# The Efficacy and Safety of Switching From Originator Infliximab to Single or Double Switch Biosimilar Among a Nationwide Cohort of Inflammatory Bowel Disease Patients

*Nabeel Khan, MD,[*,†,]* *Dhruvan Patel, MD,[‡]* *Tyler Pernes, BS,[*]* *Manthankumar Patel, MS,[*]* *Chinmay Trivedi, MBBS,[*]* *Elina Medvedeva, MS,[*]* *Dawei Xie, PhD,[§]* *and Yu-Xiao Yang, MD[*,†,§,¶]*

**Background:** Data on safety and efficacy of switching to Renflexis (SB2) from originator Infliximab (IFX) (single switch) or from originator IFX to Inflectra (CT-P13) to Renflexis (double switch) are limited.

**Methods:** We conducted a retrospective cohort study in a nationwide cohort of patient with inflammatory bowel disease (IBD) in remission who were switched to SB2. The main exposure was the treatment course of SB2. There are 2 levels in this variable: single switch (IFX to SB2) and double switch (IFX to CT-P13 to SB2). The outcome is SB2 drug discontinuation rate and/or not being in remission after 1 year. Logistic regression was used to estimate the adjusted and unadjusted odds ratios with 95% confidence intervals to study the efficacy difference between single switch and double switch.

**Results:** A total of 271 IBD patients were started on SB2. Among them 52 (19.2%) patients did not achieve remission at 1 year and 14 (5.1%) patients had to discontinue SB2 due to adverse events). In logistic regression analysis after controlling for covariates, there was no statistically significant difference observed in regard to efficacy or safety of the single switch versus double switch to SB2 (adjusted odds ratio for double switch compared to single switch = 1.33 (95% confidence interval 0.74–2.41, $P = 0.3432$).

**Conclusions:** Among IBD patients in remission, double switch was equally effective as compared to a single switch. This will help reassure the gastroenterologists who have concerns regarding the safety and efficacy of switching between multiple biosimilars for treating IBD.

### Lay Summary

Almost 81% of patients remained in remission after switching to a biosimilar at the end of 1 year. A double switch was not associated with a worse outcome as compared to a single switch.

**Key Words:** biosimilars, inflammatory bowel disease, single switch, double switch, Renflexis, Inflectra, Infliximab

Received for publications December 30, 2020; Editorial Decision February 18, 2021.

*Corporal Michael J Crescenz VA Medical Center, Department of Gastroenterology, Philadelphia, Pennsylvania, USA; †University of Pennsylvania, Perelman School of Medicine, Department of Medicine, Philadelphia, Pennsylvania, USA; ‡University of Pennsylvania, Perelman School of Medicine, Department of Gastroenterology, Philadelphia, Pennsylvania, USA; §Department of Epidemiology and Biostatistics, Center of Clinical Epidemiology and Biostatistics, University of Pennsylvania, Perelman School of Medicine, Philadelphia, Pennsylvania, USA; ¶Department of Epidemiology and Biostatistics, University of Pennsylvania, Perelman School of Medicine, Philadelphia, Pennsylvania, USA

Funding: This study was supported by an unrestricted research grant from Samung BioEpis Co., Ltd. Samsung BioEpis had no role in the study concept and design, acquisition of data, analysis and interpretation of data, or preparation of the manuscript.

Conflict of Interest: Nabeel Khan has received an unrestricted research grant from Pfizer Pharmaceuticals, Luitpold Pharmaceuticals, and Takeda Pharmaceuticals as well as Samsung BioEpis Co,. Ltd. Dhruvan Patel, Tyler Pernes, Manthankumar Patel, Chinmay Trivedi, Elina Medvedeva, Dawei Xie, and Yu-Xiao Yang have nothing to disclose regarding conflicts of interest.

Author Contribution: Nabeel Khan has participated in the study concept and design, study supervision, funding acquisition, interpretation of data, preparation of the manuscript as well as critical review of the manuscript. Dhruvan Patel has participated in study concept and design, interpretation of data, and preparation of the manuscript. Tyler Pernes has participated in study concept and design, acquisition of data, interpretation of data, preparation of manuscript, as well as study coordination. Manthankumar Patel has participated in acquisition and interpretation of the data. Chinmay Trivedi has participated in interpretation of the data and preparation of the manuscript. Elina Medvedeva has participated in the data analysis. Dawei Xie has participated in study design, interpretation of data, and critical review of the manuscript. Yu-Xiao Yang has participated in study concept and design, interpretation of data, and critical review of the manuscript.

Address correspondence to: Nabeel Khan, MD, Department of Gastroenterology, Corporal Michael J Crescenz VA Medical Center, 3900 Woodland Avenue, Philadelphia, PA-19104, USA (nabeelk@pennmedicine.upenn.edu; Nabeel.Khan@va.gov).



doi: 10.1093/crocol/otab022
Published online 26 April 2021

## INTRODUCTION

Inflammatory bowel disease (IBD), comprising of ulcerative colitis (UC) and Crohn disease (CD), is a chronic inflammatory disorder involving the gastrointestinal tract.[1] The biologic agents [Infliximab (IFX) and other antitumor necrosis factor (anti-TNF) medications] were first introduced 2 decades ago for the treatment of moderate to severe IBD.[2,3] These agents revolutionized the approach to the treatment of IBD and have proven their therapeutic efficacy over decades of follow-up.[2,4–6] Despite the clinical efficacy of biologics, there are various barriers to their widespread use. Foremost among them is the cost associated with the use of these agents. This has led to criteria being developed for their use among healthcare systems across different nations.[7–9] These economic considerations have led to the development and introduction to biosimilar agents because of their potential to reduce the financial burden on the healthcare systems.[10]

The first biosimilar agent CT-P13 (Remsima; Inflectra) was approved by the US Food and Drug Administration (FDA) in April 2016 and since then, there are few more biosimilars approved, such as other IFX biosimilars (Renflexis, Ixifi) and Adalimumab biosimilars (Amjevita, Cyltezo, Hyrimoz, Hadlima, Abrilada).[11] Previous literature has predicted a widespread use of biosimilars for IBD due to their efficacy and the cost saving.[12,13] A recent systemic review, identifying 70 published studies and abstracts, revealed that there was no difference in terms of efficacy and safety between the IFX biosimilar and reference agents.[14] Most of the studies were focused on patients with Rheumatoid arthritis, psoriasis, and ankylosing spondylitis and few studies were performed among patients with IBD.[15] Nonmedical switching (ie, biosimilar switching in IBD patients in remission) from originator IFX to an IFX biosimilars has gained recent attention. Limited data focusing on nonmedical switching in stable IBD patients indicate that it is safe to switch with no efficacy, safety, and immunogenicity concerns.[16,17] All the studies evaluated a "single switch" from original IFX to CT-P13 (Inflectra) and the data on efficacy and safety on switching to newer biosimilar, SB2 (Renflexis), are not enough.[16,17]

We decided to conduct a retrospective cohort study to determine the efficacy and safety regarding the switch from originator IFX to SB2 in the nationwide Veterans Affairs (VA) cohort of IBD patients focusing especially on patients with 2 switches (double switch). The Veterans Affairs Healthcare System (VAHS) is the largest integrated healthcare system in the US serving approximately 9 million veterans every year.[18] The VA recommended that all IBD patients on CT-P13 and originator IFX should be evaluated for possible switch to SB2 in view of cost saving. The final decision on the switch was left to the treating physician. A significant number of patients underwent the switch thus providing the ideal population in which to do the study. Our aim was to evaluate the efficacy of switching to SB2 and examine the difference, if any, in the efficacy of single switch from IFX to SB2 versus double switch ie, from IFX to CT-P13 to SB2 at 1 year.

## MATERIALS AND METHODS

We conducted a retrospective cohort study among the US national VAHS. To be included in our study, patients had to meet the following criteria: (1) followed in the VAHS with a diagnosis of IBD, which was based upon an algorithm outlined below, (2) had a Current Procedural Terminology (CPT) code for IFX before starting SB2, (3) started SB2 within the VAHS between January 1, 2000 to May 1, 2019, and (4) switched to SB2 following at least 3 months of stable IBD, defined as not requiring oral or intravenous steroids due to IBD reasons, not being hospitalized for disease flare, and not requiring an increase in drug dose or frequency for management of IBD.

IBD diagnoses were determined using a previously validated algorithm. Specifically, we obtained inpatient and outpatient International Classification of Diseases (ICD), Version 9 and 10, Clinical Modification (ICD-9-CM, ICD-10-CM) diagnosis codes, encounters, procedures, pharmacy, and demographic data for the study population. To create a source cohort, we applied our previously validated algorithm using the following criteria: (1) ≥1 ICD-9 or ICD-10 diagnosis code for CD and/or UC, (2) ≥1 outpatient visit in VA healthcare system, (3) at least 1 outpatient pharmacy claim for any of the IBD medications [ie, 5-Aminosalicylic acid (5-ASA) and its derivatives, Thiopurines (TPs), anti-TNF agents, and Vedolizumab], (4) at least 2 prescriptions of 1 distinct medication in the following 5 IBD medication groups (ie, 5-ASA only, TPs, anti-TNF agents, a combination of TPs and anti-TNF, and Vedolizumab), and (5) the censor date could not be preceded by the date of the first prescription of IBD medication/pharmacy claim. The positive predictive value of this algorithm for IBD diagnosis was 94.5%, confirmed on chart review by 2 reviewers with 100% concordance.[19]

Follow-up began on date of first SB2 infusion. Patients were censored if they died, were lost to follow up, stopped SB2, were followed up for 1 year, or if the study period ended on May 1, 2020.

### Exposure

The main exposure was the treatment course of SB2. There are 2 levels in this variable: single switch (IFX to SB2) and double switch (IFX to CT-P13 to SB2).

### Outcomes

The primary outcome is a composite outcome looking at SB2 drug discontinuation rate and/or not being in remission after 1 year. This outcome is set to "true" if any of the following is true during the first year of follow-up: (1) patient required steroid use for disease control, (2) patient required hospitalization or surgery for control of the disease, (3) patient required an increase in the dosing or frequency of SB2, or (4) patient stopped taking SB2.

The secondary outcome breaks down the reason the patient was not in remission and/or stopped the drug, which will be used in a descriptive analysis. All the outcomes were confirmed via a manual chart review of the electronic medical records of the patients. More specifically, physician notes were evaluated to confirm the accuracy of all the outcomes reported. A patient was considered to have an adverse event (which led to drug discontinuation) only if the physician, after a detailed evaluation, confirmed the adverse event in the electronic medical record.

## Covariates

For all patients, we collected baseline data for the following covariates: sex, race (Caucasian, African American, other, and unknown), district (Continental, Midwest, North Atlantic, Pacific, and Southeast), type of IBD (CD and UC), disease duration, comorbid conditions based on the Charlson Comorbidity Index, body mass index (BMI), smoking status, and exposure to other medications (5-ASA or derivatives, combination therapy of TPs or Methotrexate) within 3 months preceding the start of SB2.

## Statistical Analysis

Patient baseline characteristics were compared between patients with the 2 treatment courses using frequencies and percentages for categorical variables and means for continuous variables. Differences were assessed using the chi-square test, Fisher exact test, or *t* test.

For the primary outcome, we first fit an unadjusted logistic regression model for the main exposure (treatment course). We then determined whether a covariate was a confounder by adding it to the unadjusted model. If the regression coefficient for the main exposure changed more than 10%, we called the covariate as a confounder. All confounders were then added to the unadjusted model. Statistical significance was determined by a double-sided $P$ value <0.05. For the secondary outcome, we only did a descriptive analysis.

# RESULTS

We included 271 eligible patients. Table 1 presents the baseline characteristics of these patients stratified by the exposure (single switch/double switch). The 2 groups of patients were significantly different in terms of race and BMI. Specifically, the single-switch group had a higher percent of Caucasian patients (85% vs 82%) and higher BMI (mean 30.4 vs 29.0).

In the unadjusted logistic regression, treatment course was not associated with poor outcome and the unadjusted odds ratio (OR) of double vs single switch was 1.13 [95% confidence interval (CI) 0.64–1.98, $P$ = 0.6764]. In the next step, gender,

**TABLE 1.** Patient Characteristics of Our Study

| | | Overall (N = 271) | Single Switch (N = 101) | Double Switch (N = 170) | *P* |
|---|---|---|---|---|---|
| Age (mean ± SD) | | 53.00 ± 16.66 | 52.30 ± 15.72 | 53.41 ± 17.23 | 0.595 |
| Gender | Male | 248 (92) | 96 (95) | 152 (89) | 0.107 |
| | Female | 23 (8) | 5 (5) | 18 (11) | |
| Race | Caucasian | 226 (83) | 86 (85) | 140 (82) | 0.045 |
| | African American | 27 (10) | 11 (11) | 16 (9) | |
| | Others | 14 (5) | 1 (1) | 13 (8) | |
| | Unknown | 4 (1) | 3 (3) | 1 (1) | |
| IBD type | CD | 149 (55) | 58 (57) | 91 (54) | 0.533 |
| | UC | 122 (45) | 43 (43) | 79 (46) | |
| Basal Metabolic Index (mean ± SD) | | 29.55 ± 5.33 | 30.40 ± 5.46 | 29.03 ± 5.20 | 0.036 |
| Disease duration (mean ± SD) | | 13.20 ± 10.34 | 12.59 ± 10.03 | 13.57 ± 10.52 | 0.451 |
| CCI* (mean ± SD) | | 0.66 ± 1.26 | 0.59 ± 1.01 | 0.69 ± 1.38 | 0.528 |
| Smoking status | Nonsmoker | 177 (65) | 66 (65) | 111 (65) | 0.892 |
| | Active smoker | 40 (15) | 16 (16) | 24 (14) | |
| | Prior smoker | 54 (20) | 19 (19) | 35 (21) | |
| 5-ASA† use | Yes | 38 (14) | 14 (14) | 24 (14) | 0.953 |
| | No | 233 (86) | 87 (86) | 146 (86) | |
| Combination therapy | Yes | 65 (24) | 30 (30) | 35 (21) | 0.089 |
| | No | 206 (76) | 71 (70) | 135 (79) | |
| Primary outcome | Yes | 71 (26) | 25 (25) | 46 (27) | 0.676 |
| | No | 200 (74) | 76 (75) | 124 (73) | |

*Charlson Comorbidity Index.
†Amino salicylic acid.

race, and disease duration were determined to be confounders for the association between treatment course and the outcome. In the model adjusted for all these confounders, the treatment course and outcome association were still insignificant with OR 1.33 (95% CI 0.74–2.41, $P$ = 0.3432). In the adjusted model, race ($P$ = 0.0133) and disease duration (adjusted OR = 0.97 per year increase, 95% CI 0.94–1.00, $P$ = 0.0469) were found to be significant. The adjusted OR for the African Americans vs Caucasians was 3.45 (95% CI 1.48–8.07) (Table 2).

Within the single-switch group, 12.9% of patients discontinued SB2 within 1 year and 11.9% of patients continued SB2 but were not in disease remission after 1 year. Within the double-switch group, 17.6% of patients discontinued SB2 within 1 year and 9.4% of patients continued SB2 but were not in IBD remission after 1 year. Detail regarding reasons for discontinuing SB2, as well as reasons patients were not in remission, are also shown (Table 3).

## DISCUSSION

In this large nationwide retrospective cohort study in the IBD population who had a stable disease activity at baseline, we found that there was no statistically significant difference observed in regard to efficacy or safety on evaluating the single switch from IFX to SB2 vs double switch to SB2 (IFX to CP-T13 to SB2). A total of 52 (19.2%) patients from our cohort who had switched to SB2 (single or double switch) did not achieve remission at 1 year and a total of 14 (5.1%) patients had to discontinue their SB2 due to adverse events.

Biosimilars are the alternate to reference agents because of their potential cost-saving option.[11] Previous randomized controlled trial and observational studies found that nonmedical switching from IFX to CT-P13 biosimilar in stable IBD patients is safe with no concerns regarding safety, efficacy, or immunogenicity.[16,17] However, none of the studies evaluated the efficacy of switching to SB2 in stable IBD patients. In the rheumatoid arthritis population, there have been 2 studies that have evaluated the efficacy of SB2.[20,21] A randomized double blinded phase 3 transition study by Smolen et al demonstrated that the safety, immunogenicity, and efficacy profiles remained similar in patients who switched from originator IFX to SB2 vs patients who continued the IFX originator.[20] A study by Fiorino et al in IBD patients showed that switching to SB2 has the same immunogenicity.[22] But the data on safety and efficacy on switching from originator IFX to SB2 in patients with IBD are not enough.

**TABLE 2.** Adjusted Association Between Treatment Course and Drug Discontinuation Rate and/or Lack of Remission at 1 Year

| Variable (Reference) | | Adjusted OR (95% CI) | $P$ |
|---|---|---|---|
| Treatment course (single switch) | Double switch | 1.33 (0.74, 2.41) | 0.3432 |
| Gender (male) | Female | 0.54 (0.18, 1.62) | |
| Race (Caucasian) | African American | 3.45 (1.48, 8.07) | 0.0133 |
| | Others | 0.44 (0.09, 2.06) | |
| | Unknown | 3.43 (0.45, 26.23) | |
| Disease duration (per year) | | 0.97 (0.94, 1.00) | 0.0469 |

**TABLE 3.** Reasons That the Patients Were Not in Remission and/or Stopped the Drug

| | Single Switch | | Double Switch | | Total | |
|---|---|---|---|---|---|---|
| Primary Outcome Reason | N | % | N | % | N | % |
| Discontinued SB2 within 1 year | 13 | 12.9 | 30 | 17.6 | 43 | 15.9 |
| Loss of response | 9 | 8.9 | 15 | 8.8 | 24 | 8.9 |
| Hypersensitivity reaction | 2 | 2.0 | 6 | 3.5 | 8 | 3.0 |
| Refused treatment | 0 | 0.0 | 3 | 1.8 | 3 | 1.1 |
| Secondary to infection | 0 | 0.0 | 2 | 1.2 | 2 | 0.7 |
| Secondary to malignancy | 1 | 1.0 | 3 | 1.8 | 4 | 1.5 |
| Other | 1 | 1.0 | 1 | 0.6 | 2 | 0.7 |
| Continued SB2, not in remission after 1 year | 12 | 11.9 | 16 | 9.4 | 28 | 10.3 |
| Required dosage increase | 8 | 7.9 | 9 | 5.3 | 17 | 6.3 |
| Steroids utilization | 3 | 3.0 | 4 | 2.4 | 7 | 2.6 |
| Hospitalized for IBD | 1 | 1.0 | 3 | 1.8 | 4 | 1.5 |

In our study, we found that switch to SB2 (either single or double switch) was not efficacious in 71 (26%) of patients. Of those 71 patients, 19.2% did not achieve remission, 5.2% discontinued SB2 due to adverse events (such as hypersensitive reaction, infectious or malignant complications), and 2% patients either refused to continue SB2 or discontinued SB2 for other reasons. This result was similar to the data from previous studies evaluating CT-P13 switch. Loss of response was seen in 13.2%, 12.4%, and 15.7% at 1 year when patients with IBD switched from IFX to CT-P13 biosimilar.[23–25] Also, 15 patients ie, 4.8% of the total IBD patients had to discontinue CT-P13 because of adverse effects.[23]

Due to a continuing trend in the invention of newer biosimilars since 2015 and the increasing utilization of these agents, the evaluation regarding the efficacy and safety of a double switch (from originator IFX to a biosimilar and then to another biosimilar) compared to a single switch is important. Currently, to the best of our knowledge, there have been very few studies which have evaluated the efficacy of a double switch as compared to a single switch among different biosimilars in the IBD population subgroup. A study by Mazza et al showed that the double switch strategy was noninferior to the single switch strategy in the IBD population subgroup. However, this study comprised of only 52 IBD patients.[26] There have been a few studies in the past examining the effects of double and/or cross switches in various inflammatory and skin diseases. Although these studies concluded that double/cross switching does not change the efficacy or immunogenicity, none of this study was done in the IBD population subgroup which makes our study the first of its kind.[27,28] Our study demonstrated that in the IBD population subgroup, a double switch has the same efficacy when compared to single switch, after accounting for all confounding factors. Also, there was no difference in the safety of double switch when compared to a single switch. The other factors that impacted efficacy were disease duration and race. As expected, patients with longer disease duration were more like to continue the biosimilar and remain in remission. Surprisingly, African American race was associated with a higher failure rate; a finding which needs further evaluation. African American patients with CD have a higher frequency of perianal involvement along with a higher proportion of penetrating and a lower proportion of nonpenetrating, nonstricturing disease.[29] Genetic factors may also play a role as risk variants at ZNF649 and LSAMP were specific to those of African ancestry.[30]

The strengths of our study include a large retrospective cohort from the nationwide VAHS serving a geographically diverse population of more than 9 million veterans every year.[18] Furthermore, all the prescriptions filled inside the VAHS are recorded in the VA pharmacy records, which means that if a patient switched various VA stations during his/her follow-up, the prescriptions were still recorded in the central VA pharmacy records, leading to accurate capturing of the prescriptions for the biosimilars, IFX medications, and IBD medications. Furthermore, the accuracy regarding the receipt of prescriptions and the diagnosis of IBD was confirmed by a manual chart review of individual patient records minimizing the probability of misclassification to almost zero. However, our study is not without its limitations. Firstly, the data on potential confounders may be lacking due to the inherent retrospective nature of our study. Also, the prescriptions filled outside the VA may be missed by us, however the probability of this happening is very minimal as previous studies have shown that the veterans have a very good adherence to the VA pharmacy.[31–34]

## CONCLUSIONS

This nationwide retrospective cohort study, which to the best of our knowledge, is the first study evaluating the efficacy of a double switch from IFX to 2 subsequent biosimilars in the IBD population subgroup demonstrated equal efficacy of a double switch as compared to a single switch. This study will potentially aid in reassuring the gastroenterologists who have concerns regarding the safety and efficacy of switching between multiple biosimilars for treating IBD owing to the lack of data on the subject.

## DATA AVAILABILITY

Data are not publicly available.

## REFERENCES

1. Feuerstein JD, Cheifetz AS. Crohn disease: epidemiology, diagnosis, and management. *Mayo Clin Proc.* 2017;92:1088–1103.
2. Côté-Daigneault J, Bouin M, Lahaie R, et al. Biologics in inflammatory bowel disease: what are the data? *United European Gastroenterol J.* 2015;3:419–428.
3. Tracey D, Klareskog L, Sasso EH, et al. Tumor necrosis factor antagonist mechanisms of action: a comprehensive review. *Pharmacol Ther.* 2008;117:244–279.
4. Kuek A, Hazleman BL, Ostör AJ. Immune-mediated inflammatory diseases (IMIDs) and biologic therapy: a medical revolution. *Postgrad Med J.* 2007;83:251–260.
5. Schnitzler F, Fidder H, Ferrante M, et al. Long-term outcome of treatment with infliximab in 614 patients with Crohn's disease: results from a single-centre cohort. *Gut.* 2009;58:492–500.
6. Willert RP, Lawrance IC. Use of infliximab in the prevention and delay of colectomy in severe steroid dependant and refractory ulcerative colitis. *World J Gastroenterol.* 2008;14:2544–2549.
7. Putrik P, Ramiro S, Kvien TK, et al.; Working Group 'Equity in access to treatment of rheumatoid arthritis in Europe'. Inequities in access to biologic and synthetic DMARDs across 46 European countries. *Ann Rheum Dis.* 2014;73:198–206.
8. Balzola F, Bernstein C, Van Assche G. Cost-effectiveness of biological therapy for Crohn's disease: Markov cohort analyses incorporating United Kingdom patient-level cost data: commentary. *Inflamm Bowel Dis Monitor*. 2010;10:93–94.
9. Putrik P, Ramiro S, Kvien TK, et al.; Equity in Clinical Eligibility Criteria for RA treatment Working Group. Variations in criteria regulating treatment with reimbursed biologic DMARDs across European countries. Are differences related to country's wealth? *Ann Rheum Dis.* 2014;73:2010–2021.
10. Singh SC, Bagnato KM. The economic implications of biosimilars. *Am J Manag Care.* 2015;21:s331–s340.
11. Buchner AM, Schneider Y, Lichtenstein GR. Biosimilars in inflammatory bowel disease. *Am J Gastroenterol*. 2021;116:45–56. doi:10.14309/ajg.0000000000000844 [Epub ahead of print]. PMID: 33110013.
12. Papamichael K, Van Stappen T, Jairath V, et al. Pharmacological aspects of anti-TNF biosimilars in inflammatory bowel diseases. *Aliment Pharmacol Ther*. 2015;42:1158–1169.
13. Rinaudo-Gaujous M, Paul S, Tedesco ED, et al. Biosimilars are the next generation of drugs for liver and gastrointestinal diseases. *Aliment Pharmacol Ther*. 2013;38:914–924.
14. Feagan BG, Lam G, Ma C, et al. Systematic review: efficacy and safety of switching patients between reference and biosimilar infliximab. *Aliment Pharmacol Ther.* 2019;49:31–40.

15. Queiroz NS, Saad-Hossne R, FrÓes RD, et al. Discontinuation rates following a switch from a reference to a biosimilar biologic in patients with inflammatory bowel disease: a systematic review and meta-analysis. *Arq Gastroenterol.* 2020 [Epub ahead of print].
16. Bernard EJ, Fedorak RN, Jairath V. Systematic review: non-medical switching of infliximab to CT-P13 in inflammatory bowel disease. *Dig Dis Sci.* 2020;65:2354–2372.
17. Milassin Á, Fábián A, Molnár T. Switching from infliximab to biosimilar in inflammatory bowel disease: overview of the literature and perspective. *Therap Adv Gastroenterol.* 2019;12:1756284819842748.
18. U.S. Department of Veterans Affairs. Selected Veterans Health Administration Characteristics: FY 2002 to FY 2015 [online]. 2017. https://va.gov/vetdata/docs/Utilization/VHAStats_2015.xlsx. Accessed 1 May 2020.
19. Khan N, Patel D, Trivedi C, et al. Overall and comparative risk of herpes zoster with pharmacotherapy for inflammatory bowel diseases: a nationwide cohort study. *Clin Gastroenterol Hepatol.* 2018;16:1919–1927.e3.
20. Smolen JS, Choe JY, Prodanovic N, et al. Safety, immunogenicity and efficacy after switching from reference infliximab to biosimilar SB2 compared with continuing reference infliximab and SB2 in patients with rheumatoid arthritis: results of a randomised, double-blind, phase III transition study. *Ann Rheum Dis.* 2018;77:234–240.
21. Choe JY, Prodanovic N, Niebrzydowski J, et al. A randomised, double-blind, phase III study comparing SB2, an infliximab biosimilar, to the infliximab reference product Remicade in patients with moderate to severe rheumatoid arthritis despite methotrexate therapy. *Ann Rheum Dis.* 2017;76:58–64.
22. Fiorino G, Ruiz-Argüello MB, Maguregui A, et al. Full interchangeability in regard to immunogenicity between the infliximab reference biologic and biosimilars CT-P13 and SB2 in inflammatory bowel disease. *Inflamm Bowel Dis.* 2018;24:601–606.
23. Bergqvist V, Kadivar M, Molin D, et al. Switching from originator infliximab to the biosimilar CT-P13 in 313 patients with inflammatory bowel disease. *Therap Adv Gastroenterol.* 2018;11:1756284818801244.
24. Petitdidier N, Gagniere C, Rentien AL, et al. Patients' perspectives on switching from reference infliximab to CT-P13 biosimilar in patients with inflammatory bowel disease: a 12-month prospective observational cohort study [ECCO Abstract P528]. Presented at 13th Congress of ECCO, February 14–17, 2018, Vienna, Austria.
25. Guerra Veloz MF, Belvis Jiménez M, Valdes Delgado T, et al. Long-term follow up after switching from original infliximab to an infliximab biosimilar: real-world data. *Therap Adv Gastroenterol.* 2019;12:1756284819858052.
26. Mazza S, Fascì A, Casini V, et al. P360 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.
27. 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;50:1449–1456.
28. Gisondi P, Virga C, Girolomoni G. Cross-switch from CT-P13 to sb2 infliximab biosimilars in patients with chronic plaque psoriasis. Abstract P049, SPIN 2019, April 25–27, Paris, France.
29. Shi HY, Levy AN, Trivedi HD, et al. Ethnicity influences phenotype and outcomes in inflammatory bowel disease: a systematic review and meta-analysis of population-based studies. *Clin Gastroenterol Hepatol.* 2018;16:190–197.e11.
30. Brant SR, Okou DT, Simpson CL, et al. Genome-wide association study identifies African-specific susceptibility loci in African Americans with inflammatory bowel disease. *Gastroenterology.* 2017;152:206–217.e2.
31. Klein RESD. Data on the Socioeconomic Status of Veterans and on VA Program Usage. Office of the Actuary, Veterans Health Administration; 2013. http://www.va.gov/vetdata/docs/SpecialReports/sesprogramnet5-31-01.pdf. Accessed 1 May 2020.
32. Morgan RO, Petersen LA, Hasche JC, et al. VHA pharmacy use in veterans with Medicare drug coverage. *Am J Manag Care.* 2009;15:e1–e8.
33. Wolinsky FD, Miller TR, An H, et al. Dual use of Medicare and the Veterans Health Administration: are there adverse health outcomes? *BMC Health Serv Res.* 2006;6:131.
34. Veterans Health Council. Use of VA Services by Medicare-Eligible Veterans. Washington, DC: Veterans Health Council; 2013. http://www.gao.gov/assets/230/220386.pdf. Accessed 1 May 2020.