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EFFECTIVENESS AND SAFETY OF ADALIMUMAB BIOSIMILAR SB5 IN IBD: OUTCOMES IN ORIGINATOR TO SB5 SWITCH, DOUBLE BIOSIMILAR SWITCH AND BIO-NAIEVE SB5 OBSERVATIONAL COHORTS

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Authors' contributions

LD, NP, ML, GJ, CL contributed to the design of the study. LD, HD, NP, LL, CR, SIS, PJ, SS, CH, LK, LM, CN, AI contributed to the data collection. LD, HD, NP, ML, GJ, CL analyzed the data. LD drafted the first version of the manuscript. All authors critically revised the manuscript for important intellectual content. All authors have approved the final version of this manuscript.

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LIST OF ABBREVIATIONS

ADA	Adalimumab
AE	Adverse event
BMI	Body mass index
CD	Crohn’s disease
CI	Confidence interval
CRP	C-Reactive Protein
EIM	Extra-intestinal manifestation
ELISA	Enzyme-linked immunosorbent assay
FCAL	Faecal calprotectin
GBP	Great British Pounds
HBI	Harvey Bradshaw Index
IBD	Inflammatory bowel disease
IBD-U	Inflammatory bowel disease unclassified
IQR	Interquartile Range
n	Number
PYF	Person years of follow-up
NHS	National Health Service
TNF	Tumor necrosis factor
UC	Ulcerative colitis

ABSTRACT

Background and aims

Multiple adalimumab (ADA) biosimilars are now approved for use in IBD; however, effectiveness and safety data remain scarce. We aimed to investigate long-term outcomes of the adalimumab (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 biologic prescription database that prospectively registered all ADA start and stop dates including brand names. Data on IBD phenotype, CRP, drug persistence, ADA drug and antibody levels, and faecal calprotectin were collected.

Results

481 patients were treated with SB5, 256 in the SB5-switch cohort (median follow-up: 13.7 months [8.6-15.2]) and 225 in the SB5-start cohort (median follow-up: 8.3 months [4.2-12.8]). 70.8% of the SB5-switch cohort remained on SB5 beyond one 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 one 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.

Keywords

Crohn's disease, ulcerative colitis, biosimilar

INTRODUCTION

Monoclonal antibodies directed against tumor 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 hospitalisations.[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 randomised 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-naive patients as well as patients switching to biosimilar ADA from originator, however 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 program 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 program.

METHODS

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 7,000 patients in NHS Lothian are diagnosed with IBD, referred to as the Lothian IBD cohort.[12]

Since 1 February 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 1 December 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 CRP), therapeutic drug monitoring and faecal calprotectin (FCAL) were collected by protocol if these data were not collected in the last 2 months.

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 28 October 2020. We performed an additional cross-check with the Lothian

IBD Biologics Database, containing all biological prescriptions for IBD patients since 1 August 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 one month follow-up after starting SB5.

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 ($\pm$ 10 weeks). Biochemical remission was defined as a CRP < 5 mg/l; biomarker remission was defined as a FCAL < 250 µg/g[13]; and clinical remission was defined as a Harvey Bradshaw Index (HBI) $\leq$ 4 for Crohn's disease patients or a partial Mayo index $\leq$ 1 for ulcerative colitis 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.

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 hospitalisation. 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.

Adalimumab trough and antibody assay

Until December 2017, ADA trough and antibody levels were processed at the Exeter Hospital Laboratories, United Kingdom, using the Immundiagnostik monitor enzyme-linked immunosorbent assay (ELISA) as per the manufacturer's protocol. Trough levels and antibody levels were expressed in ug/mL and AU/mL, respectively. The assay detects drug levels ≥0.8 ug/mL and total antibodies to ADA ≥10 AU/ml. Drug assays were validated for both the ADA originator and for SB5.[19]

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

Faecal calprotectin analyses

FCAL was measured as part of routine clinical monitoring and as directed by patient symptoms. Patients received a 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 hours of collection. Upon arrival at the laboratories, samples were stored at –20°C. FCAL was measured using a standard ELISA technique (Calpro AS, Lysaker, Norway). Numerical values were generated between 20 and 2500 ug/g. All assays were performed in the Department of Clinical Biochemistry at the Western General Hospital, Edinburgh, United Kingdom. The same assay has been utilized since 2004.

Statistics

All analyses were performed with IBM SPSS statistical software package version 25 [Armonk, NY]. 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 versus 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 both 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 patients' 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 ($\pm$ 10 weeks) and week 52 ($\pm$ 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 continues and categorical variables, respectively. We considered antibody levels of >10 AU/ml as detectable antibodies, whereas levels $\leq$10 AU/ml or absent measurements (due to adequate trough levels) were considered as indetectable antibodies. A p value <0.05 was considered statistically significant.

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.

RESULTS

Patients

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 (8.6-15.2) in the SB5-switch cohort and 8.3 months (4.2-12.8) in the SB5-start cohort, corresponding with 254 and 170 person years of follow-up (PYF), respectively. 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 Table 1 and Table 2.

SB5-switch cohort

Most patients in the SB5-switch cohort were diagnosed with CD (228/256, 89.1% versus 28/256, 11.0% with UC/IBD-U). 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). 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. 21.9% were on combination therapy with thiopurines

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

SB5-start cohort

The majority of patients included in the SB5-start cohort had CD (175/225, 77.8%). 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. 68.6% (153/225) was biological-naive. 11/225 patients who started on SB5 previously used ADA. This was stopped median 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 since they used ADA in the past. Combination therapy with a thiopurine or methotrexate was prescribed in 37/225 patients (16.5%). 21.3% (48/225) of patients required SB5 dose intensification during treatment.

Drug persistence

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). Main reasons to stop therapy were adverse events (n = 46/90) and secondary loss of response (n = 37/90). 213/252 (84.6%) and 163/236 (70.8%) patients remained on SB5 at week 26 and week 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.

SB5-start cohort

81/225 patients (36%) discontinued SB5 in 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. 140/179 (80.1%) and 67/130 (62.8%) patients remained on ADA at week 26 and 52, respectively.

Disease activity

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 ug/g (30-390). 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, 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 ug/g [35-585], median FCAL week 52: 129 [37-574], p = 0.47).

Immunogenicity

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 ug/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). 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 week 52, SB5 was continued in 213 and 163 patients, respectively. 26/213 patients underwent dose adjustments before week 26 (16/26 dose intensification, 7/26 dose de-escalation, 3 temporarily suspended), resulting in a median ADA trough level of 11.6 ug/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 temporarily suspended) with subsequently trough levels of 7.8 ug/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).

27/256 patients (10.5%) had detectable antibodies following the switch to SB5. 8/27 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 detectable antibodies. These antibodies were detected after median 40 weeks (16-55). 17/19 patients received an immunosuppressant before switch and 4/19 were treated with azathioprine (n = 3) or methotrexate (n =1) during SB5 treatment.

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. Median ADA trough level was 9.4 ug/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). 2/28 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.

In a median follow-up duration of 8.3 months (4.2-12.8) 182/225 patients underwent therapeutic drug monitoring at some point. 40/182 patients (22.0%) developed newly detectable antibodies over time after median 21 weeks (14-36).

Safety

Adverse events that required SB5 suspension or discontinuation, or hospitalisation 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. 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.

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). 33 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 of whom two patients switched back to the originator. Five patients developed an infection requiring (temporary) SB5 discontinuation.

SB5-start cohort

The most frequently reported adverse event in patients who started on SB5 were infections (n = 17; 10.0 per 100 PYF). 7/17 infections (41.2%) required permanent treatment discontinuation, whereas 10 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.

Double biosimilar switch

35 patients underwent a double biosimilar switch from the ADA originator to SB5 and subsequently to ABP 501. Most of these patients had CD (CD: 31/35, 88.6%; UC: 3/35, 8.6%; IBD-U 1/35, 2.9%). They were treated for median 30 months (18-50) with the originator. After median 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. In respective, median trough levels were 10.0 ug/ml (7.4 – 21.7), 12.0 ug/ml (8.7 – 18.5) and 12.0 (7.9 – 12.0; Supplementary Figure 3). ADA trough levels were available at all three timepoints 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 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.

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 as much in 2019/2020 compared to 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]

DISCUSSION

In our managed switch program, 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 is 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 is 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 safety[22]) after one 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 one-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 analyzed safety and effectiveness of SB5 in IBD patients. They reported that 66.7% of ADA-naive patients (n = 48) and 81.6% of patients who switched from the originator to SB5 (n = 98) remained on SB5 beyond one year.[9] Moreover, similar proportions of clinical remission were found in this study one 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 week 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 or response after cessation of anti-TNF.[28] Since we used the latter definition, relatively low loss of response percentages were expected. Furthermore, not all patients in our study have completed three month or one year follow-up yet, meaning that these patients are still at risk to develop loss of response. As such, 193/225 patients of the SB5-start cohort completed three month follow-up and only 65/225 patients had follow-up beyond one year. One previous study describing their SB5 experience in IBD reported primary loss of response in 1/48 patients (2.1%) after three months and 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 in 28.5% of patients antibodies to ADA 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 versus 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 IBD[32] and rheumatological 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 provided one of the first data 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, a recent IBD study described a double IFX biosimilar switch in 115 patients and they 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 infliximab 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 the allowance of a double biosimilar switch.

Our data are of major importance for socioeconomic society and our supportive evidence for biosimilar use may improve access to ADA, especially in countries where healthcare costs and policies may limit the appropriate prescription of it. In recent years, the number of ADA prescriptions has significantly increased as emphasized in our cohort.[2, 6] In line, 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 is one of world's top selling drugs in the last decade.[43] In addition, the Global Monoclonal Antibodies Market has 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 for monoclonal antibodies.[6] Biosimilars bear a great cost-saving potential and ADA costs were significantly reduced in NHS Lothian by the managed switch program.

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 both data 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, significantly contributes to completeness of 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, which impede 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 were used since January 2018 when the Scottish Biologic drug monitoring was relocated from Exeter to Glasgow. However, this took place one year before the first patients started on SB5 and almost all drug assays were performed in Glasgow limiting the impact of it. Finally, the cohort was heterogenous in terms of disease activity, ADA dosing, and dose adjustments. Treatment changes could be made at the responsible clinicians' discretion, 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.

TABLE 1

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

Variable	**SB5-switch cohort** (n = 256)	**SB5-start cohort** (n = 225)	**Missing Values** (SB5-switch / SB5-start cohort, n)
Male sex, n (%)	135 (52.7)	113 (50.2)	0
Smoking behavior, n (%)			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 Adalimumab start (years), median	6.5 (2.5 – 12.4)	6.3 (1.5 – 17.1)	0 / 3
Duration ADA originator until SB5 (years), median (IQR) Duration ADA originator until SB5 (months), median (IQR)	2.7 (1.4 – 4.7) 32.5 (16.4-55.9)	-	0
IBD type, n (%)			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, n (%)			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, n (%)			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, n (%)			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, n (%)	87 (34.0)	64 (28.4)	0
Previous IBD-related medical therapy, n (%)			
- 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

IBD, inflammatory bowel disease; TNF, tumor necrosis factor; n, number; IQR, interquartile range

TABLE 2

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

Variable	**SB5-switch cohort** (n = 256)	**SB5-start cohort** (n = 225)	**Missing Values** (SB5-switch / SB5-start cohort, n)
Adalimumab dose at switch to SB5, n (%)			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, n (%)			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, n (%)			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, n (%)	90 (35.2)	81 (36.0)	0
Adalimumab treatment discontinuation, n (%)	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, n (%)			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; IQR, interquartile range; EIM, extra-intestinal manifestation

TABLE 3

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

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)*	AEs (n, % of total cohort)	AEs requiring permanent treatment discontinuation (n, % of total cohort)	Median time to permanent treatment discontinuation (weeks, IQR)*
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)

* In case of ≤ 3 reported adverse events, absolute week numbers of permanent treatment discontinuation are reported.

AE, adverse event; n, number

FIGURE 1

Patient inclusion flowchart

* 11/225 patients previously used the adalimumab originator; however, last injection with the originator was discontinued median 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

FIGURE 2

Drug persistence of SB5 and ADA in both the SB5-switch (A) and SB5-start cohort (B).

ADA, Adalimumab

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 $\leq$ 5mg/l), faecal biomarker remission (faecal calprotectin $\leq$ 250 µg/g) and clinical remission (Crohn's disease HBI $\leq$ 4; ulcerative colitis $\leq$ 1)

(B): Adalimumab trough levels

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

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Figure 1

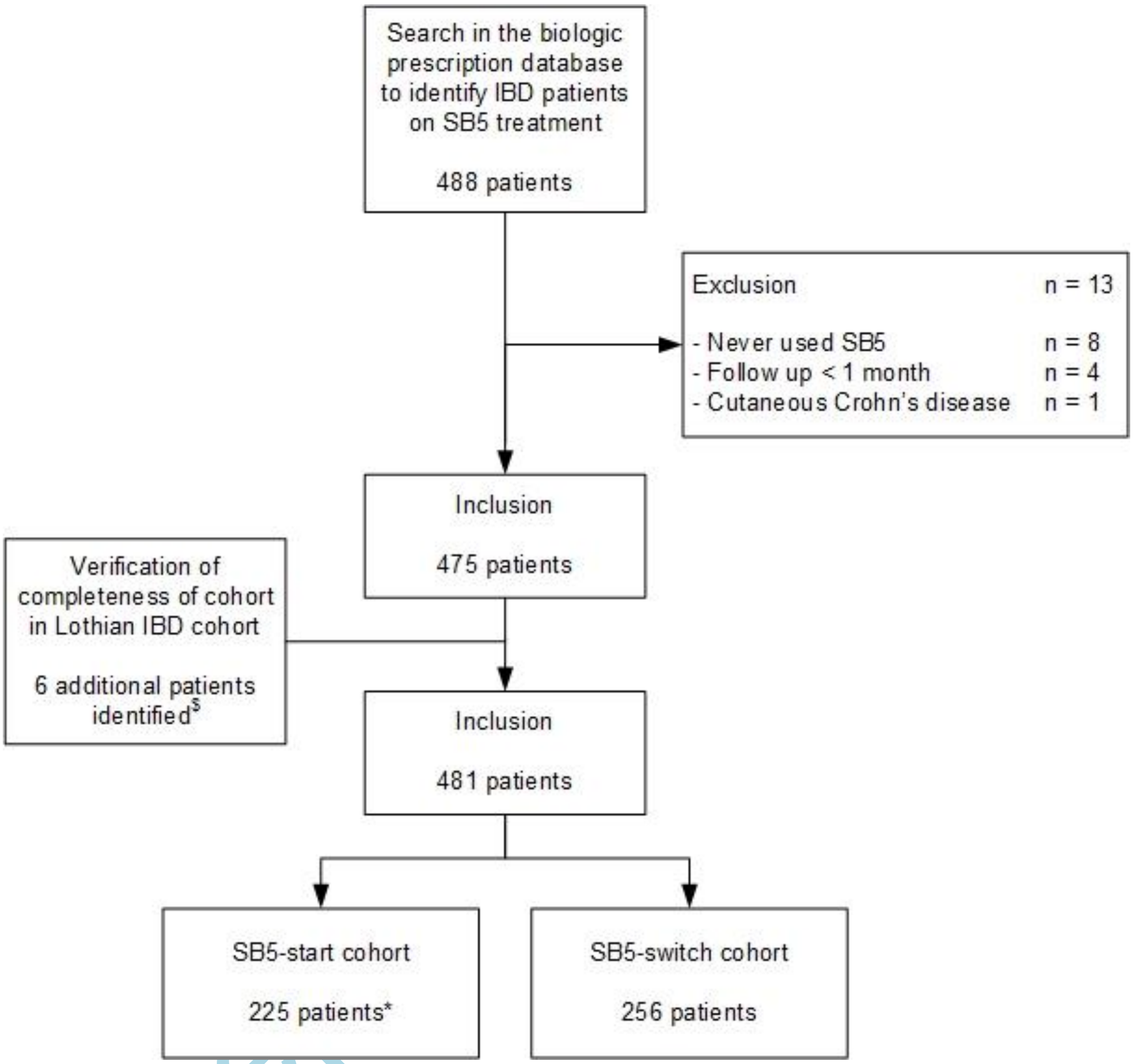
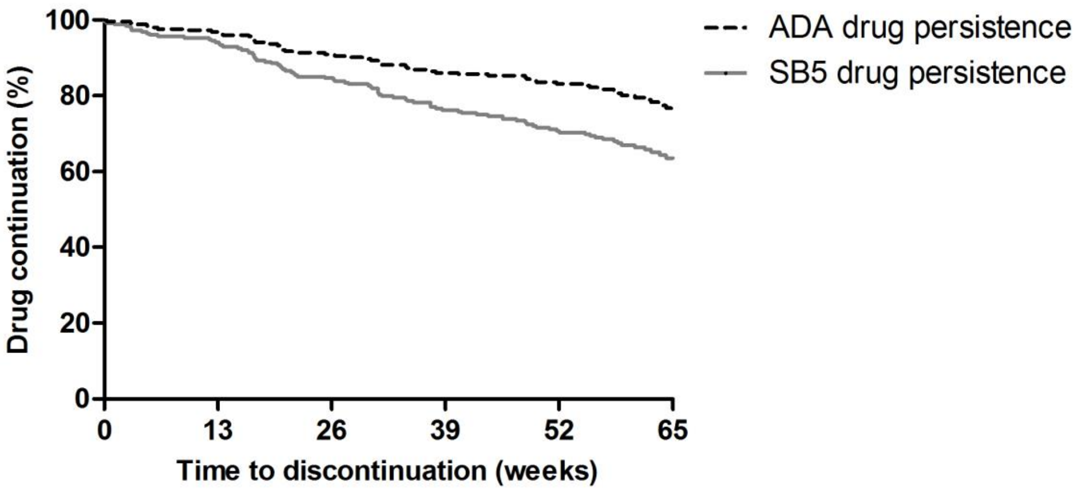
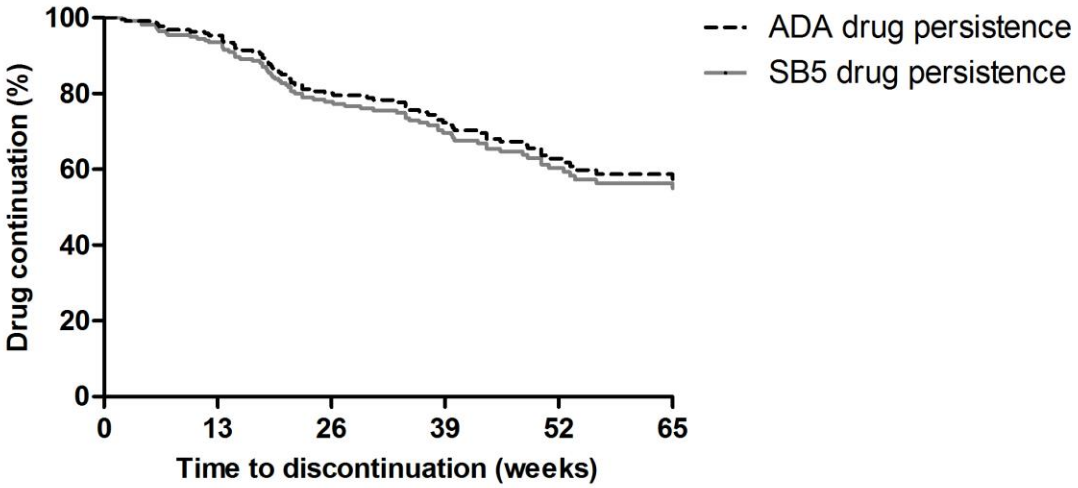

Search in the biologic prescription database to identify IBD patients on SB5 treatment
488 patients
Exclusion n = 13
- Never used SB5 n = 8
- Follow up < 1 month n = 4
- Cutaneous Crohn's disease n = 1
Inclusion
475 patients
Verification of completeness of cohort in Lothian IBD cohort
6 additional patients identified$
Inclusion
481 patients
SB5-start cohort
225 patients*
SB5-switch cohort
256 patients

Figure 2

A


100
80
60
40
20
0
Drug continuation (%)
0
13
26
39
52
65
Time to discontinuation (weeks)
ADA drug persistence
SB5 drug persistence

B


100
80
60
40
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Drug continuation (%)
0
13
26
39
52
65
Time to discontinuation (weeks)
ADA drug persistence
SB5 drug persistence

Figure 3

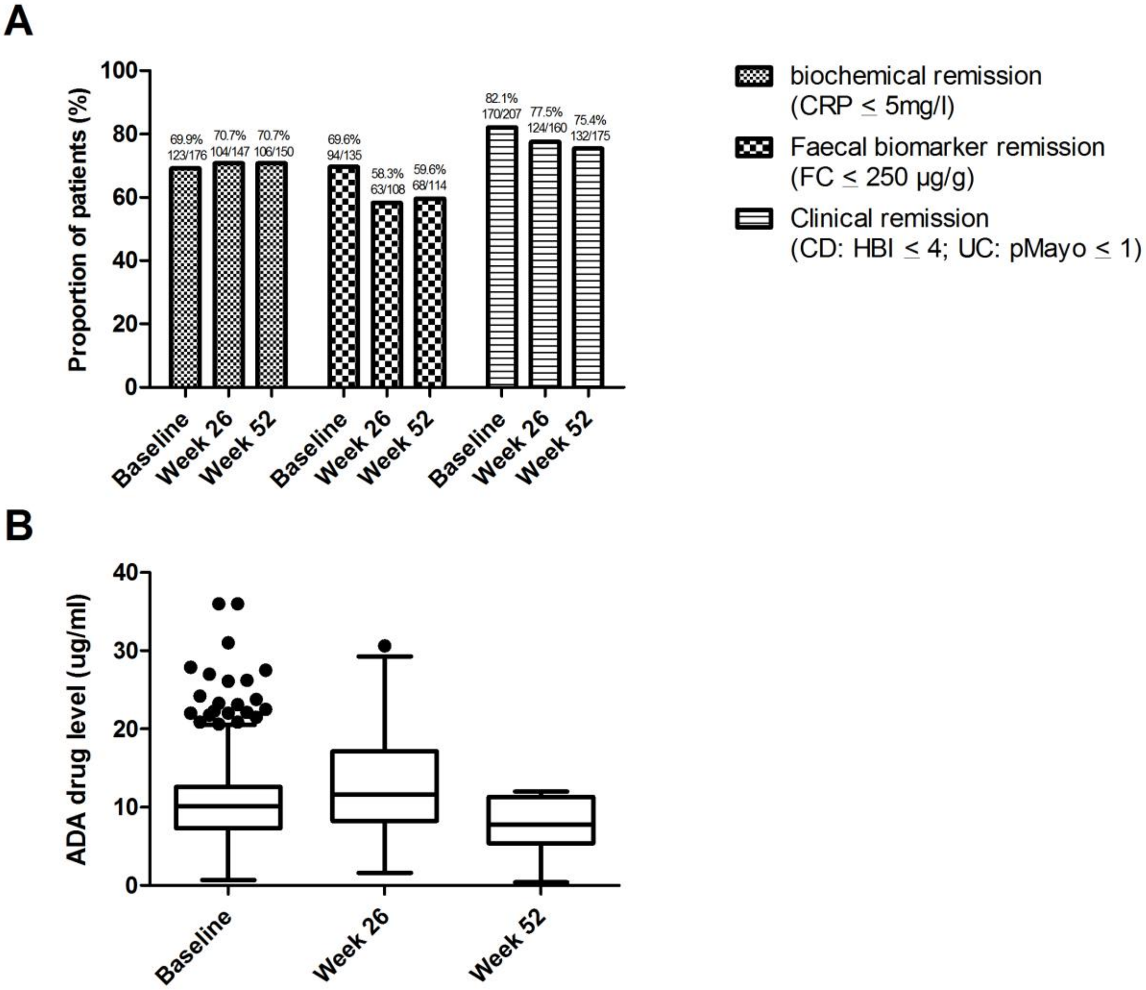
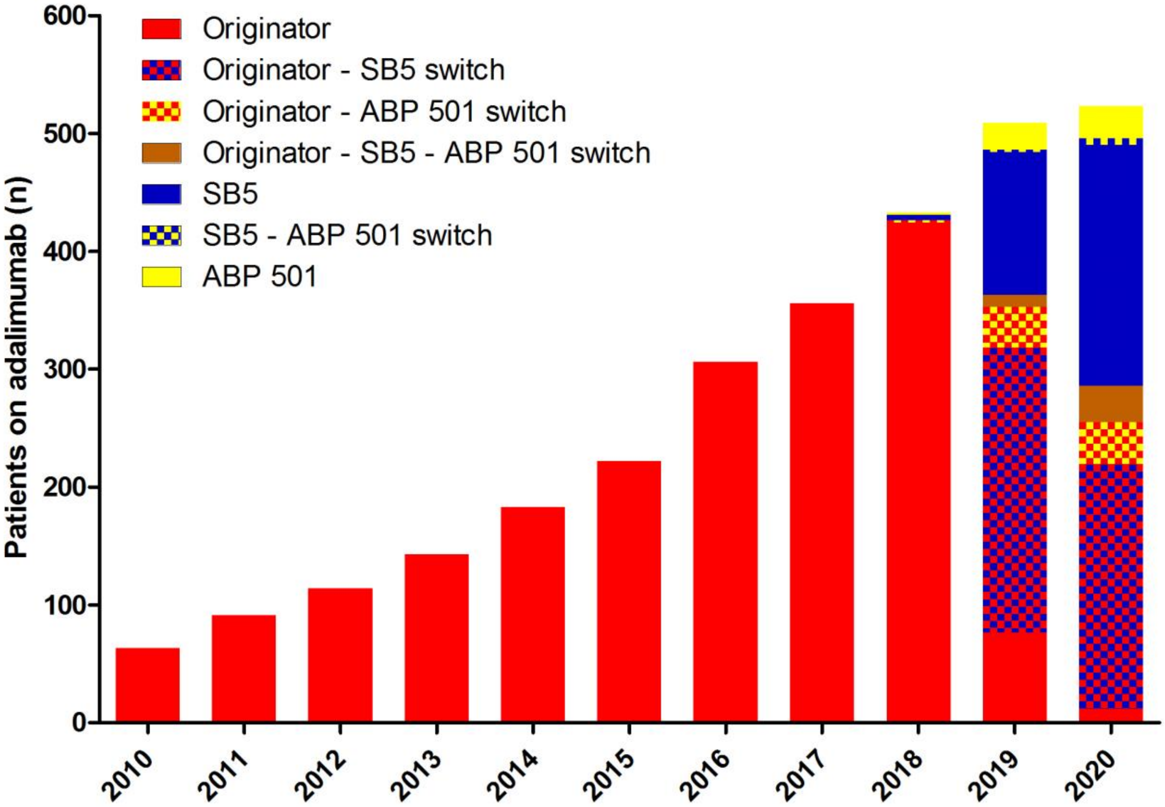

A
Proportion of patients (%)
100
80
60
40
20
0
69.9% 123/176
70.7% 104/147
70.7% 106/150
69.6% 94/135
58.3% 63/108
59.6% 68/114
82.1% 170/207
77.5% 124/160
75.4% 132/175
Baseline
Week 26
Week 52
Baseline
Week 26
Week 52
Baseline
Week 26
Week 52
biochemical remission (CRP ≤ 5mg/l)
Faecal biomarker remission (FC ≤ 250 µg/g)
Clinical remission (CD: HBI ≤ 4; UC: pMayo ≤ 1)
B
ADA drug level (ug/ml)
40
30
20
10
0
Baseline
Week 26
Week 52

Figure 4



Originator
Originator - SB5 switch
Originator - ABP 501 switch
Originator - SB5 - ABP 501 switch
SB5
SB5 - ABP 501 switch
ABP 501
Patients on adalimumab (n)
600
500
400
300
200
100
0
2010
2011
2012
2013
2014
2015
2016
2017
2018
2019
2020