used concurrently with an immunomodulator. Again, IFX and ADA were evaluated in TNF-a inhibitor naive and non-naive patients with CD in another real-life study by Macaluso et al[26], and equal efficacy was discovered in both groups. Our research used real-life data from biologically unexposed patients to compare ADA and IFX treatments for CD. Both anti-TNF therapies were shown to have comparable long-term efficacy and safety.

In a meta-analysis from 2022, Yang et al[29] examined the efficacy and safety of ADA and IFX therapies for Crohn's patients. The researchers examined a total of 14 studies and discovered that both naive and non-naive individuals showed identical efficacy and safety results for ADA and IFX. In another meta-analysis, Gangwani et al[30] examined the efficacy and side-effect profiles of the ADA and IFX therapies for preventing the postoperative recurrence of CD. In their study, published in 2021, Tursi et al[31] examined the long-term effectiveness and safety profiles of IFX and ADA therapies in individuals with ulcerative colitis and CD. Their research led them to conclude that both anti-TNF medications were equally effective over the long term, with ADA treatment showing fewer adverse effects. In a retrospective cohort study, Osterman et al[18] examined 2,310 CD patients who received ADA or IFX therapies using the US Medicare database. Hospitalization and abdominal surgery associated with CD, as well as disease status at week 26 were the study's primary outcomes. In terms of treatment effectiveness, abdominal surgery, and hospitalization, there was no discernible difference between the ADA and IFX groups. Singh et al[22] examined 3,205 patients in a different, large, retrospective, and database-based cohort analysis. In the study's effectiveness outcomes, which included all-cause hospitalization, CD-related hospitalization, major abdominal surgery, and serious infections, there was no substantial difference between IFX and ADA. Again, Singh et al[25] conducted a retrospective cohort study comparing the efficacy and safety of IFX and ADA using administrative claims from 827 biologic-naive patients with CD. They found no significant differences in the rates of all-cause hospitalization, CD-related hospitalization, abdominal surgery, and serious infection. In 852 individuals with CD, Targownik et al[27] reported that there were no differences in hospitalization, intestinal resection, corticosteroid use, or change in anti-TNF medication. In our study, results regarding the long-term efficacy and safety of IFX and ADA in biologic-naïve patients with CD, which are comparable with respect to steroid use, CD-related hospitalization, CD-related major abdominal surgery, and serious infections in both groups are usually consistent with the results of above-mentioned long-term, real-life larger cohort observational studies[18,25,27], except only one study in which lower risks of abdominal surgery, CD-related hospitalization, and corticosteroid use were observed in the IFX group compared to the ADA group[22].

In a multicenter, retrospective study, Inokuchi et al[28] examined the efficacy of IFX and ADA in treating 263 CD patients, with the endpoint being a steroid-free remission rate. There was no discernible difference in the long-term prognosis between biologic-naïve CD patients who began treatment with IFX or ADA first. In a retrospective cohort study by Kestens et al[17], 100 anti-TNF-naïve patients were given IFX, while 100 patients received ADA, and the patients' steroid-free clinical response – defined as the absence of hospitalization or CD-related surgery, discontinuation of anti-TNF, and steroid dependency – was assessed. No significant difference was found between the two groups. In the study conducted by Narula et al[19], 362 CD patients who had never received anti-TNF therapy were prospectively examined; 251 patients received IFX treatment, and 111 received ADA treatment. At 12 weeks and 12 months, clinical remission, clinical response, and steroid-free remission were assessed with the Harvey-Bradshaw Index (HBI), which revealed no discernible difference between the two groups. In our study, we observed no significant differences between biologic-naïve CD patients who began IFX or ADA treatment first in terms of steroid necessitation during follow-up, which is consistent with studies examining steroid-free clinical remission only[28,17,19].

Despite few conflicting results and discussion regarding the comparison of IFX and ADA, overall outcomes have shown that the two have similar effectiveness and safety profiles, which is consistent with our results. Nevertheless, comparisons of IFX and ADA in CD patients treated with monotherapy or in combination with an IM agent revealed distinctive results. While Cosnes et al[21] and Targownik et al[27] observed that combination therapy was superior to monotherapy, Kestens et al[17] and Benmassaoud et al[23] revealed superiority in CD patients treated with IFX only, but not ADA. However, Osterman et al[18], Narula et al[19], Inokuchi et al[22] and Singh et al[25,28] (2016 and 2018) observed similar effectiveness and safety among the combinations of both IFX and ADA with IM therapy and monotherapy. In our study, there were no significant differences in main outcomes between monotherapy and combination therapy with an IM agent in patients using IFX or ADA. In our study, the majority of patients (90.1%) who were administered TNF antagonists with IM combination therapy were already exposed to IM agents, which they had developed resistance to. Furthermore, the rate of IFX with IM combination was more than that of ADA with IM combination, which may reveal that patients treated with IFX have had more extensive and severe disease. Therefore, similar effectiveness rates may be confounded by higher disease burden and more experienced IM therapies previously. Our results regarding IM combination therapy are concomitant with some studies[18,19,22,25,28], nevertheless not with SONIC results[13] and others[21,27]. In the SONIC trial[13], concomitant immunosuppressant therapy with thiopurines has been demonstrated to minimize the response to IFX treatment in patients already exposed to thiopurines[13]. Further studies regarding the combination anti-TNF with IM therapy will provide additional information for long-term outcomes.

Its single-center design, and being the first anti-TNF treatment, long-term outcome study providing real-life data are the two major strengths of our study. Our limitations include its retrospective design, and lack of measurement of drug levels, anti-drug antibodies, fecal calprotectin, or endoscopic activity.

Conclusions

CD is a chronic, inflammatory, relapsing disease that negatively affects the quality of life.

Two of the most used anti-TNF agents are ADA and IFX, and there are not enough publications comparing these two agents head-to-head with real-life data. In this retrospective, observational, tertiary single-center study, we compared IFX and ADA head-to-head in biologically naïve Crohn's patients and found that IFX and ADA were comparable in terms of steroid use, CD-related hospitalization, CD-related major abdominal surgery, and significant infections leading to treatment discontinuation. The patient outcomes were similar whether IFX and ADA were given as monotherapy or in conjunction with an IM. Patients with moderate to severe CD who are biological-agent naïve can start treatment with either IFX or ADA. It would be appropriate to individualize the patient's treatment to include IM during treatment.

Declaration of Previous Publication

The study was presented as an abstract at the 16th Congress of ECCO, Virtual, 2021.

Authors' Contributions

Author contributions: CE, IY and MBD planned the conception and design of the study. VK, FK, CE and KK performed the data collection. IY and AA performed data analyses. IY and AA interpreted the data. IY, CE and AA drafted the manuscript. All authors revised and approved the final version of the manuscript to be submitted.

Data Availability
The data underlying this article are available within the article. Any additional information will be shared on reasonable request to the corresponding author.

Informed Consent
Informed consent was obtained from all patients included in the study.

Ethics Approval
This study complied with the ethical guidelines of the 1975 Helsinki Declaration, later modified in 2013. The study protocol was approved by Ankara City Hospital Ethics Committee (E1-20-862).

Conflict of Interest
Authors have no conflicts of interest to declare.

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