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A Propensity Score-matched Comparison of Infliximab and Adalimumab in Tumour Necrosis Factor-α Inhibitor-naïve and Non-naïve Patients With Crohn's Disease: Real-Life Data From the Sicilian Network for Inflammatory Bowel Disease

Fabio Salvatore Macaluso,[a,*] Walter Fries,[b] Antonio Carlo Privitera,[c] Maria Cappello,[d] Sebastiano Siringo,[e] Gaetano Inserra,[f] Antonio Magnano,[g] Roberto Di Mitri,[h] Filippo Mocciaro,[h] Nunzio Belluardo,[i] Giuseppe Scarpulla,[j] Giovanni Magrì,[k] Antonino Trovatello,[l] Antonio Carroccio,[m] Salvatore Genova,[n] Carmelo Bertolami,[o] Roberto Vassallo,[p] Claudio Romano,[q] Michele Citrano,[r] Salvatore Accomando,[s] Marco Ventimiglia,[a] Sara Renna,[a] Rosalba Orlando,[a] Giulia Rizzuto,[a] Serena Porcari,[b] Concetta Ferracane,[c] Mario Cottone,[a] Ambrogio Orlando[a]; Sicilian Network for Inflammatory Bowel Diseases [SN-IBD]

[a]Inflammatory Bowel Disease Unit, A.O.O.R. 'Villa Sofia-Cervello', Palermo, Italy [b]Inflammatory Bowel Disease Unit, A.O.U. Policlinico 'G. Martino', Messina, Italy [c]Inflammatory Bowel Disease Unit, A.O. 'Cannizzaro', Catania, Italy [d]Gastroenterology and Hepatology Unit, A.O.U. Policlinico 'G. Giaccone', Palermo, Italy [e]Gastroenterology Unit, A.R.N.A.S. 'Garibaldi', Catania, Italy [f]Internal Medicine Unit, A.O.U. Policlinico 'Vittorio Emanuele', Catania, Italy [g]Gastroenterology Unit, A.O.U. Policlinico 'Vittorio Emanuele', Catania, Italy [h]Gastroenterology and Endoscopy Unit, A.R.N.A.S. 'Civico Di Cristina Benfratelli', Palermo, Italy [i]Gastroenterology Unit, A.O. 'Guzzardi', Vittoria, Italy [j]Gastroenterology Unit, A.O.O.R. 'S. Elia- M. Raimondi', Caltanissetta, Italy [k]Gastroenterology Unit, A.O. 'Santa Marta e S. Venera', Acireale, Italy [l]Surgery Unit, A.O. 'Umberto I', Siracusa, Italy [m]Internal Medicine Unit, A.O. 'Giovanni Paolo II', Sciacca, Italy [n]Gastroenterology and Endoscopy Unit, A.O. 'S. Antonio Abate', Trapani, Italy [o]Gastroenterology Unit, A.O.O.R. 'Papardo Piemonte', Messina, Italy [p]Gastroenterology and Endoscopy Unit, A.O. 'Buccheri La Ferla Fatebenefratelli', Palermo, Italy [q]Pediatric Gastroenterology Unit, A.O.U. Policlinico 'G. Martino', Messina, Italy [r]Pediatric Unit, A.O.O.R. 'Villa Sofia-Cervello', Palermo, Italy [s]Pediatric Unit, A.O.U. Policlinico 'G. Giaccone', Palermo, Italy

Corresponding author: Fabio Salvatore Macaluso, MD; Inflammatory Bowel Disease Unit, 'Villa Sofia-Cervello' Hospital, Via Trabucco 180, 90146 Palermo, Italy. Tel.: +39 0916802966; fax: +39 0916802042; email: fsmacaluso@gmail.com

Abstract

Background and Aims: There is an unmet need to better understand the effectiveness of different biologics in inflammatory bowel diseases. We aimed at performing a multicentre, real-life comparison of the effectiveness of infliximab [IFX] and adalimumab [ADA] in Crohn's disease [CD].
Methods: Data of consecutive patients with CD treated with IFX and ADA from January 2013 to May 2017 were extracted from the cohort of the Sicilian Network for Inflammatory Bowel Disease.

We used propensity score-matching accounting for the main baseline characteristics in TNF-α inhibitor-naïve and non-naïve patients.

Results: A total of 632 patients [735 total treatments] were included. Among naïve patients, a clinical benefit [the sum of steroid-free remission plus clinical response] was achieved in 81.8% patients treated with ADA and in 77.6% patients treated with IFX (adjusted odds ratio [OR]: 1.23, 95% CI 0.63-2-44, $p = 0.547$] at 12 weeks; after 1 year, a clinical benefit was achieved in 69.2% of patients treated with ADA and in 64.5% patients treated with IFX [adjusted OR: 1.10, 95% CI 0.61–1.96, $p = 0.766$]. Among non-naïve patients, a clinical benefit was achieved in 61.7% of patients treated with ADA and in 68.1% of patients treated with IFX [adjusted OR: 0.72, 95% CI 0.21–2.44, $p = 0.600$] at 12 weeks; after 1 year, a clinical benefit was achieved in 48.9% of patients treated with ADA and in 40.4% patients treated with IFX [adjusted OR: 1.23, 95% CI 0.54–2.86, $p = 0.620$].

Conclusions: In this propensity score-matched comparison of ADA and IFX in CD, both drugs showed high rates of clinical benefit, without significant differences between them.

Key Words: Adalimumab; infliximab; propensity score

1. Introduction

Tumor necrosis factor-α [TNFα] inhibitors, particularly infliximab [IFX] and adalimumab [ADA], have dramatically changed the management of moderate to severe Crohn's disease [CD].[1] Even in the rapidly evolving scenario of the therapeutic weaponry for CD—including novel biologics and small molecule drugs with different mechanisms of actions[2]—TNF-α inhibitors are still considered a milestone for the treatment of this complex disease.[3] Anyway, although these drugs have been available in clinical practice for several years, there are many aspects that have not been fully understood yet: we know that they are effective, but we do not know whether there may be differences in effectiveness among them, and which subsets of patients could benefit more from one drug or another. As a consequence, the choice of a TNF-α inhibitor is currently based on patient and clinician preferences, or on insurance coverage. This relevant lack of knowledge is mainly due to the absence of comparative head-to-head trials between the various drugs, whose efficacy and safety were always compared against placebo.[4] Furthermore, there is a sharp discrepancy between the patients enrolled in phase II/III clinical trials of all biologics currently used in CD, and clinical practice: it is estimated that at least one-third of inflammatory bowel disease [IBD] patients would not be eligible to participate in a clinical trial of biological therapy.[5] The poor external validity of the results obtained in clinical trials and the difference in their designs confer limited value to the findings obtained with any indirect comparison of IFX and ADA by network meta-analyses.[6,7] More useful indications may be provided by real-life observational studies comparing the two drugs.[8–15] Unfortunately, bias in patient selection, short follow-up, evaluation of the effectiveness with endpoints such as hospitalisations and surgery—and not with clinical outcomes, such as steroid-free remission and clinical response—and use of administrative claims only could limit the meaningfulness of the observed results. In addition, most of these observational studies focused on TNF-α inhibitor-naïve patients, and data on non-naïve patients are less represented.

On these premises, web-based data from the cohort of the Sicilian Network for Inflammatory Bowel Disease [SN-IBD] were extracted to perform a multicentre, real-life comparison of the effectiveness of ADA and IFX in CD through a propensity score-matched cohort study. Since the clinical response to a second TNF-α inhibitor is often inferior to that of the first TNF-α inhibitor,[16] we performed two distinct analyses for biologic-naïve and non-naïve patients, rather than a cumulative—and probably too heterogeneous—analysis of the overall population.

2. Materials and Methods

2.1. Patients

The SN-IBD is a group composed by all 16 centres prescribing biologics in Sicily. The choice of the 16 centres was made by the highest regional health authority, taking into account predefined requirements for an expert management of patients with IBD. Since January 2013, these centres have continuously entered into web-based software all real-life prospective data on patients with IBD treated with biologics, with the aim of monitoring efficacy, safety, appropriateness, and costs of these therapeutics in Sicily. So, all consecutive patients treated with IFX or ADA from January 2013 to May 2017, with at least 1 year of follow-up, were extracted from the cohort of SN-IBD for the purposes of this study. IFX and ADA were used in patients with moderately to severely active luminal CD according to recommended dosages,[3] with the possibility of treatment optimisation, i.e. shortening the administration intervals and/or increasing the dose for IFX up to a maximum of 10 mg/kg every 4 weeks, and shortening the administration intervals to every week for ADA. Both originator and biosimilar versions of IFX were used, even if patients treated with IFX biosimilars were all naïve to IFX [no switch nor past exposure to IFX originator]. Subjects without luminal active disease, who received IFX or ADA for ano-perineal CD or for extra-intestinal manifestations as the only indications for biological therapy, and those with less than 1 year of follow-up, were excluded from the analysis.

2.2. Data collection and measures of outcome

The following data were collected for each patient at baseline, i.e. at the initiation of IFX or ADA treatment: age, gender, smoking habit, age at diagnosis, disease duration, disease localisation, disease behaviour, presence of perianal disease, presence of extra-intestinal manifestations, type of TNFα inhibitor [IFX vs ADA], concomitant immunosuppressive therapy, previous resections, previous use of biologics [distinguishing between TNF-α inhibitor-naïve and non-naïve patients], and number of previous biologic treatments [for non-naïve patients only]. The reasons for previous discontinuation of anti-TNF therapy in pre-exposed

patients included lack of effectiveness and adverse events, but no case of patient/physician practice preference was reported. The need for therapeutic optimisation was evaluated at 1 year. Patients were then divided in TNF-α inhibitor-naïve and non-naïve patients, and the two groups were analysed separately. The effectiveness was evaluated at 12 weeks and at 1 year. As clinical endpoint, we assessed steroid-free remission, defined as resolution of abdominal pain and normalisation of bowel habit without steroid use, and clinical response, defined as the presence of mild or no abdominal pain plus a reduction of at least 50% of the number of bowel movements compared with baseline, without attaining the criteria defining the steroid-free remission. Patients with steroid-free remission or clinical response were deemed as having clinical benefit, so that the percentage of patients with clinical benefit was given by the sum of patients with steroid-free remission plus clinical response, whereas treatment failure was defined as discontinuation of IFX or ADA due to adverse events or inefficacy.

2.3. Statistics

Continuous variables were reported as medians with interquartile ranges [IQR], and categorical variables as frequency and percentage. Mann–Whitney U tests and χ^2 tests [or Fisher's exact test, where needed] were used for comparison of continuous and categorical variables, respectively.

Since patients were not randomly assigned to receive ADA or IFX treatment, a propensity score-adjusted analysis was performed to reduce the effect of treatment-selection bias and simulate the effects of randomisation[17] among both subgroups of TNF-α inhibitor-naïve and non-naïve patients. Propensity scores [the conditional probabilities of receiving IFX treatment, given the observed covariates] were evaluated using a non-parsimonious logistic regression model based on age, gender, smoking habit, age at diagnosis, disease duration, disease localisation, disease behaviour, presence of perianal disease, presence of extra-intestinal manifestations, concomitant immunosuppressive therapy, previous resections, need of therapeutic optimisation, and number of previous biologic treatments [for non-naïve patients only]. Overlap of the propensity-score distributions [i.e. the region of common support] was assessed by examining a graph of propensity scores across treatments. One-to-two [for the naïve patients subgroup], and one-to-one [for the non-naïve patients subgroup] nearest neighbour matching without replacement was performed with a caliper of width equal to 0.1 of the standard deviation of the logit of the propensity score, and the resulting score-matched pairs were used in subsequent analyses to assess the effectiveness of the drugs and the predictors of clinical benefit. Covariate balance was checked with standardised differences [absolute values <0.1 supported the assumption of balance between the groups]. The matched nature of data, and their repeated nature in the non-naïve patients group, were considered using a conditional logistic regression model for the assessment of the clinical outcomes at 12 weeks and 1 year. A double adjustment approach was also used to protect from potential propensity-score model mis-specification, by fitting propensity score-matching analysis models adjusted for all the above mentioned covariates. Results were considered statistically significant when $p \leq 0.05$ or when the 95% confidence intervals did not overlap. All statistical analyses were performed using R version 3.4.2 [R Foundation for Statistical Computing, Vienna, Austria].[18]

3. Results

3.1. Overall cohort

A total of 632 consecutive CD patients [735 total treatments] were included. In detail, 563 naïve [437 treated with ADA and 126 treated with IFX] and 147 non-naïve patients [172 total treatments: 59 ADA and 113 IFX] were analysed. The sum of naïve and non-naïve patients is superior to the total number of subjects with CD included in the study because a patient may be included in the naïve group during the first-line biologic treatment, and then—in case of multiple treatments—may be considered also in the non-naïve group during the subsequent line[s] of treatment.

After 2:1 propensity score-matching, the cohort for primary analysis of the naïve subgroup was restricted to 321 patients [214 treated with ADA and 107 with IFX], and their baseline demographic, clinical, and treatment characteristics, and the subsequent rates of treatment optimisation, were comparable [Table 1]. A plot of absolute standardised mean differences, before and after propensity score-matching, is shown in Figure 1; Supplementary Figure 1 [available as Supplementary data at *ECCO-JCC* online] depicts the density distribution of propensity scores of the two treatment groups, before and after matching. After 1:1 propensity score-matching, the cohort for primary analysis of the non-naïve subgroup was restricted to 81 patients [94 total treatments: 47 ADA and 47 IFX], and all baseline demographic, clinical, and treatment characteristics, lines of biological treatment, and the subsequent rates of treatment optimisation, were comparable [Table 2]. Figure 2 shows the plot of absolute standardised mean differences, before and after propensity score-matching, and the density distribution of propensity scores of the two treatment groups is depicted in Supplementary Figure 2, available as Supplementary data at *ECCO-JCC* online.

3.2. Comparative effectiveness of ADA vs IFX in naïve patients

After 12 weeks, a clinical benefit was achieved in 175/214 [81.8%] patients treated with ADA and in 84/107 [77.6%] patients treated with IFX [crude OR: 1.27, 95% CI 0.74–2.17, $p = 0.392$; adjusted OR: 1.23, 95% CI 0.63-2-44, $p = 0.547$; Figure 3]. A steroid-free remission was reported in 98/214 [45.8%] patients in the ADA group and in 35/107 [32.7%] patients in the IFX group [crude OR: 1.82, 95% CI 1.09–3.03, $p = 0.023$]. The logistic regression model, fitted considering the matched nature of the data, showed that previous surgery [adjusted OR: 0.17, 95% CI 0.04–0.69, $p = 0.013$] and increasing age at diagnosis [adjusted OR: 0.96, 95% CI 0.93–0.99, $p = 0.019$] were independent risk factors for a reduced rate of clinical benefit at 12 weeks.

After 1 year, a clinical benefit was achieved in 148/214 [69.2%] patients treated with ADA and in 69/107 [64.5%] patients treated with IFX [crude OR: 1.23, 95% CI 0.76–2.00, $p = 0.402$; adjusted OR: 1.10, 95% CI 0.61–1.96, $p = 0.766$; Figure 3]. A steroid-free remission was reported in 106/214 [49.5%] patients in the ADA group and in 38/107 [35.5%] patients in the IFX group [crude OR: 1.79, 95% CI 1.11–2.86, $p = 0.017$]. The conditional logistic regression model showed that previous surgery [adjusted OR: 0.19, 95% CI 0.04–0.78, $p = 0.021$], upper gastrointestinal localisation [adjusted OR: 0.20, 95% CI 0.05–0.84, $p = 0.028$], and internal fistulising disease at baseline [adjusted OR: 0.29, 95% CI 0.10–0.87, $p = 0.027$] were independent risk factors for a reduced rate of clinical benefit at 1 year.

Forty adverse events occurred in patients treated with ADA [incidence rate = 209.9/1000 person-years] and 33 events in patients treated with IFX [incidence rate = 359.8/1000 person-years]; the rate of adverse events was significantly higher in patient treated with IFX [incidence rate ratio = 1.71, p-value = 0.020—Supplementary Table 1, available as Supplementary data at *ECCO-JCC* online].

Table 1. Baseline characteristics of TNF-α inhibitor-naïve patients in the overall cohort and the propensity score-matched cohort.

		Overall cohort [*n* = 563]			2:1 PS-matched cohort [*n* = 321]		
		ADA	IFX	*p*	ADA	IFX	*p*
		n = 437	*n* = 126		*n* = 214	*n* = 107	
Gender [%]	Female	185 [42.3]	51 [40.5]	0.787	96 [44.9]	44 [41.1]	0.605
	Male	252 [57.7]	75 [59.5]		118 [55.1]	63 [58.9]	
Age at diagnosis, years, median [IQR]		27.00 [20.00, 38.00]	25.00 [17.25, 36.75]	0.052	23.00 [19.00, 35.00]	25.00 [17.00, 36.50]	0.991
Age at initiation of therapy. median [IQR]		38.34 [26.57, 49.73]	36.12 [22.00, 47.39]	0.050	34.45 [23.26, 47.02]	36.68 [22.15, 47.00]	0.872
CD duration, years, median [IQR]		6.00 [2.00, 13.00]	5.00 [1.00, 12.75]	0.592	5.00 [2.00, 11.75]	6.00 [2.00, 14.00]	0.860
Smoking habits [%]	Never	264 [60.4]	89 [70.6]		146 [68.2]	73 [68.2]	
	Former	50 [11.4]	12 [9.5]	0.104	21 [9.8]	11 [10.3]	0.989
	Current	123 [28.1]	25 [19.8]		47 [22.0]	23 [21.5]	
Localisation of disease [%]	Ileal	169 [38.7]	36 [28.6]		68 [31.8]	35 [32.7]	
	Colic	36 [8.2]	28 [22.2]	<0.001	28 [13.1]	15 [14.0]	0.990
	Ileo-colic	207 [47.4]	49 [38.9]		101 [47.2]	49 [45.8]	
	Upper GI	25 [5.7]	13 [10.3]		17 [7.9]	8 [7.5]	
Disease behaviour [%]	Inflammatory	154 [35.2]	57 [45.2]		87 [40.7]	45 [42.1]	
	Stricturing	219 [50.1]	52 [41.3]	0.117	104 [48.6]	47 [43.9]	0.604
	Fistulising	64 [14.6]	17 [13.5]		23 [10.7]	15 [14.0]	
Perianal disease [%]	No	361 [82.6]	104 [82.5]	1.000	176 [82.2]	88 [82.2]	1.000
	Yes	76 [17.4]	22 [17.5]		38 [17.8]	19 [17.8]	
Extra-intestinal manifestation [%]	No	334 [76.4]	95 [75.4]	0.903	157 [73.4]	81 [75.7]	0.752
	Yes	103 [23.6]	31 [24.6]		57 [26.6]	26 [24.3]	
Previous surgery [%]	No	311 [71.2]	104 [82.5]	0.015	173 [80.8]	86 [80.4]	1.000
	Yes	126 [28.8]	22 [17.5]		41 [19.2]	21 [19.6]	
Combination therapy [%]	No	429 [98.2]	121 [96.0]	0.284	207 [96.7]	104 [97.2]	1.000
	Yes	8 [1.8]	5 [4.0]		7 [3.3]	3 [2.8]	
Therapeutic optimisation [%]	No	362 [82.8]	102 [81.0]	0.721	175 [81.8]	87 [81.3]	1.000
	Yes	75 [17.2]	24 [19.0]		39 [18.2]	20 [18.7]	

PS, propensity score; ADA, adalimumab; IFX, infliximab; IQR, interquartile range; CD, Crohn's disease; GI, gastrointestinal.

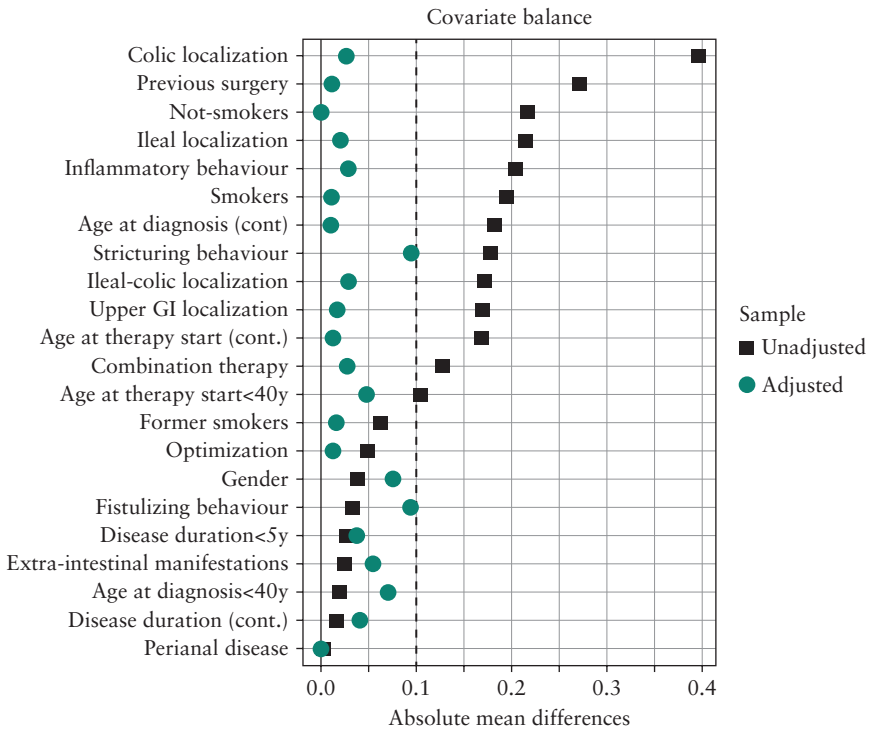

Figure 1. Plot of absolute standardised mean differences before and after propensity scorematching in tumour necrosis factor [TNF]-α inhibitor-naïve patients.

No difference was observed at 12 weeks [p = 0.347] or after 1 year [p = 0.205] when the effectiveness of infliximab originator [78 out of 107 IFX patients, 72.9%] was compared with that of biosimilars of infliximab [29 out of 107 IFX patients, 27.1%].

Of note, after 2 years, a clinical benefit was achieved in 67/146 [45.9%] patients treated with ADA and in 30/73 [41.1%] patients treated with IFX [crude OR: 1.22, 95% CI 0.69–2.16, p = 0.501; adjusted OR: 1.16, 95% CI 0.64–2.11, p = 0.621].

3.3. Comparative effectiveness of ADA vs IFX in non-naïve patients

After 12 weeks, a clinical benefit was achieved in 29/47 [61.7%] patients treated with ADA and in 32/47 [68.1%] patients treated with IFX [crude OR: 0.77, 95% CI 0.34–1.75, p = 0.533; adjusted OR: 0.72, 95% CI 0.21–2.44, p = 0.600; Figure 4]. A steroid-free remission was reported in 16/47 [34.0%] patients in the ADA group and in 10/47 [21.3%] patients in the IFX group [crude OR: 1.75, 95% CI 0.74–4.17, p = 0.207].

After 1 year, a clinical benefit was achieved in 23/47 [48.9%] patients treated with ADA and in 19/47 [40.4%] patients treated with IFX [crude OR: 1.32, 95% CI 0.64–2.70, p = 0.467; adjusted OR: 1.23, 95% CI 0.54–2.86, p = 0.620; Figure 4]. A steroid-free remission was reported in 13/47 [27.7%] patients in the ADA group and in 9/47 [19.1%] patients in the IFX group [crude OR: 1.56, 95% CI 0.61–4.00, p = 0.350]. The logistic regression model, fitted considering the matched nature of data, showed no significant prognostic factors of clinical benefit at 12 weeks or at 1 year.

Ten adverse events occurred in patients treated with ADA [incidence rate = 267.7/1000 person-years] and 33 events in patients treated with IFX [incidence rate = 688.7/1000 person-years]; the rate of adverse events was significantly higher in patients treated with IFX (incidence rate ratio [IRR]; 2.57, p-value = 0.009—(Supplementary Figure 2, available as Supplementary data at *ECCO-JCC* online).

Only seven out of 47 patients [14.9%] were treated with biosimilars of infliximab. Of note, after 2 years, a clinical benefit was obtained in 8/31 [25.8%] patients treated with ADA and in 9/36 [25.0%] patients treated with IFX [crude OR: 1.04, 95% CI 0.34–3.16, p = 0.940; adjusted OR: 1.14, 95% CI 0.31–4.32, p = 0.840].

4. Discussion

This real-life, multicentre study of patients with CD—extracted from the cohort of the SN-IBD—aimed at comparing the clinical effectiveness of IFX and ADA, using a propensity score-matched analysis. Our results provide relevant data about the effectiveness of the two drugs in everyday practice, showing that—over a temporal span of 1 year—there was no significant difference in the effectiveness of the two biologics, either in naïve or in non-naïve patients. A higher incidence of adverse events leading to treatment discontinuation, mainly infusion reactions, was reported for IFX, as expected.

The results of our study are generally in line with findings derived from smaller observational studies dealing with TNF-α inhibitor-naïve patients. A recent Dutch study[14] reported no significant difference in 1-year rates of steroid-free clinical response between ADA- [62%] and IFX-treated [65%] TNF-α inhibitor-naïve patients, and similar findings were observed in a consecutive series of 362 naïve patients with CD from four centres in Austria.[13] Furthermore, in a large prospective registry-based study, Cosnes *et al.*[15] showed similar rates of clinical response and drug survival in ADA- and IFX-treated patients at 6 months and at 2 years. Other studies comparing ADA and IFX in patients with CD were based on administrative claims, thus focusing not on clinical benefit, but on different outcomes such as all-cause or CD-related hospitalisation, major abdominal surgery, and serious infections. Osterman *et al.*[9] observed no significant difference in the risks of hospitalisation and abdominal surgery between ADA- and IFX-treated patients with CD, whereas

Table 2. Baseline characteristics ofTNF-α inhibitor non-naïve patients in the overall cohort and the propensity score-matched cohort

		Overall cohort [*n* = 172]			1:1 PS matched cohort [*n* = 94]		
		ADA	IFX	*p*	ADA	IFX	*p*
		n = 59	*n* = 113		*n* = 47	*n* = 47	
Gender [%]	Female	25 [42.4]	45 [39.8]	0.873	20 [42.6]	21 [44.7]	1.000
	Male	34 [57.6]	68 [60.2]		27 [57.4]	26 [55.3]	
Age at diagnosis, years, median [IQR]		23.00 [17.00, 33.50]	28.00 [20.00, 38.00]	0.065	25.00 [19.00, 34.50]	25.00 [17.50, 31.00]	0.454
Age at initiation of therapy, median [IQR]		33.22 [23.93, 44.18]	38.95 [28.39, 52.94]	0.025	35.74 [24.17, 45.83]	31.65 [26.57, 44.73]	0.777
CD duration, years, median [IQR]		7.00 [4.00, 13.00]	8.00 [4.00, 15.00]	0.412	7.00 [3.50, 11.50]	7.00 [4.00, 14.00]	0.612
Smoking habits [%]	Never	35 [59.3]	66 [58.4]		28 [59.6]	28 [59.6]	
	Former	7 [11.9]	11 [9.7]	0.865	5 [10.6]	5 [10.6]	1.000
	Current	17 [28.8]	36 [31.9]		14 [29.8]	14 [29.8]	
Localisation of disease [%]	Ileal	18 [30.5]	33 [29.2]		13 [27.7]	13 [27.7]	
	Colic	7 [11.9]	14 [12.4]	0.991	6 [12.8]	7 [14.9]	0.964
	Ileo-colic	30 [50.8]	57 [50.4]		25 [53.2]	25 [53.2]	
	Upper GI	4 [6.8]	9 [8.0]		3 [6.4]	2 [4.3]	
Disease behaviour [%]	Inflammatory	19 [32.2]	38 [33.6]		17 [36.2]	17 [36.2]	
	Stricturing	30 [50.8]	63 [55.8]	0.494	24 [51.1]	25 [53.2]	0.946
	Fistulising	10 [16.9]	12 [10.6]		6 [12.8]	5 [10.6]	
Perianal disease [%]	No	45 [76.3]	89 [78.8]	0.857	39 [83.0]	39 [83.0]	1.000
	Yes	14 [23.7]	24 [21.2]		8 [17.0]	8 [17.0]	
Extra-intestinal manifestation [%]	No	46 [78.0]	81 [71.7]	0.479	36 [76.6]	38 [80.9]	0.801
	Yes	13 [22.0]	32 [28.3]		11 [23.4]	9 [19.1]	
Previous surgery [%]	No	40 [67.8]	76 [67.3]	1.000	32 [68.1]	30 [63.8]	0.828
	Yes	19 [32.2]	37 [32.7]		15 [31.9]	17 [36.2]	
Combination therapy [%]	No	56 [94.9]	107 [94.7]	1.000	45 [95.7]	45 [95.7]	1.000
	Yes	3 [5.1]	6 [5.3]		2 [4.3]	2 [4.3]	
Therapeutic optimisation [%]	No	47 [79.7]	71 [62.8]	0.037	36 [76.6]	36 [76.6]	1.000
	Yes	12 [20.3]	42 [37.2]		11 [23.4]	11 [23.4]	
Number of previous biologic treatments	Two	42 [71.2]	99 [87.6]	0.014	35 [74.5]	35 [74.5]	1.000
	More than two	17 [28.8]	14 [12.4]		12 [25.5]	12 [25.5]	

PS, propensity score; ADA, adalimumab; IFX, infliximab; IQR, interquartile range; CD, Crohn's disease; GI, gastrointestinal.

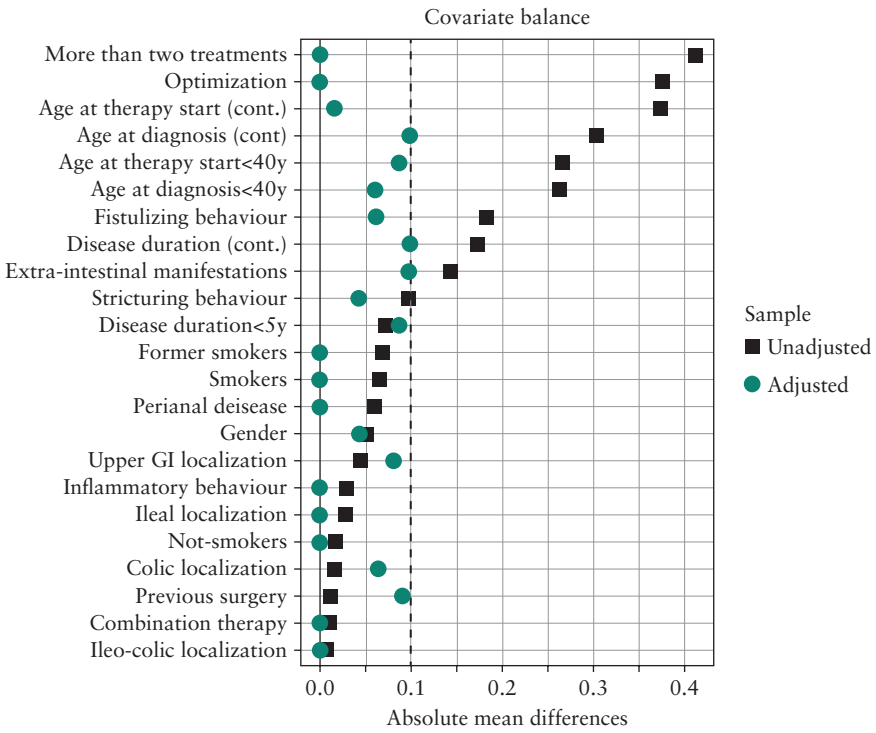

Figure 2. Plot of absolute standardised mean differences before and after propensity-score matching in tumour necrosis factor [TNF]-α inhibitor non-naïve patients.

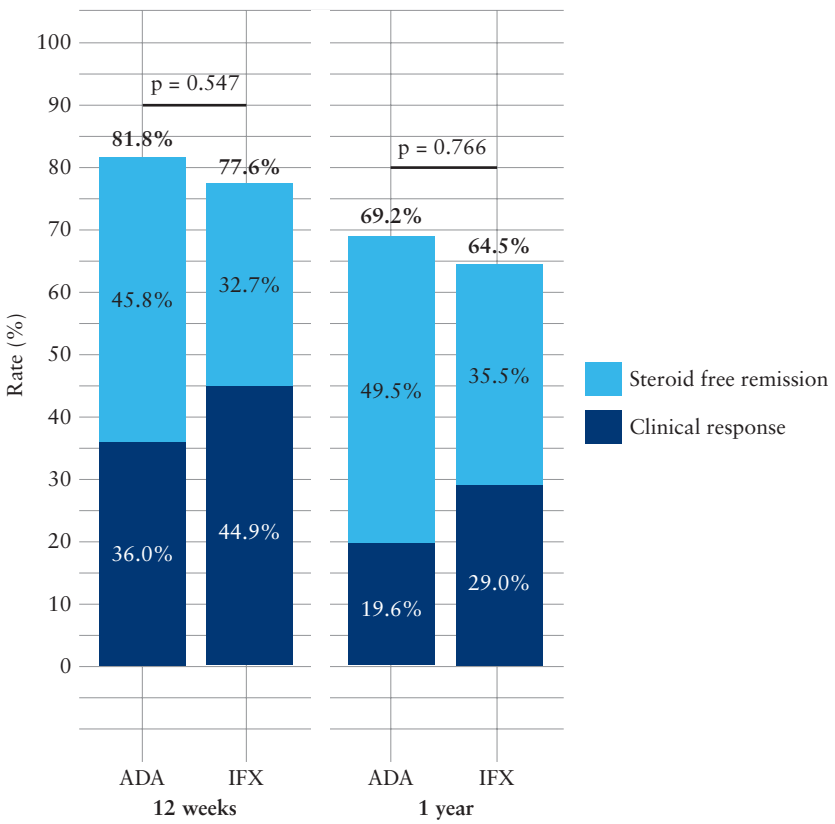

Figure 3. Clinical benefit [rate of remission plus clinical response] among tumour necrosis factor [TNF]-α inhibitor-naïve patients treated with adalimumab [ADA] and infliximab [IFX] at Week 12 and at 1 year.

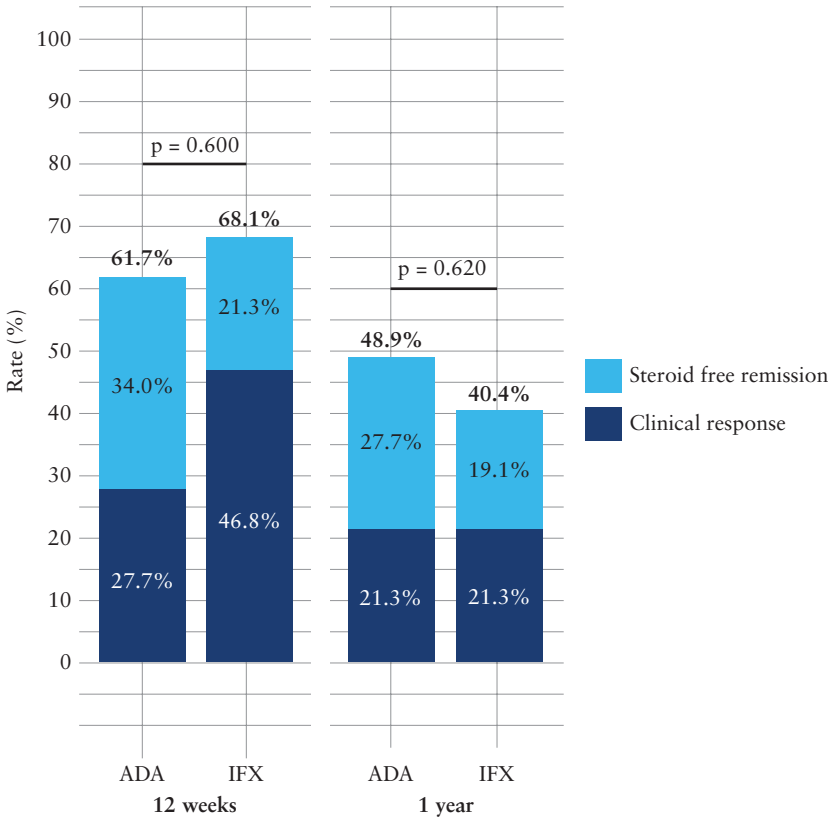

Figure 4. Clinical benefit [rate of remission plus clinical response] among tumour necrosis factor [TNF]-α inhibitor non-naïve patients treated with adalimumab [ADA] and infliximab [IFX] at Week 12 and at 1 year.

a large administrative claims-based study of 3205 TNF-α inhibitor-naïve patients with CD showed a lower risk of abdominal surgery, CD-related hospitalisation, and corticosteroid use in patients treated with IFX compared with those treated with ADA.[11] Conversely, a Canadian study by Targownik *et al.*[12] observed that there was no significant difference in 1-year rates of IBD-related surgery, hospitalisation, need for re-initiation of corticosteroids, or drug discontinuation between the two biologics.

Differently from the aforementioned papers, our analysis was based on the use of the propensity score, this representing the main strength of our study. We believe that this methodology is necessary when comparing the effectiveness of drugs, to tackle the effect of treatment-selection bias—an ineluctable issue in all real-life studies—and simulate the effects of randomisation. In particular, we adjusted for numerous variables in order to place the two drugs on the same starting line. The only other study which applied propensity score-matching to compare ADA and IFX revealed no significant difference in the effectiveness and safety of the two drugs among biologic-naïve patients with CD.[10] However, this elegant study differed from ours because it was based on administrative claims, and thus it focused on different outcomes such as hospitalizstion, surgery, and serious infections, but not on a pure clinical assessment. Furthermore, we identified some predictors of reduced clinical benefit among TNF-α inhibitor-naïve patients. After 12 weeks, previous surgery and increasing age at diagnosis were found to be independent risk factors for a reduced rate of clinical benefit.

Unexpectedly, the finding about age at diagnosis is not in agreement with the existing literature considering early age as a risk factor. Indeed, the lower rate of clinical benefit found in patients with age at diagnosis greater than 50 years, combined with a higher [than expected] rate of clinical benefit in very young patients [not older than 16 years], led to this statistically significant result; however, patients in the range 17–30 years had a worse response than those in the range 30–50 years. Furthermore, upper gastrointestinal localisation, internal fistulising disease at baseline, and previous surgery were associated with reduced rate of clinical benefit after 1 year. They are well-known negative prognostic factors in patients with CD treated with biologics, and this should be taken into account for any therapeutic decision in this setting.

Of note, the use of a concomitant immunosuppressant was not found to be associated with the clinical outcomes. This is probably due to the very low number of patients treated with combination therapy [approximately 3% in the matched cohort of naïve patients, and 4% among non-naïve patients]. Indeed, there is a homogeneous tendency among all the centres composing the Sicilian network to employ anti-TNF monotherapy, instead of the combination therapy, reserving this latter for a very small proportion of patients with strongly unfavourable prognostic factors. In addition, our study analysed the effectiveness of ADA and IFX among TNF-α inhibitor non-naïve patients, a population poorly represented in this kind of study. Even if the sample size of this specific subgroup was inferior to that of naïve patients, we confirmed the overall similar effectiveness of the two drugs also in this specific setting.

Another finding emerging from our analysis lies in the significantly higher rates of steroid-free remission both at 12 weeks and after 1 year among naïve patients treated with ADA compared with those treated with IFX. Although this result may lead to the hypothesis that ADA could induce and maintain a deeper remission compared with IFX, caution is warranted, because the propensity score-matching accounted for the main baseline characteristics of

patients but was not able to correct for the activity of the disease, as we did not use clinical scores. As a consequence, we can not exclude that patients treated with ADA may have had a less severe activity at baseline compared with those treated with IFX. Here, the absence of clinical scores represents a drawback of our study. Furthermore, data on endoscopic outcomes and markers of inflammation—such as C-reactive protein and faecal calprotectin—were not available; however, lack of systematically collected endoscopic or biochemical data is quite inevitable in real-life study and, even if our clinical endpoints were basically patient-reported, we believe that these methodological flaws may be counterbalanced by the rigorous application of the propensity score and the large sample size, making this cohort highly representative of clinical practice in IBD centres. Of note, the higher use of ADA in naïve patients may be explained by the limited number of seats for infusion therapy among the centres of our Sicilian network. Therefore, once the possibility of infusion therapy was saturated, there was an almost mandatory necessity to prescribe the subcutaneous drug instead of infliximab.

In conclusion, our large, propensity score-matched, real-life, multicentre study of CD patients extracted from the cohort of SN-IBD highlighted the overall equal—and good—effectiveness of ADA and IFX, in both TNF-α inhibitor-naïve and non-naïve patients. These findings can support physicians in the therapeutic decision-making processes for this complex disease.

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None.

Conflict of Interest

FSM served as an advisory board member for MSD, and received lecture grants from MSD and Takeda Pharmaceuticals. MC served as an advisory board member for AbbVie, MSD, Takeda Pharmaceuticals, and received lecture grants from AbbVie, MSD, Chiesi, and Takeda Pharmaceuticals. FM served as an advisory board member for AbbVie and MSD Pharmaceuticals, and received lecture grants from AbbVie, MSD, and Takeda Pharmaceuticals. SR served as an advisory board member for AbbVie and MSD Pharmaceuticals, and received lecture grants from AbbVie, MSD, and Takeda Pharmaceuticals/AO served as an advisory board member for AbbVie, MSD, Takeda Pharmaceuticals, and received lecture grants from AbbVie, MSD, Sofar, Chiesi, and Takeda Pharmaceuticals.

Author Contributions

FSM, AO, and MC planned the study, interpreted the data, and wrote the manuscript. MV performed the statistical analysis. All other authors were involved in data collection.

Supplementary Data

Supplementary data are available at *ECCO-JCC* online.

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