A propensity score-weighted comparison between adalimumab originator and its biosimilars, ABP501 and SB5, in inflammatory bowel disease: a multicenter Italian study

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Abstract

Background: Adalimumab is an effective and safe biological drug for the treatment of inflammatory bowel disease (IBD). Nowadays, several biosimilar agents are available, but data regarding their efficacy and safety in patients with IBD are still lacking. We aimed to compare the effectiveness and tolerability between adalimumab originator, ABP501 and SB5 biosimilars in patients with IBD in the short term (after induction and after 6 months of treatment) through a propensity score-weighted multicenter cohort study.

Methods: We included 156 patients with IBD, 69 patients with ulcerative colitis and 87 patients with Crohn's disease (CD) receiving ABP501 or SB5 biosimilars from January 2019 to April 2020 for moderate-to-severe disease. For comparison, a group of age- and sex-matched patients treated with adalimumab originator was used. We collected clinical and biochemical data after induction and at 6 months of treatment. Endoscopic data were recorded only at baseline.

Results: Overall, clinical benefit was achieved by 86.4% and 85.3% after induction and at 6 months, respectively, without a statistically significant difference between the three treatment groups ($p = 0.68$ and $p = 0.46$). However, after induction, we found significant differences between the two types of the disease (ulcerative colitis or CD, $p = 0.004$), with a greater clinical benefit achieved by patients with CD. Also, the therapeutic optimization rate between the three drugs was not statistically significant different ($p = 0.30$). All treatments showed a good safety profile, with only 10 patients who needed to stop therapy because of adverse events.

Conclusion: Adalimumab biosimilars seem to be as effective and safe as the originator in patients with IBD. Surely, they represent a great opportunity to reduce the costs of biological therapies, however larger and longer real-life studies are necessary.

Keywords: ABP501, adalimumab, anti-TNF, biosimilar, Crohn's disease, inflammatory bowel disease, SB5, ulcerative colitis

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Introduction

Inflammatory bowel disease (IBD), including Crohn's disease (CD) and ulcerative colitis (UC), are chronic inflammatory disorders which are characterized by periods of remission and relapses,[1] and can severely affect quality of life of

the patients.[2–6] However, their prognosis dramatically changed after the introduction of biological agents, particularly anti-tumor necrosis factor (TNF)-α,[7] which is demonstrated to reduce recurrence rate as well as hospitalization, and prevent complications.[8] Among these agents, adalimumab (ADA) is well recognized to be effective in treating IBD.[8,9] Indeed, registration trials and then the real-life studies demonstrated that it is effective and well tolerated in patients with UC as well as in those with CD.[10–13] Last but not least, it offers the convenience of self-injection, making this therapy particularly appropriate for outpatients with moderate steroid-dependent/refractory disease activity.[14]

ADA originator, Humira®, was introduced in 2002 and soon became one of the main therapies for moderate-to-severe IBD.[15] Since expiration of its patent, several biosimilars (i.e. a biologic drug highly similar to a previously approved existing biologic therapy) have been developed with substantial cost reduction for IBD-related healthcare.[16,17] ABP501 (Amgevita®) was the first biosimilar of ADA approved by both the US Food and Drug Administration (FDA) in 2016 and European Medicines Agency (EMA) in 2017 for all the clinical indications of ADA originator, including IBD.[17,18] One year later, in 2017, SB5 (Imraldi®) biosimilar was approved by the EMA as well.[19] For both biosimilars, however, there is a paucity of data in the IBD setting, since their approval for indications other than rheumatologic diseases was based on the principle of extrapolation.[20–23] That is one of the reasons why, as with other anti-TNF biosimilars already on the market, real-life data and pharmacovigilance studies are needed to develop long-term evidence on effectiveness and safety of these drugs in the IBD population.

Therefore, we aimed to compare the effectiveness and tolerability among ADA originator, ABP501 and SB5 biosimilars in the short term (after induction and after 6 months of treatment) in patients with IBD who started these drugs through a propensity score-weighted multicenter cohort study.

Methods

Study design and population

This is a multicenter prospective cohort study, coordinated by the IBD Unit of Padua University (Veneto, Italy), with the involvement of other five Italian IBD centers (Pordenone, Pisa, Genoa, Santorso and Feltre). We included all consecutive patients receiving for the first time ABP501 or SB5 biosimilars from January 2019 to April 2020 for a moderate-to-severe IBD, who completed at least the induction regimen. For comparison, we matched them by age and sex with an historical cohort of patients who took ADA originator and completed the induction regimen. The drug was administered at standard dose to all patients (160 mg, 80 mg and then 40 mg every 2 weeks). However, during outpatient follow-up visits (after induction, 6 months or in case of disease recurrence), each physician could decide whether or not to optimize the drug based on clinical and biochemical response. The methods of therapeutic optimization were 40 mg every week or 80 mg every 2 weeks.

The study was approved by our Ethics Committee as part of a larger study aimed to evaluate disease course and characteristics of IBD patients from the introduction of biologics in clinical practice (N. 3312/AO/14). Written informed consent was obtained from all eligible participants or their legal representatives before participation. The study protocol was performed according to the ethical guidelines of the 1964 Declaration of Helsinki (6th revision, 2008) as reflected in *a priori* approval by the institution's Human Research Committee.

Data collection

For the purpose of our study, various demographic and clinical data for each patient were collected at baseline (T_0), after induction (8 weeks, T_1) and after 6 months (32 weeks) from the start of treatment (T_2). In particular, the following data were recorded at baseline: age, sex, smoking habits, age at diagnosis, disease duration, disease extent, previous biological treatments, presence of extraintestinal manifestations, concomitant immunosuppressive (azathioprine, 6-mercapthopurine, methotrexate), steroid or mesalamine treatments. Clinical activity was measured by using partial Mayo (p-Mayo) score and Harvey–Bradshaw index (HBI) for UC and CD, respectively. As previously stated, clinical activity was further measured after induction and 6 months from the start of treatment. C-reactive protein (CRP) levels (positive if >0.5 mg/dl) and fecal calprotectin (FC) values >250 μg/g[24] were

also evaluated at the same time points. Finally, Mayo Endoscopic score and Simple Endoscopic Score for CD (SES-CD) or Rutgeerts score were evaluated at baseline. Patients with a p-Mayo ≥ 5, and/or Mayo Endoscopic score ≥ 2 and HBI > 7 and/or SES-CD ≥ 7 and/or Rutgeerts ≥ 2 at baseline were considered affected by a moderate-to-severe disease.

Outcomes

As to the major endpoints evaluated, according to medical literature, we defined respectively for UC and CD, steroid-free clinical remission as p-Mayo score <2 and HBI < 5 without steroid use for at least 1 month and clinical response in case of more than a two-point reduction of the baseline p-Mayo score and in case of more than a three-point reduction of baseline HBI score, with a concomitant decrease of steroid dosage until its discontinuation within 8 weeks, in absence of a clinical remission. Clinical benefit was defined as the sum of steroid-free clinical remission and clinical response. Finally, treatment failure was defined as discontinuation of biological therapy due to adverse events (AEs), lack of clinical response and need of hospitalization/surgery. All AEs, not only those which led to therapy discontinuation, were recorded.

Statistical analysis

The effects of different ADA drugs on clinical benefit (main outcome) and steroid-free clinical remission were evaluated through an intention to treat analysis, at two different time points after treatment assignment: after induction and after 32 weeks. To evaluate the distribution of the baseline characteristics in relation to treatments and outcomes, and between these two, a Chi-square test was performed. First, a multivariate logistics analysis was used to analyze the relationship between treatments and outcomes, adjusting by all pre-treatment characteristics: sex, age at the beginning of the follow-up, smoking habit, type of disease (UC or CD), endoscopic score, clinical score and presence of previous biological therapy.

Since treatments were not randomly assigned to patients, a propensity score approach was also performed, to control for confounding factors by balancing differences in the baseline characteristics among the three groups. An inverse probability-weighting method was used to estimate the average treatment effect among treated [Figure 1(a) and (b)]. Weights were estimated through generalized boosted modelling, a machine-learning method, which aimed to minimize the loss function for complex and nonlinear relationships between the pre-treatment characteristics and the assigned treatments, after building a series of regression trees (10,000 in our analysis). This approach was chosen due to its flexibility in presence of multiple treatments (≥ 3). Observation with missing values on relevant covariates were excluded from the sample in this first step. The balanced sample was analyzed using inverse probability weighting-adjusted logistics models for both outcomes and three different models were performed. The first included only the treatment, without any other covariate, while the others were also adjusted by different subsets of variables to control for residual confounding. One model was adjusted by the most unbalanced variables, previous biological therapy and disease, while the other included all the covariates with maximum standardized mean difference $>20\%$. Models after 32 weeks were also adjusted by the variable therapy optimization, which refers to a change in the administration of the therapy for some subjects. Since this variable is not a baseline characteristic, it was not included in the propensity score estimation.

The statistical software package R (R Foundation for Statistical Computing, Vienna, Austria), was used to perform all statistical analyses. In particular, we used the WeightIt package to balance the sample, the cobalt package for assessing balance and the survey package to estimate the effect of treatments on the outcome in the balanced population.

Results

Study population and disease characteristics at baseline

At study entry, 156 IBD patients (69 patients with UC, 87 patients with CD) who started ADA originator or biosimilars were considered, with one of them excluded because did not complete the induction phase. Overall, 155 (69 UC and 86 CD) patients completed induction (T_1), out of whom 136 completed at least 6 months of therapy (T_2).

The main characteristics of the population are reported in Table 1. In our multicenter cohort,

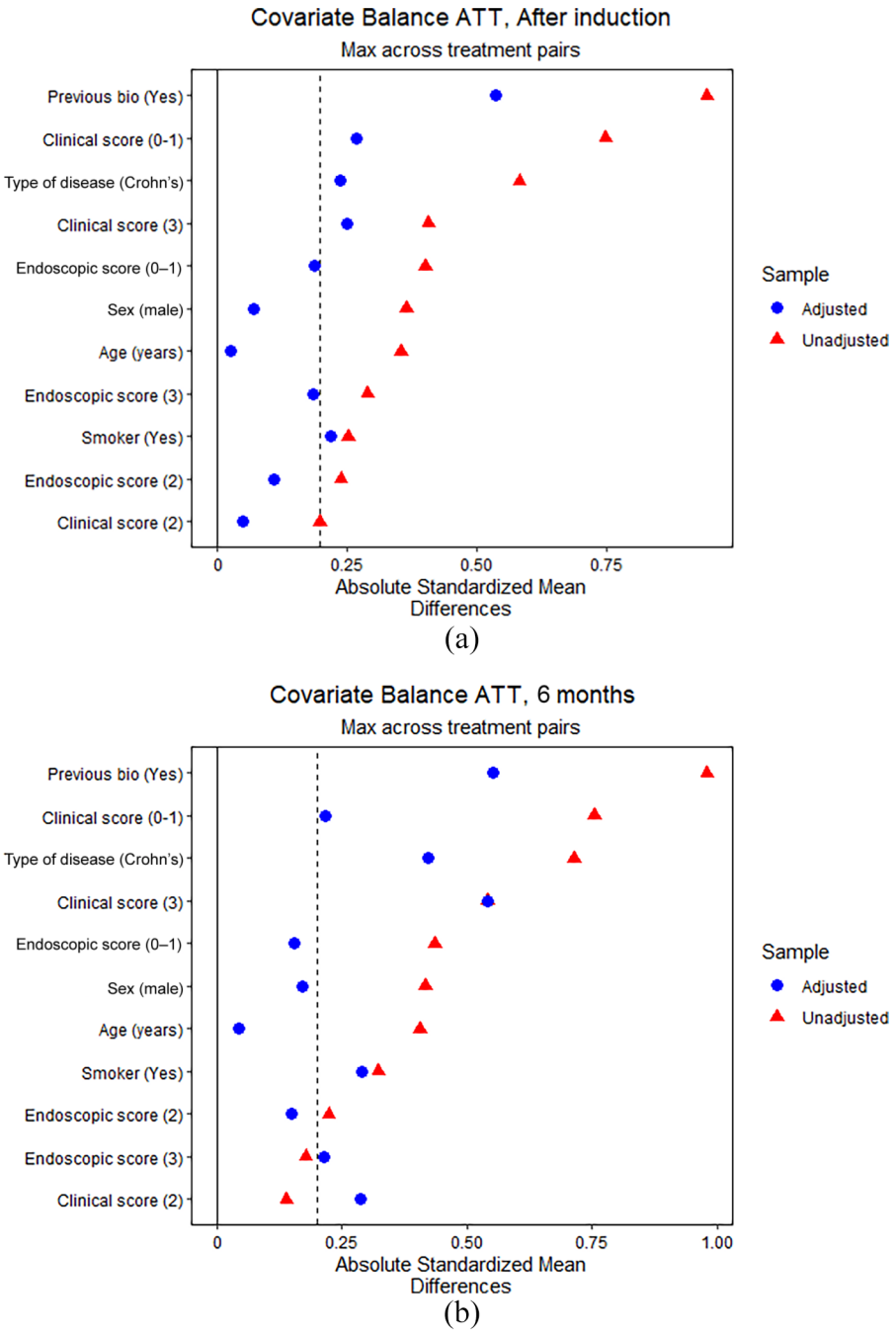

Figure 1. Covariate balance (a) after induction and (b) after 6 months
ATT, average treatment effect among treated.

55 (35.5%) patients started biologic treatment with ADA originator, 54 (34.8%) with ABP501 and 46 (29.7%) with SB5 biosimilars. We observed a statistically significant difference regarding the clinical activity of disease between the three treatment groups in patients with CD ($p = 0.02$, based on HBI score), while this was not found in patients with UC ($p = 0.17$, based on p-Mayo score). Regarding biochemical disease activity, CRP was positive in 17 (30.9%) patients treated with ADA, in 13 (24.1%) patients treated with ABP501 and in 28 (60.9%) patients treated

Table 1. Study population characteristics at baseline.

	Total number of patients (*n* = 155)	ADA originator (*n* = 55)	ABP501 (*n* = 54)	SB5 (*n* = 46)	*p*-value
Disease					
UC	69 (44.5)	31 (56.4)	25 (46.3)	13 (28.3)	0.02
CD	86 (55.5)	24 (43.6)	29 (53.7)	33 (71.7)	
Males *n* (%)	94 (60.7)	36 (65.5)	36 (66.7)	22 (47.8)	0.10
Median age (years) at diagnosis (1Q–3Q)	29 (23–45)	28 (23–39)	30.5 (23–45)	30 (21–47)	0.86
Median age (years) at baseline (1Q–3Q)	45 (32–55)	48 (36–58)	42.5 (30–53)	40.5 (30–52)	0.13
Smoke					
Ex-smoker	23 (14.8)	7 (12.7)	6 (11.1)	10 (21.7)	0.10
Smoker	19 (12.3)	9 (16.4)	9 (16.7)	1 (2.2)	
CD: Montreal Classification *n* (%)					
L1	16 (18.6)	6 (25.0)	6 (20.7)	4 (12.1)	0.07
L2	49 (57.0)	15 (62.5)	15 (51.7)	19 (57.6)	
L3	19 (22.1)	1 (4.2)	8 (27.6)	10 (30.3)	
L4 + others	2 (2.3)	2 (8.3)	0 (0.0)	0 (0.0)	
B1	50 (58.8)	15 (62.5)	18 (64.3)	17 (51.5)	0.66
B2	8 (9.4)	1 (4.2)	2 (7.1)	5 (15.2)	
B3	24 (28.2)	7 (29.2)	8 (28.6)	9 (27.3)	
B2+B3	3 (3.5)	1 (4.2)	0 (0.0)	2 (6.1)	
UC: Montreal Classification *n* (%)					
E1	3 (4.4)	0 (0.0)	3 (12.0)	0 (0.0)	0.07
E2	26 (37.7)	10 (32.3)	12 (48.0)	4 (30.8)	
E3	40 (58.0)	21 (67.7)	10 (40.0)	9 (69.2)	
HBI score (median, 1Q–3Q)	8 (8–10)	9 (8–10)	8 (8–10)	8 (8–9)	0.02
SES-CD score (median, 1Q–3Q)	8 (8–10)	9.5 (9–10.5)	8 (7–9)	8 (8–12)	0.03
Rutgeerts score *n* (%)					
i0	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	0.38
i1	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	
i2	9 (39.1)	1 (12.5)	3 (50.0)	5 (55.6)	

(Continued)

Table 1. (Continued)

	Total number of patients (*n* = 155)	ADA originator (*n* = 55)	ABP501 (*n* = 54)	SB5 (*n* = 46)	*p*-value
i3	5 (21.7)	2 (25.0)	1 (16.7)	2 (22.2)	
i4	9 (39.1)	5 (62.5)	2 (33.3)	2 (22.2)	
p-Mayo score (median, 1Q–3Q)	6 (5–7)	5 (5–6)	5 (5–6)	6.5 (6–7)	0.17
Mayo endoscopic score *n* (%)					
0	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	0.47
1	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	
2	51 (73.9)	23 (74.2)	20 (80.0)	8 (61.5)	
3	18 (26.1)	8 (25.8)	5 (20.0)	5 (38.5)	
Fecal calprotectin value (μg/g) (median, 1Q–3Q)	613 (373–1153)	756 (521–1296)	600 (244–1024)	531.5 (296–1029)	0.03
Positive CRP (mg/l, NV < 6) *n* (%)	58 (37.4)	17 (30.9)	13 (24.1)	28 (60.9)	<0.0001
Naïve biologic *n* (%)	103 (66.5)	23 (41.8)	42 (77.8)	38 (82.6)	<0.0001
Concomitant steroids *n* (%)	39 (25.2)	10 (18.2)	19 (35.2)	10 (21.7)	0.10
Concomitant immunosuppressants *n* (%)	20 (12.9)	9 (16.4)	10 (18.5)	1 (2.2)	0.03
Previous surgery *n* (%)	30 (20.7)	9 (16.4)	7 (13.0)	14 (30.4)	<0.0001
Extraintestinal manifestation *n* (%)	45 (29.0)	21 (38.2)	13 (24.1)	11 (23.9)	0.18

1Q, first quartile; 3Q, third quartile; ADA, adalimumab; CD, Crohn's disease; CRP, C-reactive protein; HBI, Harvey–Bradshaw index; NV normal value; UC, ulcerative colitis.

with SB5 ($p < 0.0001$). We also found statistically significant differences in FC median values among the different groups ($p = 0.03$): they were higher in patients treated with ADA than those treated with ABP501 or SB5 biosimilars, as illustrated in Table 1. Moreover, we found a statistically significant different number of patients who were naïve to biological therapies between the three groups ($p < 0.0001$), with a higher percentage of them in the SB5 group (SB5 82.6% *versus* ADA 41.8% *versus* ABP501 77.8%). More patients treated with ABP501 (18.5%) took concomitant immunosuppressants compared with patients treated with ADA (16.4%) and SB5 biosimilar (2.2%) ($p = 0.03$). Conversely, higher rate of patients who underwent surgery was found in SB5 group (SB5 30.4% *versus* ADA 16.4% *versus* 13.0% ABP501, $p < 0.0001$).

Study population and disease characteristics after induction

After induction, clinical benefit was achieved by 86.4% of patients ($n = 134$ out of 155). In particular, it was obtained by 89.1% of the patients taking ADA originator, by 87.0% of the patients taking SB5 and by 83.3% of patients taking ABP501, without a statistically significant difference between the three groups ($p = 0.68$) [Figure 2(a) and Supplemental Table 1]. Moreover, we found a statistically significant difference between the two types of the disease (UC or CD, $p = 0.004$), with a greater clinical benefit achieved by patients with CD (Supplemental Table 1).

We observed that steroid-free clinical remission was overall achieved by 49.0% of patients. Specifically, it was obtained by 40.0% of patients

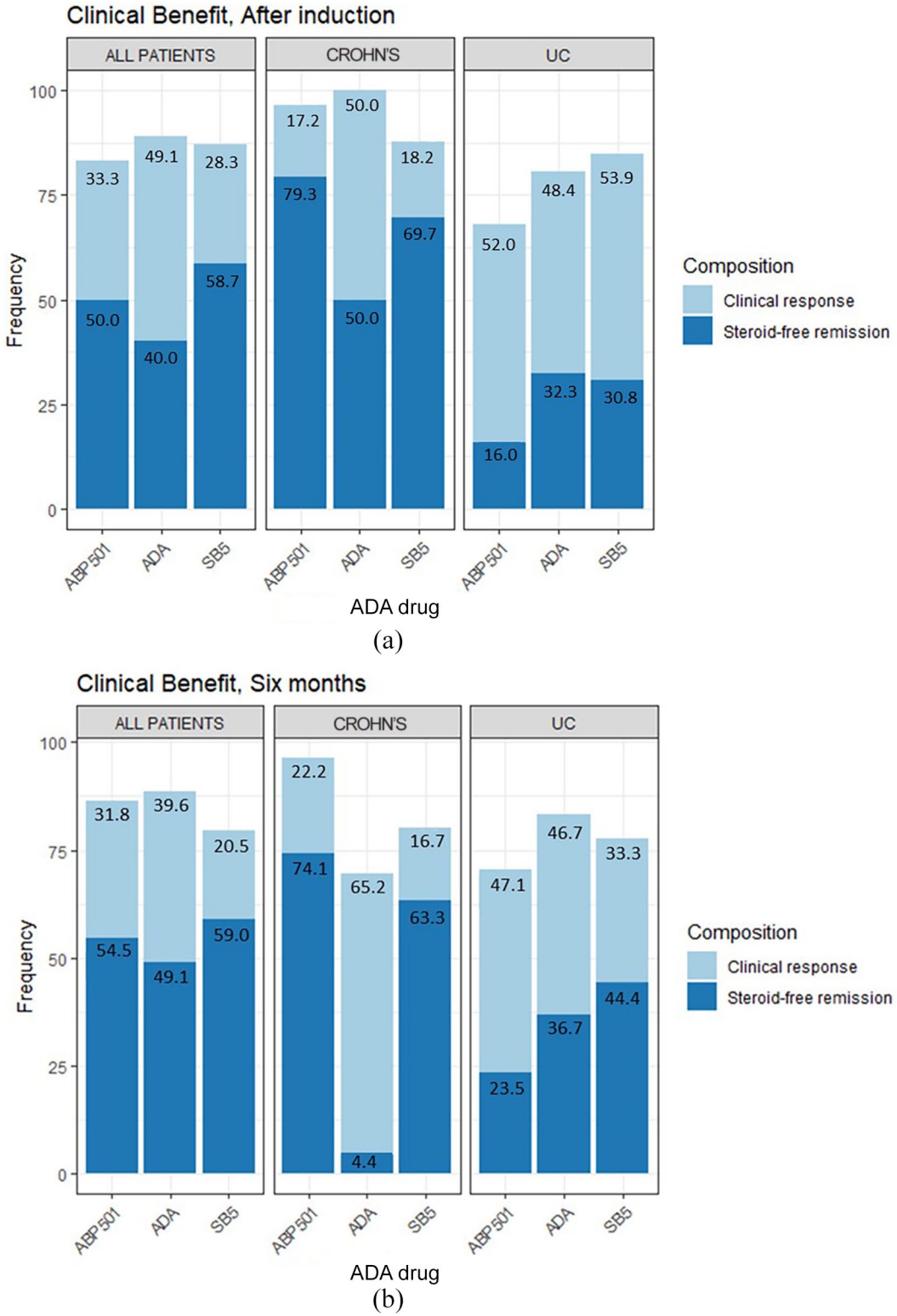

Figure 2. Clinical benefit in patients with IBD treated with ADA originator, ABP501 and SB5 (a) after induction and (b) after 6 months

ADA, adalimumab; IBD, inflammatory bowel disease; UC, ulcerative colitis.

Table 2. Multivariate analyses.

(a) Clinical benefit, OR (CI 95%).						
	T_1			**T_2**		
	Originator	**ABP501**	**SB5**	**Originator**	**ABP501**	**SB5**
Multivariate analyses	1	0.41 (0.10; 1.50)	0.41 (0.08; 1.93)	1	0.56 (0.13; 2.34)	0.44 (0.09; 2.12)
PS IPW analysis						
Unadjusted	1	0.53 (0.15; 1.83)	0.67 (0.17; 2.7)	1	0.45 (0.12; 1.64)	0.86 (0.2; 3.72)
Adjusted§	1	0.4 (0.11; 1.5)	0.55 (0.13; 2.31)	1	0.19 (0.04; 1.00)	0.52 (0.09; 3.09)
Adjusted$	1	0.41 (0.11; 1.53)	0.52 (0.12; 2.35)	1	0.19 (0.04; 1.00)	0.52 (0.09; 3.09)
(b) Steroid-free remission, OR (CI 95%).						
	T_1			**T_2**		
	Originator	**ABP501**	**SB5**	**Originator**	**ABP501**	**SB5**
Multivariate analyses	1	1.26 (0.51; 3.11)	1.32 (0.48; 3.61)	1	0.99 (0.36; 2.66)	0.88 (0.29; 2.67)
PS IPW analysis						
Unadjusted	1	1.22 (0.51; 2.9)	1.16 (0.46; 2.96)	1	1.01 (0.4; 2.53)	1.28 (0.44; 3.75)
Adjusted§	1	1.03 (0.42; 2.49)	1.02 (0.34; 3.06)	1	0.98 (0.34; 2.79)	0.9 (0.25; 3.15)
Adjusted$	1	0.93 (0.38; 2.28)	0.85 (0.27; 2.66)	1	1.12 (0.37; 3.34)	0.22; 3.04)
(c) Clinical response, OR (CI 95%).						
	T_1			**T_2**		
	Originator	**ABP501**	**SB5**	**Originator**	**ABP501**	**SB5**
Multivariate analyses	1	0.54 (0.22; 1.29)	0.53 (0.19; 1.40)	1	0.73 (0.26; 2.02)	0.74 (0.22; 2.37)
PS IPW analysis						
Unadjusted	1	0.6 (0.24; 1.47)	0.72 (0.27; 1.87)	1	0.61 (0.23; 1.64)	0.71 (0.22; 2.29)
Adjusted§	1	0.63 (0.25; 1.59)	0.75 (0.26; 2.12)	1	0.42 (0.14; 1.27)	0.84 (0.22; 3.14)
Adjusted$	1	0.68 (0.27; 1.73)	0.83 (0.28; 2.46)	1	0.44 (0.13; 1.45)	1.08 (0.28; 4.20)

§Adjusted by previous biologic therapy, disease and therapy optimization (only T_2).
$Adjusted by previous biologic therapy, disease, therapy optimization (only T_2), endoscopic score and clinical score.
T_1, after induction; T_2, after 6 months of treatment; CI, confidence interval; PS IPW, Inverse Probability Weighted Propensity Score; OR, odds ratio.

treated with ADA, 50.0% of patients treated with ABP501 and 58.7% of those treated with SB5 ($p = 0.17$). To note, lower rates of steroid-free clinical remission were found in patients with UC ($p < 0.0001$). Moreover, clinical response was obtained by 37.4% of our patients (49.1%, 33.3% and 28.3% of patients treated with ADA originator, ABP501 and SB5, respectively) ($p = 0.07$) [Figure 2(a) and Supplemental Table 2].

From t_0 to t_1, FC values decreased significantly in all groups of treatment ($p < 0.05$). Regarding optimization of therapy, 4 in ADA group, 11 patients in ABP501 group and 3 under treatment with SB2 needed to optimize the dosage after the induction regimen ($p = 0.23$). Overall, 16 patients discontinued treatment ($n = 2$ ADA, $n = 8$ ABP501, $n = 6$ SB5, $p = 0.1$): 5 patients needed to stop therapy due to an adverse event ($n = 1$ ADA,

$n=3$ ABP501, $n=1$ SB5); 9 patients discontinued biological drugs for inefficacy ($n=1$ ADA, $n=3$ ABP501, $n=5$ SB5) and 2 patients needed to stop therapy because of abdominal surgery ($n=2$ ABP501).

Study population and disease characteristics after 6 months of therapy (T_2)

At six months we calculated the outcomes of 136 patients, because 16 patients discontinued treatment after induction, as reported above, and three patients were taking therapy without reaching the end of follow-up (i.e. 32 weeks).

Clinical benefit was achieved by 85.3% ($n=116/155$) of all patients. In particular, 88.7%, 86.3% and 79.5%, of patients treated with ADA, ABP501 and SB5, respectively, achieved clinical benefit, without statistically significant difference among the different drugs. We also did not find significant difference between UC and CD patients ($p=0.11$) [Figure 2(b) and Supplemental Table 1].

Steroid-free clinical remission was observed in 53.7% of overall population. Particularly, it was achieved by 49.1% of patients treated with ADA, 54.5% of patients treated with ABP501 and 59.0% of those treated with SB5, without statistically significant difference between groups ($p=0.64$) [Figure 2(b) and Supplemental Table 2]. Overall, patients with CD had a significantly higher rate of steroid-free clinical remission compared to those with UC ($p<0.0001$). However, a low steroid-free clinical remission rate was found in patients with CD treated with originator at 6 months.

Clinical response was observed in 39.6% of patients in ADA originator group, in 31.8% of patients in ABP501 group and in 20.5% of those in SB5 group without significantly difference among the three groups of treatment ($p=0.15$) [Figure 2(b) and Supplemental Table 2].

Regarding biochemical values, FC values significantly decreased in all groups of treatment ($p<0.05$). A need for drug optimization was observed in five patients treated with ADA originator, in two patients treated with ABP501, and in seven of those treated with SB5 ($p=0.30$). Finally, 17 patients discontinued therapy ($n=6$ ADA, $n=7$ ABP501, $n=4$ SB5, $p=0.30$): 5 of them because of AEs ($n=2$ ADA, $n=2$ ABP501, $n=1$ SB5) and 12 patients for inefficacy ($n=4$ ADA originator, $n=5$ ABP501, $n=3$ SB5).

Multivariate analysis

We included in the multivariate logistic regression model all statistically significant different variables at baseline among groups after a propensity score-weighted analysis. However, we did not find a statistically significant difference among the different drugs for all outcomes evaluated both at T_1 and T_2 (Table 2).

Tolerability profile of drugs

During the study period, all AEs, not only those which lead to therapy discontinuation, were reported. Overall, 10 patients stopped therapy because of AEs, without statistically significant difference between the three groups ($p=0.65$). All of these caused discontinuation of treatment. In general, the following AEs were registered (Table 3): allergic reaction (mostly skin rash; we never observed severe allergic reactions during the follow-up); recurrent infections; cough; paradoxical psoriasis; alopecia.

Discussion

In our study, we aimed to compare the effectiveness and tolerability between ADA originator and two biosimilar drugs (ABP501 and SB5) using a three-arm propensity score-weighted analysis. We found that clinical benefit (including clinical response and steroid-free clinical remission) was achieved by 86.4% and 85.3% of all patients at T_1 and T_2, respectively. Particularly, after induction, it was obtained with a similar percentage in all groups of treatment (89.1% in ADA originator, 87.0% in SB5 and 83.3% in ABP501 groups), without a statistically significant difference between the three populations ($p=0.68$). However, we found a statistically significant differences between the two types of the disease (UC or CD, $p=0.004$), with a greater clinical benefit achieved by patients with CD. After 6 months of therapy, clinical benefit was achieved by 88.7%, 86.3% and 79.5%, of patients treated with ADA, ABP501 and SB5, respectively, without statistically significant difference among the different adalimumab drugs ($p=0.46$). In this case, we did not find significant difference between UC and CD patients ($p=0.11$). Also,

Table 3. Adverse events after induction and after 6 months of treatment.

	After induction			6 months		
	n	Type of adverse events	Therapy discontinued	*n*	Type of adverse events	Therapy discontinued
Adalimumab originator	1	Dyspnea, cough and chest pain	Yes	1	Conjunctivitis, blepharitis, vitreous detachment	Yes
				1	Psoriasis	Yes
ABP501	4	Allergic reaction, skin rash and dyspnea (×2)	Yes	1	Psoriasis	Yes
				1	Alopecia	Yes
		Skin rash	No			
		Multiple infections	Yes			
SB5	1	Multiple infections	Yes	1	Psoriasis	Yes

the therapeutic optimization rate among the three groups of treatment was not statistically significant different ($p = 0.30$), and all treatments showed a good safety profile, with only 10 patients stopping therapy because of AEs at the end of follow-up.

Looking at real-life studies in existing literature, to the best of our knowledge, there are few investigations available and mostly about ADA originator. Orlando *et al.*[25] conducted a study enrolling CD patients and observed a clinical benefit of 91.0% and a steroid-free clinical remission of 45.5% after induction. Likewise, at the same time point, we found that all patients with CD (100%) achieved clinical benefit, while 50.0% of them obtained steroid-free clinical remission. Moreover, Renna *et al.*[11] conducted a real-life study on UC patients in therapy with ADA originator, observing that 40.7% of patients was in steroid-free clinical remission after induction. Our results showed a lower percentage of patients with UC achieving a steroid-free clinical remission (32.3%), although it was higher than those obtained in patients treated with ABP501 (16.0%) and SB5 (30.8%).

These data are in line with those extrapolated from studies on rheumatological patients. In particular, a recent systematic literature review, including two large phase III randomized studies which sustained efficacy and tolerability of ABP501 and SB5 in rheumatoid arthritis, confirmed the non-inferiority of ADA biosimilar drugs compared with the reference product.[20]

Currently, only a few studies with a small sample size have directly evaluated ADA biosimilars in a real-life setting in patients with IBD. Ribaldone *et al.*[26] evaluated effectiveness and safety of ABP501 in 25 Italian patients with CD who were naïve to ADA, as well as the ability of ABP501 to maintain the response in 62 patients switched from ADA originator. In the first group, at 3 months, clinical remission was 56.0%, while in our study steroid-free clinical remission was 79.3% in patients with CD treated with ABP501. An Indian study by Kamat *et al.*[27] evaluated in real life, the efficacy of another ADA biosimilar (Exemptia®, ZRC-3197). After induction, 46.9% of patients with CD and 52.4% of patients with UC achieved clinical remission. At the same time point, in our study we found a higher percentage of steroid-free clinical remission in patients with CD and lower in those with UC treated with biosimilar drugs. In fact, steroid-free remission was achieved by 79.3% and by 69.7% of patients with

CD treated with ABP501 and SB5, respectively, but only by 16.0% of patients with UC treated with ABP501 and 30.7% of those treated with SB5. Finally, another multicenter Italian study recently published by our group evaluated effectiveness and safety of ADA biosimilars in 55 patients who switched from to the originator to ABP501 and in 25 patients who switched to SB5. In addition, an age- and sex-matched control group ($n = 38$) who continued ADA originator for at least 2 years and who did not switch to a biosimilar drug was included. Drug survival curves of patients who switched from originator to ABP501 and those who continued ADA originator were similar ($p = 0.20$), and the drugs were well tolerated.[28]

Regarding the discontinuation of treatment for adverse events, Kamat *et al.*[27] found that 3.5% and 4.7% of patients with CD treated with ZRC-3197 stopped the therapy for AEs after induction and after 26 weeks, respectively. In our study population, we observed similar figures: three patients (5.6%) treated with ABP501 and one (2.2%) of those treated with SB5 discontinued treatment due to an adverse event after induction, while 3.7% and 2.2%, respectively, after 6 months of treatment.

It is worth noting that, as previously reported in the literature, overall the clinical benefit was higher in patients with CD than those with UC. In fact, a recent study, comparing efficacy and safety of different anti-TNF-α between patients with moderate-to-severe UC and CD, demonstrated a better clinical response to anti-TNF-α treatment, including ADA originator, in patients with CD.[13]

With the introduction of various ADA biosimilars, we might be able to significantly reduce the healthcare costs related to IBD treatments. However, as a biosimilar is likely to be less expensive than the comparator (e.g. the reference biopharmaceutical), the assessment of the cost-effectiveness of a biosimilar depends on the relative effectiveness.[29] Thus, we deeply believe that the results of our study, showing similar effectiveness and safety between originator and biosimilars, might improve knowledge on this field. However, a recent study conducted in Thailand suggested that even though biosimilars provided equivalent effectiveness with the originator with less cost, they are not cost-effective at their current price in this country.[30] Therefore, further studies evaluating the cost-effectiveness of biosimilars according to the different rules in each country are necessary.

A major strength of our study is that it is one of the first multicenter studies comparing head-to-head effectiveness and tolerability of ADA originator and two of its biosimilars in patients with IBD in a real-life setting. Further, we applied propensity score-based weighted analysis, which is considered as one of the most reliable techniques to account for possible baseline differences between the treatment groups. However, weaknesses of this study include the fact that the sample size was limited. Nevertheless, this drawback is balanced by the fact that every patient was strictly followed-up by a maximum of two physicians with the same standardized management approach. Second, follow-up was not long enough to gather reliable data about the long-term response and correlation of serious AEs with biological therapy. Finally, the study population showed a remarkable heterogeneity, including patients already exposed to biologics, as well as naïve patients treated with biological monotherapy or patients receiving immunosuppressant concomitant therapy. On the other hand, this can be considered a representation of the clinical reality of heterogeneous groups rather than the selected cohorts of registration trials.

In conclusion, we found that ADA biosimilar drugs seem to be as effective as the originator. Surely, biosimilars represent a great opportunity to reduce the costs of biological therapies and lighten the impact on healthcare resources, however larger and longer studies in real life are needed to improve our knowledge about their effectiveness and safety in patients with IBD.

Author contributions

BB, LC, EVS, FZ conceived and drafted the study. BB, LC, RS, MTU, LB, FC, GB, MGD, AF, AB, PM, DM collected all data. FZ, CC, GB analyzed all data. BB, LC, EVS, FZ interpreted the data. BB, LC, EVS, FZ drafted the manuscript. All authors commented on drafts of the paper. All authors approved the final draft of the manuscript.

Conflict of interest statement

EVS has received lecture or consultancy fees from Takeda, Merck & Co, Bristol-Myers Squibb, Abbvie, Amgen, Novartis, Fresenius

Kabi, Sandoz, Sofar and Janssen. FZ had received lecture fees from Takeda, Janssen and Norgine. The remaining authors declare no competing interests.

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Guarantor of the article

FZ and EVS are guarantors.

Ethical approval

The study was approved by our Ethics Committee as part of a larger study aimed to evaluate disease course and characteristics of IBD patients from the introduction of biologics in clinical practice (N. 3312/AO/14).

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Data availability statement

The data underlying this study are available within the manuscript and supplemental materials.

Supplemental material

Supplemental material for this article is available online.

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