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Alimentary Tract

Non-medical switch from the originator to biosimilar and between biosimilars of adalimumab in inflammatory bowel disease – a prospective, multicentre study

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ABSTRACT

Introduction: Clinical data on the efficacy and safety of non-medical switch between adalimumab(ADA) biosimilars are limited.
Aims: The aim of this study was to evaluate medium-term clinical efficacy, drug sustainability and safety comparing non-medical switches from the originator to biosimilar ADA, and between ADA biosimilars.
Methods: 276 consecutive patients on maintenance ADA therapy (n = 205 Crohn's disease, n = 71 ulcerative colitis) were included. Data on clinical efficacy, biomarkers and adverse events were collected at four time points: 8–12 weeks prior switch, at baseline/switch, 8–12 weeks and 20–24 weeks after switch. Drug survival was evaluated after a median 40(IQR:35–42) weeks follow-up.
Results: A total 174 patients underwent a non-medical switch from the originator to a biosimilar, and 102 patients had a biosimilar-to-biosimilar switch. No significant difference was found in clinical remission rates at any time point in patients switching from originator to biosimilar(87.3%/88.5%/86.5%/85.7%) or biosimilar to biosimilar(74.5%/78.4%/85.3%/79.8%). Mean C-reactive protein levels remained unchanged in both cohorts(p = 0.856 and p = 0.525). Drug survival was similar between the two cohorts with a probability of 91.6%(SE: 2.2) and 87.0%(SE:3.4) to stay on drug after 40 weeks(log-rank:0.96; p = 0.327). Five cases of injection related adverse events were reported.
Conclusion: Clinical benefit was sustained following non-medical switch from originator to biosimilar, or between biosimilars in adalimumab treated IBD patients.

1. Introduction

Biological therapies are now representing the mainstay of medical treatment in moderate- to severe inflammatory bowel disease (IBD). The global financial expenditure on biological treatments has however augmented rapidly over the last decade and now approaching almost unaffordable costs [1]. The recent expiry of patents for biologicals – anti-TNF agents mainly – have led to the development of biosimilar products, expected to offer options for both patients and physicians towards easier access to these medications and with more affordable economic burden.

Biosimilar biological products had undergone stringent, although expedited approval processes by European (EMA) and American (FDA) regulatory authorities, using extrapolation of clinical trial data on safety and efficacy performed in other autoimmune diseases (e.g. rheumatoid arthritis), thus approval was granted without the need for formal clinical trials in IBD [2,3]. The acceptance of biosimilars among physicians encountered resistance in the early phase after approval, especially when considering switching from the originator product to its biosimilar, or between biosimilars [4]. CT-P13 infliximab was the first anti-TNF

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biosimilar approved in IBD in 2013 by the EMA, and compelling data has accumulated from real-life cohorts and a randomized controlled trial on the similarity of clinical efficacy, safety, and immunogenicity between biosimilar and originator infliximab since [5,6,7]. In 2017, based on clinical evidence mainly derived from the use of biosimilar infliximab, a position statement by the European Crohn's and Colitis organisation highlighted that non-medical switching from the originator to an approved biosimilar product is acceptable [8].

Few years after the introduction of infliximab biosimilars, adalimumab biosimilar products emerged to the market. More recently successful switching from the originator to an adalimumab (ADA) biosimilar was reported in some IBD cohorts, however considerably less 'real-word' data are available compared to infliximab biosimilars. Biosimilars of ADA showed equivalent clinical efficacy to the originator product in other immune-mediated diseases [9,10,11], yet post-marketing data in IBD patients are still of great importance for reassuring the efficacy and safety of ADA biosimilars. Moreover, because of the increasing number of biosimilar ADA agents and changing reimbursement policies by health authorities (especially the tender system in certain European countries) [12,13], physicians have to face non-medical mandatory cross-switching, or multiple switching among biosimilars in the forthcoming years. Currently, clinical data examining non-medical switch between ADA biosimilars are limited.

In Hungary, Humira® was the only available ADA agent until the end of 2019. The National Health Insurance Fund of Hungary (NEAK) adopted two ADA biosimilar products for reimbursement: ABP 501 (Amgevita®) and MSB11022 (Idacio®). Biosimilars were mandatory to be used in new patients, while a non-medical switch was optional in patients with maintenance therapy, based on physicians' discretion. Since December of 2020, the GP2017 (Hyrimoz®) became the only available adalimumab agent in the country. As a result, a non-medical switch became mandatory in all new- and maintenance patients on adalimumab therapy, irrespective of the therapeutic situation [14].

Federal regulation changes in Hungary presented a unique opportunity to prospectively evaluate short- and medium-term clinical efficacy, drug sustainability and safety in patients with mandatory non-medical switches from the originator to biosimilar ADA, and between ADA biosimilars in a large cohort of IBD patients.

2. Materials and methods

2.1. Study design and patients

The present prospective observational study enrolled unselected IBD patients from 4 academic IBD centers receiving ADA therapy. Patients were eligible with an age of 18 years or older. 276 consecutive patients – $n = 205$ Crohn's disease (CD) and $n = 71$ ulcerative colitis (UC) – were included who underwent a non-medical switch between September 2019 and December 2020 based on actual reimbursement regulations (regulations changed on two occasions in this period). Patients received subcutaneous injections of ADA at standard doses of 40 mg every other week, or at a dose intensified regimen with administration of 40 mg every week.

A harmonized monitoring strategy was applied in all participating centers (as well as in all biological centers in Hungary) as mandated by the NEAK [12,13]. Data on patient demographics, disease phenotype, treatment history (surgical history, previous and present concomitant medications) were collected from electronic medical records at inclusion. Disease location and behavior were assessed according to the Montreal classification [15]. Clinical and biochemical assessment was performed 8–12 weeks prior the switch, at baseline (switch), 8–12 weeks and 20–24 weeks after switch, as mandated by the NEAK. Data on concomitant corticosteroid and immunosuppressive medication use was collected. Total follow-up time for evaluating drug sustainability and recording adverse events was a median of 40 weeks (IQR: 35–42). Clinical remission was defined as a Crohn's Disease Activity Index (CDAI) <150 points or no fistula drainage in CD patients. A partial Mayo (pMayo) score of less than 3 points defined clinical remission in UC patients. Patients with induction treatment at baseline were excluded from analysis. Biochemical inflammatory activity was evaluated using serum C-reactive protein (normal cut-off value: 10 mg/L).

The primary outcomes of the present study were evaluation of clinical disease activity changes and drug sustainability following a non-medical switch between adalimumab agents. One hundred and seventy-four of the total 276 patients underwent a switch from originator ADA to biosimilar, and 102 of 246 patients had a switch from one biosimilar to another. In our analysis, we evaluated clinical and biochemical remission rates, drug sustainability rates concomitant corticosteroid treatment and adverse events in both cohorts.

2.2. Statistical analysis

For the evaluation of baseline demographic data, disease characteristics, remission rates and adverse events descriptive statistics were applied. Medians and interquartile ranges (IQR) were calculated for continuous variables. Nominal variables of clinical remission rates were compared by chi-square tests. Continuous variables, such as CRP were compared by analysis of variance (ANOVA). Kaplan–Meier survival curves were plotted to evaluate drug sustainability. Statistical analysis was performed using SPSS software v. 20.0 (Chicago, IL); $P < 0.05$ was considered statistically significant. Remission rates were calculated based on intention-to-treat analysis.

2.3. Ethical considerations

Ethical approval of the study was acquired from the Hungarian Medical Research Council's Committee of Scientific and Research Ethics [IV/ 4532–3/EKU]. Consent forms of all patients were obtained in accordance with the Helsinki Declaration.

3. Results

Out of the total 276 IBD patients, $n = 174$ patients [133CD/41UC, median age: 38y(IQR: 28–47)] underwent a non-medical switch from the originator to a biosimilar ADA and $n = 102$ patients [72CD/30UC, median age: 32.5y(IQR: 26–41)] had a switch from a biosimilar to another biosimilar ADA in the inclusion period. For detailed description of the switches between available ADA agents see Fig. 1. Both originator-to-biosimilar and biosimilar-to-biosimilar cohorts are characterized by high rates of severe disease phenotype, high exposure to immunosuppressives and previous biological therapy, and high rates of previous resective surgery. In total, 15.9% ($n = 44$) patients received ADA at a dose intensified regimen at the time of switch. Of note, patients with biosimilar-to-biosimilar switch had shorter duration of maintenance ADA therapy. Detailed baseline characteristics of the two patient cohorts are shown in Table 1.

The proportion of patients in clinical remission remained unchanged before and after the non-medical switch including all patients, either undergoing an originator-to-biosimilar or biosimilar-to-biosimilar switch: 82.5% / 84.8% / 86.1% / 83.6% at week 8–12 prior switch / switch / week 8–12 and week 20–24 after switch ($N = 276$; $p = 0.697$ among groups). Systemic corticosteroid use as concomitant therapy was 6.5% / 5.8% / 3.7% / and 5.2% at times of clinical evaluation.

Fig. 1. Distribution of originator-to-biosimilar and biosimilar-to-biosimilar switches in the study period
* Eleven patients initially switched to ABP-501 and one patient switched to MSB11022 underwent a second consecutive non-medical switch to the biosimilar GP2017 according to renewed regulations in December 2020.

Table 1
Baseline patient characteristics.

	Originator > biosimilar switch $N = 174$	Biosimilar > biosimilar switch $N = 102$
Gender (male/female)	74/100 (42.5%/57.5%)	36/66 (35.3%/67.4%)
CD / UC	133/41	72/30
Age at disease onset (median (IQR); years)	23 (18–32)	24 (20–32)
Disease duration (median (IQR); years)	12.5 (8–17)	8 (3–13)
Location (L1/L2/L3/all+L4;%)	12/22.6/65.4 /15.8	12.5/18.1/69.4 /19.4
extent (e1/e2/e3;%)	2.4/46.3/51.2	3.3/46.7/50.0
behavior (b1/b2/b3/b2+b3;%)	39.8/38.3/18.0/3.8	37.5/40.3/16.7/5.6
Perianal (%)	39.8	36.1
Previous resective surgery or colectomy (%)	24.7	24.5
Concomittant steroid/AZA (%)	4.0 / 32.1	8.8 / 31.4
Previous biologicals (%)	42.8%	23.5%
Dose intensified regimen (%)	14.7%	16.7%
Duration of ADA therapy (median (IQR); months)	42 (24–61)	6 (3–11)

[IQR, inter-quartile region; CD, Crohn's disease; UC, ulcerative colitis; AZA, azathioprin; ADA, adalimumab].

Table 2
A) Clinical disease activity scores and biomarkers in patients with an originator-to-biosimilar, and a biosimilar-to-biosimilar switch with adalimumab.

	Week 8–12 before switch	Switch	Week 8–12	Week 20–24
Originator-to-biosimilar SWITCH				
CD ($n = 133$)				
Median CDAI (IQR)	70 (35–98.25)	66 (34–104)	68 (40–98)	64 (39–105)
Mean CRP* (SD)	6.41 (12.31)	5.63 (8.85)	6.45 (13.72)	6.79 (15.26)
UC ($n = 41$)				
Median pMayo (IQR)	1 (1–2)	1 (1–2)	1 (0–2)	1 (0.25–2)
Mean CRP* (SD)	3.82 (3.85)	2.86 (3.44)	3.09 (3.28)	4.16 (8.50)
Biosimilar-to-biosimilar SWITCH				
CD ($n = 72$)				
Median CDAI (IQR)	75 (40–135)	75 (40.5–108.5)	72.5 (36.25–99)	70 (30.25–113.75)
Mean CRP* (SD)	5.84 (6.50)	6.81 (15.23)	6.34 (10.76)	5.72 (6.24)
UC ($n = 30$)				
Median pMayo (IQR)	2 (0.5–3)	2 (0–3)	1 (0–2)	1 (0.25–2)
Mean CRP* (SD)	3.13 (3.06)	9.46 (24.5)	4.56 (4.88)	3.92 (3.44)

*mg/L.
[IQR, *inter-quartile region*; SD, *standard deviation*; CD, *Crohn's disease*; UC, *ulcerative colitis*; CDAI, *Crohn's Disease Activity Index; pMayo, partial Mayo Score*, CRP, C-*reactive protein*].

3.1. Clinical outcomes after non-medical switch from the originator to biosimilar adalimumab

Median CDAI and pMayo scores were 66 (IQR, 34–104) and 1 (IQR, 1–2) at the time of switch, and 64 (IQR, 39–105) and 1 (IQR, 0–2) at week 20–24 thereafter in patients with originator-to-biosimilar switch. Median clinical activity scores and mean CRP levels during the complete follow-up are shown in Table 2. CDAI and pMayo scores at week 8–12 prior switch, baseline, week 8–12 and week 20–24 were compared with 1-way ANOVA, showing no statistically significant variance between clinical activity scores at these time points (CDAI: $p = 0.997$; pMayo: $p = 0.724$). CRP levels between the evaluation time points remained unchanged in both CD ($p = 0.925$) and UC patients ($p = 0.752$).

No significant difference was found among the proportion of patients in clinical remission at week 8–12 prior switch / switch

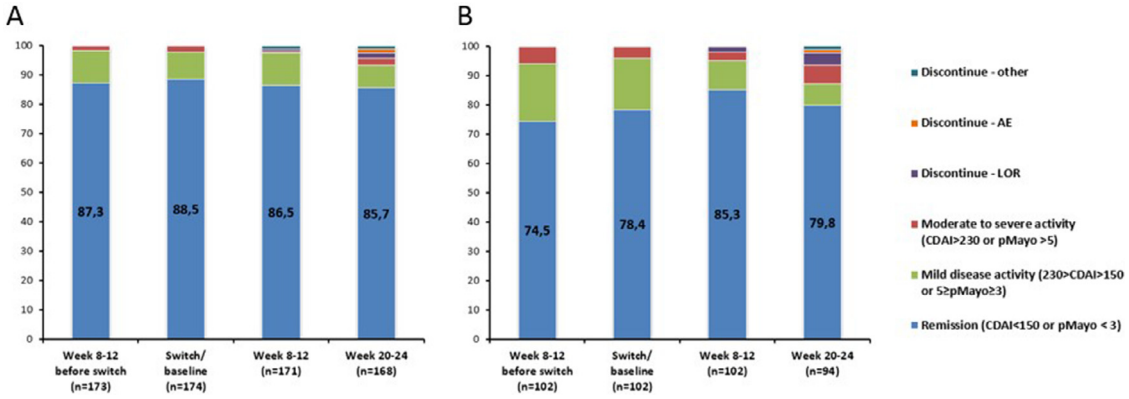

Fig. 2. A) Change in clinical disease activity following a switch from the originator adalimumab to biosimilar in IBD patients; B) Change in clinical disease activity following a switch from biosimilar to biosimilar adalimumab in IBD patients.

Table 3
Concomitant systemic corticosteroid medication in patients with an originator-to-biosimilar, and a biosimilar-to-biosimilar switch with adalimumab.

	Week 8–12 before switch	Switch	Week 8–12	Week 20–24
Total population (n = 276)	6.5%	5.8%	3.7%	5.2%
Originator >> biosimilar (n = 174)	2.9%	4.0%	3.5%	6.7%
Biosimilar >> biosimilar (n = 102)	12.7%	8.8%	4.0%	2.2%

/ week 8–12 and week 20–24 after switch in patients switched from originator to biosimilar ADA treatment (87.3% / 88.5% / 86.5% / 85.7%; p = 0.888 among groups). Fig. 2/a. Among patients in clinical remission at switch/baseline, 93.4% sustained clinical remission at week 8–12 and 89.9% up to week 20–24.

Concomitant systemic corticosteroid medication was required at an even rate between evaluation points. Table 3. In a sub-analysis of patients with corticosteroid-free clinical remission at the time of switch, considerably lower corticosteroid therapy rates were observed at week 8–12 (1.3%) and week 20–24 (4.2%) after the switch. Amongst these patients, corticosteroid-free remission was sustained in 92.6% at week 8–12. For detailed corticosteroid-free remission rates see Supplementary Figure 1/a.

3.2. Clinical outcomes after non-medical switch from biosimilar to biosimilar adalimumab

In patients with a switch from a biosimilar ADA to another biosimilar, median CDAI and pMayo scores were 75 (IQR, 41–109) and 2 (IQR, 0–3) at the time of switch, and 70 (IQR, 30–114) and 1 (IQR, 0–2) at week 20–24 thereafter. Median clinical activity scores and mean CRP levels during the complete follow-up are shown in Table 2. By comparing CDAI and pMayo scores at week 8–12 prior switch, baseline, week 8–12 and week 20–24 no statistically significant difference between clinical activity scores was observed (CDAI: p = 0.688; pMayo: p = 0.504). CRP levels between the evaluation time points remained unchanged in both CD (p = 0.942) and UC patients (p = 0.383).

No statistically significant difference was found in the proportion of patients in clinical remission at week 8–12 prior switch / switch / week 8–12 and week 20–24 after switch in patients who were switched from biosimilar to biosimilar ADA treatment (74.5% / 78.4% / 85.3% / 79.8%; p = 0.291 among groups). Fig. 2/b. Among patients who were in clinical remission at switch/baseline, 96.3% sustained clinical remission at week 8–12 and 84.9% up to week 20–24.

Rates of concomitant systemic corticosteroid medication required at evaluation points are shown in Table 3. In a sub-analysis of patients with corticosteroid-free clinical remission at switch, corticosteroid therapy rates remained 0% at both week 8–12 and week 20–24 after switch. Among patients with corticosteroid-free remission at the time of switch, 96.0% sustained corticosteroid-free remission at week 8–12. For detailed corticosteroid-free remission rates see Supplementary Figure 1/b.

3.3. Drug survival, dose intensification and adverse events

Drug survival was evaluated after a median of 40 weeks (IQR: 35–42) total patient follow-up. In Kaplan-Meier analysis no significant difference was observed between the originator-to-biosimilar and biosimilar-to-biosimilar switch cohorts in drug survival (log-rank: 0.961; p = 0.327). Fig. 3. Patients who switched from the originator to a biosimilar ADA had a probability of 95.4% (SE:1.6) to remain on medication after 20 weeks, and 91.6% (SE: 2.2) after 40 weeks. In the biosimilar-to-biosimilar cohort, drug survival probabilities were 94.1% (SE: 2.3) and 87.0% (SE: 3.4) after 20 and 40 weeks following the switch.

Dose intensification rates at the time of switch were 16.7% in the original-to-biosimilar group, and 14.7% in the biosimilar-to-biosimilar group. During the 24 weeks follow-up, 2.9% (n = 5) of the patients with originator-to-biosimilar switch required dose intensification, whereas 5.8% (n = 6) of the patients in the biosimilar-to-biosimilar group needed to escalate to weekly ADA regimen.

In total, n = 29 patients discontinued ADA therapy (n = 16 patients after originator-to-biosimilar switch, and n = 13 patients with biosimilar-to-biosimilar switch). Reasons for therapy discontinuation were loss of response (n = 20), pregnancy (n = 2), adverse events (n = 4), cancer (n = 1), other cause/compliance (n = 2).

In total, n = 5 therapy related adverse events were registered. Two cases of skin erythema at the injection site were registered. One patient on Hyrimoz® therapy (switched from Idacio®), and one with Idacio® (switched from Humira®), the latter discontinued and switched back to Humira®. Liver enzyme elevation was detected with one patient, switched from Humira® to Hyrimoz®. One patient developed adalimumab induced psoriasis 20 weeks after switched from Amgevita® to Hyrimoz®. Both patients discon-

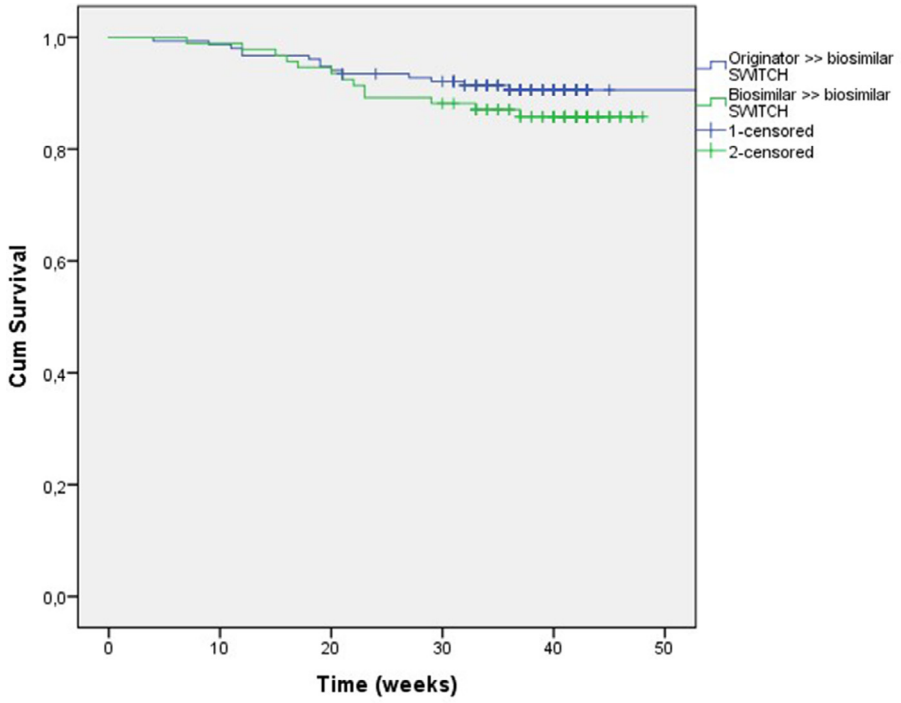

Fig. 3. Drug survival following originator-to-biosimilar and biosimilar-to-biosimilar non-medical switches in patients with adalimumab therapy.

tinued ADA therapy and were switched to other drug class. Finally, one patient switched from Humira® to Hyrimoz® therapy developed symptoms of difficulty breathing and fatigue presenting 3 days after injection, suggestive of late hypersensitivity reaction and discontinued therapy after 18 weeks following the switch.

In the total study population, $n = 12$ patients experienced multiple switches among ADA agents. Eleven patients were switched first to Amgevita® and one patient to Idacio®, who later underwent a second consecutive non-medical switch to the biosimilar Hyrimoz® according to renewed regulations in December 2020. No adverse events and no treatment discontinuation was registered in these patients.

4. Discussion

The results of the present prospective multicenter study provide data on the efficacy and safety of originator-to-biosimilar ADA switching in a 'real-world' setting. We are also one of the first to present data on biosimilar-to-biosimilar ADA switching in a patient cohort of considerable size. Clinical remission rates following the switch remained unchanged in both cohorts during the 24-week monitoring period. Medium-term clinical benefit was maintained in both originator-to-biosimilar and biosimilar-to-biosimilar switching. Drug sustainability was high and not different between the two groups. No new safety signals were detected in either originator-to-biosimilar or biosimilar-to-biosimilar switching.

As global expenditures on monoclonal antibodies used for immune-mediated inflammatory diseases grow rapidly every year [16], the advent of biosimilar monoclonal antibodies represent one of the most recent revolutions in the field of biological therapies. Following the infliximab biosimilars, adalimumab biosimilars also became available for the treatment of IBD patients in the past two years. In fact, several of them (SB5, ABP501, BI 695,501, MSB11022, and GP2017) have been approved by the EMA, after initial preclinical data proved strong similarity between all biosimilars and the originator product [17]. Clinical data of comparative phase 3 studies in rheumatoid arthritis and chronic plaque psoriasis showed no differences in terms of efficacy, safety, and immunogenicity [9,10]. Consequently, only post-marketing clinical data exist on the efficacy and safety of ADA biosimilars in IBD patients and the number of these studies is still limited. In addition, safety and efficacy data on cross-switching among biosimilars, and multiple switching is missing. Choosing between available biosimilars, or switching amongst them is the next challenge in biological therapies.

A small number of 'real-world' prospective studies have investigated the efficacy and safety of switching to the biosimilar ADA from the originator in IBD, but they are limited by cohort size or follow-up time, and mainly focus on the SB5 biosimilar. An Italian prospective study enrolled patients who underwent a non-medical switch from the ADA originator to SB5 biosimilar [18]. Out of the 98 patients in clinical remission at switch, 72.4% were in clinical remission at one year. The study found no differences in ADA serum trough levels at baseline, 3, and 6 months after switching, and no patient developed antidrug antibodies after the switch. In another Czech study, a cohort of 93 patients switched to biosimilar SB5 was matched to 93 controls remaining on originator ADA [19]. No difference in the clinical disease activity, or CRP and fecal calprotectin (FCAL) concentrations was found between the switch and originator cohorts between weeks 0 and 10. A small North Italian retrospective cohort showed conflictive results that almost 1/3 of the patients experienced disease worsening after switching from the originator ADA to ABP 501 [20]. In the present paper, we found that a high proportion of patients maintained clinical remission (>80–85%) and remained on the therapy (>85–90%) at 24 and 40 weeks after switching from the originator to a biosimilar ADA or in the biosimilar-to-biosimilar switch cohort.

A recent large observational cohort from the UK investigated outcomes in patients after switching from the ADA originator to the biosimilar SB5 (256 patients), and in patients with a new biological therapy start on SB5 (225 patients) [21]. No differences in clinical remission, CRP, FCAL and ADA trough levels were found between baseline, week 26 and week 52 following switch. In concordance, we did not find changes in biochemical activity as measured by CRP values after the switch in the present study. In the switch

cohort, 70.8% remained on SB5 beyond 1 year. Among naïve patients with SB5 start, drug persistence was 60.3% beyond 1 year, which is in line with available data on drug persistence with the originator ADA after one year [22]. A small number of patients ($n = 35$) underwent a double biosimilar switch from the ADA originator to SB5 and subsequently to ABP 501 in this study, none of those patients discontinued during a median follow-up 34 weeks.

The only available randomized phase 3 trial comparing biosimilar versus ADA reference product in IBD is the VOLTAIRE-CD trial [23]. Patients were randomly assigned 1:1 to start biological therapy with ADA originator product or biosimilar BI 695,501, then responders were treated until week 46, with those assigned to ADA reference product switched to BI 695,501 at week 24. Treatment benefits were maintained in patients receiving ADA reference product who switched to BI 695,501 with no statistically significant difference in clinical remission rates, CRP and FCAL levels by week 48, compared to the biosimilar arm. Safety signals were also comparable between the originator ADA and BI 695,501 biosimilar.

As for biosimilar-to-biosimilar switching, our results confirm that clinical benefit was maintained following the switch. Among patients who were in corticosteroid-free remission at the time of switch, 96.0% sustained corticosteroid-free remission at week 8–12, and 85.5% up to week 20–24. The drug sustainability rates was over 94% at 20 weeks following a biosimilar-to-biosimilar switch, and 87% after 40 weeks in these patients. These drug survival rates were not different from that in our originator-to-biosimilar switch cohort and were also in line with other data of available studies on originator-to-biosimilar switching [21]. Currently, very limited number of studies are available on biosimilar-to-biosimilar switching with ADA. An Italian prospective study provided data on switching from ABP 501 to SB5 biosimilar in $n = 61$ patients – of whom 43/61 underwent multiple switches (Humira® → ABP 501 → SB5) [24]. After 6 months of follow up, 88.5% of patients maintained on SB5 therapy.

In contrast, more data are available on multiple switching among ADA biosimilars in other immune mediated diseases. In a phase 3 randomized study in psoriasis, the impact of multiple switches between GP2017 and the originator ADA was demonstrated including 465 patients randomly assigned to start GP2017 or originator ADA therapy [25]. At week 17, each arm was re-randomized to continue their original treatment or to receive either GP2017 or originator ADA during three alternating 6-week periods. Psoriasis Area and Severity Index (PASI) improved over time and was similar between all treatment groups at every time point up to a total follow-up of 51weeks. In our cohort, $n = 12$ patients underwent a double biosimilar switch safely without registering adverse events or treatment discontinuation during the follow-up of these patients. Of note, the ECCO position statement on the use of biosimilars (2017) advises against a sequential biosimilar switch within 6 months due to possible immunological effects and lack of evidence.

The rate of concomitant systemic corticosteroid medication was overall low during the study period. Corticosteroid need was relatively stable across the evaluation time points in the originator-to-biosimilar group, however a decrease was seen among biosimilar-to-biosimilar switch patients over time. This may be explained by the shorter duration of ADA maintenance therapy (median 6 months) among biosimilar-to-biosimilar switch patients.

Previous studies examining the originator-to-biosimilar switch in ADA patients detected no new safety signals [18,19,21]. Injection site pain was the most common adverse event in patients treated with the SB5 biosimilar, which was interestingly more frequent in patients who underwent an originator-to-SB5 switch [18,19,21]. This phenomenon could be explained by the fact that SB5 contains sodium citrate, a compound may be responsible for more painful administration. In one study, all but one (1/31) patient continued to have pain at the injection site after a second switch to another biosimilar (from SB5 to ABP 501) [21]. In a recent study, following a biosimilar-to-biosimilar switch to SB5, adverse events occurred in 11.5% of the patients up to 6 months, which was a statistically significant increase compared to the adverse event rate of 1.6% in last 6 months of therapy with ABP 501 [24]. These registered adverse events were injection site pain in over 90% of the cases. In our study, the total adverse event rate is in line with that of the originator ADA compound and we did not detect an increased number of injection site pain / erythema with the biosimilars used in this study (ABP 501, MSB11022, GP2017).

To the best of our knowledge, this is one of the first, and the largest real-life prospective multicenter cohort that examines biosimilar-to-biosimilar switches in IBD patients on maintenance ADA therapy. Strengths of our study is the large sample size and the parallel investigation of multiple biosimilar ADA agents. Further strength is the methodological design: a mandatory harmonized monitoring strategy is applied in all participating centers, as well as in all biological centers in Hungary as mandated by the National Health Insurance Fund (NEAK), which allowed standardized data collection on clinical disease activity scores and biomarkers in all time points. Limitation to our study is the relatively short follow-up time and the lack of data on FCAL levels. Fecal calprotectin test is not reimbursed by the national healthcare provider, thus not routinely available in Hungary. However, FCAL measurement has a more important role in UC, where CRP levels show a weaker correlation to biochemical disease activity, as opposed to CD patients, especially in patients with ileal disease. Further limitation to our study that ADA serum drug trough level and anti-drug antibody measurements (TDM-therapeutic drug monitoring) were not performed. Nonetheless, the impact of TDM measurements on the clinical decision making and the correlation with clinical outcomes in ADA treated patients is less important compared to patients treated with infliximab [26].

In conclusion, we demonstrated that non-medical switching between ADA biosimilars or switching from the originator ADA to a biosimilar had no impact on treatment efficacy and safety. Drug sustainability following the switch was high and not different between originator-to-biosimilar and biosimilar-to-biosimilar switches. Our study showed amongst the first that a biosimilar-to-biosimilar non-medical switch in ADA therapy is safe with no changes in clinical or biochemical disease activity over time, providing comforting evidence for the everyday clinical practice. Further research is warranted, especially on cross-switching among biosimilars. Because of the growing number of biosimilars and rapidly changing regulations, physicians may need to face multiple switch scenarios in the near future.

Conflict of interest

LL, LG, FB, NK, TS and ES declare no conflict of interest. KF has been a speaker and/or advisory board member: Abbvie and Ferring. TM, PM, TSZ have been a speaker and/or advisory board member: AbbVie, EGIS, Ferring, MSD and Takeda. AI has been a speaker and/or advisory board member: MSD. PAG. has been a speaker for AbbVie, Takeda, Fresenius, Ferring. PLL has been a speaker and/or advisory board member: AbbVie, Amgen, Arena Pharmaceuticals, Fresenius Kabi, Genetech, Gilead, Janssen, Merck, Mylan, Organon, Pharmacosmos, Pfizer, Roche, Takeda,Tillots and Viatris and has received unrestricted research grant: AbbVie, Gilead, Takeda and Pfizer.

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NK contributed to the data collection. TR, KF, TM, PM, PG, ES, TS, and AI equally contributed to the data collection and manuscript revision. LPL was responsible for research planning and result interpretation, and supervised the manuscript preparation. LPL is acting as guarantor of submission. All authors read and approved the final manuscript.

Disclosures

LL, LG, FB, NK, TS and ES declare no conflict of interest. KF has been a speaker and/or advisory board member: Abbvie and Ferring. TM, PM, TSZ have been a speaker and/or advisory board member: AbbVie, EGIS, Ferring, MSD and Takeda. AI has been a speaker and/or advisory board member: MSD. PAG. has been a speaker for AbbVie, Takeda, Fresenius, Ferring. PLL has been a speaker and/or advisory board member: AbbVie, Amgen, Arena Pharmaceuticals, Fresenius Kabi, Genetech, Gilead, Janssen, Merck, Mylan, Organon, Pharmacosmos, Pfizer, Roche, Takeda,Tillots and Viatris and has received unrestricted research grant: AbbVie, Gilead, Takeda and Pfizer.

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Supplementary materials

Supplementary material associated with this article can be found, in the online version, at doi:10.1016/j.dld.2022.07.004.

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