Evaluation of the safety and effectiveness after switch from adalimumab originator to biosimilar SB5 in patients with inflammatory bowel disease in a real-life setting

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Abstract

Background and study aims: **Prospective data are lacking on evolution of trough levels, effectiveness, acceptance rate and patient satisfaction after switch from the adalimumab originator to a biosimilar in patients with inflammatory bowel disease.**

Patients and methods: **Patients in clinical remission or stable response and treated with adalimumab originator in 2 Belgian centers were offered to participate in this phase IV, prospective trial in which patients were switched to adalimumab biosimilar SB5. The primary outcome was the description of adalimumab trough levels over time. Secondary outcomes were secondary loss of response, disease activity, patient satisfaction score and drug persistence over 12 months.**

Results: **The study included 110 patients. Mean baseline adalimumab trough level was 9.21 µg/ml. Concentration remained within the therapeutic range over time. No changes were observed in disease activity scores nor in biochemical parameters over time. The acceptance rate of switch was 84.6%. By month 12, 74.5% was still treated with SB5. The most frequent reason for discontinuation was occurrence of adverse events. 50% of these adverse events were injection site pain. The local discomfort was only significant the first 30 minutes after injection. Satisfaction with the decision to switch to SB5 was high and remained stable over time.**

Conclusions: **After being well informed the great majority of patients treated with the adalimumab originator is willing to switch to biosimilar SB5. In our study, there was a persistence rate of 75% over one year. The trough levels remained within the therapeutic range and no change in disease activity was seen over time.** (Acta gastroenterol. belg., **2022,** 85, **557-564**).

Keywords: inflammatory bowel disease, adalimumab, biosimilar

Introduction

Although biologic therapy is effective in the treatment of inflammatory bowel disease (IBD), the high cost represents a disadvantage. It's estimated that the treatment with anti-tumor necrosis factor-α (anti-TNFα) therapy accounts for the largest part of the costs in the management of IBD (1). The development of biosimilars offers an opportunity to reduce these costs. According to a Dutch study, cost savings seen over a period of 5 years were on average € 9.850 per Crohn's Disease (CD) patient and € 2.250 per ulcerative colitis (UC) patient, yielding a total of € 493 million in cost savings or a reduction of 28% (2).

Since October 2018, in most European Union countries, different adalimumab (ADA) biosimilars received marketing authorization from the European Medicines Agency (EMA), among them SB5 (3).

In 2017, the European Crohn's and Colitis Organisation (ECCO) stated that switching from originator to biosimilar in patients with IBD is an acceptable option (4). However, in contrast to infliximab, less data are available concerning effectiveness and safety after switch from ADA originator to ADA biosimilars. Two recent studies in IBD describe no differences in disease activity during short-term and long-term follow-up after switch from ADA originator to SB5 (5, 6).

Nevertheless, doubts among patients and health care professionals about switching from originator to biosimilar are extremely relevant to account for. The nocebo effect is defined as a negative effect of a medical treatment induced by patient's expectations and unrelated to the physiological action of the treatment (7). This is an important clinical challenge in the use of biosimilars. Negative expectations in combination with adverse symptoms can lead to a decrease in the patient's subjective well-being, worse adherence and can attribute to a detrimental effect on treatment outcomes (8). In a recently published consensus report, recommendations were made for the management of the nocebo effect in IBD patients treated with biosimilars, among them minimizing the lack of knowledge about the effectiveness and safety of biosimilars among patients and health care providers (9).

We performed a multicenter, phase IV interventional cohort study to evaluate the ADA trough levels after non-medical switch from ADA originator to SB5 in a real-world setting over a period of 12 months. The aim of the study was to analyze ADA trough levels over time and to collect data concerning disease activity, acceptance and discontinuation rate and adverse events.

In our study, patients were switched from ADA originator to SB5 after education about biosimilars. Patients were followed for 12 months and data concerning trough levels, disease activity, acceptance rate, discontinuation rate and reasons for discontinuation, adverse events, and visual analogue scores (VAS) were

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collected. To our knowledge, our study represents the largest dataset on prospective evolution of ADA trough levels over time in a real-life IBD population.

Material and methods

Study design

This is a multicenter, phase IV, prospective, interventional cohort study to evaluate the effectiveness and safety after non-medical switch from ADA originator to SB5 in a real-world setting. Patients from 2 Belgian centers were included: Maria Middelares General Hospital in Ghent (AZ Maria Middelares) and the Onze-Lieve-Vrouw General Hospital in Aalst (OLV Aalst). The study was registered on clinicaltrials.gov under the number NCT04045782 and in the EudraCT database under 2019-002041-38.

Study population

Adult patients (≥ 18 years of age) with CD or UC on ADA originator for at least 8 weeks were invited to enter the study. Patients were informed about the possibility to switch to SB5 and to participate in this study, regardless the disease response status. Irrespective of their intention to switch, all patients were offered a standardized evaluation of their current disease status. Patients were excluded if they had an allergy to latex, if they were already included in an interventional study or if they were pregnant or breastfeeding.

Study plan

Physicians and IBD nurses received a personalized thorough briefing with dedicated information regarding biosimilars in general and SB5 in particular with the possibility to ask questions or share concerns on the topic. Information about biosimilars was primarily given by the treating physician before the decision to switch and further fine-tuned by the IBD-nurse or physician in consecutive follow-up visits. For patients willing to switch, a follow-up period of 12 months after switch was scheduled. Baseline characteristics were collected, and patients were followed at baseline and subsequently 8 weeks, 6 months, and 12 months after switch. The treating physician could change dosing-intervals from week 8 on, based on the trough level determination at baseline. At the different time points blood samplings for analysis for ADA trough level (measured by enzyme-linked immunosorbent assay (ELISA), using the apDia ADA ELISA kit with a detection range between 0.1 and 12 µg/mL), anti-drug antibodies, peripheral blood count and C reactive protein (CRP) were collected. In addition, fecal calprotectin (fCal) was measured and disease scores as Crohn's Disease Activity Index (CDAI) for CD patients, Partial Mayo Score (PMS) for UC patients and Physician Global Assessment (PGA) for both were assessed. Finally, data on safety and subjective satisfaction of the patient was captured.

Outcomes

The primary outcome was the ADA trough level over time after switch from originator to SB5. Secondary outcomes were secondary loss of response (SLOR), changes in disease activity scores or objective disease markers over time, adverse events, acceptance of switch, satisfaction with the therapy, discontinuation of SB5 and possible associations between patient or disease characteristics and acceptance of switch and discontinuation of treatment with SB5.

Statistical analysis

The participating centers collected pseudonymous data by assigning a unique subject identification number to each patient. Data handling has been conducted according to the Data Management Plan and Data Validation Plan, specifically developed for this study. Statistical analysis was done according to the pre-planned statistical analysis plan (SAP) developed for this study. Continuous variables are reported as mean, standard deviation (SD), median, 25th and 75th percentile (Q1, Q3), 95% confidence intervals (CI), minimum and maximum where appropriate. Categorical variables are summarized as frequencies and percentage. Proportions will be presented with 95% confidence interval (CI). ADA trough level was analyzed with a mixed model repeated measures analysis (MMRM) with the use of the change of the log-transferred values. For each disease activity score a similar MMRM analysis was used. The comparison of the changes compared to baseline was made with a McNemar's Chi-Square test. Objective disease markers are described with the absolute levels and a change from baseline. For each marker a MMRM comparable to the other was used. A Kaplan-Meier (KM) estimate of the probability of persistence on treatment with SB5 at each timepoint plus a 95% CI, as well as the median and quartiles (25^{th} and 75^{th}) of persistence time were calculated. All statistical analysis was done using SAS version 9.4. As detailed in the SAP, a linear mixed model was fitted to the data with following covariates: sex, age, site, IBD type, disease activity at baseline, duration of disease at baseline, duration of prior ADA originator treatment at baseline, concomitant medication.

Ethical consideration

The study was registered on clinicaltrials.gov (NCT04045782) and in the EudraCT database (2019-002041-38). Approval was obtained on 29/07/2019 from the central ethics committee of Maria Middelares Hospital in Ghent (under internal reference number MMS.2019.026) and the Federal Agency for Medicines and Health Products (FAGG) to proceed with the study.

Results

Baseline characteristics

One hundred and thirty patients were screened at both centers for inclusion of which 110 patients (84.6%) agreed to switch (Figure 1), 84 had CD (76.4%) and 26 had UC (23.6%). The mean age of our population was 45.3 years and 52.7% were female. The median disease duration was 11.3 years and the median duration of treatment with ADA originator was 4.5 years. All patients were on the formula 40 mg/0.4 mL, most patients had a dosing frequency of two-weekly (90.0%) and two third of the patients used a pen as application device (66.4%). Immunodulators were co-administered in 6.4% of patients and corticosteroids were used in 5.5%

Table 1. — **Baseline characteristics**

	CD (N = 84)	**UC** (N = 26)	**Total** (N = 110)
Age, mean (SD)	44.8 (15.3)	47.2 (11.2)	45.3 (14.4)
Gender, n (%)			
Male	37 (44.0)	15 (57.7)	52 (47.3)
Female	47 (56.0)	11 (42.3)	58 (52.7)
Smoking status, n (%)			
Active	18 (21.4)	3 (11.5)	21 (19.1)
Former	16 (19.0)	9 (34.6)	25 (22.7)
Duration of disease, median months (min; max)	136.94 (4.7; 569.1)	124.40 (28.7; 498.1)	136.13 (4.7; 569.1)
Disease extension, n (%)			
Ileal	32 (39.5)		
Colonic	11 (13.6)		
Ileocolonic	38 (46.9)		
Upper GI disease (isolated or concomitant)	5 (6.3)		
Concomitant perianal disease	18 (22.8)		
Proctitis		2 (8.0)	
Left-sided colitis		13 (52.0)	
Pancolitis		10 (40.0)	
Previous surgery due to IBD, n (%)			
Yes	38 (45.2)	0	38 (34.5)
Ileocecal resection	21 (25.0)		
Partial colectomy	9 (10.7)		
Total colectomy	4 (4.8)		
Segment resection	1 (1.2)		
Surgery for fistula	11 (13.1)		
Anal surgery	11 (13.1)		
Presence of stoma, n (%)	4 (4.8)	0	4 (3.6)
Extraintestinal disease, n (%)	12 (14.3)	5 (19.2)	17 (15.5)
Psoriasis	8 (9.5)	2 (7.7)	10 (9.1)
Psoriatic arthritis	1 (1.2)	1 (3.8)	2 (1.8)
Ankylosing spondylitis	4 (4.8)	2 (7.7)	6 (5.5)
Baseline treatment			
Duration on ADA* originator, median months (min; max)			54.14 (2.3; 142)
Dosing volume ADA originator 40mg/0.4ml, n (%)	84 (100)	26 (100)	110 (100)
Dosing frequency ADA originator 2 weekly, n (%)	76 (90.5)	23 (88.5)	99 (90.0)
Pen/syringe, n (%)	55/29 (65.5/34.5)	18/8 (69.2/30.8)	73/37 (66.4/33.6)
Concomitant use immunomodulators, n (%)	5 (6.0)	2 (7.7)	7 (6.4)
Concomitant use corticosteroids, n (%)	4 (4.8)	2 (7.7)	6 (5.5)
Disease scores			
CDAI †, mean (SD)	62.3 (54.1)		
PMS ‡, median (IQR)		0.0 (0.0; 1.0)	
PGA ¥, median (IQR)	0.0 (0.0; 0.0)	0.0 (0.0; 0.0)	0.0 (0.0; 0.0)
Disease remission, n (%) °	75 (89.3)	22 (84.6)	97 (88.2)
Biochemical parameters, mean (SD)			
Leukocytes (x10/uL)	7.81 (2.14)	7.81 (2.49)	7.81 (2.22)
CRP ¤ (mg/L)	3.04 (4.82)	3.04 (3.96)	3.04 (4.61)
Fecal calprotectin (ug/g)	129.0 (215.7)	136.4 (263.0)	130.8 (226.6)

* ADA: Adalimumab, † CDAI: Crohn's Disease Activity Index, ‡ PMS: Partial Mayo Score, ¥ PGA: Physician's Global Assessment, ° Remission: CDAI ≤ 150 for CD or PMS < 2 for UC, ¤ CRP: C Reactive Protein.

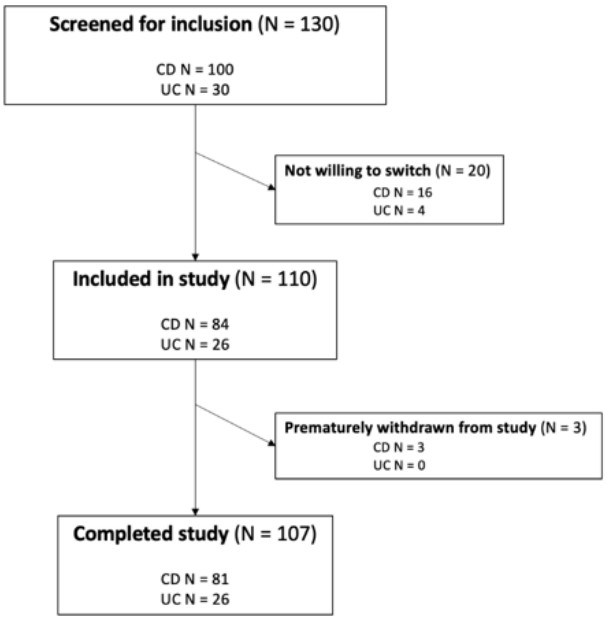

Figure 1. — Flowchart of patients.

of patients. The large majority (88.2%) of the patients were in clinical and biochemical remission based on low CDAI, PMS and PGA scores, normal leukocytes and CRP and low fCal (table 1).

Escalation/de-escalation

De-escalation was performed in 3 patients with the reason of supratherapeutic trough level and clinical remission while 9 patients received escalation of therapy because of low trough level and/or active disease (clinical or biochemical). In 2 patients, de-escalation has been performed on request of the patient itself and was followed by escalation because of flare.

Adalimumab trough levels

Mean trough level at baseline of ADA was 9.21 µg/ml. From all the covariates that were fitted in the model, hospital site significantly affected the mean change from baseline with a higher reduction of the ADA trough level over time in OLV Aalst compared to AZ Maria Middelares (table 2). The trough levels remained within the therapeutic range over time although a statistically significant reduction in mean ADA trough level was observed in the primary regression analysis from baseline compared to week 8, month 6 and month 12. However, no statistically significant change between month 6 and month 12 was observed (table 3).

Acceptance of switch

The acceptance rate of switch was 84.6% (110/130 patients) for all patients and 84.0% and 86.7% for CD and UC patients respectively. Fifteen patients reported 22 reasons for non-switch, while 5 patients preferred not to reveal their motivation. The most frequent reasons given for non-switch were fear for flare in 8 patients (40.0%), ease to stay on the ADA originator in 4 patients (20.0%), absence of trust in biosimilars in 3 patients (15.0%) and too much negative experiences with disease burden in 2 patients (3.8%). Patient characteristics correlating with non-switch could not be detected.

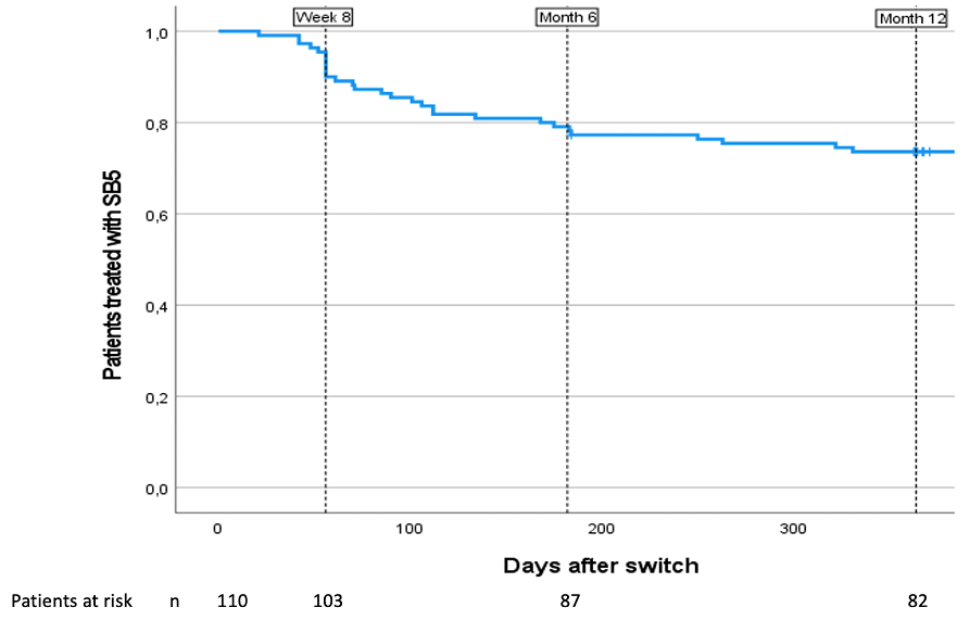

Figure 2. — Kaplan Meier estimate curve of the discontinuation of treatment with SBS over time.

Table 2. — **Adjusted mean change from baseline and 95% CI of ADA trough levels**

	ADA Through Level
Fixed Effects	Estimate [95% CI] p-value
Dose regimen at the visit	
Weekly	<reference>
2-Weekly	-0.582 [-1.957, 0.793] 0.404
Concomitant Medication at the visit	
Yes	<reference>
No	0.409 [-0.756, 1.574] 0.489
Sex	
Female	<reference>
Male	0.326 [-0.573, 1.225] 0.473
Disease cohort	
Chron's Disease	<reference>
Ulcerative Colitis	-0.206 [-1.238, 0.827] 0.693
Disease activity at baseline	
Remission	<reference>
Active	0.706 [-0.776, 2.187] 0.346
Site	
AZ Maria Middelares	<reference>
OLV Aalst	-1.613 [-2.658, -0.568] 0.003

Of the 110 patients who decided to switch to SB5, 103 patients (93.6% [87.1, 96.9]) were still on SB5 at week 8, 87 patients (79.1% [70.2, 85.6]) at month 6 and 82 patients (74.5% [65.2, 81.6]) completed the study with SB5 at month 12 (figure 2). Three patients prematurely left the study: 1 patient died (not related to the treatment with SB5), 1 patient was lost to follow-up and 1 patient reported adverse events, stopped treatment and withdrew the informed consent for the study.

Twenty-eight patients (25.4%) stopped treatment with SB5 of which 64.3% switched back to the ADA originator. Twenty-eight reasons were reported to discontinue the treatment with SB5. The most frequent being adverse events (n = 16), followed by high ADA anti-drug antibodies (n = 5) and patient's decision to switch back to ADA originator (n = 3). The remaining reasons were secondary loss of response (n=3) and long-term remission (n=1). Half of the adverse events resulting in treatment discontinuation were severe injection site pain (ISP).

Disease activity scores and objective disease markers

The median value (IQR) at baseline of the PGA, PMS and the CDAI were 0.0 (0.0 to 0.0), 0.0 (0.0 to 1.0) and 50.5 (25.5 to 93.0) respectively. Mean (SD) LC, CRP and fCal at baseline were respectively 7.81 (2.22) x 10/µl, 3.04 (4.61) mg/L and 130.8 (226.6) µg/g. The regression analysis showed no change in disease activity scores neither in biochemical parameters from baseline to week 8, month 6 and month 12 after switching to SB5, as displayed in table 4.

Satisfaction with treatment and switch

All the satisfaction scores were high at baseline and remained high at the different timepoints as displayed in table 5. The perceived early (up to 30 minutes after injection) local discomfort was low at baseline with ADA originator with a median VAS of 1.0, which significantly increased after switch to SB5 with a median VAS of 3.0, 2.5, 3.0 and 3.0 at baseline, week 8, month 6 and month 12 respectively. The late (after 30 minutes post injection) local discomfort was low with the ADA originator with a median VAS of 1.0 and remained low after switch to SB5 with a median VAS of 0.0, 1.0 and 1.0 respectively at week 8, month 6 and month 12 (p ns).

Serious treatment emergent adverse events

Twenty serious treatment emergent adverse events (TEAEs) were reported in 15 patients (13.6%) with the most frequent being intestinal obstruction (3.6%). One serious TEAE had an outcome of death, however this was not considered to be related to the study treatment. Two serious TEAE were considered to be related to the study treatment (Streptococcal sepsis and rectal abscess) and led to discontinuation of SB5.

Table 3. — **Mean and median ADA trough levels over time (µg/ml)**

	Baseline	**Week 8**	**Month 6**	**Month 12**
n	109	100	87	79
Mean (SD)	9.21 (5.72)	9.16 (5.31)	7.98 (4.21)	7.87 (4.03)
Median (Q1, Q3)	9.30 (4.80, 12.00)	8.50 (5.20, 12.00)	7.70 (5.00, 10.90)	7.70 (4.60, 10.40)
Adjusted mean change from baseline (SD)		-0.51 (0.254)	-1.63 (0.323)	-2.05 (0.424)
95% CI		[-1.02, 0.00]	[-2.27, -0.99]	[-2.90, -1.21]
p-value		0.048	<0.001	<0.001
Adjusted mean change from month 6 (SD)				-0.42 (0.285)
95% CI				[-0.99, 0.14]
p-value				0.140

n - number of subjects; SD – standard deviation; GM – Geometric Mean; CV – Coefficient of Variation; Q1 – 25th quartile; Q3 – 75th quartile

Table 4. — **Mean change from baseline of disease activity scores and biochemical parameters**

	CDAI	PMS	PGA	LC (x10/µl)	CRP (mg/L)	fCal (µg/g)
Baseline						
n	80	26	110	110	110	105
Mean (SD)	62.3 (54.1)	0.7 (0.8)	0.1 (0.4)	7.81 (2.22)	3.04 (4.61)	130.8 (226.6)
Median (Q1, Q3)	50.5 (25.5, 93.0)	0.0 (0.0, 1.0)	0.0 (0.0, 0.0)	7.42 (6.41, 9.35)	1.35 (0.60, 3.44)	55.0 (23.0, 116.0)
Week 8						
n	78	26	108	105	105	98
Mean change from baseline (SE)	4.43 (6.54)	0.14 (0.16)	0.04 (0.03)	0.42 (0.30)	0.10 (0.48)	61.49 (41.66)
95% CI	[-8.60, 17.46]	[-0.20, 0.48]	[-0.03, 0.11]	[-0.18, 1.01]	[-0.85, 1.05]	[-21.19, 144.18]
Month 6						
n	58	21	86	87	86	83
Mean change from baseline (SE)	0.53 (6.53)	0.00 (0.248)	0.07 (0.05)	-0.09 (0.20)	1.22 (1.02)	85.58 (76.10)
95% CI	[-12.56, 13.62]	[-0.52, 0.52]	[-0.04, 0.18]	[-0.49,0.30]	[-0.81, 3.24]	[-65.81, 236.96]
Month 12						
n	56	21	80	79	79	74
Mean change from baseline (SE)	-6.66 (5.11)	-0.16 (0.23)	-0.01 (0.04)	-0.21 (0.22)	-0.25 (0.31)	34.76 (25.96)
95% CI	[-16.92, 3.60]	[-0.64, 0.33]	[-0.09, 0.07]	[-0.65, 0.23]	[-0.89, 0.39]	[-18.03, 87.54]

n- number of subjects at the timepoint; SE – standard error; CI – confidence interval ; CDAI – Crohn's Disease Activity Index; PMS – Partial Mayo Score; PGA – Physician Global Assessment Score; LC – leucocyte count; CRP – C-reactive protein- fCal – fecal calprotectin

Table 5. — **Visual analogue scores (VAS) of satisfaction parameters**

	Score	p*
Ease to use, VAS median (IQR)		
Baseline ADA originator	9.0 (8.0; 10.0)	
Baseline SB5	9.0 (8.0; 10.0)	0.001
Week 8	9.0 (8.0; 10.0)	< 0.001
Month 6	8.0 (7.0; 9.0)	< 0.001
Month 12	9.0 (8.0; 9.0)	< 0.001
Satisfaction with medication in general, VAS median (IQR)		
Baseline ADA originator	9.0 (8.0; 10.0)	
Week 8	8.0 (6.0; 9.0)	< 0.001
Month 6	8.0 (7.0; 9.0)	< 0.001
Month 12	8.0 (6.0; 9.0)	< 0.001
Comfortable with decision to switch to SB5, VAS median (IQR)		
Baseline ADA originator	8.0 (5.0; 9.0)	
Week 8	7.0 (5.0; 9.0)	0.085
Month 6	8.0 (7.0; 9.0)	0.168
Month 12	8.0 (6.0; 9.0)	0.774
Local discomfort up to 30 minutes, VAS median (IQR)		
Baseline ADA originator	1.0 (0.0; 2.0)	
Baseline SB5	3.0 (0.0; 6.0)	< 0.001
Week 8	2.5 (1.0; 7.0)	< 0.001
Month 6	3.0 (1.0; 7.0)	< 0.001
Month 12	3.0 (2.0; 7.0)	< 0.001
Local discomfort after 30 minutes and up to next injection, VAS median (IQR)		
Baseline ADA originator	1.0 (0.0; 2.0)	
Week 8	0.0 (0.0; 2.0)	0.890
Month 6	1.0 (0.0; 2.0)	0.460
Month 12	1.0 (0.0; 2.0)	0.346

*Timepoint compared to baseline. IQR: interquartile range

Discussion

We performed a multicenter, phase IV, prospective, interventional cohort study to evaluate the ADA trough levels after non-medical switch from ADA originator to SB5 in a real-world setting.

The key strength of this study is the prospective design with regular schedule of measurements of trough level for a period of 12 months together with objective disease markers. Only 1 prospective study reported the evolution of ADA trough levels after switch in time with a follow-up up to 6 months, however ADA trough levels were available for only a small proportion of their study population: 17 patients (17.3%) (6).

In our study, ADA trough levels remained within the therapeutic range after switch from originator to SB5. However, in the first 6 months after the switch, a statistically significant reduction of trough levels has been detected while the levels remained stable between month 6 and 12. This observation cannot fully be explained; although there might be an effect of the fact that physicians could change dosing-intervals from week 8 on, based on the trough level determination at baseline. On the other hand, knowledge is lacking on evolution of trough level over time in patients on ADA. Our findings are in line with previously reported retrospective data described by Lukas et al. They observed a reduction of the median trough level from 14.8 to 13.7 µg/ml in the ADA originator group after 10 weeks and a reduction from 14.2 to 13.0 µg/ml in the SB5 group. This reduction however was not statistically significant between both groups (5).

As we studied a real-life IBD population in which elective switch was offered to every patient treated with ADA also patients not in clinical or endoscopic remission were prospectively monitored. Importantly, no change

in disease activity was observed in patients persisting on SB5, based on both disease activity scores and biochemical parameters. In line with previous described studies (5, 10), our study confirms that switching from ADA originator to SB5 does not affect treatment efficacy. In fact, only 3 patients (6.6%) in our study showed SLOR.

Another strength of our study is that it is the first prospectively designed study in IBD in which the acceptance of switch to a biosimilar is investigated and subjective perceptions of patients linked to the switch are described. In a study with an etanercept biosimilar where no specific information was given to the patients, only 51.6% of the patients accepted to switch (11). In contrast, another study reported acceptance rates of 92 to 99% in series in which patients were well informed and physicians and pharmacists were trained (12). In our study, both physicians and IBD nurses received a thorough briefing with dedicated information regarding biosimilars in general and SB5 in particular with the possibility to ask questions or share concerns on the topic. This approach might explain the rather high acceptance of switch rate of 84.6% in our study. In patients not willing to switch, fear for flare, absence of trust in biosimilars and too much negative experience with disease burden, were the main reasons for non-switch.

As the focus of the study was – amongst others – on acceptance of switch, it was important to minimize interventions which might influence the willingness to participate; therefore, no endoscopic evaluation was performed at the time of the switch or afterwards, except if flare was suspected, as being done according to good clinical practice. The lack of endoscopic data can be perceived as a weakness of our study.

Eighty-two of the 110 patients (74.5%) were still treated with SB5 at month 12.

A recent retrospective study reported a persistence rate with SB5 of 60.3% beyond 1 year and a prospective study reported a persistence rate with SB5 of 81.6% at 12 months (6, 10). Our results are in line with these reports.

Of note, as the study design stipulated that patients could be withdrawn from the study at week 8 in case of detection of high antibodies to ADA or unmeasurable levels of ADA, this negatively impacted on the persistence rate. Indeed, as these parameters were assessed at baseline, with patients still on ADA originator, it's fair to state that persistence rate would have been higher if these 6 patients would have been excluded prior to the study. This represents a methodological weakness in our real-life study.

The most frequently reported adverse event was injection site pain. The VAS for early discomfort was significantly higher with SB5 compared to ADA originator. In 8 patients this adverse event was perceived as so important that treatment with SB5 was stopped. Patients especially felt pain/discomfort from the moment the injection started and lasted for a few seconds to maximum of a few minutes. The VAS for late injection site pain, set from 30 minutes after injection, showed no difference between SB5 and the ADA originator. No difference was observed in pain sensation when using a syringe or pen. We speculate that 2 reasons may account for the pain. First, all patients who switched were on the low volume (0,4 ml) ADA originator; meaning that by switching to SB5 the volume doubled for the same ADA dose. Secondly, citrate was used in the formulation of SB5 as a buffer which can be associated with injection site pain (13).

Ten of 25 (40.0%) adverse events leading to discontinuation of treatment with SB5 at the request of the patient were not related to ISP and the fact that 76.6% of the patients who discontinued treatment with SB5, returned to the ADA originator, suggests that at least in these cases a nocebo effect comes into play.

In conclusion, after being well informed the great majority of patients treated with ADA originator is willing to switch to biosimilar SB5. A gradual decline of the ADA trough levels is observed after switch; however no change is disease activity scores or biochemical parameters is seen. There is a persistence rate of 75% after one year which is in line with previous reported studies. The most important reasons for discontinuation were adverse events, most frequently attributable to injection site pain. Of note, patients in general report a higher, early and temporary local discomfort within 30 minutes after injection with SB5 compared to the ADA originator. It seems likely that in case of switch to a formulation with a smaller volume and without citrate, the persistence rate would be higher.

Author's Contributions

Thomas De Somer, Pieter Dewint, Nina Van Heddegem contributed to the design of the study. Thomas De Somer, Inge Huys, An Sterckx, Nina Van Heddegem, Pieter Dewint contributed to the data collection. Thomas De Somer, Nele Deprez, Pieter Dewint, Nina Van Heddegem analyzed the data. Thomas De Somer and Nele Deprez wrote the manuscript. Pieter Dewint critically revised the manuscript. All authors revised the manuscript for important intellectual content. All authors have approved the final version of this manuscript.

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Conflict of interest statement

P. Dewint received a speaker's fee from Biogen and consultancy fee from Samsung Bioepis. The other authors have declared no conflict of interest.

Conference presentation and posters

– Belgian Week of Gastroenterology, Belgium, 2021, 2 presentations

– European Crohn's and Colitis Organisation (ECCO), Virtual, 2021, 2 posters
– United European Gastroenterology Week (UEGW), Virtual, 2021, 2 posters

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