

Original Article

Effectiveness and Safety of Adalimumab Biosimilar SB5 in Inflammatory Bowel Disease: Outcomes in Originator to SB5 Switch, Double Biosimilar Switch and Bio-Naïve SB5 Observational Cohorts

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Abstract

Background and Aims: Multiple adalimumab [ADA] biosimilars are now approved for use in inflammatory bowel disease [IBD]; however, effectiveness and safety data remain scarce. We aimed to investigate long-term outcomes of the ADA biosimilar SB5 in IBD patients following a switch from the ADA originator [SB5-switch cohort] or after start of SB5 [SB5-start cohort].

Methods: We performed an observational cohort study in a tertiary IBD referral centre. All IBD patients treated with Humira underwent an elective switch to SB5. We identified all these patients in a biological prescription database that prospectively registered all ADA start and stop dates including brand names. Data on IBD phenotype, C-reactive protein [CRP], drug persistence, ADA drug and antibody levels, and faecal calprotectin were collected.

Results: In total, 481 patients were treated with SB5, 256 in the SB5-switch cohort (median follow-up: 13.7 months [IQR 8.6–15.2]) and 225 in the SB5-start cohort [median follow-up: 8.3 months [4.2–12.8]]. Of the SB5-switch cohort, 70.8% remained on SB5 beyond 1 year; 90/256 discontinued SB5, mainly due to adverse events [46/90] or secondary loss of response [37/90]. In the SB5-start cohort, 81/225 discontinued SB5, resulting in SB5-drug persistence of 60.3% beyond 1 year. No differences in clinical remission [$p = 0.53$], CRP [$p = 0.80$], faecal calprotectin [$p = 0.40$] and ADA trough levels [$p = 0.55$] were found between baseline, week 26 and week 52 following switch. Injection site pain was the most frequently reported adverse event.



Conclusion: Switching from ADA originator to SB5 appeared effective and safe in this study with over 12 months of follow-up.

Key Words: Crohn's disease; ulcerative colitis; biosimilar

1. Introduction

Monoclonal antibodies directed against tumour necrosis factor [TNF], such as adalimumab [ADA] and infliximab [IFX], are widely used in the treatment of moderate to severe inflammatory bowel disease [IBD]. They can successfully induce and maintain remission as well as reduce surgical rates and IBD-related hospitalizations.^{1,2} However, anti-TNF therapy is costly and accounts for up to 73% of the annual IBD-related healthcare costs.^{3,4} Indeed, it has been estimated that the United Kingdom National Health Service [NHS] treats more than 46 000 patients with ADA, spending more than £400 million per year [GBP].⁵

Biosimilar agents represent a great potential in cost savings given their reduced pricing and their use may help improve patient access to anti-TNF therapy.⁶ In 2013, the first biosimilar for IFX [CT-P13] was licensed for use in IBD, whereas biosimilars for ADA have only been available since 2017. Although several studies have now demonstrated the safety and effectiveness of IFX biosimilars, data on ADA biosimilars are scarce. Currently, no randomized controlled trials comparing ADA biosimilars with the originator are available for IBD.^{6,7} A small number of real-world studies have looked at outcomes of bio-naïve patients as well as patients switching to biosimilar ADA from originator, but they are limited by size and long-term follow-up.^{8,9} Furthermore, there are no data available looking at IBD patients who have undergone a double biosimilar ADA switch.

In the Edinburgh IBD unit we previously implemented a managed switch programme to guide the transition from the originator IFX to biosimilar CT-P13.¹⁰ In 2019, a similar process was adopted for patients switching to biosimilar SB5 from originator ADA. We aimed to investigate the effectiveness and safety of SB5 [Imraldi] in [1] IBD patients who underwent a switch from the ADA originator [Humira] to the biosimilar SB5, and in [2] IBD patients who commenced SB5 without previously being treated with the ADA originator. Moreover, we aimed to describe the prescribing trends of ADA over time to understand the impact and relevance of our managed switch programme.

2. Methods

2.1. Study design

We performed a retrospective observational cohort study in NHS Lothian [Scotland] to investigate the long-term effectiveness and safety of SB5. NHS Lothian provides all healthcare for a population of 907 580 people in Edinburgh and the surrounding areas [estimate 2019].¹¹ Four hospitals serve this area including the Western General Hospital [principal IBD unit], the Royal Infirmary of Edinburgh, St John's Hospital and the Royal Hospital for Sick Children. More than 7000 patients in NHS Lothian are diagnosed with IBD, referred to as the Lothian IBD cohort.¹²

Since February 1, 2019, all adult [≥ 18 years] IBD patients in NHS Lothian who were on maintenance therapy with the ADA originator underwent an elective switch to the biosimilar SB5 regardless of IBD phenotype, disease activity and ADA dosing. This

switch took place after careful patient counselling, giving patients the opportunity to discuss this switch process further via a telephone consultation. Dosing and interval remained unchanged following the switch to SB5 unless clinical need dictated therapy adjustments. Adult patients who started ADA after December 1, 2018, directly commenced on the biosimilar SB5. All patients were reviewed regularly [approximately every 6 months] in a virtual biologic clinic. At this time, clinical disease activity, laboratory parameters (including C-reactive protein [CRP]), therapeutic drug monitoring and faecal calprotectin [FCAL] were collected by protocol if these data were not collected in the last 2 months.

2.2. Patient identification

Lloyds Pharmacy Clinical Homecare provides ADA for all NHS Lothian IBD patients since 2016. They prospectively register all ADA prescriptions including brand names, start dates and stop dates. Prescribed ADA brands included Humira, Imraldi [SB5] and Amgevita [ABP 501], noting that ABP 501 was the first-choice biosimilar in paediatric patients. A search in the Lloyds Pharmacy homecare prescription database was performed to identify all IBD patients in NHS Lothian who were on SB5 treatment before October 28, 2020. We performed an additional cross-check with the Lothian IBD Biologics Database, containing all biological prescriptions for IBD patients since August 1, 2009.¹²

All patients with a confirmed IBD diagnosis and at least one dose of SB5 were eligible for inclusion. We included both patients who switched from the ADA originator to the biosimilar SB5 [SB5-switch cohort] and ADA-naïve patients who commenced SB5 [SB5-start cohort]. Previous anti-TNF exposure was allowed. Patients who previously used ADA and discontinued ADA treatment before starting SB5 were included in the SB5-start cohort. We excluded patients with less than 1 month follow-up after starting SB5.

2.3. Outcomes

The primary outcome of this study was SB5 drug persistence in both the SB5-switch and SB5-start cohort. Secondary endpoints included biochemical, faecal biomarker and clinical remission, immunogenicity parameters [ADA drug and antibody levels], and safety parameters [adverse events]. We assessed remission in the SB5-switch cohort as close to week 26 and week 52 [± 10 weeks]. Biochemical remission was defined as a CRP ≤ 5 mg/L; biomarker remission was defined as a FCAL ≤ 250 μ g/g;¹³ and clinical remission was defined as a Harvey Bradshaw Index [HBI] ≤ 4 for Crohn's disease [CD] patients or a partial Mayo index ≤ 1 for ulcerative colitis [UC] patients.¹⁴⁻¹⁷

Furthermore, we assessed ADA drug use over time in the Lothian IBD cohort. To this end, we reported the prevalent number of IBD cases on ADA per brand per year since 2010.

2.4. Data collection

Patient demographics and disease characteristics were extracted from electronic medical health records [TrakCare]. We collected the following baseline characteristics: sex, medical history, smoking history, body mass index [BMI], IBD type, age at IBD diagnosis, disease

extent and phenotype according to the Montreal classification, previous IBD-related surgery, and both previous and ongoing exposure to IBD-related medical therapies. Start and stop dates of the different ADA brands [Humira, and/or Imraldi, and/or Amgevita] were verified in TrakCare. Reasons for treatment discontinuation were recorded. Primary non-response was defined as lack of clinical or biochemical improvement after at least 8 weeks of induction therapy, requiring drug discontinuation. Secondary loss of response was defined as initial response to induction therapy but subsequent loss of response to maintenance therapy, requiring drug discontinuation.¹⁸ Furthermore, we collected data regarding the ADA dose and dose adjustments. Adverse events during follow-up were documented. Given the retrospective nature of this study, adverse events were not systematically recorded in the medical records. Therefore, we only documented adverse events that led to SB5 suspension or discontinuation, or hospitalization. To assess treatment effectiveness, we extracted clinical scores and several biochemical parameters, including CRP, FCAL and ADA drug and antibody levels, at baseline [start SB5] and during follow-up.

2.5. Adalimumab trough and antibody assay

Until December 2017, ADA trough and antibody levels were processed at the Exeter Hospital Laboratories, UK, using the Immundiagnostik monitor enzyme-linked immunosorbent assay [ELISA] as per the manufacturer's protocol. Trough levels and antibody levels were expressed in $\mu\text{g/mL}$ and AU/mL, respectively. The assay detects drug levels $\geq 0.8 \mu\text{g/mL}$ and total antibodies to ADA $\geq 10 \text{ AU/mL}$. Drug assays were validated for both the ADA originator and SB5.¹⁹

Since January 2018, ADA drug monitoring has been delivered by the Queen Elizabeth University Hospital site, Glasgow, UK, using Immundiagnostik monitor ELISA as per the manufacturer's protocol. The lower and upper limits are respectively < 0.4 and $> 12 \mu\text{g/mL}$ for trough level measurement, and < 10 and $> 200 \text{ AU/mL}$ for ADA antibody level testing. Antibody testing is only performed when trough levels are below the therapeutic range [$< 5 \mu\text{g/mL}$] or when ADA antibodies have previously been detectable.²⁰

2.6. Faecal calprotectin analyses

FCAL was measured as part of routine clinical monitoring and as directed by patient symptoms. Patients received an FCAL collection kit with instructions and were asked to return their sample to the hospital biochemistry laboratories either directly or via their general practitioner's practice [samples forwarded the same day]. They were advised to obtain a sample from the first bowel movement of the day and return their samples within 24 h of collection. Upon arrival at the laboratories, samples were stored at -20°C . FCAL was measured using a standard ELISA technique [Calpro AS]. Numerical values were generated between 20 and $2500 \mu\text{g/g}$. All assays were performed in the Department of Clinical Biochemistry at the Western General Hospital, Edinburgh, UK. The same assay has been utilized since 2004.

2.7. Statistics

All analyses were performed with IBM SPSS statistical software package version 25. Descriptive statistics were used to describe baseline characteristics. Continuous variables are expressed as medians and interquartile range or mean and standard deviation, depending on distribution. Since the SB5-switch and SB5-start cohorts represent two different non-comparable cohorts [an IBD cohort which

already started ADA therapy in the past vs a cohort with active IBD commencing SB5], it is of limited relevance to compare both groups. To this end, we have not compared descriptive statistics between the two cohorts.

Drug persistence was established with Kaplan–Meier curves. Time-to-event was calculated from the start of SB5 treatment until SB5 discontinuation. Patients were censored at the end of follow-up, which was defined as last gastroenterology-related medical contact or the patient's death.

Clinical, biochemical and faecal biomarker remission were analysed as categorical variables. Data were collected as close to baseline [within 26 weeks before SB5 commencement], week 26 [± 10 weeks] and week 52 [± 10 weeks]. We performed an intention-to-treat analysis with the last observation carried forward for patients who discontinued SB5. Comparison of parameters at the three different time points [baseline, week 26 and week 52] was performed via Friedman analysis.

ADA trough levels and antibody levels were analysed as continuous and categorical variables, respectively. We considered antibody levels of $> 10 \text{ AU/mL}$ as detectable antibodies, whereas levels $\leq 10 \text{ AU/mL}$ or absent measurements [due to adequate trough levels] were considered as undetectable antibodies. A p value < 0.05 was considered statistically significant.

2.8. Ethics

This work was considered a service evaluation/audit as all data were collected as part of routine clinical care. Therefore, no written consent or formal ethical approval was necessary as per departmental policy and Health Research Authority guidance. Caldicott guardian approval [NHS Lothian] was granted for anonymized data collection, analysis and submission for publication without the need for formal written consent.

3. Results

3.1. Patients

In total, 481 patients, including 256 patients who switched from the ADA originator to SB5 and 225 patients who started on SB5, were included [Figure 1]. The median duration of follow-up was 13.7 months [range 8.6–15.2] in the SB5-switch cohort and 8.3 months [4.2–12.8] in the SB5-start cohort, corresponding to 254 and 170 person years of follow-up [PYF], respectively. In total, 88.1% [SB5-switch cohort] and 36.7% [SB5-start cohort] of patients who continued ADA had over 12 months of follow-up after starting SB5. The baseline characteristics of both the SB5-switch and SB5-start cohort are displayed in Tables 1 and 2.

3.1.1. SB5-switch cohort

Most patients in the SB5-switch cohort were diagnosed with CD (228/256, 89.1% vs 28/256, 11.0% with UC/IBD-unclassified [IBD-U]). In total, 52.7% were male [135/256] with a median IBD duration of 10 years [5.8–16.2] before commencing SB5. The majority of patients had ileocolonic CD [46.9%] and 27.6% [63/256] had perianal disease activity. Patients were treated for a median of 32.5 months [16.4–55.9] with the originator prior to switching [minimum duration of treatment with the originator: 6 months]. In total, 53.9% [138/256] patients were biologic-naïve before use of ADA.

At switch from the originator to SB5, 60.8% [155/256] received 40 mg ADA every other week and 39.1% [97/256] received once weekly dosing. In total, 21.9% were on combination therapy with thiopurines

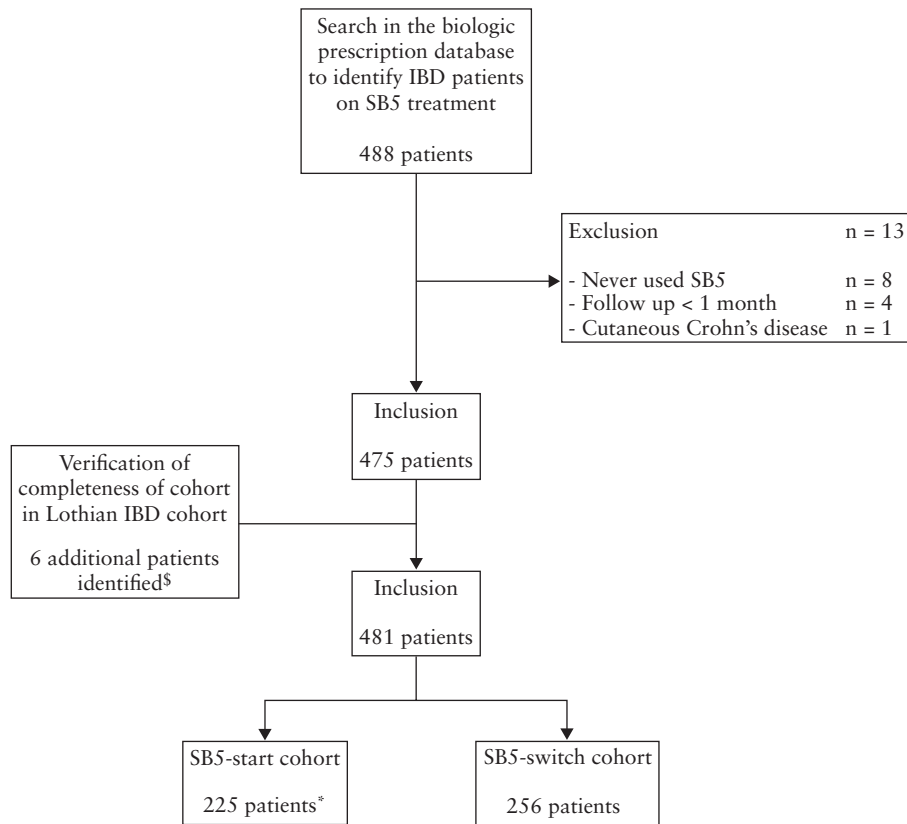


Figure 1. Patient inclusion flowchart.

*Eleven of 225 patients previously used the adalimumab originator; however, last injection with the originator was discontinued a median of 27.3 [11.1–35.5] months before the start of SB5.

§Six patients with both IBD and a rheumatological condition were not identified in the homecare prescription database since adalimumab was prescribed by the rheumatologist. IBD, inflammatory bowel disease; *n*, number.

[45/256, 17.6%] or methotrexate [11/256, 4.3%], and 10.6% [27/256] patients underwent an SB5 dose intensification during treatment.

3.1.2. SB5-start cohort

The majority of patients included in the SB5-start cohort had CD [175/225, 77.8%]. In total, 50.2% [113/225] were male with a median IBD duration of 6.3 years [1.5–17.1] before starting SB5. Penetrating disease occurred in 30.6% [53/225] of the patients and 27.7% [48/207] had perianal disease. In total, 68.6% [153/225] were biologic-naïve. Eleven of 225 patients who started on SB5 previously used ADA. This was stopped a median of 27.3 [11.1–35.5] months before start of SB5 due to secondary loss of response [$n = 3$], pregnancy [$n = 2$], adverse events [$n = 2$], disease remission [$n = 2$], IBD-related surgery [$n = 1$] or loss of patient contact for drug delivery [$n = 1$].

Almost all patients received a dose of 40 mg every other week [220/225, 97.8%]. Two patients started on 40 mg weekly because they had used ADA in the past. Combination therapy with a thiopurine or methotrexate was prescribed in 37/225 patients [16.5%], and 21.3% [48/225] of patients required SB5 dose intensification during treatment.

3.2. Drug persistence

3.2.1. SB5-switch cohort

In total, 90/256 [35.2%] patients discontinued SB5 treatment during a median follow-up time of 13.7 months [8.6–15.2]. The main

reasons for stopping therapy were adverse events [$n = 46/90$] and secondary loss of response [$n = 37/90$]. In total, 213/252 [84.6%] and 163/236 [70.8%] patients remained on SB5 at week 26 and 52, respectively [Figure 2]. The majority of patients who stopped SB5 due to side effects switched to another ADA brand [see paragraph with safety outcomes], resulting in higher ADA drug persistence. As such, 228/251 [90.9%] and 190/232 [83.1%] patients remained on ADA at week 26 and 52, respectively.

3.2.2. SB5-start cohort

In total, 81/225 patients [36%] discontinued SB5 within 18.3 months [4.2–12.8] of follow-up, mainly due to primary non-response [$n = 22/81$], secondary loss of response [$n = 26/81$] and adverse events [$n = 24/81$]. At week 26 and 52, 137/181 [77.8%] and 65/134 [60.3%] patients remained on SB5 treatment, respectively [Figure 2]. A minority of patients [7/225; 3.1%] who discontinued SB5 switched to another ADA brand, resulting in overlapping ADA and SB5 drug persistence curves. In total, 140/179 [80.1%] and 67/130 [62.8%] patients remained on ADA at week 26 and 52, respectively.

3.3. Disease activity

3.3.1. SB5-switch cohort

At baseline, 69.9% [123/176] of patients were in biochemical remission, 69.6% [94/135] were in faecal biomarker remission and 82.1% [170/207] were in clinical remission [Figure 3]. Median CRP was 2 mg/L [1–6] and median FCAL was 95 μ g/g [30–390]. The

Table 1. IBD baseline characteristics of the SB5-switch cohort and SB5-start cohort

Variable	SB5-switch cohort [<i>n</i> = 256]	SB5-start cohort [<i>n</i> = 225]	Missing values [SB5-switch/SB5-start cohort, <i>n</i>]
Male sex, <i>n</i> [%]	135 [52.7]	113 [50.2]	0
Smoking behaviour, <i>n</i> [%]			28/16
Never	139 [61.0]	116 [55.5]	
Former	51 [22.4]	53 [25.4]	
Current	38 [16.7]	40 [19.1]	
Body mass index [kg/m ²], median [IQR]	25.2 [22.6–29.6]	26.9 [23.5–30.5]	44/31
Age at IBD diagnosis [years], median [IQR]	26.8 [18.5–37.9]	29.0 [21.9–40.4]	0/3
IBD duration until SB5 start [years], median [IQR]	10.0 [5.8–16.2]	6.3 [1.5–17.1]	0/3
IBD duration until ADA start [years], median	6.5 [2.5–12.4]	6.3 [1.5–17.1]	0/3
Duration of ADA originator until SB5 [years], median [IQR]	2.7 [1.4–4.7]	—	0
Duration of ADA originator until SB5 [months], median [IQR]	32.5 [16.4–55.9]		
IBD type, <i>n</i> [%]			0
Crohn's disease	228 [89.1]	175 [77.8]	
Ulcerative colitis	23 [9.0]	37 [16.4]	
IBD-unclassified	5 [2.0]	13 [5.8]	
Ulcerative colitis extent, <i>n</i> [%]			5/5
Proctitis [Montreal E1]	4 [17.4]	9 [20.0]	
Left sided colitis [Montreal E2]	10 [43.5]	23 [51.1]	
Extended colitis [Montreal E3]	9 [39.1]	13 [28.9]	
Crohn's disease extent, <i>n</i> [%]			0/2
Ileal [Montreal L1]	68 [29.8]	59 [34.1]	
Colonic [Montreal L2]	53 [23.2]	52 [30.1]	
Ileocolonic [Montreal L3]	107 [46.9]	62 [35.8]	
Upper gastrointestinal disease [Montreal L4]	45 [19.7]	13 [7.5]	
Perianal disease activity	63 [27.6]	48 [27.7]	
Crohn's disease phenotype, <i>n</i> [%]			0/2
Non-stricturing, non-penetrating [Montreal B1]	122 [53.5]	94 [54.3]	
Stricturing [Montreal B2]	54 [23.7]	26 [15.0]	
Penetrating [Montreal B3]	52 [22.8]	53 [30.6]	
Previous IBD-related surgery, <i>n</i> [%]	87 [34.0]	64 [28.4]	0
Previous IBD-related medical therapy, <i>n</i> [%]			
Thiopurines	213 [84.2]	141 [63.2]	3/2
Methotrexate	44 [17.2]	8 [3.6]	0/2
Calcineurin inhibitors	3 [1.2]	5 [2.2]	0/2
Anti-TNF	115 [45.1]	63 [28.3]	1/2
Vedolizumab	4 [1.6]	19 [8.5]	0/1
Ustekinumab	3 [1.2]	6 [2.7]	0/1
Tofacitinib	0 [0]	0 [0]	0/1

ADA, adalimumab; IBD, inflammatory bowel disease; TNF, tumour necrosis factor; *n*, number; IQR, interquartile range.

proportions of patients in biochemical remission, faecal biomarker remission and clinical remission were similar at baseline, week 26 and week 52 following switch [Figure 3; *p* = 0.80, *p* = 0.40 and *p* = 0.53, respectively]. In addition, no differences were observed among median CRP and FCAL levels at different time points (median CRP week 26: 2 mg/L [1–6], median CRP week 52: 2 mg/L [1–8.3], *p* = 0.48; median FCAL week 26: 171 µg/g [35–585], median FCAL week 52: 129 µg/g [37–574], *p* = 0.47).

3.4. Immunogenicity

3.4.1. SB5-switch cohort

ADA trough levels and antibodies were measured within 18 months before switch in 207/256 patients. Median trough level was 10.1 µg/mL [7.3–12.6] with 10.1% [21/207] of patients found to have detectable antibodies to ADA >10 AU/mL; Figure 3 and Supplementary Figure 1. In total, 47.6% of these patients [10/21] discontinued SB5, whilst 38.1% [8/21] continued therapy and 14.3% [3/21] switched to the biosimilar ABP 501. Patients with detectable antibodies before

switch had a significantly shorter SB5 drug persistence following switch [*p* < 0.01; Supplementary Figure 2].

At week 26 and 52, SB5 was continued in 213 and 163 patients, respectively. In total, 26/213 patients underwent dose adjustments before week 26 [16/26 dose intensification, 7/26 dose de-escalation, 3/26 temporarily suspended], resulting in a median ADA trough level of 11.6 µg/mL [8.3–17.2; *n* = 65 measurements available] at week 26. Before week 52, 31/163 patients underwent therapy adjustments [15/31 dose intensification, 11/31 dose de-escalation, 5/31 temporarily suspended] with subsequent trough levels of 7.8 µg/mL [5.4–11.3; *n* = 44 measurements available] at week 52. Allowing therapy adjustments dictated by clinical care, trough levels were not significantly different over time [baseline vs week 26 vs week 52: *p* = 0.55].

In total, 27/256 patients [10.5%] had detectable antibodies following the switch to SB5. Eight of 27 patients had pre-existing detectable ADA levels at baseline and 5/27 patients never underwent a drug assay prior to switch. Thus, 19 patients developed new

Table 2. Details of adalimumab dosing and follow-up in the SB5-switch cohort and SB5-start cohort

Variable	SB5-switch cohort [<i>n</i> = 256]	SB5-start cohort [<i>n</i> = 225]	Missing values [SB5-switch/SB5-start cohort, <i>n</i>]
Adalimumab dose at switch to SB5, <i>n</i> [%]			1/0
40 mg every other week	155 [60.8]	220 [97.8]	
40 mg weekly	97 [39.1]	2 [0.9]	
80 mg weekly	2 [0.8]	0 [0]	
40 mg every 3 weeks	1 [0.4]	0 [0]	
Received loading dose[s] only	0 [0]	3 [1.3]	
Concomitant IBD therapy during SB5 treatment, <i>n</i> [%]			1/1
Systemic steroids	25 [9.8]	72 [32.1]	
Systemic aminosalicylates	15 [5.9]	24 [10.7]	
Thiopurines	45 [17.6]	34 [15.2]	
Methotrexate	11 [4.3]	3 [1.3]	
SB5 dose adjustments after switch, <i>n</i> [%]			1/2
No	206 [80.8]	172 [76.4]	
Yes, dose intensification	27 [10.6]	48 [21.3]	
Yes, dose de-escalation	17 [6.7]	2 [0.9]	
Yes, temporarily [>6 weeks] suspended	5 [2.0]	3 [1.4]	
SB5 treatment discontinuation, <i>n</i> [%]	90 [35.2]	81 [36.0]	0
Adalimumab treatment discontinuation, <i>n</i> [%]	55 [21.5]	75 [33.3]	0
Time to SB5 treatment discontinuation [months], median [IQR]	7.1 [3.9–11.1]	5.2 [3.4–10.0]	0
SB5 stop reasons, <i>n</i> [%]			0
Primary non-response	0 [0]	22 [9.8]	
Secondary loss of response	37 [14.5]	26 [11.6]	
Adverse events	46 [18.0]	24 [10.7]	
Adverse events and active disease	0 [0]	1 [0.4]	
Patient request	2 [0.8]	3 [1.3]	
Long-term remission	2 [0.8]	0 [0]	
Pregnancy	0 [0]	1 [0.4]	
Peri-operative discontinuation of therapy	1 [0.4]	4 [1.8]	
Active EIM, requiring new therapy	1 [0.4]	0 [0]	
Patient deceased	1 [0.4]	0 [0]	
Duration of follow-up [months], median [IQR]	13.7 [8.6–15.2]	8.3 [4.2–12.8]	0

n, number; IBD, inflammatory bowel disease; IQR, interquartile range; EIM, extra-intestinal manifestation.

detectable antibodies. These antibodies were detected after a median of 40 weeks [16–55]. In total, 17/19 patients received an immunosuppressant before switch and 4/19 were treated with azathioprine [*n* = 3] or methotrexate [*n* = 1] during SB5 treatment.

3.4.2. SB5-start cohort

Therapeutic drug monitoring was performed 3 months after SB5 commencement as part of standard clinical care in the virtual IBD clinic. At this time point, ADA trough levels and antibodies were available in 153/225 patients. The median ADA trough level was 9.4 µg/mL [6.1–12.0], and 28/153 [18.3%] patients had detectable antibodies to ADA. Most patients who developed detectable antibodies were on ADA monotherapy [24/28 monotherapy, 4/28 combination therapy with azathioprine]. Two of 28 patients who developed antibodies were previously treated with the ADA originator [treatment duration 6.6 and 8.4 years] and discontinued the originator 28 and 36 months before commencement of SB5.

Over a median follow-up duration of 8.3 months [4.2–12.8], 182/225 patients underwent therapeutic drug monitoring at some point. Forty of 182 patients [22.0%] developed newly detectable antibodies over time after a median of 21 weeks [14–36].

3.5. Safety

Adverse events that required SB5 suspension or discontinuation, or hospitalization were reported in 51/256 patients in the SB5-switch cohort [Table 3]. This results in an adverse event rate of 20.1 per 100

PYF. In total, 41 adverse events were reported in 39/225 patients in the SB5-start cohort [Table 3], resulting in an adverse event rate of 24.1 per 100 PYF.

3.5.1. SB5-switch cohort

Pain at the injection site was the most frequently reported adverse event in the SB5-switch cohort [*n* = 34; 13.4 per 100 PYF]. Thirty-three of these 34 patients switched either to another ADA biosimilar ABP 501 [*n* = 31] or back to the originator [*n* = 2]. Three additional patients developed a skin rash after SB5 administration, two of whom switched back to the originator. Five patients developed an infection requiring [temporary] SB5 discontinuation.

3.5.2. SB5-start cohort

The most frequently reported adverse event in patients who started on SB5 were infections [*n* = 17; 10.0 per 100 PYF]. In total, 7/17 infections [41.2%] required permanent treatment discontinuation, whereas ten infections required temporary suspension of SB5.

Six patients in the SB5-start cohort reported pain at the injection site and all these patients switched to the biosimilar ABP 501. In addition, skin lesions were frequently reported [*n* = 8]; 1/8 patients switched to ABP 501.

3.6. Double biosimilar switch

Thirty-five patients underwent a double biosimilar switch from the ADA originator to SB5 and subsequently to ABP 501. Most of these

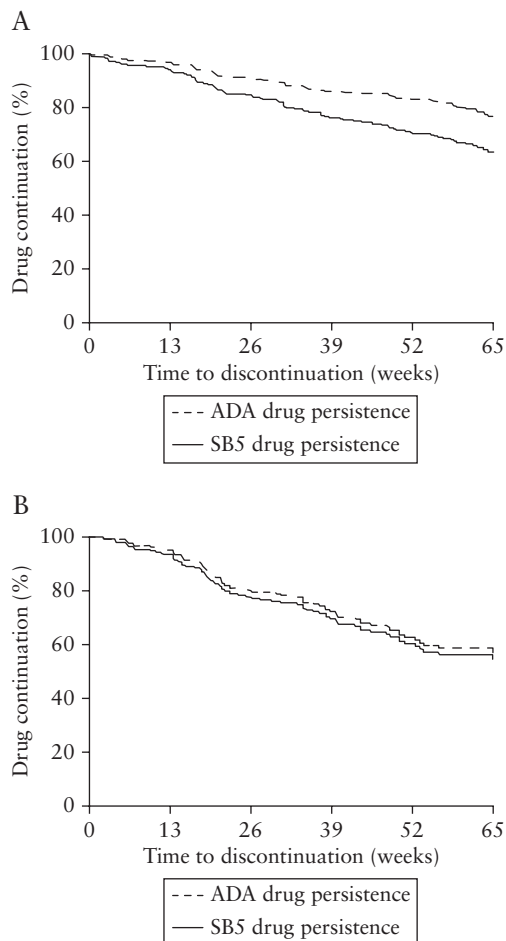


Figure 2. Drug persistence of SB5 and ADA in both the SB5-switch [A] and SB5-start cohorts [B].

ADA, adalimumab.

patients had CD [CD: 31/35, 88.6%; UC: 3/35, 8.6%; IBD-U: 1/35, 2.9%]. They were treated for a median of 30 months [18–50] with the originator. After a median of 28 weeks [15–43] patients were switched from SB5 to ABP 501 [$n = 31$] or back to the originator [$n = 4$]. All patients underwent a second switch due to side effects on SB5 [pain at the injection site: $n = 33$; skin rash: $n = 2$]. One patient continued to have pain at the injection site after a second biosimilar switch to ABP 501 and switched back to the originator. None of the patients underwent dose adjustments of the second ADA brand or discontinued ADA in a median follow-up duration of 34 weeks [24–46].

ADA trough levels before, after the initial switch and after the second switch were available in 28, 17 and 19 patients, respectively. Median trough levels were, respectively, 10.0 $\mu\text{g/mL}$ [7.4–21.7], 12.0 $\mu\text{g/mL}$ [8.7–18.5] and 12.0 $\mu\text{g/mL}$ [7.9–12.0; [Supplementary Figure 3](#)]. ADA trough levels were available at all three time points in six patients. A significant difference was found between trough levels at these time points [$p < 0.01$] with lower trough levels whilst treated with the originator. However, post-hoc comparisons between time points [including more patients] did not show any significant differences [data not shown]. Moreover, it should be noted that 6/35 patients underwent SB5 dose intensification.

Three patients had detectable ADA antibodies before switch to SB5. No detectable antibodies were found during follow-up

measurements in these patients. Two patients developed new detectable antibodies during SB5 treatment. Follow-up drug assays were not available for these patients. None of the patients developed new detectable antibodies during ABP 501 treatment.

3.7. Adalimumab use in the Lothian IBD cohort

An increase in absolute ADA prescriptions was seen over time, with on average 77 prescriptions in 2010/2011 and 516 prescriptions in 2019/2020 [[Figure 4](#)]. ADA was prescribed 6.7 times more in 2019/2020 than in 2010/2011. This increase in ADA prescriptions is not exclusively caused by rising IBD prevalence, but also by earlier and more frequent use of ADA as this increase in prescriptions outpaces the increase in IBD prevalence seen in Lothian. IBD prevalence in Lothian rose by 4.3% per year between 2008 and 2018.^{2,12}

4. Discussion

In our managed switch programme, we actively switched IBD patients from the ADA originator to the biosimilar SB5. We showed in this large real-world cohort that this was safe, with acceptable drug persistence, no changes in clinical or biochemical activity over time, and stable trough levels over 12 months of follow-up. The most common adverse event was injection site pain; these patients were successfully moved on to ABP 501, providing the first data about a double biosimilar switch. Furthermore, our data showed that the biosimilar SB5 is efficient and safe in patients who commenced new treatment with SB5.

Approval of the biosimilar SB5 was based on a phase III trial in rheumatoid arthritis patients that showed an efficacy comparable to the ADA originator in the induction of clinical remission.²¹ Through extrapolation of indications, SB5 was approved for use in IBD patients. Our real-world IBD cohort provides effectiveness data for SB5 that shows comparability with the ADA originator. ADA drug persistence [which may serve as a proxy for real-world therapeutic benefit and safety²²] after 1 year was 62.5% in our SB5-start cohort and 83.1% in our SB5-switch cohort. This is in line with drug persistence data from previous studies with the originator, reporting 1-year ADA drug persistence between 45% and 74% depending on previous biological use, disease type and sex.^{22,23} In addition, one Italian study recently analysed the safety and effectiveness of SB5 in IBD patients. They reported that 66.7% of ADA-naïve patients [$n = 48$] and 81.6% of patients who switched from the originator to SB5 [$n = 98$] remained on SB5 beyond 1 year.⁹ Moreover, similar proportions of clinical remission were found in this study 1 year after the switch to SB5 [74.5% vs 75.4% in our study].⁹ Another IBD study [$n = 93$] reported no significant differences in CRP or FCAL between weeks 0 and 10 after switching to SB5.⁸

Further evidence that supports a comparable effectiveness of SB5 to the originator is based on the proportions of primary non-response and secondary loss of response in our study. According to the literature, 10–40% of patients do not respond to induction therapy with anti-TNF [primary non-response].^{24–27} Secondary loss of response is reported in 24–46% of patients in the first year of treatment.^{24,28} Compared to the literature, we found very reassuring but relatively low percentages of non-response [9.8% primary non-response, 11.6% secondary loss of response] in our SB5-start cohort. This is partly caused by lack of a uniform definition, in which some publications consider loss of response as the need for dose escalation whereas others designate loss of response after cessation of anti-TNF.²⁸ Since we used the latter

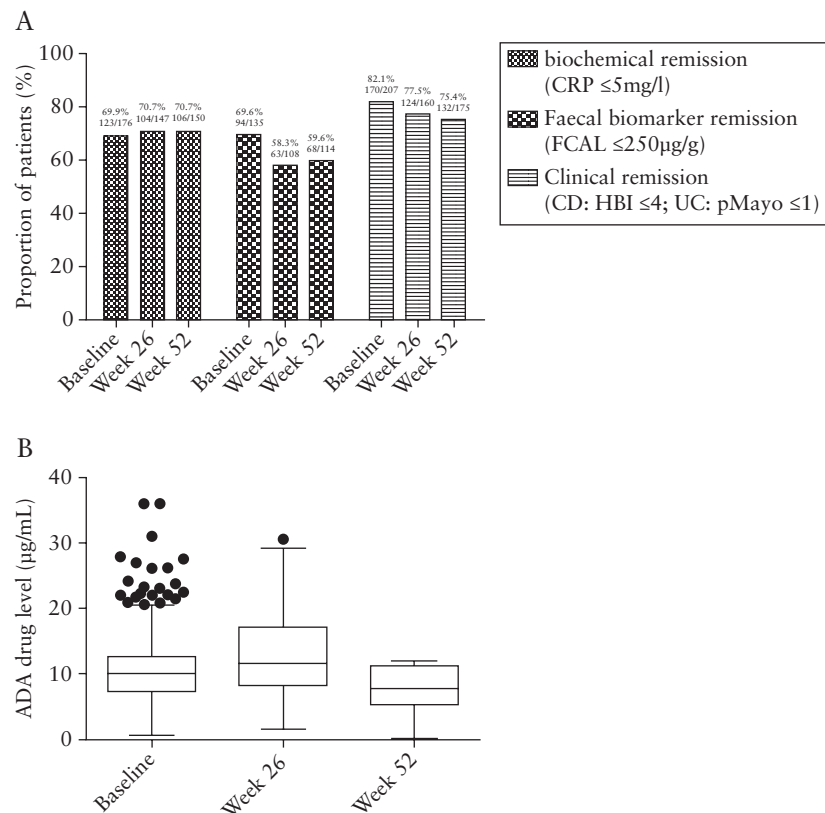


Figure 3. Clinical, biochemical and immunogenicity outcomes at baseline, week 26 and week 52 following switch in the SB5-switch cohort.

[A] Proportion of patients in biochemical remission [CRP ≤ 5 mg/L], faecal biomarker remission [faecal calprotectin ≤ 250 µg/g] and clinical remission [Crohn's disease HBI ≤ 4; ulcerative colitis ≤ 1].

[B] Adalimumab trough levels.

Table 3. Overview of adverse events in the SB5-switch cohort and SB5-start cohort requiring suspension or discontinuation of SB5, or hospitalization

Adverse event	SB5-switch cohort [n = 256]			SB5-start cohort [n = 225]		
	AEs [n, % of total cohort]	AEs requiring permanent treatment discontinuation [n, % of total cohort]	Median time to permanent treatment discontinuation [weeks, IQR] ^a	AEs [n, % of total cohort]	AEs requiring permanent treatment discontinuation [n, % of total cohort]	Median time to permanent treatment discontinuation [weeks, IQR] ^a
Total number of patients	51	48	16 [29–47]	39	31	26 [6–50]
Pain at the injection site	34 [13.3]	34 [13.3]	29 [16–43]	6 [2.7]	6 [2.7]	12 [4–28]
Infection	5 [2.0]	3 [1.2]	17, 49, 61	15 [6.7]	10 [4.4]	60 [32–72]
Joint pain	2 [0.8]	2 [0.8]	17, 38	2 [0.9]	2 [0.9]	9, 30
Infection + joint pain	0 [0]	0 [0]	-	2 [0.9]	2 [0.9]	39, 45
Rash/skin lesions	3 [1.2]	3 [1.2]	1, 17, 33	8 [3.6]	6 [2.7]	6 [2–28]
Other	7 [2.7]	6 [2.3]	41 [13–64]	6 [2.7]	5 [2.2]	19 [12–40]

AE, adverse event; n, number.

^aIn case of three or fewer reported adverse events, absolute week numbers of permanent treatment discontinuation are reported.

definition, relatively low loss of response percentages were expected. Furthermore, not all patients in our study have completed 3 months or 1 year of follow-up yet, meaning that these patients are still at risk of developing loss of response. As such, 193/225

patients of the SB5-start cohort completed 3 months of follow-up and only 65/225 patients had follow-up beyond 1 year. One previous study describing their SB5 experience in IBD reported primary loss of response in 1/48 patients [2.1%] after 3 months and

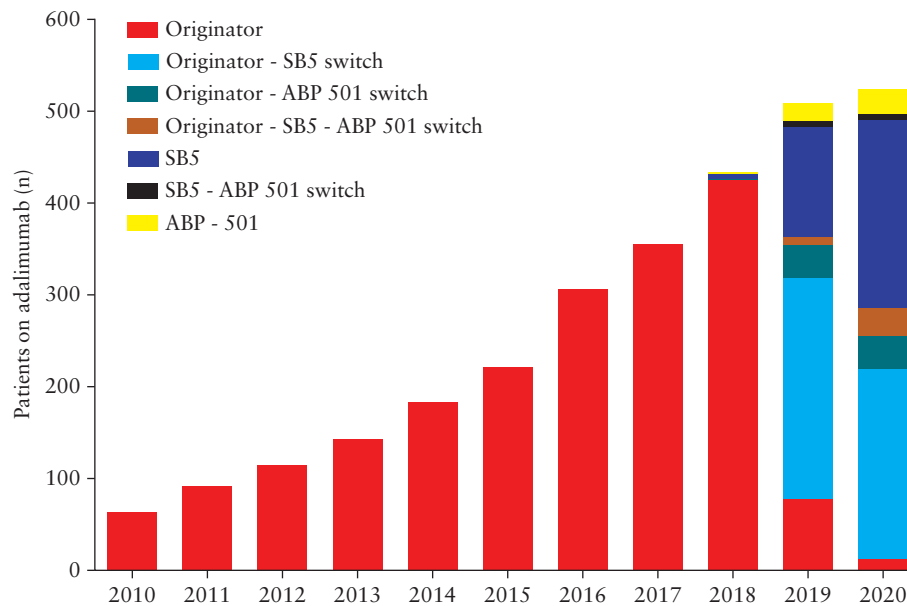


Figure 4. Prevalent number of IBD cases on ADA per brand per year.

Of note, one patient who switched from the originator to SB5, to ABP 501 switched back to the originator [included in the originator-SB5-ABP 501 group]. Three patients who switched from originator to ABP 501 switched back to the originator [included in the originator-ABP 501 switch group]. Four patients who switched from the originator to SB5 switched back to the originator [included in the originator-SB5 switch group].

IBD, inflammatory bowel disease; ADA, adalimumab.

secondary loss of response in 12.5% [6/48] and 27.1% [13/48] after respectively 6 and 12 months.⁹

We demonstrated that trough levels were adequate and stable over time, with ADA antibodies detectable in 10.5% in the SB5-switch cohort [including 3.1% with already detectable antibodies before switch] and 22.0% in the SB5-start cohort. This is in line with two previous IBD studies showing stable ADA trough levels following a switch from the ADA originator to SB5.^{8,9} The PANTS study [$n = 955$] described antibodies to ADA in 28.5% of patients at week 54 following commencement of the ADA originator.²⁴ Our immunogenicity percentage [22.0%] was slightly lower, which may be caused by differences in duration of follow-up [median 8.3 months in the SB5-start cohort in our study vs 54 weeks in the PANTS study]. Furthermore, no differences were found between SB5 and the originator with respect to the pharmacokinetic and immunogenicity profile in non-IBD trials. As such, a phase I trial in healthy volunteers and a phase III trial in rheumatoid arthritis showed comparable ADA serum concentrations and antibodies.^{21,29}

Injection site pain was the most frequently reported adverse event and occurred significantly more often in the patients who switched to SB5 [SB5-switch cohort 13.7%; SB5-start cohort 2.7%; $p < 0.01$]. This percentage might be underreported since only adverse events leading to treatment discontinuation were documented. In line with our findings, the SB5 switch study from the Italian group described injection site pain in 24.7% [88.9% occurred in the switching cohort].⁹ This may be related to the citrate buffer used for SB5, causing significantly more injection site pain compared to other buffers such as saline or histidine.^{30,31} Two previous studies compared a new citrate-free formulation of the ADA originator [with a smaller injection volume and smaller needle] with the original citrate-containing ADA originator in IBD³² and rheumatoid arthritis patients.³³ They found that the citrate-free ADA formulation was associated with statistically significant less injection site pain.^{32,33} In another study [only available in abstract form], 744 patients underwent a non-medical

switch to a citrate-containing ADA biosimilar [all rheumatology and dermatology patients] or to a citrate-free ADA biosimilar [all gastroenterology patients]. Injection site problems were more likely to be reported with the citrate-containing biosimilar.³⁴ Most patients who developed injection site pain in our cohort switched to ABP 501, a citrate-free ADA biosimilar. Only 1/39 patients who switched to ABP 501 continued to have pain at the injection site and switched back to the originator. This supports the hypothesis that injection site pain is related to the citrate buffer. Finally, it should be noted that injection site reactions are also frequently reported [13–38%] with the ADA originator.^{1,35} The fact that injection site pain is mainly reported in the SB5-switch cohort may indicate a role for the nocebo effect. No other unexpected toxicity signals were found in our study.

The current ECCO position statement on the use of biosimilars advocates against a double biosimilar switch within 6 months from an immunological point of view and due to lack of evidence.³⁶ Our study provides one of the first datasets regarding a double ADA biosimilar in IBD patients. None of the double switch patients in our study [$n = 35$] discontinued ADA after the second switch, and trough levels were stable over time. Supportive data are found in a recent phase III trial with 465 plaque psoriasis patients assessing the impact of multiple ADA biosimilar switches on safety and efficacy. No differences were found between patients who did not switch and patients who underwent four switches [reverse switching between ADA originator and biosimilar GP2017].³⁷ In line with this, a recent IBD study described a double IFX biosimilar switch in 115 patients and found a comparable drug persistence compared to the single switch group with an overall drug persistence of 94.9% in the total study population.³⁸ No changes were observed in clinical activity scores and IFX trough levels over time. Similarly, the number of received IFX biosimilars did not impact immunogenicity in another study [$n = 140$].³⁹ A Dutch study reported similar IFX drug persistence in patients who underwent a reverse switch to the IFX originator [$n = 75$] compared to patients who continued the IFX biosimilar [$n = 683$] with stable trough levels over

time.⁴⁰ These safety and effectiveness findings of a double biosimilar switch are confirmed in smaller studies.^{41,42} This advocates allowance of a double biosimilar switch.

Our data are of major socioeconomic importance and our supportive evidence for biosimilar use may improve access to ADA, especially in countries where healthcare costs and policies may limit its appropriate prescription. In recent years, the number of ADA prescriptions has increased significantly as emphasized in our cohort.^{2,6} In line with this, biological therapies are the main cost driver in IBD, accounting for 73% of costs in CD and 48% in UC after the first year of diagnosis.⁴ Indeed, Humira has been one of world's top selling drugs in the last decade.⁴³ In addition, the global monoclonal antibodies market has seen a 7.4% compound annual growth rate since 2016 for monoclonal antibodies used for immune-mediated inflammatory diseases, and it is estimated that 60 million USD will be spent in 2021 on monoclonal antibodies.⁶ Biosimilars bear a great cost-saving potential, and ADA costs were significantly reduced in NHS Lothian by the managed switch programme.

Our study has several strengths including the large sample size of the SB5 cohort [$n = 481$] and the long-term follow-up [>13 months in the SB5-switch cohort]. Furthermore, our study provides data both for patients who switched to SB5 and for patients who commenced SB5 as a new treatment strategy. The prospective registration of ADA start and stop dates, including brand names, contributes significantly to the completeness of the data. Moreover, the protocol-driven collection of clinical disease activity, blood tests, therapeutic drug monitoring and FCAL in the virtual biologic clinic limits selection bias during collection of follow-up data.

Nevertheless, some limitations should be addressed. First, the study design did not include a control arm that continued the ADA originator, hampering the comparison of safety and effectiveness data between groups. Second, some follow-up data were lacking despite prospective data collection in the virtual biologic clinic. Third, different ADA drug and antibody assays have been used since January 2018 when the Scottish Biologic drug monitoring was relocated from Exeter to Glasgow. However, this took place 1 year before the first patients started on SB5 and almost all drug assays were performed in Glasgow, limiting its impact. Finally, the cohort was heterogeneous in terms of disease activity, ADA dosing and dose adjustments. Treatment changes could be made at the discretion of the responsible clinicians, which was not standardized. However, this reflects real-world practice, allowing direct translation of results into daily clinical practice.

In conclusion, switching from the ADA originator to SB5 appeared effective and safe in this study with over 12 months of follow-up. The most common adverse event was injection site pain; these patients were successfully moved on to ABP 501, providing data about a double biosimilar switch, which seems to be safe.

Conference Presentation

1. DDW [Digestive Disease Week], May 2021, virtual conference.
2. DDD [Dutch Digestive Disease Days], March 2021, virtual conference, the Netherlands.
3. ECCO, July 2021, virtual conference.

Funding

Professor Lees is funded by a UKRI [UK research and Innovation] Future Leaders Fellowship 'Predicting outcomes in IBD'. Gareth-Rhys Jones is funded by a Wellcome Trust Clinical Research Career Development Fellowship. None of our funding bodies had any role in study design, data collection or analysis,

writing or decision to submit for publication. No writing assistance was used for this paper.

Conflict of Interest

Lauranne Derikx has served on the advisory board for Sandoz. Spyros Siakavellas received a support grant from the Greek Group for the study of IBD and he received speaker fees from Pfizer and Janssen. Nikolas Plevis has served as a speaker for Janssen, Takeda and Pfizer. Professor Charlie Lees has received research support from Abbvie and Gilead, and acted as a consultant to Abbvie, Janssen, Takeda, Pfizer, Galapagos, MSD, Hospira, Pharmacosmos, GSK, Gilead, Topivert, Vifor Pharma, Dr Falk, Oshi Health, Trellus Health and Iterative Scopes; he has received speaking fees and travel support from Pfizer, Janssen, Abbvie, Galapagos, MSD, Takeda, Shire, Ferring, Hospira, Warner-Chilcott and Dr Falk. All declarations of interest are outside the submitted work. None of the other authors have any conflicts of interest.

Author Contributions

L.D., N.P., M.L., G.J., C.L. contributed to the design of the study. L.D., H.D., N.P., L.L., C.R., S.I.S., P.J., S.S., C.H., L.K., L.M., C.N., A.I. contributed to the data collection. L.D., H.D., N.P., M.L., G.J., C.L. analysed the data. L.D. drafted the first version of the manuscript. All authors critically revised the manuscript for important intellectual content. All authors approved the final version of the manuscript.

Data Availability Statement

All data are incorporated into the article and its online supplementary material.

Supplementary Data

Supplementary data are available at *ECCO-JCC* online.

References

1. D'Haens GR, van Deventer S. 25 years of anti-TNF treatment for inflammatory bowel disease: lessons from the past and a look to the future. *Gut* 2021;70:1396–405. doi:10.1136/gutjnl-2019-320022. Epub 11 January 2021.
2. Jenkinson PW, Plevis N, Siakavellas S, et al. Temporal trends in surgical resection rates and biologic prescribing in Crohn's disease: a population-based cohort study. *J Crohns Colitis* 2020;14:1241–7.
3. van der Valk ME, Mangen MJ, Leenders M, et al.; COIN study group and the Dutch Initiative on Crohn and Colitis. Healthcare costs of inflammatory bowel disease have shifted from hospitalisation and surgery towards anti-TNF α therapy: results from the COIN study. *Gut* 2014;63:72–9.
4. Burisch J, Vardi H, Schwartz D, et al.; Epi-IBD group. Health-care costs of inflammatory bowel disease in a pan-European, community-based, inception cohort during 5 years of follow-up: a population-based study. *Lancet Gastroenterol Hepatol* 2020;5:454–64.
5. NHS set to save £150 million by switching to new versions of most costly drug. <https://www.england.nhs.uk/2018/10/nhs-set-to-save-150-million-by-switching-to-new-versions-of-most-costly-drug/>. Accessed June 25, 2021.
6. Fiorino G, Gilardi D, Correale C, et al. Biosimilars of adalimumab: the upcoming challenge in IBD. *Expert Opin Biol Ther* 2019;19:1023–30.
7. Somers M, Bossuyt P, Ferrante M, Peeters H, Baert F. Belgian IBD Research Group [BIRD] position statement 2019 on the use of adalimumab biosimilars in inflammatory bowel diseases. *J Crohns Colitis* 2020;14:680–5.
8. Lukas M, Malickova K, Kolar M, et al. Switching from originator adalimumab to the biosimilar SB5 in patients with inflammatory bowel disease: short-term experience from a single tertiary clinical centre. *J Crohns Colitis* 2020;14:915–9.

9. Tapete G, Bertani L, Pieraccini A, *et al.* Effectiveness and safety of nonmedical switch from adalimumab originator to SB5 biosimilar in patients with inflammatory bowel diseases: twelve-month follow-up from the TABLET Registry. *Inflamm Bowel Dis* 2021.
10. Plevris N, Jones GR, Jenkinson PW, *et al.* Implementation of CT-P13 via a managed switch programme in Crohn's disease: 12-month real-world outcomes. *Dig Dis Sci* 2019;64:1660–7.
11. Population Estimates Time Series Data. <https://www.nrscotland.gov.uk/statistics-and-data/statistics/statistics-by-theme/population/population-estimates/mid-year-population-estimates/population-estimates-time-series-data>. Accessed April 9, 2021.
12. Jones GR, Lyons M, Plevris N, *et al.* IBD prevalence in Lothian, Scotland, derived by capture–recapture methodology. *Gut* 2019;68:1953–60.
13. Plevris N, Lyons M, Jenkinson PW, *et al.* Higher adalimumab drug levels during maintenance therapy for Crohn's disease are associated with biologic remission. *Inflamm Bowel Dis* 2019;25:1036–43.
14. Smits LJ, Derikx LA, de Jong DJ, *et al.* Clinical outcomes following a switch from Remicade® to the biosimilar CT-P13 in inflammatory bowel disease patients: a prospective observational cohort study. *J Crohns Colitis* 2016;10:1287–93.
15. Lewis JD, Chuai S, Nessel L, Lichtenstein GR, Abera FN, Ellenberg JH. Use of the noninvasive components of the Mayo score to assess clinical response in ulcerative colitis. *Inflamm Bowel Dis* 2008;14:1660–6.
16. Higgins PD, Schwartz M, Mapili J, Krokos I, Leung J, Zimmermann EM. Patient defined dichotomous end points for remission and clinical improvement in ulcerative colitis. *Gut* 2005;54:782–8.
17. Vermeire S, Schreiber S, Sandborn WJ, Dubois C, Rutgeerts P. Correlation between the Crohn's disease activity and Harvey-Bradshaw indices in assessing Crohn's disease severity. *Clin Gastroenterol Hepatol* 2010;8:357–63.
18. Roda G, Jharap B, Neeraj N, Colombel JF. Loss of response to anti-TNFs: definition, epidemiology, and management. *Clin Transl Gastroenterol* 2016;7:e135.
19. Blood Sciences Test - Adalimumab Drug Levels. <https://www.exeterlaboratory.com/test/adalimumab-drug-levels/>. Accessed June 25, 2021.
20. Scottish Biologic Therapeutic Drug Monitoring Service –Gastroenterology Guidance. <https://www.nhs.uk/media/251621/scottish-biologic-tdm-service-gastroenterology-guidance-03122018.pdf>. Accessed June 25, 2021.
21. Weinblatt ME, Baranauskaite A, Niebrzydowski J, *et al.* Phase III randomized study of SB5, an adalimumab biosimilar, versus reference adalimumab in patients with moderate-to-severe rheumatoid arthritis. *Arthritis Rheumatol* 2018;70:40–8.
22. Chen C, Hartzema AG, Xiao H, *et al.* Real-world pattern of biologic use in patients with inflammatory bowel disease: treatment persistence, switching, and importance of concurrent immunosuppressive therapy. *Inflamm Bowel Dis* 2019;25:1417–27.
23. Rundquist S, Sachs MC, Eriksson C, Olén O, Montgomery S, Halfvarson J; SWIBREG Study Group. Drug survival of anti-TNF agents compared with vedolizumab as a second-line biological treatment in inflammatory bowel disease: results from nationwide Swedish registers. *Aliment Pharmacol Ther* 2021;53:471–83.
24. Kennedy NA, Heap GA, Green HD, *et al.*; UK Inflammatory Bowel Disease Pharmacogenetics Study Group. Predictors of anti-TNF treatment failure in anti-TNF-naïve patients with active luminal Crohn's disease: a prospective, multicentre, cohort study. *Lancet Gastroenterol Hepatol* 2019;4:341–53.
25. Hanauer SB, Sandborn WJ, Rutgeerts P, *et al.* Human anti-tumor necrosis factor monoclonal antibody (adalimumab) in Crohn's disease: the CLASSIC-I trial. *Gastroenterology* 2006;130:323–33; quiz 591.
26. Colombel JF, Sandborn WJ, Rutgeerts P, *et al.* Adalimumab for maintenance of clinical response and remission in patients with Crohn's disease: the CHARM trial. *Gastroenterology* 2007;132:52–65.
27. Rutgeerts P, D'Haens G, Targan S, *et al.* Efficacy and safety of retreatment with anti-tumor necrosis factor antibody (infliximab) to maintain remission in Crohn's disease. *Gastroenterology* 1999;117:761–9.
28. Ben-Horin S, Chowers Y. Review article: Loss of response to anti-TNF treatments in Crohn's disease. *Aliment Pharmacol Ther* 2011;33:987–95.
29. Shin D, Lee Y, Kim H, Körnicke T, Fuhr R. A randomized phase I comparative pharmacokinetic study comparing SB5 with reference adalimumab in healthy volunteers. *J Clin Pharm Ther* 2017;42:672–8.
30. Laursen T, Hansen B, Fisker S. Pain perception after subcutaneous injections of media containing different buffers. *Basic Clin Pharmacol Toxicol* 2006;98:218–21.
31. Usach I, Martinez R, Festini T, Peris JE. Subcutaneous injection of drugs: literature review of factors influencing pain sensation at the injection site. *Adv Ther* 2019;36:2986–96.
32. Patel AS, Luu P. 854 - Comparison of injection site pain with citrate free and original formulation adalimumab in pediatric IBD patients. *Am J Gastroenterol* 2019;114:S493–4.
33. Nash P, Vanhoof J, Hall S, *et al.* Randomized crossover comparison of injection site pain with 40 mg/0.4 or 0.8 mL formulations of adalimumab in patients with rheumatoid arthritis. *Rheumatol Ther* 2016;3:257–70.
34. Rosembert D, Malaviya A, How J, *et al.* Different failure rates after non-medical switching 744 patients from adalimumab originator to 2 adalimumab biosimilars. *Gut* 2021;70:A115.
35. ANNEX I: Summary of product characteristics (adalimumab). https://www.ema.europa.eu/en/documents/product-information/humira-epar-product-information_en.pdf. Accessed June 25, 2021.
36. Danese S, Fiorino G, Raine T, *et al.* ECCO position statement on the use of biosimilars for inflammatory bowel disease – an update. *J Crohns Colitis* 2017;11:26–34.
37. Blauvelt A, Lacour JP, Fowler JF Jr, *et al.* Phase III randomized study of the proposed adalimumab biosimilar GP2017 in psoriasis: impact of multiple switches. *Br J Dermatol* 2018;179:623–31.
38. Trystram N, Abitbol V, Tannoury J, *et al.* Outcomes after double switching from originator Infliximab to biosimilar CT-P13 and biosimilar SB2 in patients with inflammatory bowel disease: a 12-month prospective cohort study. *Aliment Pharmacol Ther* 2021;53:887–99.
39. Lauret A, Moltó A, Abitbol V, *et al.* Effects of successive switches to different biosimilars infliximab on immunogenicity in chronic inflammatory diseases in daily clinical practice. *Semin Arthritis Rheum* 2020;50:1449–56.
40. Mahmmod S, Schultheiss JPD, van Bodegraven AA, *et al.* Outcome of reverse switching from CT-P13 to originator infliximab in patients with inflammatory bowel disease. *Inflamm Bowel Dis* 2021.
41. Mazza S, Fasci A, Casini V, *et al.* Safety and clinical efficacy of double switch from originator infliximab to biosimilars CT-P13 and SB2 in patients with inflammatory bowel diseases [SCESICS]: a multicentre study. *J Crohns Colitis* 2020;14:S342.
42. Gisondi P, Virga C, Piaserico S, *et al.* Switching from one infliximab biosimilar (CT-P13) to another infliximab biosimilar (SB2) in patients with chronic plaque psoriasis. *Br J Dermatol* 2020;183:397–8.
43. Norman P. Humira: the impending patent battles over adalimumab biosimilars. *Pharm Pat Anal* 2016;5:141–5.