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Replacement of Adalimumab Originator to Adalimumab Biosimilar for a Non-Medical Reason in Patients with Inflammatory Bowel Disease: A Real-life Comparison of Adalimumab Biosimilars Currently Available in Italy

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ABSTRACT

Background & Aims: Adalimumab (ADA) biosimilars have been included into the therapeutic armamentarium of inflammatory bowel disease (IBD); however, comparative data on the efficacy and safety of the different ADA biosimilars after replacing the ADA originator for a non-medical reason remains scarce. We aimed to compare in a real-life setting the efficacy and safety of four ADA biosimilars SB5, APB501, GP2017, and MSB11022 in IBD patients after replacing the originator for a non-medical reason.

Methods: A multicenter retrospective study was performed on consecutive IBD patients, analyzing clinical, laboratory, and endoscopic data. The primary endpoints of the study were maintenance of clinical remission and safety of the different biosimilars.

Results: 153 patients were enrolled, 26 with UC and 127 with CD. Clinical remission was maintained in 124 out of 153 (81%) patients after a median (IQR) follow-up of 12 (6–24) months, without any significant difference between the four ADA biosimilars. ADA biosimilars dosage was optimized in five patients (3.3%). Loss of remission was significantly higher in UC patients (10/26 patients, 38.5%) than in CD patients (19/127 patients, 14.9%, $p<0.025$). Adverse events occurred in 12 (7.9%) patients; the large majority were mild.

Conclusions: No difference in efficacy and safety was found between ADA biosimilars when used to replace the ADA originator for a non-medical reason. However, in UC patients the replacement of ADA originator for this reason should be carefully assessed.

Key words: adalimumab – biosimilar – ABP501 – GP2017 – MSB11022 - SB5 – inflammatory bowel disease.

Abbreviations: ADA: adalimumab; AE: adverse event; CD: Crohn's disease; CRP: C-reactive protein; FC: fecal calprotectin; HBI: Harvey-Bradshaw index; IBD: inflammatory bowel diseases; IQR: interquartile range; MH: mucosal healing; s.c.: subcutaneous; TNF: tumor necrosis factor; UC: ulcerative colitis.

INTRODUCTION

The costs of treating inflammatory bowel disease (IBD) patients with biologics are significantly higher than with traditional therapies [1, 2]. As a result, after the patents of the original biological agent expired, the development and diffusion of biosimilars was accelerated, as they were expected to have the same efficacy and safety as the original at significantly reduced costs [3].

Adalimumab (ADA), a fully human monoclonal antibody directed against soluble and membrane-bound TNF-α, has been shown to be largely effective and safe in the treatment of both Crohn's disease (CD) and ulcerative colitis (UC) patients [4-9]. However, the approval for the use in clinical practice of ADA biosimilars in IBD is based on the concept of extrapolation of the results obtained in other diseases such as rheumatoid arthritis and psoriasis [10-13]. This type of speculation is unique to biosimilars, and the preliminary evaluation has given us some reservations about the concept of extrapolation [14]. However, the reduction in costs resulting from their wider use would allow a broader range of patients to use them. Currently, there are limited data on the safety and efficacy of ADA biosimilars in IBD when used to replace the originator for a non-medical reason [15-17]; therefore, further studies are needed. In Italy, four ADA biosimilars are available: ABP 501 (Amgevita®, Amgen Inc., Thousand Oaks, CA, USA), SB5 (Imraldi®, Samsung Bioepis UK Limited, United Kingdom), MSB11022 (Idacio®, Fresenius Kabi Deutschland GmbH, Germany), and GP2017 (Hyrimoz®, Sandoz GmbH,

Germany) [18-21]. In a previous study, we found no differences among these four ADA biosimilars in obtaining remission in UC and CD [22]. Since information about switching to ADA biosimilar is still limited, we aimed to compare the efficacy and safety of ADA biosimilars ABP 501 (Amgevita®), SB5 (Imraldi®), MSB11022 (Idacio®), and GP2017 (Hyrimoz®) in treating IBD patients in whom the replacement of the ADA originator to ADA biosimilars was made for a non-medical reason.

METHODS

This retrospective study consists of a post-hoc analysis conducted on a large population of IBD patients treated with ADA biosimilars ABP 501 (Amgevita®), SB5 (Imraldi®), MSB11022 (Idacio®), and GP2017 (Hyrimoz®) [22]. We enrolled patients in who the ADA originator was replaced for a non-medical reason as a cost reduction measure, and treated between September 1st, 2019, and May 31st, 2021. We selected only patients who had been in stable clinical remission with the originator for at least one year.

Clinical remission was defined as no need for ADA optimization or the addition of steroids or immunosuppressants. In Italy, the ADA biosimilars are chosen locally by the different regional health services, which depend on the national health system. Therefore, sales and distribution contracts were signed at the regional level without interchangeability at the pharmacy level. Patients enrolled in the study had a known diagnosis of CD or UC for at least six months, based on standard clinical, endoscopic, radiological, and histological criteria with age greater than 18 years. [23]. The clinical variables collected during the study were entered into a shared database. In detail, data collected at baseline were gender, age at diagnosis, smoking status, disease extension, disease duration, previous immunosuppressive and biologic therapies, concomitant medications, C-reactive protein (CRP) and fecal calprotectin (FC) values, Mayo score, and Mayo subscore for endoscopy for UC patients, and Harvey–Bradshaw index (HBI) for CD patients.

The study was conducted following clinical practice guidelines. All patients gave written informed consent before undergoing endoscopy and ADA treatment. The present study follows the principles of the Declaration of Helsinki. Ethics committee approval was obtained by "Brotzu" Hospital (Cagliari, Italy, PROT. PG/2021/10115).

Study Treatment

All patients were included in the study after screening for *Mycobacterium tuberculosis* infection, and active hepatitis B was negative. The ADA biosimilars were administered subcutaneously at a dose of 40 mg every two weeks after replacing the originator. No patients treated with a weekly dose of ADA originator were enrolled. Therefore, the need for discontinuation of treatment, optimization of ADA (40 mg weekly administration) or switching to other biologics, or the addition of concomitant medications for the treatment of IBD was left to the investigators.

Clinical Assessment

The extent of the disease was determined using the Montreal classification [24]. Severity was determined using the Mayo score [25] in UC patients and the HBI [26] in CD patients. All enrolled patients were in clinical remission, defined as a Mayo score of ≤2 points for UC patients and an HBI score of ≤5 points for CD patients. Patients switching from the originator to an ADA biosimilar were clinically assessed at the entry point and every six months. In the case of symptoms worsening, a clinical assessment was anticipated.

Endoscopy

All patients underwent ileocolonoscopy before switching to an ADA biosimilar for non-medical reasons. During follow-up, at least 6 months after study enrollment, patients repeated ileocolonoscopy. Endoscopic severity in UC patients was assessed according to the Mayo subscore for endoscopy [25]. Endoscopic severity in CD patients was assessed by the Simple Endoscopic Score for CD (SES-CD) [27, 28].

Primary Endpoints

The study's primary endpoints were the comparison of the efficacy in maintaining clinical remission and safety among the different ADA biosimilars used after replacing the ADA originator for a non-medical reason. Clinical remission was defined as stated in the previous paragraph.

All adverse events (AEs) occurring during treatment were registered. The AEs were classified according to their clinical severity into mild, for which treatment interruption was not necessary, and severe, which required treatment interruption. Additionally, AEs were listed by time to onset in early, occurring during injection, and late, occurring at least one week after injection. Opportunistic infections were also included among the AEs. They were defined as any infection caused by microorganisms with limited pathogenic capacity under normal circumstances. Still, it can cause disease because of the predisposing effect of another disease or its treatment [29].

Secondary Endpoint

The secondary endpoint was to see if there was any difference between the ADA biosimilars in terms of the following: a. prevention of colectomy in UC and any surgical procedure related to the disease in CD; b. optimization rate for the ADA biosimilar during the follow-up to maintain remission. The allowed methods of therapeutic optimization were considered ADA biosimilar 40 mg every week or 80 mg every two weeks; c. Return to the ADA originator, defined as return to ADA originator in those patients who experienced loss of response in the first 6 months from baseline, was also assessed for each ADA biosimilar.

Statistical Analysis

Data were analyzed using MedCalc® Release 14.8.1 software. The characteristics of the study's population were described as median (interquartile range [IQR]) for continuous non-parametric variables and as number (percentage) for categorical variables. The chi-squared test was used to compare categorical variables, and the Mann-Whitney test for continuous variables. Due to the variable duration of follow-up, the predictive value of clinical parameters was assessed using time-to-event methods for censored observations. The length

of follow-up was calculated from the baseline (inclusion in the study) to the date of the event or censorship. Time to event analysis using Kaplan – Meier estimates to draw cumulative incidence curves. P values <0.05 were considered statistically significant.

RESULTS

One-hundred-fifty-three patients were enrolled, including 26 with UC and 127 with CD. The epidemiological and clinical characteristics of the study population are shown in Table I. Overall, clinical remission was maintained in 124 of 153 patients (81%) after a median follow-up (IQR) of 12 (6-24) months. In detail, remission was maintained in 66 of 78 (84.6%) patients in the ABP 501 group, 51 of 65 (78.5%) in the SB5 group, 4 of 7 (66.7%) in the GP2017 group and 3 of 3 (100%) in the MSB11022 group (p=0.549). Loss of clinical remission was significantly higher in UC patients (10/26 patients, 38.5%) than in CD patients (19/127 patients, 14.9%, p<0.026) (Fig. 1). All AEs that occurred are shown in Table II. The incidence of AEs, including skin diseases, hematologic diseases, and arthralgia, was similar in the ABP501 and SB5 groups. The most frequent AE recorded was itch/pain at the injection site. One severe AE (leukopenia) was observed in the ABP501 group, with reversal after drug withdrawal. Colectomy occurred in one UC patient (3.9%), while no surgical procedures were recorded in the CD patients. Five patients needed ADA biosimilar optimization (3.3%), while 13 (8.5%) switched to vedolizumab. Nine patients (7.1%) switch back to the ADA originator (6 with UC and three with CD). Seven of them (77.8%) regained clinical remission, while one UC and one CD patient were switched to vedolizumab. No AEs were reported after the switch back to the originator. There was no significant difference for any of the secondary endpoints among the various ADA biosimilars.

Table I. Demographics, disease characteristics, and concomitant medications in switched patients

	N=153
Gender, male	75 (49.0)
Median (IQR) age, years	42 (30-53)
Median (IQR) BMI, Kg/m^2	24 (21-26)
Median (IQR) disease duration, years	8 (5-14)
Median (IQR) ADA treatment before switch, years	3 (2-11)
Montreal classification of extent of ulcerative colitis (26 pts)	
Proctitis	2 (7.7)
Left-sided colitis	10 (38.5)
Extensive colitis	14 (53.8)
Montreal classification of Crohn's disease (127 pts)	
Location	
Isolated ileal disease	65 (51.2)
Isolated colonic disease	15 (11.8)
Ileocolonic disease	45 (35.4)
Isolated upper gastrointestinal disease	1 (0.8)
Upper gastrointestinal and ileocolonic disease	1 (0.8)
Concomitant perianal disease	11 (8.7)
Behaviour	
Non stricturing, non-penetrating	87 (68.5)
Stricturing	25 (19.7)
Penetrating	15 (11.8)
Presence of comorbidities	47 (30.7)
Previous appendectomy	41 (26.8)
Smoking	36 (23.5)
Concomitant therapy	
Mesalazine	85 (55.6)
Systemic steroids	31 (20.3)
Topic steroids	9 (5.9)
Tiopurine	3 (1.9)
Probiotics	28 (18.3)
No previous anti-TNFα	-
Median (IQR) CRP, (mg/L)	3.0 (2.0-8.0)
Median (IQR) fecal calprotectin (μg/g)	101.0 (47.5-210.0)
Median (IQR) partial Mayo score	4 (2-7)
Median (IQR) Mayo subscore for endoscopy	2 (1-2)
Median (IRQ) HBI	3 (2-7)
Median (IRQ) SES-CD	4 (1-10)

Data are given as number (percentage) of patients unless otherwise indicated. ADA: adalimumab; IQR: interquartile range; CRP: C-reactive protein; HBI: Harvey-Bradshaw index; SES-CD: simple endoscopic score for Crohn's disease.

DISCUSSION

The availability of different ADA biosimilars for treating IBD has opened new therapeutic options, but also some concerns about their use. Recent studies found that ADA biosimilars effectively manage IBD patients naïve to biologics [15-17, 22, 30, 31]. In contrast, comparative analyses of the efficacy in maintaining remission after replacement of the originator for a non-medical reason are limited. However, the promising results of this study confirm that the replace from ADA originator to biosimilars may be an opportunity for physicians to consider when treating IBD patients.

In fact, we found that clinical remission after 12 months from baseline was maintained in about 80% of the patients, showing for the first time that there was no significant difference among all the ADA biosimilars currently available in Italy. In particular, the rate of loss of remission was similar to that reported by other studies. Tapete et al. [17] found that, after 12 months from enrollment, 74.5% were still in clinical remission after nonmedical switching to ADA biosimilar SB5. Lukas et al. [15] found that the remission rate at week 10 was similar in naïve and switched cohorts of patients under ADA SB5. Cingolani et al. [16] found that, at six months from baseline, 76.4% and 84% were still in remission under ABP501 or SB5 respectively.

Overall, these data appear satisfactory, particularly when compared with the results of a recent report summarizing the rates of maintenance of remission obtained in clinical trials by ADA originator versus placebo in CD patients [32] but worse than those achieved in the real-life setting. Indeed, in our previous experience, the percentage of patients in remission

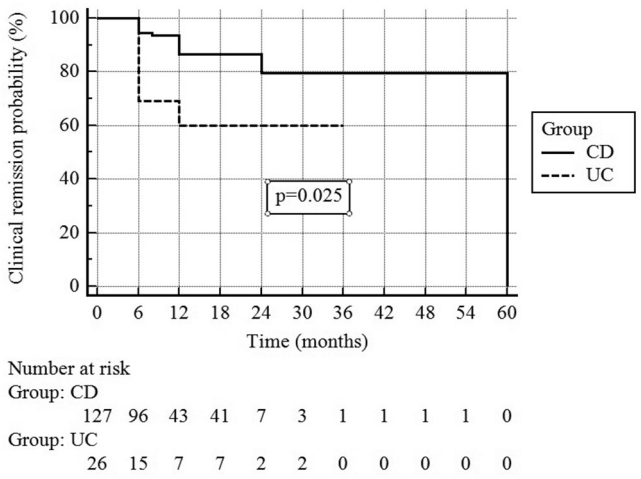

Fig. 1. Kaplan-Meier analysis about the remission maintenance during the follow-up in ulcerative colitis and Crohn's disease after nonmedical switch from adalimumab originator.

with the originator at the 108th month of follow-up was about 70% [9]. The first hypothesis that could explain this result is a "nocebo" effect that negatively influence the maintenance of remission after a nonmedical switch [33]. However, this hypothesis can only partially explain this finding because the risk of losing remission was not similar for CU and CD patients. We found that UC patients lost remission more easily than CD patients when they replaced the originator for a non-medical reason. This finding appears identical to using the originator ADA in CD or UC, where the rate of remission and the rate of long-term maintenance of remission are lower in the latter group [9]. In other words, both ADA originator and biosimilars work worse when prescribed in UC patients, both in naïve patients and after switching from the originator.

Due to the low number of patients treated with GP2017 and MSB11022, no actual data could be drawn from these ADA biosimilars.

Conversely, a full analysis can be found by comparing ABP501 and SB5. However, we did not see any difference in their efficacy between these two ADA biosimilars after switching from the ADA originator, confirming the recent experience of Cingolani et al. [16]. In addition, ADA biosimilars after replacing the originator for a non-medical reason were well tolerated with a low rate of AEs. The most frequent AE observed was hitch/pain at the injection site, occurring only in ABP501 and SB5 patients. A possible explanation could be that these two biosimilars contain sodium citrate, a compound that may be responsible for somewhat more pain [34]. Looking at the secondary endpoints of the study, an important finding is that these patients not infrequently require optimization of the dosage to maintain remission. The optimization rate was about double that required in naïve patients treated with ADA biosimilars [22] and similar to that occurring in other experiences: Ribaldone et al. [31] optimized the ABP 501 in 4.8% of patients at 6th month from baseline, Cingolani et al. [16] optimized the ABP501 in 9% and the SB5 in 3% of patients at 6th month from baseline [16], Tapete et al. [17] optimized the SB% in 9% patients at 6th month from baseline. All these data seem to show that patients who replaced the originator with ADA biosimilars for a non-medical reason often need dose escalation, which may impact the therapy's burden and make the biosimilars less attractive.

Another interesting finding of this study was that a switch back to the ADA originator was performed in 9 patients (7.1%) who experienced a loss of response during the follow-up, most of whom recovered the clinical response. These data are like those reported by Tapete et al. [17], who showed a switch back rate of 6.1% in their population treated with SB5, all regaining clinical remission and without AEs reported after the switch back. Why this occurs is unknown. The most plausible hypothesis could be that the increased immunogenicity of ADA biosimilars leads to a loss of response. Although it was recently excluded by Strand et al. [35], more in-depth studies are needed to investigate this phenomenon. Whatever the mechanisms involved, a non-negligible rate of return to the originator ADA means that, in patients who have no remission after replacing the originator for a non-medical reason, can permit the patient to regain remission and thus save therapy.

The present study has both strengths and weaknesses. The first strength is that this real-life study includes a large cohort of patients, reflecting actual clinical practice in using these drugs in Italy. The second is that it compared all ADA biosimilars available in Italy for the first time in a population of IBD patients undergoing a nonmedical switch. Moving on to the weak points, the first and stronger limit of this study is that it is not possible to draw definitive conclusions regarding

Table II. Adverse events according to the type of adalimumab biosimilar used for nonmedical switch

Adverse event	Total (153 pts)	ABP501 (78 pts)	SB5 (65 pts)	GP2017 (7 pts)	MSB11022 (3 pts)	P
Total	12 (7.84)	6 (7.6)	5 (7.7)	1 (14.3)	-	0.005
Mild-moderate	11 (4.6)	5 (6.4)	5 (7.7)	1 (14.3)	-	
Severe	1 (2.1)	1 (1.2)	-	-	-	
Type						
Allergy	3 (1.9)	1 (1.2)	1 (1.5)	1 (14.3)	-	
Alopecia	1 (0.6)	1 (1.2)	-	-	-	
Psoriasis	1 (0.6)	-	1 (1.5)	-	-	
Leukopenia	1 (0.6)	1 (1.2)	-	-	-	
Itch/pain	4 (2.6)	2 (2.5)	2 (3.0)	-	-	
Joint pain	1 (0.6)	1 (1.2)	1 (1.5)	-	-	

Data are given as number (percentage) of patients.

the patients treated with MSB11022 and GP2017 due to the small number of patients who used them and the short follow-up period due to their recent entry into the Italian market [24, 25]. In addition, a limitation lies in the study's retrospective design, which does not allow the same follow-up for all enrolled patients. Furthermore, we do not have the values of the serum levels of biosimilars and anti-drug antibodies. Finally, a comparison with the ADA originator as the control group would have been interesting to understand whether there were differences in the long-term management of these patients. However, we believe that the lack of these data does not significantly impact the management of these patients in the real world because these investigations are not widely available in Italy, and their use in clinical practice is still debated [36]. Considering the reported items, we believe this study adds interesting data for clinical practice.

CONCLUSIONS

The results of the study showed that all ADA biosimilars currently available in Italy were effective and safe for the replacement of the ADA originator for a non-medical reason. However, we should also consider the dark side of the medal: our population included patients in stable remission under ADA originator treatment, and the rate of about 20% of patients losing remission, together with a significant rate of successful switch back to the ADA originator, is a finding that requires careful evaluation in prospective studies, also for the ethical implications. This is particularly relevant for UC patients, who seem to have the worst performance when the ADA originator was replaced for a non-medical reason.

Conflicts of interest: G.Maconi served as a speaker and advisory board fees for AlfaSigma, Arena, Janssen, Gilead, Roche. F.S. served as lecturer for Sanofi. The remaining authors have no conflict of interest to declare.

Authors' contribution: A.T conceived and designed the study. A.T., G.Mocci, A.C., A.F. W.E., M.P., G.Maconi, F.S., A.P. collected data, analysed and interpreted the results. A.T., M.P. W.E. G.Maconi, A.P. drafted the work or revised it critically for important intellectual content. A.T., G.Mocci, A.C., A.F. W.E., M.P., G.Maconi, F.S., A.P. approved the final version of the manuscript.

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