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ORIGINAL RESEARCH

Self-reported efficacy and safety of infliximab and adalimumab biosimilars after non-medical switch in patients with inflammatory bowel disease: results of a multicenter survey

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ABSTRACT

Background: Few data are available on subjective disease control and perception of adverse events (AEs) during switching from original anti-TNF agents to biosimilars.

Research design and methods: Hungarian patients with inflammatory bowel disease were interviewed after a mandatory non-medical switch from an infliximab (IFX) originator to a biosimilar GP1111 or from an adalimumab (ADA) originator to a biosimilar GP2017. Drug choice was based on patient's and physician's decision. Subjective efficacy was measured using a 10-point scale, and AEs were assessed. Difference in efficacy before and after the switch was compared within and between the drugs.

Results: Seventy-three ADA and 106 IFX switching patients were interviewed. Subjective efficacy of IFX biosimilar was rated lower compared to IFX originator (8.72 ± 1.68 vs. 7.77 ± 2.34; $p = 0.001$). The ADA biosimilar was rated higher than its originator (9.02 ± 1.61 vs. 8.42 ± 1.93; $p = 0.017$). Patients receiving ADA biosimilar were more satisfied with the new treatment compared to IFX ($p = 0.032$). The incidence of new AEs was 85% in the ADA and 55% in the IFX group (1.79 vs. 0.93 AEs per patient, respectively, $p < 0.001$).

Conclusion: Subjective efficacy of switching to a biosimilar was proven in case of ADA, while reduced efficacy was experienced with IFX biosimilar. Perception of AEs was high and varied between biosimilars.

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1. Introduction

Crohn's disease (CD) and ulcerative colitis (UC) are the two major types of inflammatory bowel disease (IBD) triggered by a variety of intrinsic and extrinsic environmental factors in a genetically susceptible individual. The health-care burden and the increasing incidence of IBD of 10.4 per 100,000 person-years in Hungary correspond to the European rate [1,2].

Although the origin of IBD is still unknown, therapeutic options have expanded rapidly in recent years [3]. In addition to conventional medical treatments, such as 5-aminosalicylates, corticosteroids, and immunomodulators, biologics have been available for the last two decades for patients with moderate-to-severe IBD to induce and maintain clinical and endoscopic remissions [4,5]. In addition to evaluating personal aspects, severity, and activity of the disease, the objective treatment decision must also consider cost and availability of the drug [4,6,7].

General availability of biologics is limited due to their high development costs. As a result, interest has turned to biosimilar (BS) products after patent expiration. BSs are biologic products, similar in terms of quality, safety, and efficacy to an already licensed reference biologic product [8]. Infliximab (IFX) was the first anti-tumor necrosis factor (anti-TNF) agent approved in 1998 for the treatment of IBD. After patent protection expired in the early 2010s, many BSs have already been developed. The European Medicines Agency approved BSs of IFX in 2013 and adalimumab (ADA) in 2017 [9,10].

Therefore, in the era of market competition and easier-to-obtain BSs, not only the progression of the disease but also the current state pharmaceutical subsidy determines the decision of the next treatment option. BSs, as the treatment of IBD, are a financially sound strategy to reduce the economic burden on health-care costs and to expand the number of patients benefiting from this therapeutic modality. Health-care systems in some countries have begun to switch patients' medications from the reference product (RP) to a BS due to the financial advantages. This process, referred to as a non-medical switch, can be either on a voluntary basis or mandated by the health-care provider [11,12].

However, it is hypothesized that the uncertainty about the therapy caused by the non-medical switch may lead to a decrease in effectiveness, an increased perception of adverse

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events (AEs), up to stopping the treatment or returning to the originator [11]. This phenomenon is referred to as nocebo effect and is, like the placebo effect, influenced by several psychological, neurobiological, and environmental factors [13]. In the context of BSs, negative influences due to reduced experience with BSs and skepticism of physicians may lead to negative expectations [14].

In this cross-sectional, questionnaire-based study, we aimed to examine the subjective efficacy of two BS drugs, namely IFX and ADA, in relation to the corresponding originator, and to investigate whether the change in medication can be significantly better evaluated with one biologic than with the other. Together with the analysis of new AEs occurring during the use of BSs, we contribute to clarifying the role of the nocebo effect in the non-medical switch of patients with IBD.

2. Patients and methods

2.1. Study design and subjects

This cross-sectional, questionnaire-based survey was reported following the rules of the Checklist for Reporting of Survey Studies (CROSS) (Supplementary Table S1). The study was conducted between November 2021 and February 2022 in three academic IBD centers in Hungary (Budapest, Pecs and Szeged). It should be noted that from November 2021, Hungarian patients with IBD receiving anti-TNFα agents (IFX or ADA) had to be switched to a BS drug, due to the altered financial protocol. Patients with IBD treated with IFX-RP Remicade© or ADA-RP Humira© were switched to the corresponding BS, i.e. IFX Zessly© (GP1111, IFX-BS) or ADA Hyrimoz© (GP2017, ADA-BS). IFX is administered intravenously, while ADA is self-injected subcutaneously by the patient.

All patients aged 18 years or older who underwent the non-medical switch at the listed centers were invited to participate in this study via a structured, self-completed online questionnaire at least 1 month after switching to the BS. Accordingly, the study sample consisted of voluntary participants (voluntary response sampling). The number of IBD patients treated with ADA or IFX between 2019 and 2020 at the aforementioned centers was 707. The choice of the primary medication was made based on a shared decision between the patient and the physician and was not determined by internal guidelines.

The self-administered questionnaire itself consisted of 31 questions in four main domains: demographic data, IBD symptoms in the past week, questions regarding the switching phase (duration of RP use, duration of BS use, concomitant medication, assessment of previous and current therapies), and current therapy side effects. At the beginning of the questionnaire, patients were informed about the aim of the study and the reason for the non-medical switch in Hungary (including the information that BSs contain the same active agent with similar structure and biological activity as the RP).

Patients were required to provide their unique health insurance number, which allowed detection of multiple participation. In case of multiple participation, the last response was counted. After data validation, the health insurance number was replaced with a generated unique identifier to ensure pseudonymity.

2.2. Ethical considerations

This study was approved by the Scientific and Research Ethics Committee of the Hungarian Medical Research Council (IV/1957–3/2021/EKU). The study protocol confirms the ethical guidelines of the Declaration of Helsinki updated in 2013, as reflected in a prior approval by the institution's human research committee. Patient consent was obtained prior to data collection.

2.3. Outcome measures

The primary end point was the evaluation of the subjective efficacy of the BS compared to the previously used RP. A 10-point interval rating scale adapted from the visual analog scale of the validated IBD-Control questionnaire was used for simple measurement of efficacy [15]. Patients were asked to rate the degree of symptom control during therapy with the corresponding biologic agent, with higher scores indicating better symptom control. A 3-point Likert scale was used to assess the satisfaction with the two biologicals. Another variable indicating the efficacy of the therapy was a binary question whether patients would like to switch back to the RP if possible. This question was only asked for ADA patients due to organizational reasons.

Secondary end points were patient-reported adverse events (AEs) and adverse events of special interest (AESI) after non-medical switch. AESIs during anti-TNF treatment were infections (including tuberculosis), infusion-related reactions, skin reactions, arthralgias, cardiac abnormalities, and malignancy. Patients should report any AEs and AESIs that did not occur during treatment with the RP but with the BS, measured by a checklist.

2.4. Statistical analysis

Descriptive statistics were used to characterize the demographic and disease characteristics of the patients. For the statistical analysis, the study participants were divided into two groups depending on the biological used. The difference in subjective efficacy before and after the switch was evaluated within each patient group using Wilcoxon signed-rank test with paired groups. The difference in subjective efficacy between the two patient groups was assessed using Wilcoxon rank sum test. The difference in AE and AESI after the non-medical switch between the two patient groups was calculated with Pearson's chi-squared test.

All data are expressed as N (%) for categorical variables; for numerical variables as mean ± standard deviation (SD) or median and interquartile range (IQR). All two-sided *p*-values below 0.05 were considered significant. In case of missing entries, empty data points were excluded from the analysis. All statistical analysis was performed using R Statistical Software (version 4.2.1; R Foundation for Statistical Computing, Vienna, Austria).

3. Results

A total of 188 submissions from the questionnaires were recorded. After removing duplicate submissions, 179 unique records were included in the analysis, which represents a response rate of 25%. Ninety-four (53%) patients were female; the median age was 41 years (IQR, 32–47 years). Seventy-three (41%) patients were switched from the ADA-RP to the ADA-BS and 106 (59%) from the IFX-RP to the IFX-BS. In both groups, most patients were diagnosed with CD (77% in the ADA group and 75% in the IFX group). Baseline demographics and disease characteristics are provided in Table 1.

In the ADA group, the median duration of ADA-RP and ADA-BS treatment was 24 months (IQR, 12–48 months) and 11 months (IQR, 8–12 months), respectively. In the IFX group, the median duration of treatment with IFX-RP was 30 months (IQR, 18–60 months), and the median duration since the initiation of treatment with IFX-BS was 7.5 months (IQR, 6–10 months).

The majority of patients treated with IFX (87%) were bio-naïve, whereas in the ADA group, the ratio of bio-naïve patients was relatively balanced with 39 (53%) individuals.

3.1. Efficacy

Patients receiving ADA-BS rated the efficacy of their current therapy higher than those who previously used ADA-RP (9.02 ± 1.61 vs. 8.42 ± 1.93; $p = 0.017$, respectively). The subjective efficacy of the previously used IFX-RP product was significantly higher compared to the IFX-BS group (8.72 ± 1.68 vs. 7.77 ± 2.34; $p = 0.001$) (Figure 1).

Comparing the satisfaction rate of non-medical switch between the ADA and IFX groups, patients receiving ADA-BS were more satisfied with the new treatment as patients in the IFX-BS group ($p = 0.032$). Nevertheless, 42 (64%) patients receiving ADA-BS indicated that they would like to switch back to the RP if they had the opportunity.

3.2. Adverse events

A total of 120 (67%) patients reported new AEs that did not occur during treatment with the RP, of which 92 (51%) patients reported new AESIs. The mean reported AEs per patient were 1.28 (1.79 in the ADA-BS group vs. 0.93 in the IFX-BS group).

Comparing the incidence of AEs after the non-medical switch between the two groups of biologicals, the incidence of reported AEs was significantly higher in the ADA-BS group compared to the IFX-BS group (85% vs. 55%; $p < 0.001$; respectively). However, there was no clear difference between the groups regarding AESIs. The most frequently reported new AEs were arthralgia in 24 (33%) patients in the ADA-BS group compared to 21 (20%) patients in the IFX-BS group ($p = 0.047$). Cutaneous AEs were more common in the ADA-BS group as well (20% vs. 7.5%, $p = 0.011$). In the ADA-BS group, 48 (66%) patients reported injection-site pain at the subcutaneous injection site when using the BS injector (Table 2).

4. Discussion

The literature on non-medical switch of IFX and ADA is very limited, and conclusions are mixed. Despite similar

Table 1. General demographic data and reported efficacy in adalimumab and infliximab biosimilar-treated patients.

Characteristic	Overall, N = 179	Adalimumab, N = 73	Infliximab, N = 106	p-value
Sex, n (%)				0.042
Female	94 (53)	45 (62)	49 (46)	
Male	85 (47)	28 (38)	57 (54)	
Age (years), median (IQR)	41 (32, 47)	42 (32, 51)	41 (32, 47)	0.32
IBD Type, n (%)				0.74
CD	135 (75)	56 (77)	79 (75)	
UC	44 (25)	17 (23)	27 (25)	
UC extension, n (%)				0.85
E1, proctitis	8 (18)	3 (18)	5 (19)	
E2, left-sided	13 (30)	4 (24)	9 (33)	
E3, extensive	23 (52)	10 (59)	13 (48)	
CD location, n (%)				0.036
L1, terminal ileum	33 (24)	19 (34)	14 (18)	
L2, isolated colon	51 (38)	15 (27)	36 (46)	
L3, ileocolon	51 (38)	22 (39)	29 (37)	
Quality of life index, mean (SD)[1]	2.28 (0.79)	2.30 (0.84)	2.27 (0.76)	0.93
Stool frequency per day, mean (SD)[2]	1.44 (0.68)	1.45 (0.69)	1.44 (0.68)	0.96
Bloody stool, n (%)[2]	16 (8.9)	1 (1.4)	15 (14)	0.003
Treatment duration with RP (months), median (IQR)	30 (18, 57)	24 (12, 48)	30 (18, 60)	0.067
Treatment duration with BS (months), median (IQR)	9.0 (6.0, 12.0)	11.0 (8.0, 12.0)	7.5 (6.0, 10.0)	<0.001
Previous biological therapy, n (%)	48 (27)	34 (47)	14 (13)	<0.001
Satisfaction rate with biosimilar therapy, n (%)				0.032
- I am satisfied, I am symptom-free	118 (66)	56 (77)	62 (58)	
- I am partially satisfied, I am not completely symptom-free	55 (31)	16 (22)	39 (37)	
- I am not satisfied, my symptoms are not controlled	6 (3.4)	1 (1.4)	5 (4.7)	
Subjective efficacy of RP, mean (SD)[3]	8.60 (1.78)	8.42 (1.93)	8.72 (1.68)	0.34
Subjective efficacy of BS, mean (SD)[3]	8.18 (2.20)	9.02 (1.61)	7.77 (2.34)	<0.001
Intention to switch back to reference product, n (%)	-	42 (64)	-	

[1]1 = weak, 4 = excellent, [2]last week average, [3]1 = not effective, 10 = my complaints have completely disappeared, Abbreviations: BS: biosimilar, CD: Crohn's disease, IBD: inflammatory bowel disease, IQR: interquartile range, RP: reference product, SD: standard deviation, UC: ulcerative colitis, Significant values ($p < 0.05$) marked in bold.

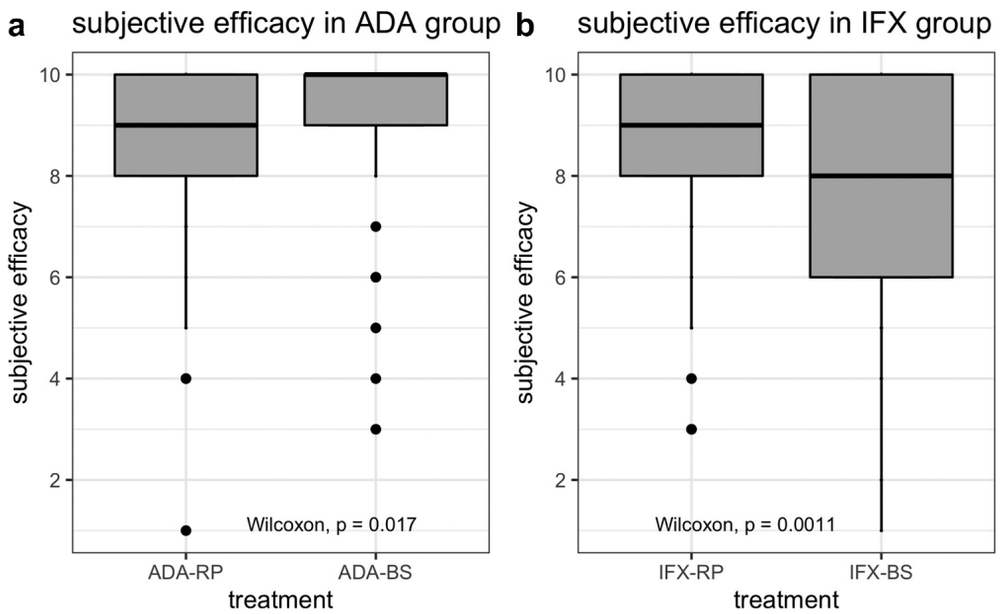

Figure 1. Subjective efficacy of adalimumab and infliximab biosimilars in patients with inflammatory bowel disease.
Abbreviations: ADA: adalimumab, IFX: infliximab, RP: reference product, BS: biosimilar.

Table 2. Reported adverse events during infliximab and adalimumab biosimilar treatment.

Characteristic	Overall, $N = 179$	Adalimumab, $N = 73$	Infliximab, $N = 106$	p-value
AE, n (%)[1]	120 (67)	62 (85)	58 (55)	<0.001
AESI, n (%)	92 (51)	41 (56)	51 (48)	0.29
Immediate allergic reaction, n (%)	11 (6.1)	3 (4.1)	8 (7.5)	0.53
Late allergic reaction, n (%)	33 (18)	14 (19)	19 (18)	0.83
Cardiac AE, n (%)	40 (22)	15 (21)	25 (24)	0.63
Infectious AE, n (%)	36 (20)	18 (25)	18 (17)	0.21
Cutaneous AE, n (%)	23 (13)	15 (20)	8 (7.5)	0.011
Arthralgia	45 (25)	24 (33)	21 (20)	0.047
Injection-site pain, n (%)	-	48 (66)	-	

Abbreviations: AE: Adverse events, AESI: Adverse events of significance, Significant values ($p < 0.05$) marked in bold.

effectiveness, recent studies have revealed negative and neutral effects of non-medical switch on health-care utilization, co-payment, and medication adherence [16–20].

During their approval, BSs had to demonstrate similar chemical composition, pharmacokinetics, and pharmacodynamics compared to the RPs [9,10]. Several randomized, blinded clinical trials have proven the safety and efficacy of switching from an originator to a BS in IBD [21,22]. However, it has been shown that these results are not always confirmed in the unblinded clinical practice, probably due to the emerging nocebo effect [23].

Our results show a significant difference in subjective efficacy in patients with IBD who switched from IFX or ADA originator to its BS during a mandatory non-medical switch. Starting with a similar rating of the efficacy of the RP, ADA-BS was rated significantly better, while IFX-BS was significantly lower than the corresponding RP. Second, two-third of patients switched to BS reported new AEs, mainly in the ADA group. However, patients sometimes give contradictory answers. For example, patients receiving ADA therapy were significantly more satisfied with the BS than with the previous product but at the same time reported more AEs and the majority also stated that they would like to switch back to the RP if possible.

The measurement of the nocebo effect is complicated and inconsistent across different studies. It is often calculated as the proportion of patients who experienced a negative and unexplained therapeutic effect that resolved after restarting the originator [24]. It ranges from 10% to 29% (median 20%) across different IFX-BS studies in IBD patients [11]. Direct measurement of the nocebo effect, i.e. the proportion of patients switching back to the original product, was not possible in our population, because the original product is no longer provided. Still, 64% of patients in the ADA group indicated a preference to switch back if possible.

The number of newly reported AEs was very high and disproportionate to other studies, for example, the NORSWITCH study reported 70% and 68% AE with the RP and the BS, respectively [21]. However, the data must be viewed critically due to possible survey biases like the retrospective study design causing patients to also report AEs that also occur with RP treatment. Another explanation for high AE incidence may lie in the structure of the questionnaire. AEs were asked by checking off a list of symptoms, which can lead to a higher number of AEs than if they were reported spontaneously [25].

The ADA group reported more injection site reactions and injection-site pain with BS than with RP. Research has shown that several factors related to drug delivery, such as the usage of a buffering agent (e.g. citrate), injection volume, needle size, or the usage of latex in the delivery device, can contribute to injection-site pain [26,27]. The ADA-BS GP2017 evaluated in this study contains citrate buffer, latex, and uses a larger injection volume (0.8 mL vs. 0.4 mL) and a larger needle size (27 G vs. 29 G) compared to RP [26,27]. These factors may account for the increase in injection-site pain following a non-medical switch. Additionally, the nocebo effect may contribute to a further increase in injection site reactions. A recent literature review identified that patients in open-label trials (where they were aware that they are receiving a BS) showed more reactions than those in blinded trials [28].

It is important to consider certain limitations of this study when interpreting the results. Since demographic data for our entire population were not available, we could not analyze the demographic representativeness of our study sample. The 25% response rate may limit the generalizability of the findings due to the potential for non-response bias, as non-responders may have systematically different characteristics or opinions from those who responded. As the online questionnaire may not be accessible to all patients, selection bias may be present. The retrospective design of the questionnaire and the one-time administration of the survey may have led to recall bias, as patients may not remember their previous medication experiences. The study captured only AEs that were reported at the time of the interview, without considering potential AEs related to duration of treatment and cumulative exposure. To increase validity, future research could use continuous monitoring of parameters over a longer period of time to examine potential time-related changes in AE perception and the long-term impact of BS use. The study assessed end points with a limited number of direct questions, and standardized scores, such as the IBD-Control, were not fully used to measure patient-reported outcomes. Additionally, the study design considered only a case group and did not include a control group. However, a control group does not exist in the current population, as all patients in Hungary have been switched to the BSs. Unfortunately, the questionnaire did not capture the preference of IFX-treated patients regarding switching back to the RP. The high frequency of new-onset AEs during the use of the BS is also questionable, and the validity of the data may be reduced because patients could not remember previous AEs or misread the request to specify only newly onset events. In order to overcome these limitations in the future research, reported AEs could be cross-checked with physician assessment. One explanation for the differences in the evaluation of BSs could be the different rates of disease progression between the two groups. Factors that may influence disease progression (such as disease duration or age at diagnosis) were not assessed, making it difficult to analyze the impact of different disease progression on the results. Finally, it should be noted that there is a significant difference in the duration of treatment between the two groups, as patients receiving ADA therapy filled out the questionnaire at a later time point, which could have influenced the evaluation of the drugs.

5. Conclusions

The results of the study show partly contradictory attitudes of patients toward BSs. The fact that there is no uniform trend in the assessment of the two BSs may indicate that this attitude may develop in different directions and thus possibly be influenced by a nocebo effect.

The precise quantification of the nocebo effect in patients with IBD during non-medical switch, as well as the possibilities of mitigating this effect, remain an open question. However, nocebo susceptibility is thought to be already high in IBD patients [29]. A mandatory non-medical switch may promote negative expectations and further increase the nocebo effect [11]. To counteract this, guidance of a non-medical switch through a managed switch program that includes patient and physician education about BSs and the development of an open communication which addresses patients' concerns and preferences may play a key role [14,30,31]. Specifying the main components of a switch program to increase patient adherence and decrease nocebo effect should form the basis of future research.

The high frequency of painful injections and subjective AEs associated with subcutaneous BS administration suggest that, in addition to objective clinical endpoints (which are considered similar for BS and RP), the patient's perspective should also be taken into account when assessing treatment success. The choice of the biologic drug used and the decision between RP and BS drug should be a joint decision of the physician and the patient [30]. In case of loss of response or increase of AEs following non-medical switch, the possibility of reverse switching to the originator should be available. In most cases, this leads to the recurrence of clinical remission [32,33].

List of abbreviations

ADA	adalimumab
ADA-BS	adalimumab biosimilar
ADA-RP	adalimumab reference product
AE	adverse events
AESI	adverse events of special interest
BS	biosimilar
CD	Crohn's disease
IBD	inflammatory bowel disease
IFX	infliximab
IFX-BS	infliximab biosimilar
IFX-RP	infliximab reference product
UC	ulcerative colitis
TNF	tumor necrosis factor

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