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Effectiveness and safety of adalimumab biosimilar ABP 501 in Crohn's disease: an observational study

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ABSTRACT

Background and objective: there are no studies in the literature about the effectiveness of adalimumab biosimilar ABP 501 in Crohn's disease. The aim of this study was to evaluate its effectiveness and safety.

Methods: an observational study was performed in Crohn's disease patients treated with ABP 501, with the classic induction and maintenance regimen and in Crohn's disease patients who were switched from the adalimumab originator to ABP 501.

Results: eighty-seven patients were included in the study, of which 25 were naïve to the adalimumab originator and 62 were switched to ABP 501. In adalimumab-naïve patients, clinical response at three months was 60% (15/25) and clinical remission at three months was 56% (14/25). At six months, 95.2% (59/62) of the patients switched to ABP 501 were still in therapy, without a significant increase of clinical activity (Harvey-Bradshaw index from 3.4, 95% CI = 2.4-4.4, to 3.8, 95% CI = 2.7-4.9, p = 0.23) and inflammatory biomarkers (C-reactive protein from 4.2

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mg/l, 95% CI = 2.5-5.9 mg/l, to 3.6 mg/l, 95% CI = 2.2-5 mg/l, p = 0.32). There were no unexpected adverse events during the study period.

Conclusions: our results support ABP 501 as an effective and well-tolerated drug, with a good interchangeability with its originator for the treatment of Crohn's disease.

Keywords: Amgevita®. Anti-TNF. Inflammatory bowel disease.

INTRODUCTION

Crohn's disease (CD) is a chronic condition with progressive damage to the gastrointestinal tract, which affects the quality of life of patients (1). We are still far from being able to cure this disease, but we have a growing number of drugs to control flares and prevent complications due to its natural history (2). Anti-tumor necrosis factor (anti-TNF) (TNF is a pleotropic pro-inflammatory cytokine) were the first approved biological drugs in CD. Among this class of drugs, adalimumab, a fully human monoclonal antibody directed against soluble and membrane-bound TNF, is highly effective in CD (3).

Although the use of biologics in CD has made it possible to reach targets such as improvement in the quality of life and clinical and endoscopic response in patients who have failed previous therapies (steroids, thiopurines, etc.) (4), they entail an increasing cost on the national health systems (5). Biosimilar drugs, which are biological drugs being developed as similar therapeutic alternatives to their originators, respond precisely to this need. However, there are few studies that support their use in inflammatory bowel disease (IBD), especially regarding adalimumab.

The use of biosimilars of adalimumab in CD, which are now widely used in the clinical practice, is based on the concept of extrapolation of the results obtained in rheumatoid arthritis (6) and in psoriasis (7). However, there is no study about the efficacy and safety in CD of the biosimilars approved in Europe and in the United States, such as ABP 501. The concept of extrapolation is unique to biosimilars. Studies about the effectiveness of this biosimilar of adalimumab in CD would allow us to answer some of the doubts raised regarding the concept of extrapolation (8-11).

ABP 501 (Amgevita®; Amgen Inc., Thousand Oaks, CA, USA) is a biosimilar of the adalimumab originator (Humira®; AbbVie Inc., North Chicago, IL, USA) approved for all the indications of its originator. The similarity between ABP 501 and adalimumab has been demonstrated by means of an analytical assessment and human pharmacokinetic evaluation (12).

The aim of this study was to analyze, for the first time, the effectiveness and safety of ABP 501 in CD patients naïve to adalimumab and the biosimilar adalimumab maintenance in CD patients who switched from the adalimumab originator.

METHODS

A prospective observational study was performed at the gastroenterology clinic of the Turin university hospital between November 2018 and May 2019, according to regional indications:

- All CD patients who began adalimumab were treated with ABP 501.
- All CD patients with stabilized disease (clinical and biochemical remission from at least six months) treated with the adalimumab originator were switched to ABP 501. According to the position paper of the Italian Group for the Study of Inflammatory Bowel Disease (IG-IBD) and ECCO, we explained to the patient that when a biosimilar is approved by the European Medicines Agency (EMA) according to the strict regulations applied to this drug class, we consider it as equivalent to its originator. Switching from the originator to a biosimilar is acceptable, because this approach is safe, effective and leads to a significant cost reduction for the health care system and, subsequently, to the possibility of treating more patients (13,14).

All CD patients who began ABP 501 as a first adalimumab treatment (160 mg, 80 mg after 14 days, 40 mg every 14 days) were prospectively followed up at three months; all CD patients who switched to ABP 501 (40 mg every 14 days) were prospectively followed up at six months.

The following parameters were prospectively collected at every visit: previous biological treatments, smoking habits, Harvey-Bradshaw index (HBI), concomitant treatments, adalimumab retention, adalimumab dose escalation, clinical response and clinical remission (for patients who began ABP 501 as first adalimumab treatment), C-reactive protein (CRP), perianal involvement, CD-related hospitalization, CD-related intestinal surgery, anal surgery and adverse events. Given the observational nature of the study, calprotectin was not included because of the cost to patients.

Inclusion criteria were: CD diagnosed according to ECCO criteria (15), age ≥ 16 years and initiation of therapy with ABP 501. Exclusion criteria was follow-up duration of less than three months for adalimumab-naïve patients and less than six months for patients who switched to ABP 501.

Primary outcomes were:

- For patients treated with ABP 501 as the first adalimumab: clinical response rate at 12 weeks. Clinical response was defined as a ≥ 3-point decrease in HBI compared to baseline and complete tapering of systemic corticosteroids. For patients with active perianal fistulising disease, fistula response was defined by a reduction of the number of draining fistulae ≥ 50%, as assessed by physical examination without the need for surgical intervention. Fistula remission was defined as a complete absence of fistula drainage and closure of all fistulae on physical examination (16). Due to the observational design of the study and the short follow-up (six months), pelvic magnetic resonance imaging that, in our clinical practice, is performed one year after the start of an anti-TNF was not included (17).
- For patients who switched to ABP 501: drug retention at 24 weeks.

Secondary outcomes were:

- Clinical remission rate at week 12 (for patients treated with ABP 501 as first adalimumab). Clinical remission was defined as HBI ≤ 4 points and complete tapering of systemic corticosteroids (18).
- HBI and CRP reduction at week 12 (for patients treated with ABP 501 as first adalimumab), no significant change in HBI and CRP values at week 24 (for patients who switched to ABP 501).
- Analysis of predictors of drug discontinuation in the whole population (i.e., combination therapy with azathioprine, previous anti-TNF use, sex, age, disease duration).
- Adverse events, defined as new events that began during or following the first and within two months after the last dose of ABP 501. With regard to the side effects, all those that occurred during the follow-up period were considered, regardless of the probability that they were consequent to the use of ABP 501.

Statistical analysis

Continuous variables were reported as the mean (range). The normality of the data was evaluated by the D'Agostino-Pearson test. The comparison of paired measurements was performed using the Student's t test for paired measurements. The cumulative retention rate of ABP 501 was calculated with the Kaplan-Meier survival curves. Multivariable Cox proportional hazards regression models were used to identify the predictors of ABP 501 discontinuation. A p value of less than 0.05 was considered as significant. The statistical analysis was performed with the MedCalc Statistical Software version 18.9.1 (MedCalc Software bvba, Ostend, Belgium;

http://www.medcalc.org; 2018).

Ethical considerations

The ethical committee of our institution approved the analysis of the data of all patients treated with adalimumab and the correlation with clinical parameters.

RESULTS

Eighty-seven patients were included in the study, of which 25 were naïve to adalimumab originator and 62 were switched to ABP 501. The demographic and clinical characteristics of the two study populations are shown in table 1.

Clinical effectiveness of ABP 501 in adalimumab-naïve patients

The cumulative retention rate of ABP 501 in adalimumab-naïve patients is shown in figure 1.

After three months, 96% (24/25) of the patients were still on ABP 501 therapy, and after six months, 92% (23/25) of the patients were still on ABP 501 therapy. The reason for discontinuation was adverse events in all patients, such as backache, headache and vomiting in one patient and abdominal pain in the other patient. Clinical response at three months was 60% (15/25) (Fig. 2). Clinical remission at three months was 56% (14/25). The mean HBI score at baseline was 6.1 (95% confidence interval, CI = 4.3-7.9), which decreased at week 12 (4.7, 95% CI = 2.6-6.8, p = 0.10). The mean of the CRP values at baseline was 14.9 mg/l (95% CI = 4.8 mg/l-25.1 mg/l), which decreased at week 12 (6.2 mg/l, 95% CI = 2.4-10.1 mg/l, p = 0.11). The ABP 501 dose was escalated in two patients (8%).

Clinical effectiveness of ABP 501 in patients who switched from adalimumab originator

The cumulative retention rate of ABP 501 in patients who switched from adalimumab originator is shown in figure 3.

After six months, 95.2% (59/62) of the patients were still on ABP 501 therapy. The reason for discontinuation was secondary failure in all patients. The mean HBI value at baseline was 3.4 (95% CI = 2.4-4.4) and did not change significantly after six months of therapy (3.8, 95% CI = 2.7-4.9, p = 0.23). The mean of the CRP values at baseline was 4.2 mg/l (95% CI = 2.5-5.9 mg/l) and did not change significantly after six months of therapy (3.6 mg/l, 95% CI = 2.2-5 mg/l, p = 0.32). The ABP 501 dose was escalated in three patients (4.8%).

Factors predicting drug discontinuation in the whole population

The Cox proportional-hazards regression analysis for predictors of drug discontinuation is reported in table 2. Female sex (p = 0.047) was associated with a worse outcome of drug persistence.

Safety

Twenty-two patients experienced at least one adverse event (25.3%). Four of the patients suffered from a rash; eight, abdominal pain; four, diarrhea; five, arthralgia; five, vomiting; one, anemia; one, rectal bleeding; two, headaches; one, bronchitis; one, herpes simplex type 1 clinical reactivation; three, fever; and one, weight loss. Some patients experienced more than one side effect. There were no cases of malignancy, tuberculosis or death reported during the study. The CD-related hospitalizations rate during ABP 501 therapy was 1.1% (n = 1/87). No CD-related surgery events were recorded during the study.

DISCUSSION

In recent years, the interest in biosimilar drugs has constantly grown thanks to the great economic savings that their use entails. Generic drugs are identical from the point of view of the active ingredient with respect to the drugs from which they derive. However, biosimilars cannot be identical to their originators because of the complex and proprietary protein structure of which they are made, requiring unique cell lines (19). Biosimilars are not identical to their originators.

The efficacy and safety of the adalimumab biosimilar ABP 501 has been established in multi-center, randomized, clinical trials (RCTs) in psoriasis (7) and rheumatoid arthritis (6). Therefore, there is a great expectation for data concerning the effectiveness of adalimumab biosimilars in IBD. Unfortunately, to date, the studies in this regard are absolutely lacking. This study describes for the first time the efficacy and adverse events of the adalimumab biosimilar ABP 501 in a population of 87 CD patients, of which 25 are naïve to adalimumab and 62 switched from the adalimumab originator to ABP 501.

A significant proportion of patients treated with ABP 501 showed clinical benefit until the end of follow-up. The rate of clinical remission at week 12 was 56%, which was comparable to the rates of the adalimumab originator in the CHARM trial at week 26 (40%) (3) and in the CLASSIC trial at four weeks (36%) (20). The same was true for the data regarding drug retention rate, which was 92% at six months for the patients that had received an induction dose of 160 mg of ABP 501. This

was comparable with data from the real-life experience of adalimumab originator (81% at 12 months [21]).

HBI and CRP values decreased in a clinical significantly way after 12 weeks of ABP 501 160 mg first dose compared to baseline. However, these differences did not reach statistical significance due to the sample size ($p = 0.10$ and $p = 0.11$, respectively). Only one study analyzed the efficacy of one adalimumab biosimilar (Exemptia®) in IBD patients in a real-life setting in India (22). This retrospective study only included patients (49 CD) treated with Exemptia® as a first adalimumab induction therapy. At week 8, 47% of CD patients were in clinical remission and the clinical response was 57%; at 26 weeks, 41% of patients were in clinical remission. During the two years of follow-up, 17% of patients underwent surgery and 10% had serious adverse events (three patients developed pulmonary tuberculosis). No studies about interchangeability of an adalimumab biosimilar, including ABP 501 with its originator in IBD have been published.

In our study, 62 CD patients switched from the adalimumab originator to ABP 501 and 95.2% were still on ABP 501 therapy after six months; data confirm those of the biosimilar of infliximab CT-P13 (23). Female sex as a prognostic factor of precocious ABP 501 discontinuation confirmed what had already been reported for the adalimumab originator (21), but the possible biological explanation it is not yet known. With regard to adverse events, there were no unexpected safety findings including death during the study period. Our results suggest that, at least in the short-term, treatment with ABP 501 was generally well-tolerated in CD and the safety profile of ABP 501 seems to be not inferior to that of the adalimumab originator. Our results support that ABP 501 is interchangeable with its originator in the treatment of CD.

A potential limitation of our study is the relatively small sample size, which limited the generalizability of our findings. The observational design of this study could have overestimated the efficacy and underestimated the rate of side effects of ABP 501 in CD compared to RCTs. However, these are unlikely to be performed in this setting due to their high costs as long-term surveillance would be needed to further assess the safety profile. Data on endoscopic effectiveness were very limited, as follow-up colonoscopy was performed in only a few cases at various time points. Thus, they have not been reported in our analysis. With regard to patients who switched from the originator to a biosimilar, a concern about the nocebo effect should be raised (24). According to the IG-IBD position paper (13), reliable, up-to-date information to help patients understand biosimilars and enable them to make informed choices about their treatment options was provided. Thus, this should have limited the nocebo effect (25). Finally, ABP 501 was

not directly compared with its originator and as the use of ABP 501 derived from a regional indication, it was impossible to directly compare ABP 501 and the adalimumab originator in two comparable patient cohorts.

Despite these limitations, our data provide meaningful information that reflects the actual experience (effectiveness, safety) of the short-term treatment with ABP 501 in a real-life cohort of CD patients. Another strength of our study is that it was not supported by Amgen Inc. Thus, we have no conflicts of interest compared to the studies about the efficacy of ABP 501 in psoriasis (7) and rheumatoid arthritis (6).

In conclusion, our findings support the use of the adalimumab biosimilar ABP 501 in CD as an effective and well-tolerated drug, at least in the short-term. These data contribute to the confirmation of the similarity between ABP 501 and the adalimumab originator. Further multicenter studies with a larger sample size and a longer follow-up are needed to confirm our preliminary results.

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309 **Table 1. Demographic and clinical characteristics of patients treated with ABP 501, naïve to**
310 **adalimumab (n = 25) or who switched from adalimumab originator to ABP 501 (n = 62)**
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Characteristics	*Patients naïve to adalimumab*	*Patients who switched to ABP 501*
Sex, n (%)		
Male	17 (68)	39 (62.9)
Female	8 (32)	23 (37.1)
Age at ABP 501 first dose, mean years (range)	45.9 (18-66)	42.8 (16-68)
Smoking habits n (%)		
Current	9 (36)	29 (46.8)
Ex-smokers	6 (24)	13 (21)
Never	10 (40)	20 (32.3)
Disease duration, mean years (range)	16.5 (0-46)	17.3 (1-49)
HBI at first treatment, mean score (95% CI)	6.1 (4.3-7.9)	N/A
Perianal involvement, n (%)	5 (20)	13 (21)

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313 CI: confidence interval; N/A: not applicable (all patients were in clinical remission).

314 **Table 2. Cox proportional-hazards regression analysis for predictors of ABP 501 discontinuation**

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Characteristics	p value
Age	0.78
Disease duration	0.11
Experienced to adalimumab originator	0.97
Female	0.047
Current smoker	0.66
Infliximab-naïve	0.97
History of perianal disease	0.92
Combinational therapy with azathioprine	0.33
Steroids at baseline	0.97

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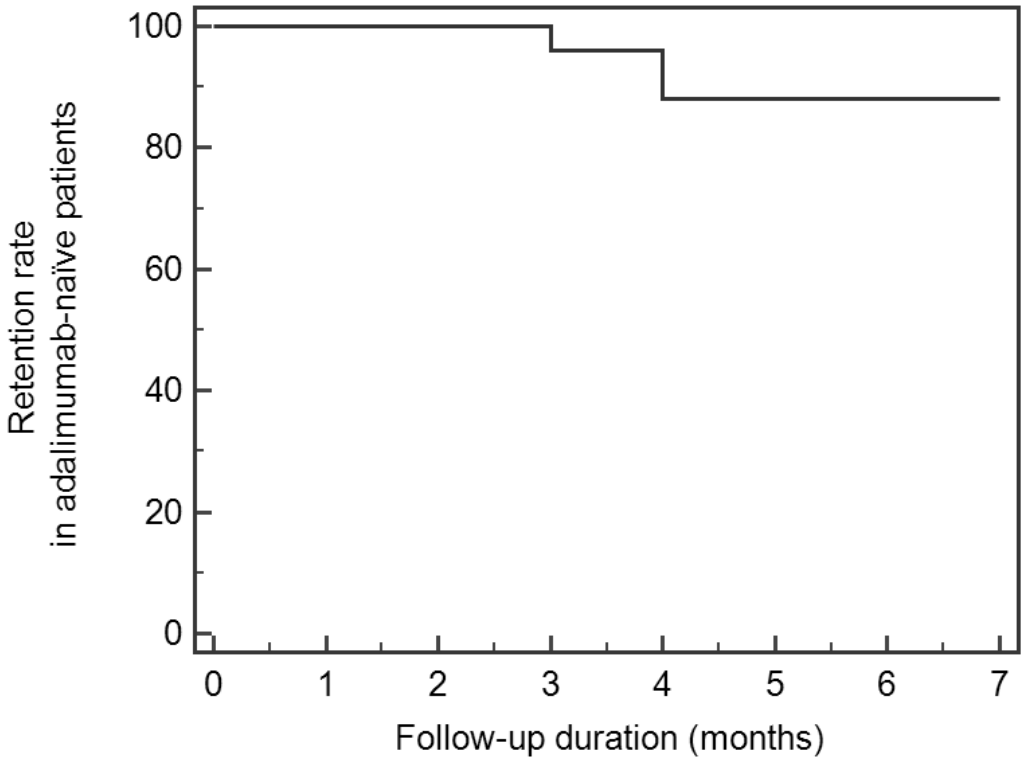

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319 Fig. 1. ABP 501 retention rate in patients naïve to adalimumab.

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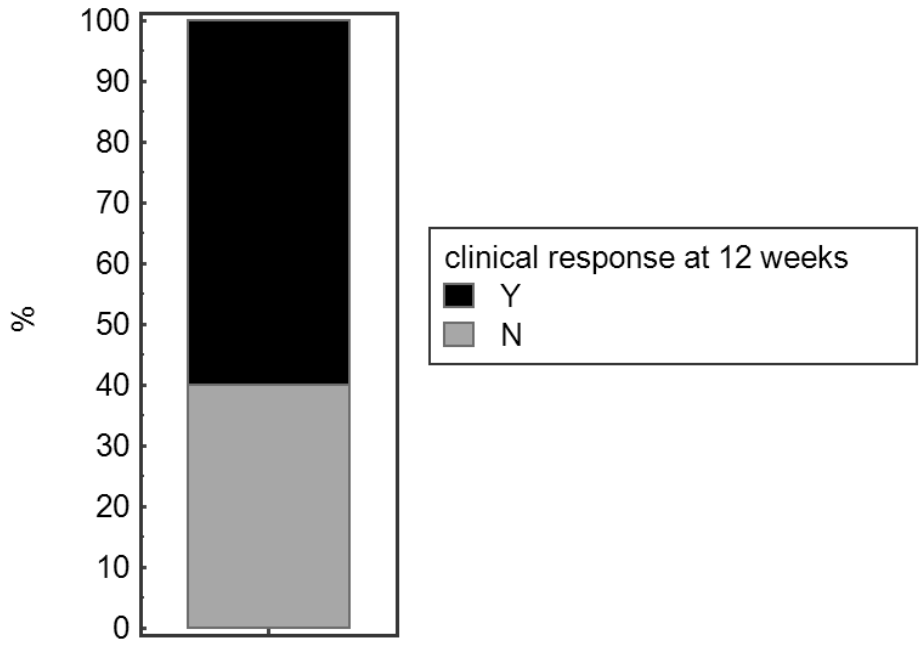

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322 Fig. 2. Clinical response at week 12 to ABP 501 in patients naïve to adalimumab.

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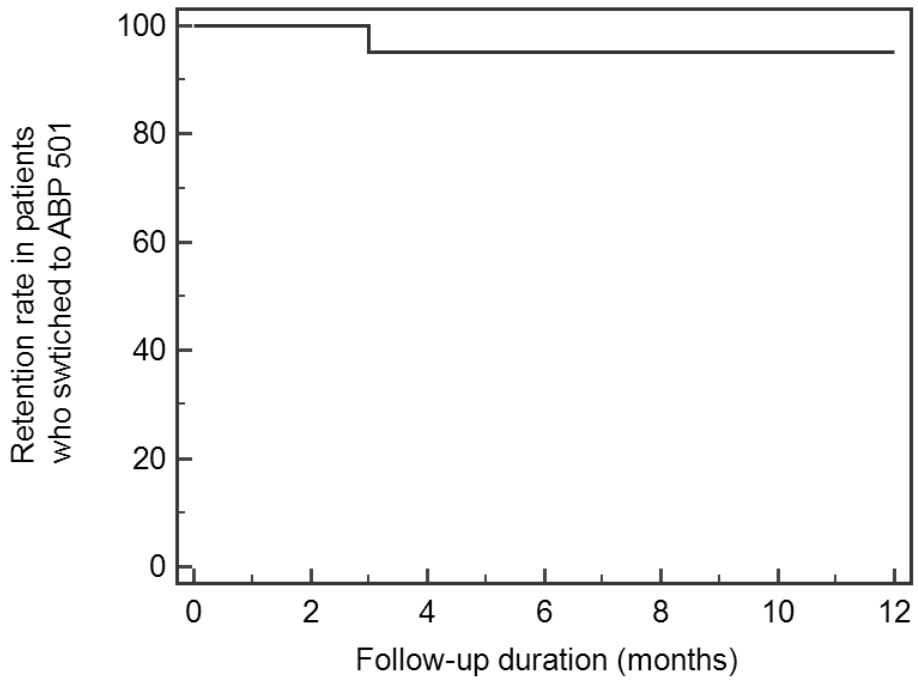

Fig. 3. ABP 501 retention rate in patients who switched from the adalimumab originator.