



Impact of Infliximab-dyyb (Infliximab Biosimilar) on Clinical and Patient-Reported Outcomes: 1-Year Follow-up Results from an Observational Real-World Study Among Patients with Inflammatory Bowel Disease in the US and Canada (the ONWARD Study)

Bincy Abraham · Bertus Eksteen · Khan Nedd · Hrishikesh Kale ·
Dipen Patel · Jennifer Stephens · Ahmed Shelbaya · Richard Chambers ·
Arif Soonasra

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ABSTRACT

Introduction: To date, there are limited real-world studies published on the use of infliximab-dyyb, a biosimilar to reference product (RP) infliximab approved for the treatment of moderate to severe inflammatory bowel disease (IBD), including Crohn's disease (CD) and ulcerative colitis (UC) in North America. This study examined utilization patterns and the effects of infliximab-dyyb on clinical outcomes, patient-reported outcomes (PROs), and

healthcare resource use (HCRU) in IBD patients in a real-world setting.

Methods: In this prospective, observational study, adult IBD patients in the US and Canada were recruited to initiate treatment with infliximab-dyyb and followed for 12 months. Patients included biologic-naïve users of infliximab-dyyb and patients switching from RP infliximab or other biologics to infliximab-dyyb. Partial Mayo (pMAYO) and Harvey Bradshaw Index (HBI) scores measured clinical outcomes for the UC and CD cohorts, respectively. Key PRO measures included the SIBDQ, EQ-VAS, and psychological outcomes. In addition, work productivity, HCRU, and adverse events (AEs) were assessed.

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B. Abraham
Houston Methodist Hospital, Houston, TX, USA
e-mail: BPAbraham@houstonmethodist.org

B. Eksteen
Aspen Woods Clinic, Calgary, AB, Canada
e-mail: bertuseksteen@me.com

K. Nedd
Infusion Associates, Grand Rapids, MI, USA
e-mail: khan.nedd@infusionassociates.com

H. Kale · D. Patel · J. Stephens (✉)
OPEN Health, 4350 East-West Hwy #1100, Bethesda,
MD 20814, USA
e-mail: jenniferstephens@openhealthgroup.com

H. Kale
e-mail: hrishikale@openhealthgroup.com

D. Patel
e-mail: dipenpatel@openhealthgroup.com

A. Shelbaya
Mailman School of Public Health, Columbia
University, New York, NY, USA

A. Shelbaya
Pfizer, New York, NY, USA
e-mail: ahmed.shelbaya@pfizer.com

R. Chambers · A. Soonasra
Pfizer, PA, USA
e-mail: richard.chambers@pfizer.com

A. Soonasra
e-mail: Arif.Soonasra@pfizer.com

Results: A total of 67 CD and 48 UC patients were enrolled (51% female; mean age 44 years; 87% Caucasian; mean BMI 27.9). Thirty-nine patients were biologic-naïve, 57 switched from RP infliximab, and 19 switched from other biologics. Among UC biologic-naïve users, pMAYO decreased from 5.67 to 1.09 ($p < 0.0001$) and the remission rate increased from 5.6 to 90.9% ($p = 0.0015$). For UC patients switching from RP infliximab, pMAYO decreased from 1.38 to 0.29 ($p = 0.0103$). For CD biologic-naïve users, HBI scores and remission rates did not significantly change. The scores on all the PROs significantly improved from baseline to 12 months. A total of 22 AEs occurred consistent with the known AE profile for infliximab.

Conclusions: Clinical outcomes among biologic-naïve users of infliximab-dyyb improved for UC and were maintained for CD patients. Biologic-naïve users of infliximab-dyyb showed significant improvements in PROs. Patients switching from RP infliximab to infliximab-dyyb maintained their clinical outcomes and PROs.

Trial Registration: ClinicalTrials.gov Registration Number: NCT03801928 (February 23, 2018).

Keywords: Biosimilars; Exploratory Treatment Effectiveness Study; Inflammatory bowel disease; Infliximab; Real-world outcomes

Key Summary Points

Why carry out this study?

The approval of infliximab-dyyb for use in Crohn's disease (CD) and ulcerative colitis (UC) was granted based on extrapolation.

To date, only limited real-world data have been published on the use of infliximab-dyyb and the clinical and patient-reported outcomes in inflammatory bowel disease (IBD) patients treated with infliximab-dyyb in the North American population.

In this prospective, observational study, we evaluated real-world clinical outcomes, patient-reported outcomes, and healthcare resource utilization associated with the use of infliximab-dyyb to treat inflammatory bowel disease (IBD) among biologic-naïve patients and patients switching from reference product (RP) infliximab or other biologics.

What was learned from the study?

Among biologic-naïve patients, clinical outcomes improved significantly for UC patients and were maintained for CD ones.

Consistent with findings across other immunological diseases, our study found that patients who switched from RP infliximab to infliximab-dyyb maintained clinical outcomes and remission status.

Patient-reported quality-of-life and work productivity outcomes improved among biologic-naïve patients and were maintained for patients switched from RP infliximab.

Although the number of patients in this study is small and direct comparisons cannot be made, adverse events occurred at a rate consistent with the known adverse event profile for RP infliximab.

INTRODUCTION

Crohn's disease (CD) and ulcerative colitis (UC) are collectively known as inflammatory bowel disease (IBD) [1]. Both conditions are characterized by chronic inflammation of the bowel, a relapsing and remitting clinical course, lifelong medication use, and often significant morbidity.

The advent of biologics, such as infliximab, in the treatment of IBD has progressively changed the therapeutic landscape in this disease. Several studies of infliximab have demonstrated a benefit for disease outcome and control, a decrease in hospitalizations, and

improvements in quality of life [2–5]. Despite the clinical benefits of infliximab for IBD, cost remains a concern; therefore, biosimilars that are less expensive than reference product (RP) biologics but have similar effectiveness have been of high interest to payers and managed care organizations.[6].

Biosimilars are biological medicines that were developed to be highly similar to originator or reference medicines, and to offer the potential of lower treatment cost [7]. The introduction of biosimilars offers an opportunity for increased patient access and decreased health expenditures across a number of immunologic indications. Biosimilar infliximab-dyyb (also known as CT-P13, branded as Inflectra[®]) was approved in the US and Canada in 2016 for IBD as a biosimilar to RP infliximab (branded as Remicade[®]) based on the concept of extrapolation [8].

Recently, a few studies outside North America have compared safety outcomes, such as hepatitis and tuberculosis infections, and the pharmacokinetic profile of infliximab biosimilar and the originator in the real-world IBD population. These studies found that infliximab biosimilar had similar safety and pharmacokinetic profile in real-world settings [9, 10]. Additional real-world studies from outside North America, where approval for infliximab-dyyb for IBD occurred before 2016, suggest no clinically meaningful differences in safety and effectiveness when patients either remain on RP infliximab or switch to an infliximab biosimilar [11–17].

To date, only limited real-world data have been published on the use of infliximab-dyyb, and the clinical and patient-reported outcomes in IBD patients treated with infliximab-dyyb, in the North American population. Post-approval non-interventional studies evaluating comparative outcomes can play a key role in building a real-world evidence base to help inform clinical practices and policy decisions [18]. Therefore, the goal of this study was to understand real-world treatment patterns of infliximab-dyyb and to assess its effects on clinical outcomes, patient-reported outcomes (PROs), and health-care resource use in adult UC and CD patients

treated with infliximab-dyyb in a real-world North American setting.

METHODS

Study Design and Participants

This was a prospective observational study performed in 24 sites across the US and Canada. A geographically dispersed group of gastroenterologists in these countries recruited study patients. Physician inclusion and exclusion criteria are described below.

Physician inclusion criteria

- Is certified to practice in the US or Canada;
- Agrees to study rules including resolution of data queries, including missing data;
- Routinely uses standard laboratory testing to monitor patient health;
- Has access to certified laboratory for basic laboratory testing;
- Can make available medical records and proper documentation for patients.

Physician exclusion criteria

- Is unwilling or unable to follow study procedures;
- Is unwilling to prescribe biosimilars.

Physicians recruited adult (≥ 18 years) patients initiating treatment with infliximab-dyyb for IBD (CD or UC) between February 2018 and February 2019. Patients were enrolled within 2 weeks of their first infusion with infliximab-dyyb. Patient inclusion and exclusion criteria are described below.

Patient inclusion criteria

- Has a confirmed diagnosis of UC or CD;
- Has evidence of a personally signed and dated informed consent document indicating that they have been informed of all pertinent aspects of the study;
- Is eligible to receive infliximab-dyyb for the treatment of their disease per approved drug label (patients with fistula or stoma are eligible).

Patient exclusion criteria (any of the below)

- Is less than 18 years old at the time of consent;
- Previously failed treatment with RP infliximab or infliximab-dyyb;
- Has reported contraindications for RP infliximab or infliximab-dyyb;
- Has a known hypersensitivity (including severe, acute infusion reactions) to infliximab, its excipients, or other murine proteins;
- Has difficulty reading or understanding the study consent or questionnaires.

Recruited individuals included IBD patients with no previous biologics use (biologic-naïve users), IBD patients switching from RP infliximab to infliximab-dyyb, and IBD patients switching to infliximab-dyyb from other biologics. Enrolled patients were followed prospectively for 12 months after initiating infliximab-dyyb treatment. There were no protocol-required medical procedures for this study.

As this was an observational study, the decision to treat a patient with infliximab-dyyb was made prior to that patient's enrollment. Recruited physicians and/or their assigned staff were responsible for: patient identification, qualification, and selection; patient interviews; exam recording; data abstraction; and completion of patient case report forms. Study protocol and informed consent were reviewed and approved by the institutional review board at each site. Written informed consent was obtained from all patients enrolled in the study. Full details of institutional review boards that approved the study, along with relevant reference numbers, can be found in the Supplementary Material.

Study Measures

At baseline (the time of initiating infliximab-dyyb treatment), patient demographics (sex, age, race/ethnicity, insurance status) and clinical characteristics [body mass index (BMI), Charlson Comorbidity Index score, IBD type, duration of disease, and reason for treatment

initiation] were recorded. Information about drug utilization patterns, clinical outcomes, PROs, and healthcare resource use was collected at infusion visits corresponding with the baseline visit and the 3-month, 6-month, and 12-month post-enrollment follow-up visits.

To describe infliximab-dyyb utilization patterns, the study assessed patients' history of previous biologics use, patients' reasons for initiating infliximab-dyyb, and discontinuation rates.

Clinical endpoints included disease remission status and disease response to treatment, as defined in disease-specific composite measures. In CD patients, disease remission was defined as a Harvey-Bradshaw Index (HBI) score of < 5 and response to treatment was defined as a reduction from baseline HBI ≥ 3 points. In UC patients, disease remission was defined as a Partial Mayo Score (pMAYO) score of < 3 , and response to treatment was defined as a reduction from baseline pMAYO ≥ 3 points.

PROs measures were the Short Inflammatory Bowel Disease Questionnaire (SIBDQ); the EuroQol Visual Analogue Scale (EQ-VAS), the Treatment Satisfaction Questionnaire for Medication (TSQM), the Work Productivity and Activity Impairment (WPAI) questionnaire, and, to assess psychological outcomes, the General Anxiety Disorder-7 (GAD-7) questionnaire and the Patient Health Questionnaire-8 (PHQ-8; for depression).

Healthcare resource use measurements included the presence of IBD-related hospitalizations, presence of emergency department (ED) visits, and number of gastroenterologist visits. Visits recorded as part of resource use excluded visits to receive infliximab-dyyb infusions.

Adverse events (AEs) were monitored from each patient's first infusion of infliximab-dyyb until their last follow-up visit. Enrolling physicians classified AEs as related to or unrelated to study treatment.

Statistical Analysis

Baseline demographic and clinical characteristics of biologic-naïve patients, patients

switching from RP infliximab, and patients switching from other biologics were compared using the chi-square test or Fisher's exact test (in case of a small sample size) for categorical variables (e.g., gender). The analysis of variance (ANOVA) or the Wilcoxon rank sum test was used to compare continuous variables (e.g., BMI).

Changes in outcomes over time from baseline were calculated using a mixed model for repeated measures (MMRM) for continuous outcomes and a generalized estimating equation (GEE) for categorical outcomes, accounting for the repeated nature of the data. Given the overall sample size, all analytical models were bivariate in nature, which included a specific outcome of interest as a dependent variable and a study visit as an independent variable. All analyses were conducted at an α level of 0.05 using SAS v.9.4. (SAS Institute, Cary, NC, USA.)

RESULTS

From February 2018 to February 2020, 115 IBD patients (67 CD and 48 UC) initiated infliximab-dyyb treatment and were followed for 12 months (Fig. 1). Of 115 patients who completed the baseline visit (visit 1), 109 completed the 3-month visit (2), 99 completed the 6-month visit (3), and 84 completed the 12-month visit (4). Among the CD cohort, 20 (29.9%) had B1 (non-stricturing, non-penetrating disease). Among the UC cohort, 28 (58.3%) had E3 extensive disease. Overall, 24 (20.9%) patients had a history of IBD-related surgery. A total of 66 (57.3%) patients received endoscopy at baseline (Table 1), and 37 had endoscopy during the follow-up period. Of 66 patients, 60 patients (90.9%) received colonoscopy, and 6 (9.1%) received sigmoidoscopy. The most common reasons for endoscopy were routine surveillance ($n = 22$; 33.3%), diagnosis ($n = 18$; 27%), and assessment for disease activity ($n = 22$; 33.3%).

Infliximab-dyyb Utilization Patterns

Of 115 patients, 39 were biologic naïve, 57 were switched from RP infliximab, and 19 were

switched from other biologics. Patient demographics are summarized in Table 1. There were no statistically significant demographic differences between groups except in BMI.

In patients switching from RP infliximab, the majority (80.4%) of patient reasons for infliximab-dyyb treatment initiation were related to reimbursement, insurance coverage, or out-of-pocket costs. In biologic-naïve patients, the most frequent reasons for infliximab-dyyb treatment initiation were targeted therapy (64.1%), improved efficacy (15.4%), and new drug availability (12.8%).

Thirty-three patients had dose escalation at some point during the follow-up [16 (41%) in biologic naïve, 12 (21%) in patients switching from RP infliximab, and 5 (26%) in patients switching from other biologics]. A total of 13 patients had dose reductions at any time during the follow-up period [9 (23%) in biologic naïve, 3 (5%) in patients switching from RP infliximab, and 1 (5%) in patients switching from other biologics.]

Thirty-one patients in total (27%) did not reach 12 months' follow-up. Six patients discontinued due to an AE, 1 discontinued due to lack of efficacy, 17 were lost to follow-up, 3 patients chose to withdraw, and 4 patients discontinued for other reasons. The 6 AEs that caused study withdrawal were 1 development of antidrug antibodies, 1 case of community-acquired pneumonia, 1 hypersensitivity reaction, 1 liver abscess, 1 case of drug-induced lupus, and 1 case of psoriasisiform dermatitis and joint pain.

Clinical Results

Descriptive results for clinical outcomes are presented in Table 2. Figures depicting remission and response results over time are presented in the Supplementary Material. In CD patients during the follow-up period, HBI scores did not change significantly. Mean (SD) HBI scores were 3.45 (3.04) at baseline, 3.11 (3.27) at 3 months' follow-up, and 2.98 (2.61) at 12 months' follow-up ($p = 0.3988$).

In UC patients, the mean (SD) baseline pMAYO score was 3.85 (3.05). The pMAYO

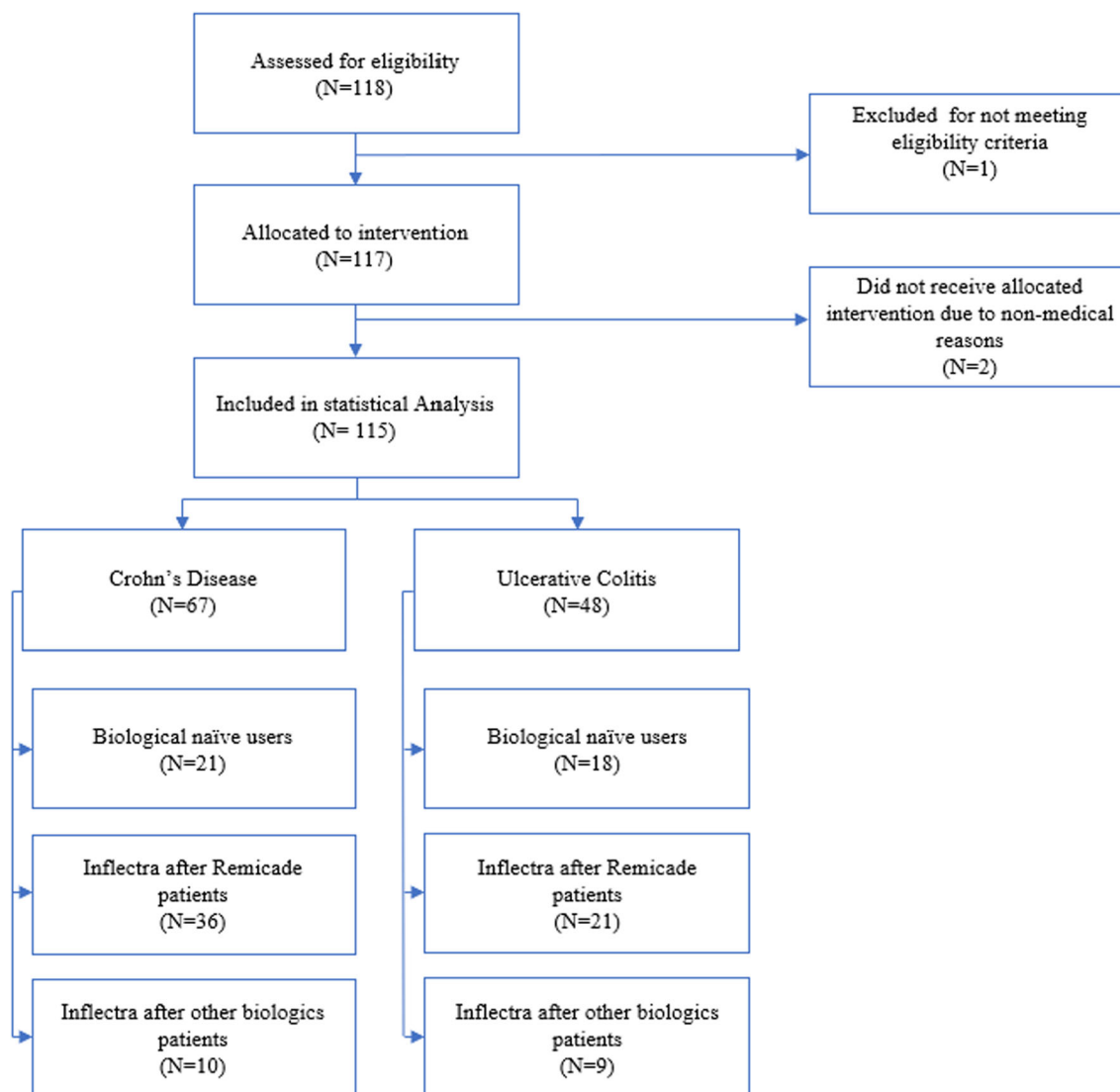


Fig. 1 Patient selection in this study

score improved significantly, to 1.44 (1.94) at 3 months' follow-up and 0.90 (1.47) at 12 months' follow-up ($p < 0.0001$). Among UC patients who were biologic-naïve, pMAYO scores improved significantly over the course of the intervention, from a mean (SD) of 5.67 (2.25) at baseline to 1.41 (1.42) at 3 months' follow-up and 1.09 (1.22) at 12 months' follow-up ($p < 0.0001$). Among the subgroup of UC patients switched from RP infliximab, the pMAYO score did not change significantly over the course of the intervention, from a mean

(SD) of 1.38 (1.83) at baseline to 0.56 (1.20) at 3 months' follow-up and to 0.29 (0.85) at 12 months' follow-up ($p = 0.0103$).

At baseline, 35.4% of enrolled UC patients were classified as in remission (Table 2). At 12 months' follow-up, 87.1% of enrolled UC patients were classified as in remission ($p < 0.0001$). In UC patients who were biologic naïve, 5.6% were classified as in remission at baseline. This proportion increased significantly at 12 months' follow-up to 90.9% ($p = 0.0015$). UC patients switched from RP infliximab

Table 1 Patient demographic and clinical characteristics

	All (<i>n</i> = 115)	Biologic-naïve users (<i>n</i> = 39)	Switched from RP infliximab (<i>n</i> = 57)	Switched from other biologics ^a (<i>n</i> = 19)
Sex [<i>n</i> (%)]				
Female	59 (51.3%)	16 (41.0%)	31 (54.4%)	12 (63.2%)
Male	56 (48.7%)	23 (59.0%)	26 (45.6%)	7 (36.8%)
Age (years) [mean (SD)]	44.25 (16.29)	45.97 (17.65)	42.79 (15.43)	45.00 (16.34)
BMI [mean (SD)]*	27.86 (6.00)	25.99 (4.26)	28.57 (6.99)	29.45 (4.84)
Race/ethnicity [<i>n</i> (%)]				
Asian	3 (2.6%)	1 (2.6%)	1 (1.8%)	1 (5.3%)
African American	8 (7.0%)	2 (5.1%)	4 (7.0%)	2 (10.5%)
Hispanic or Latino	3 (2.6%)	2 (5.1%)	0 (0.0%)	1 (5.3%)
Caucasian	100 (87.0%)	34 (87.2%)	51 (89.5%)	15 (78.9%)
Other	1 (0.9%)	0 (0.0%)	1 (1.8%)	0 (0.0%)
Insurance status [<i>n</i> (%)]*				
Canada Medicare	16 (13.9%)	8 (20.5%)	0 (0.0%)	8 (42.1%)
HMO	46 (40.0%)	4 (10.3%)	40 (70.2%)	2 (10.5%)
Medicare/Medicaid	25 (21.7%)	9 (23.1%)	12 (21.1%)	4 (21.1%)
POS	1 (0.9%)	0 (0.0%)	0 (0.0%)	1 (5.3%)
PPO	26 (22.6%)	18 (46.2%)	4 (7.0%)	4 (21.1%)
Unknown	1 (0.9%)	0 (0.0%)	1 (1.8%)	0 (0.0%)
Charlson Comorbidity Index (CCI)				
CCI [mean (SD)]	0.30 (0.98)	0.56 (1.43)	0.19 (0.69)	0.11 (0.32)
0 [<i>n</i> (%)]	101 (87.8%)	32 (82.1%)	52 (91.2%)	17 (89.5%)
1	4 (3.5%)	1 (2.6%)	1 (1.8%)	2 (10.5%)
2	6 (5.2%)	3 (7.7%)	3 (5.3%)	0 (0.0%)
3 +	4 (3.5%)	3 (7.7%)	1 (1.8%)	0 (0.0%)
IBD type [<i>n</i> (%)]				
CD	67 (58.3%)	21 (53.8%)	36 (63.2%)	10 (52.6%)
UC	48 (41.7%)	18 (46.2%)	21 (36.8%)	9 (47.4%)
Duration of disease (years) [mean (SD)]	8.24 (8.34)	5.92 (6.20)	9.88 (9.48)	8.63 (8.22)
Behavior of disease (CD cohort only)	(<i>n</i> = 67)	(<i>n</i> = 21)	(<i>n</i> = 36)	(<i>n</i> = 10)
B1 Non-stricturing, non-penetrating	20 (29.9%)	11 (52.4%)	3 (8.3%)	6 (60.0%)
B2 Stricturing	11 (16.4%)	4 (19.0%)	6 (16.7%)	1 (10.0%)

Table 1 continued

	All (<i>n</i> = 115)	Biologic-naïve users (<i>n</i> = 39)	Switched from RP infliximab (<i>n</i> = 57)	Switched from other biologics ^a (<i>n</i> = 19)
B3 Penetrating	5 (7.5%)	4 (19.0%)	0 (0.0%)	1 (10.0%)
P Perianal disease	3 (4.5%)	0 (0.0%)	2 (5.6%)	1 (10.0%)
Unknown	28 (41.8%)	2 (9.5%)	25 (69.4%)	1 (10.0%)
Age at onset in years (CD cohort only)	(<i>n</i> = 67)	(<i>n</i> = 21)	(<i>n</i> = 36)	(<i>n</i> = 10)
16 or younger	8 (11.9%)	2 (9.5%)	4 (11.1%)	2 (20.0%)
17–40	35 (52.2%)	11 (52.4%)	18 (50.0%)	6 (60.0%)
Over 40	17 (25.4%)	8 (38.1%)	7 (19.4%)	2 (20.0%)
Unknown	7 (10.4%)	0 (0.0%)	7 (19.4%)	0 (0.0%)
Location (CD cohort only)	(<i>n</i> = 67)	(<i>n</i> = 21)	(<i>n</i> = 36)	(<i>n</i> = 10)
L1 Terminal ileum	22 (32.8%)	7 (33.3%)	12 (33.3%)	3 (30.0%)
L2 Colon	22 (32.8%)	6 (28.6%)	12 (33.3%)	4 (40.0%)
L3 Ileocolon	18 (26.9%)	8 (38.1%)	7 (19.4%)	3 (30.0%)
L4 Upper GI	1 (1.5%)	0 (0.0%)	1 (2.8%)	0 (0.0%)
Unknown	4 (6.0%)	0 (0.0%)	4 (11.1%)	0 (0.0%)
Extent of disease (UC cohort only)	(<i>n</i> = 48)	(<i>n</i> = 18)	(<i>n</i> = 21)	(<i>n</i> = 9)
E1 Ulcerative proctitis	5 (10.4%)	3 (16.7%)	1 (4.8%)	1 (11.1%)
E2 Left-sided UC	13 (27.1%)	6 (33.3%)	3 (14.3%)	4 (44.4%)
E3 Extensive UC	28 (58.3%)	8 (44.4%)	16 (76.2%)	4 (44.4%)
Unknown	2 (4.2%)	1 (5.6%)	1 (4.8%)	0 (0.0%)
IBD-related surgery (yes)	24 (20.9%)	4 (10.3%)	17 (29.8%)	3 (15.8%)
Reason for surgery				
Management of IBD	9 (37.5%)	4 (100.0%)	4 (23.5%)	1 (33.3%)
Management of side effects/ adverse experiences related to IBD	13 (54.2%)	0 (0.0%)	11 (64.7%)	2 (66.7%)
Unknown	2 (8.3%)	0 (0.0%)	2 (11.8%)	0 (0.0%)
Use of corticosteroids (yes)	8 (7.0%)	5 (62.5%)	1 (12.5%)	2 (25.0%)
Endoscopy at baseline (yes)	66 (57.4%)	33 (84.6%)	19 (33.3%)	14 (73.7%)

BMI body mass index, *CCI* Charlson Comorbidity Index, *CD* Crohn's disease, *HMO* health maintenance organization, *IBD* inflammatory bowel disease, *POS* point-of-service, *PPO* preferred provider organization, *SD* standard deviation, *UC* ulcerative colitis

*Indicates statistically significant difference for the variable across patient groups

^aAnother biologic included anti-TNF (e.g., adalimumab) or others (e.g., vedolizumab)

indicated an improving trend for rate of remission from 71.4% at baseline to 94.1% at 12 months' follow-up; however, it was not statistically significant ($p = 0.1007$).

Of the enrolled CD patients, 72.7% were classified as in remission at baseline (Table 2). After 12 months of infliximab-dyyb treatment, 77.1% of CD patients were classified as in remission ($p = 0.8011$). In CD patients switched from RP infliximab, the remission rate was maintained over the duration of the study from a baseline rate of 77.8% to a 12-month remission rate of 76.7% ($p = 0.1077$). In CD patients, 30.8% of biologic-naïve users and 6.7% of those who switched from RP infliximab demonstrated a clinical response to treatment.

Patient-Reported Outcomes

PROs improved significantly from baseline to 12 months' follow-up in nearly all questionnaires administered to participants. Descriptive results at each visit are presented in Table 3. Results for changes from baseline from the MMRM model are depicted in Figs. 2 and 3. Higher scores reflect better quality of life in all the instruments except the WPAI, GAD-7, and PHQ-8, where lower scores reflect better quality of life. SIBDQ, EQ-VAS, all domains of WPAI, the effectiveness domain of TSQM, GAD-7, and PHQ-8 scores significantly improved from baseline to 12 months' follow-up. Significant improvements were observed in SIBDQ scores from baseline to 12 months in each cohort (all $p < 0.05$). The SIBDQ score for the IBD cohort increased by 7 points at 3 months and by 9 points at the 12-month visit. Biologic-naïve users showed an improvement of 16 points, whereas patients who switched from RP infliximab showed an increase of 3 points (Fig. 2). EQ-VAS scores improved in the cohort of all enrolled patients compared to baseline (9-point improvement; $p < 0.001$), in biologic-naïve users (14-point improvement; $p = 0.002$), and in switchers from RP infliximab (5-point improvement; $p = 0.010$) (Fig. 2).

IBD-related impairment in daily activities, measured by the WPAI, decreased significantly in the cohort of all patients and in biologic-naïve users (all $p < 0.05$) (Table 3). Results from

MMRM analysis indicated that the WPAI score decreased by 12 points at the 3-month visit and by 20 points at the 12-month visit for the IBD cohort. Biologic-naïve users showed a decrease of 25 points at the 3-month visit and 36 points at the 12-month visit. Switchers from RP infliximab had a decrease of 8 points by 12 months (Fig. 3). Patient-perceived treatment effectiveness, measured by the TSQM, also improved significantly in the cohort of all patients and in biologic-naïve users (both $p < 0.001$) (Table 3). Results from the MMRM model indicated that patient-perceived treatment effectiveness increased by 6 points at 3 months and 13 points at 12 months for the IBD cohort. Biologic-naïve users showed an increase of 17 points at 3 months and 26 points at 12 months. Switchers from RP infliximab had an increase of 2 points (Fig. 3). The PHQ-8 and GAD-7 scores decreased over time for the IBD cohort and for biologic-naïve patients, indicating improved quality of life (Table 3). Results from an MMRM analysis indicated that, for the IBD cohort, PHQ-8 and GAD-7 scores decreased by 3.15 and 2.65 at 12 months, respectively. Biologic-naïve users showed a decrease of 4.54 points and 2.65 points for the PHQ-8 and GAD-7 at 12 months, respectively. Switchers from RP infliximab had a decrease of 1.21 for the PHQ-8 and 0.39 for the GAD-7 at 12 months (Fig. 3).

Healthcare Resource Use

An IBD-related hospitalization was recorded in 9.6% of patients within the baseline period and in 1.2% of patients within the 12-month observation period (Table 4). An ED visit was recorded in 10.4% of patients within the baseline period and in 3.6% within the 12-month observation period. The mean (SD) number of non-infusion gastroenterologist visits was 0.78 (1.67) visits per patient during the baseline period and 0.69 (0.78) visits per patient at 12 months.

Adverse Events

Fifty-nine AEs were reported in 40 (40/115; 34.8%) patients. Of these, 29 (49.2%) were mild,

Table 2 Clinical outcomes at baseline and follow-up in IBD patients administered Infliximab-dyyb

		Baseline (<i>n</i> = 115)	3 months (<i>n</i> = 109)	6 months (<i>n</i> = 99)	12 months (<i>n</i> = 84)	<i>p</i> value
All infliximab-dyyb users						
All IBD						
Remission	<i>n</i> (%)	65 (57.0%)	81 (76.4%)	68 (73.9%)	64 (81.0%)	0.0005
Response ^a	<i>n</i> (%)	–	28 (26.4%)	29 (31.5%)	19 (24.1%)	0.6117
UC patients						
Remission	<i>n</i> (%)	17 (35.4%)	34 (79.1%)	29 (78.4%)	27 (87.1%)	< 0.0001
Response	<i>n</i> (%)	–	18 (41.9%)	18 (48.6%)	12 (38.7%)	0.9792
CD patients						
Remission	<i>n</i> (%)	48 (72.7%)	47 (74.6%)	39 (70.9%)	37 (77.1%)	0.8011
Response	<i>n</i> (%)	–	10 (15.9%)	11 (20.0%)	7 (14.6%)	620.5068
Biologic-naïve users of infliximab-dyyb						
All IBD						
Remission	<i>n</i> (%)	14 (36.8%)	30 (83.3%)	24 (75.0%)	21 (87.5%)	0.0002
Response	<i>n</i> (%)	–	16 (44.4%)	18 (56.3%)	12 (50.0%)	0.3447
UC patients						
Remission	<i>n</i> (%)	1 (5.6%)	14 (82.4%)	12 (75.0%)	10 (90.9%)	0.0015
Response	<i>n</i> (%)	–	12 (70.6%)	13 (81.3%)	8 (72.7%)	0.7079
CD patients						
Remission	<i>n</i> (%)	13 (65.0%)	16 (84.2%)	12 (75.0%)	11 (84.6%)	0.1619
Response	<i>n</i> (%)	–	4 (21.1%)	5 (31.3%)	4 (30.8%)	0.4277
Patients switching from RP infliximab						
All IBD						
Remission	<i>n</i> (%)	43 (75.4%)	39 (73.6%)	38 (77.6%)	39 (83.0%)	0.3510
Response	<i>n</i> (%)	–	5 (9.4%)	6 (12.2%)	4 (8.5%)	0.3806
UC patients						
Remission	<i>n</i> (%)	15 (71.4%)	16 (88.9%)	14 (93.3%)	16 (94.1%)	0.1007
Response	<i>n</i> (%)	–	2 (11.1%)	2 (13.3%)	2 (11.8%)	0.4724
CD patients						
Remission	<i>n</i> (%)	28 (77.8%)	23 (65.7%)	24 (70.6%)	23 (76.7%)	0.1077
Response	<i>n</i> (%)	–	3 (8.6%)	4 (11.8%)	2 (6.7%)	0.4036

p values were obtained from generalized estimating equations (GEEs)

CD Crohn's disease, IBD inflammatory bowel disease, RP reference product, UC = ulcerative colitis

^aResponse was measured as change from baseline; therefore, values for baseline visit are not applicable

Table 3 Patient-reported outcomes results at baseline and follow-up in IBD patients administered Infliximab-dyyb

		Baseline (<i>n</i> = 115)	3 months (<i>n</i> = 109)	6 months (<i>n</i> = 99)	12 months (<i>n</i> = 84)	<i>p</i> value
All infliximab-dyyb users						
Health-related quality of life						
SIBDQ	Mean (SD)	43.77 (14.13)	50.41 (11.82)	52.75 (10.91)	54.47 (11.06)	< 0.0001
EQ-VAS score	Mean (SD)	73.11 (19.38)	78.83 (16.90)	81.56 (14.82)	83.79 (14.55)	< 0.0001
Work productivity						
Absenteeism score %	Mean (SD)	12.39 (25.53)	4.33 (14.93)	3.84 (13.68)	2.23 (9.30)	0.0059
Presenteeism score %	Mean (SD)	31.38 (30.97)	20.44 (26.68)	15.34 (23.74)	10.68 (19.55)	< 0.0001
Overall work impairment score %	Mean (SD)	35.34 (32.53)	22.08 (27.74)	18.82 (26.67)	11.78 (21.03)	< 0.0001
Daily activity impairment score %	Mean (SD)	37.79 (31.62)	26.98 (27.99)	20.16 (25.19)	15.63 (25.60)	< 0.0001
Treatment satisfaction						
TSQM effectiveness	Mean (SD)	63.94 (26.00)	68.69 (26.65)	72.25 (25.35)	76.56 (25.44)	0.0035
TSQM side effects	Mean (SD)	74.88 (26.11)	78.75 (25.03)	81.51 (20.17)	84.54 (19.11)	0.0523
TSQM convenience	Mean (SD)	75.19 (18.88)	77.67 (16.84)	78.55 (16.54)	77.61 (15.20)	0.3524
Psychological outcomes						
GAD-7 score	Mean (SD)	5.37 (5.32)	4.14 (4.60)	3.84 (4.53)	3.14 (3.69)	0.0005
PHQ-8 score	Mean (SD)	7.82 (6.29)	5.70 (5.14)	4.74 (4.43)	3.90 (4.08)	< 0.0001
Biologic-naïve users of infliximab-dyyb						
Health-related quality of life						
SIBDQ	Mean (SD)	39.85 (14.20)	51.49 (13.09)	54.76 (10.30)	57.80 (9.76)	< 0.0001
EQ-VAS score	Mean (SD)	68.05 (20.71)	78.54 (18.49)	82.52 (15.27)	85.36 (13.30)	0.0135
Work productivity						
Absenteeism score %	Mean (SD)	19.41 (32.33)	2.30 (5.66)	6.59 (22.15)	4.50 (15.66)	0.811
Presenteeism score %	Mean (SD)	43.81 (36.53)	16.19 (22.69)	12.38 (21.66)	7.37 (18.81)	0.0008
Overall work impairment score %	Mean (SD)	51.49 (37.20)	15.89 (24.31)	19.00 (28.57)	8.89 (23.24)	0.0038
Daily activity impairment score %	Mean (SD)	46.58 (31.99)	21.62 (25.00)	17.50 (23.56)	9.60 (19.89)	< 0.0001
Treatment satisfaction						
TSQM effectiveness	Mean (SD)	56.31 (22.05)	73.20 (24.54)	74.24 (27.11)	81.33 (22.86)	0.0003
TSQM side effects	Mean (SD)	70.63 (23.86)	85.14 (20.05)	89.69 (17.70)	92.19 (19.36)	0.0020
TSQM convenience	Mean (SD)	74.39 (17.28)	78.15 (15.69)	75.76 (18.95)	77.00 (17.78)	0.3924

Table 3 continued

		Baseline (<i>n</i> = 115)	3 months (<i>n</i> = 109)	6 months (<i>n</i> = 99)	12 months (<i>n</i> = 84)	<i>p</i> value
Psychological outcomes						
GAD-7 score	Mean (SD)	5.82 (5.68)	3.84 (4.75)	2.64 (4.69)	2.48 (4.46)	0.0001
PHQ-8 score	Mean (SD)	8.59 (7.00)	4.89 (5.07)	3.64 (4.59)	3.00 (4.71)	0.0009
Patients switching from RP infliximab						
Health-related quality of life						
SIBDQ	Mean (SD)	49.16 (12.16)	51.06 (10.13)	52.02 (11.31)	54.36 (11.35)	0.1348
EQ-VAS score	Mean (SD)	78.49 (16.74)	80.13 (17.02)	81.39 (14.48)	84.77 (12.79)	0.0675
Work productivity						
Absenteeism score %	Mean (SD)	5.84 (11.66)	1.78 (5.83)	2.86 (6.52)	0.57 (2.85)	0.0262
Presenteeism score %	Mean (SD)	22.70 (23.53)	19.47 (24.49)	17.63 (24.87)	11.71 (20.51)	0.1565
Overall work impairment score %	Mean (SD)	25.71 (25.91)	20.73 (24.92)	19.33 (26.17)	12.21 (20.48)	0.0342
Daily activity impairment score %	Mean (SD)	27.14 (27.28)	25.93 (27.71)	22.35 (26.48)	16.09 (27.45)	0.3327
Treatment satisfaction						
TSQM effectiveness	Mean (SD)	73.46 (24.39)	66.98 (27.78)	72.62 (25.97)	76.27 (24.84)	0.2358
TSQM side effects	Mean (SD)	81.09 (23.43)	79.73 (23.53)	76.75 (21.29)	80.14 (19.07)	0.977
TSQM convenience	Mean (SD)	78.43 (19.50)	78.45 (17.65)	82.87 (13.15)	79.67 (14.11)	0.1742
Psychological outcomes						
GAD-7 score	Mean (SD)	4.33 (4.24)	4.17 (4.41)	4.69 (4.51)	3.49 (3.44)	0.2876
PHQ-8 score	Mean (SD)	5.86 (4.87)	5.31 (4.39)	5.24 (4.25)	3.98 (3.36)	0.0807

p Values were obtained from mixed model for repeated measures (MMRM)

IBD inflammatory bowel disease, *SIBDQ* Short Inflammatory Bowel Disease Questionnaire, *EQ-VAS* EuroQol-Visual Analogue Scale questionnaire, *WPAI* Work Productivity and Activity Index, *TSQM* Treatment Satisfaction Questionnaire for Medication, *GAD-7* General Anxiety Disorder-7, *PHQ-8-8-item* Patient Health Questionnaire

23 (39.0%) were moderate, and 7 (11.9%) were severe. Twenty-two AEs occurred that were classified by the enrolling physician as related to study treatment. The most frequently reported AEs related to study treatment were: gastrointestinal disorders (*n* = 8; 6.95%); infusion-related reactions (*n* = 4; 3.5%); platelet, bleeding, and clotting disorders (*n* = 2; 1.72%); and hypersensitivity reactions (*n* = 2; 1.72%). Of

severe AEs that occurred during the study period, all but one were deemed by the enrolling physician to be unrelated to the intervention. The severe AE related to infliximab-dyyb treatment was a severe hypersensitivity reaction. Overall, AEs occurred at rates consistent with the known AE profile for infliximab.

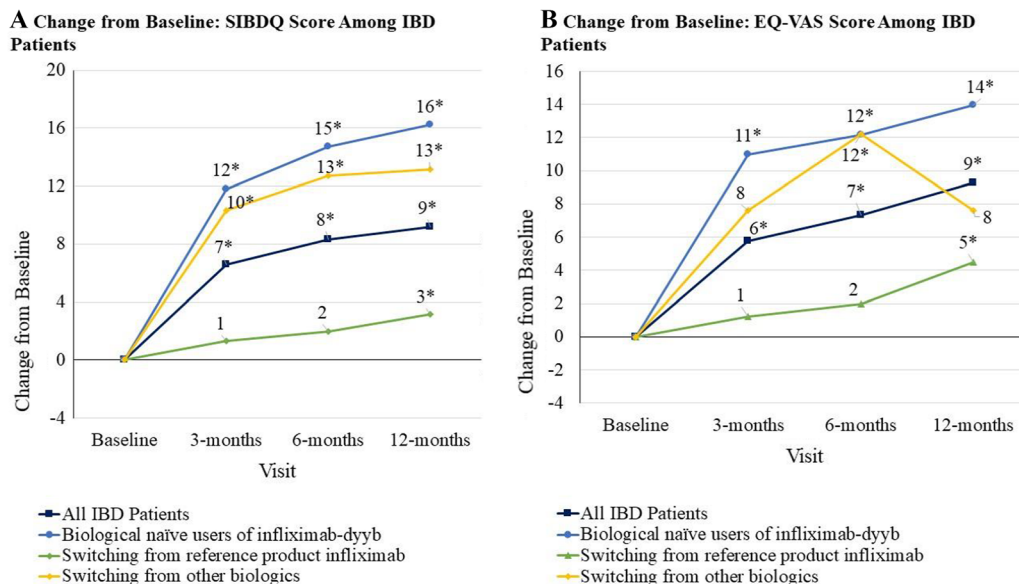


Fig. 2 Changes from baseline in SIBDQ and EQ-VAS scores. *Denotes statistically significant ($p < 0.05$) change from mixed model for repeated measures (MMRM). *EQ-*

VAS EuroQol Visual Analogue Scale, *IBD* inflammatory bowel disease, *SIBDQ* Short Inflammatory Bowel Disease Questionnaire

DISCUSSION

This study assessed the effectiveness of infliximab-dyyb among IBD patients in terms of clinical outcomes, quality of life, work productivity, and resource utilization. These outcomes were examined among patients who switched from RP infliximab or other biologics and biologic-naïve patients initiating infliximab. Overall, this study showed positive response and remission outcomes in biologic-naïve IBD patients. Clinical response was observed in 72.7% of UC and 30.8% of CD biologic-naïve users initiating infliximab-dyyb treatment. However, 65.0% of CD biologic-naïve users were already in remission at baseline (scoring < 5 on HBI), which limited their room for clinical response (defined as an HBI improvement of ≥ 3 points). At the end of 12 months' follow-up, 90.9% of UC and 84.6% of CD biologic-naïve users were in remission. These rates are consistent with other studies of infliximab-dyyb as a patient's first biologic therapy for IBD. A 2017 meta-analysis by Komaki et al. reviewed 11 observational studies of patients with active CD or UC treated with CT-P13 (switched from RP infliximab or biologic naïve) [19]. Consistent

with our findings, pooled clinical response rates at 24–30 weeks were 77% in UC and 77% in CD, and pooled clinical remission rates were 42% in UC and 60% in CD. Several other studies have suggested that infliximab-dyyb is effective and safe in biologic-naïve patients [20–24]. A large comparative study of infliximab-naïve patients with IBD initiating either RP infliximab or CT-P13 concluded that infliximab-dyyb was equally efficacious, with no clinically meaningful differences [25].

Our findings on clinical outcomes among patients switching from RP infliximab to infliximab-dyyb are consistent with those of prior studies [13, 16, 22, 26–39]. In the present study, at 12 months' follow-up, clinical remission was observed in 94.1% of UC and 76.7% of CD patients switched from RP infliximab to infliximab-dyyb. Jung et al. studied 59 IBD patients switching from RP infliximab to CT-P13, and observed that 92.6% of CD patients and 66.7% of UC patients maintained similar efficacy compared with infliximab [13]. Smits et al. [16] studied 83 RP infliximab-treated IBD patients who switched to CT-P13, and similarly found that over 80% of those patients maintained clinical remission. Furthermore, Smits

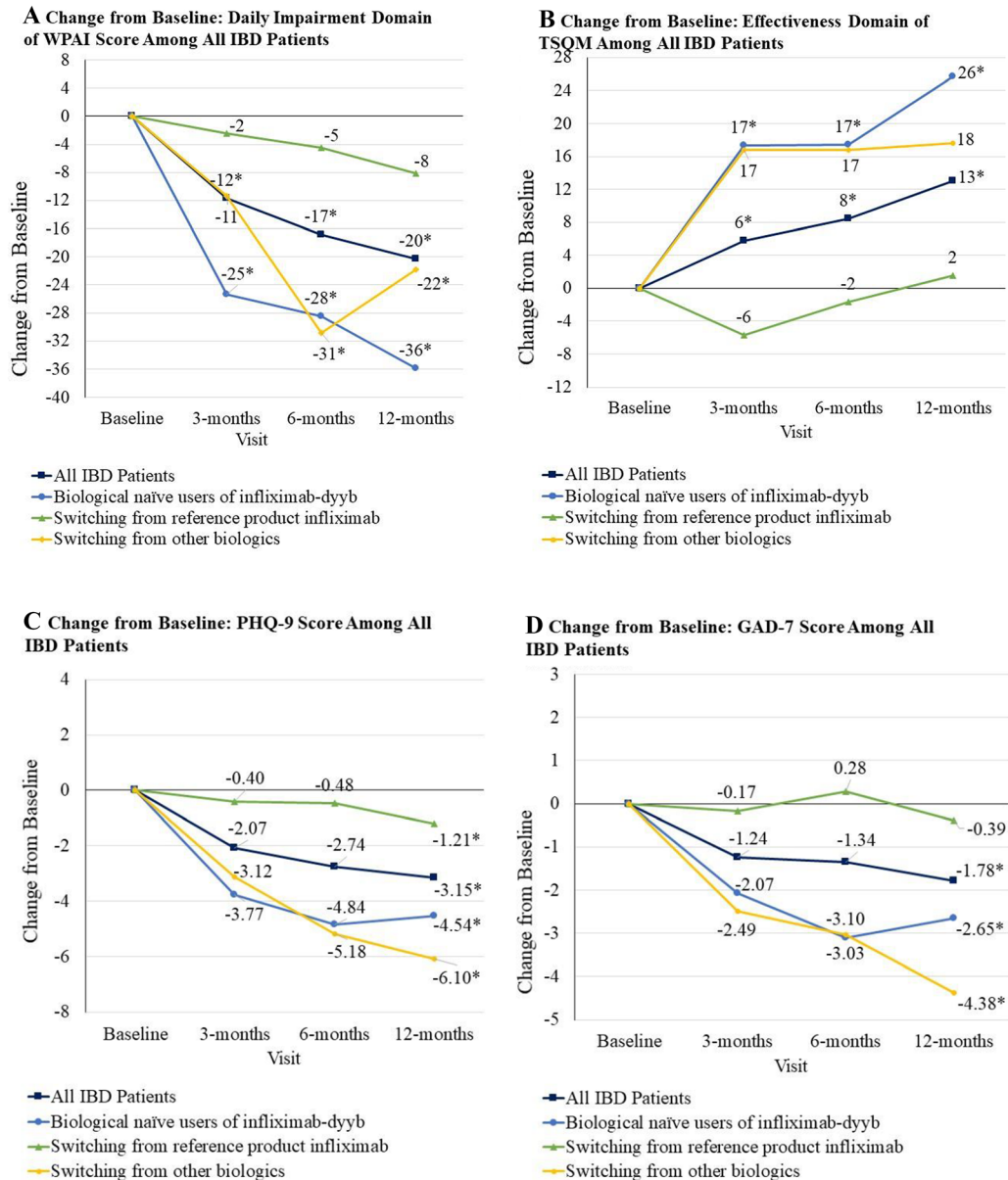


Fig. 3 Changes from baseline in daily impairment (WPAI), effectiveness (TSQM), PHQ-8, GAD-7. *Denotes statistically significant ($p < 0.05$) change from mixed model for repeated measures (MMRM). IBD

inflammatory bowel disease, *SIBDQ* Short Inflammatory Bowel Disease Questionnaire, *EQ-VAS* EuroQol Visual Analogue Scale

et al. found that IBD activity remained stable after switching. In another published study, Chaparro et al. found unfavorable results in users who switched from RP infliximab to CT-P13 [40]. However, Chaparro et al. explained that the higher risk of clinical relapse observed in patients switched to CT-P13 was not

supported by objective markers of inflammation and may have been due to the nocebo effect.

PROs showed significant improvements over time for all IBD patients initiating infliximab-dyyb ($n = 115$). Scores on the *SIBDQ*, the *EQ-VAS*, all domains of the *WPAI*, the effectiveness domain of the *TSQM*, the *GAD-7*, and the *PHQ-*

Table 4 Resource utilization at baseline and during the follow-up period in IBD patients administered Infliximab-dyyb

		Baseline (n = 115)	3 months (n = 109)	6 months (n = 99)	12 months (n = 84)
All patients					
Presence of an IBD-related hospitalization	n (%)	11 (9.6%)	6 (5.5%)	1 (1.0%)	1 (1.2%)
Presence of an ED visit	n (%)	12 (10.4%)	8 (7.3%)	3 (3.0%)	3 (3.6%)
Mean number of gastroenterologist visits	Mean (SD)	0.78 (1.67)	0.61 (0.71)	0.52 (0.75)	0.69 (0.78)
Biologic-naïve users of infliximab-dyyb					
Presence of an IBD-related hospitalization	n (%)	6 (15.4%)	2 (5.4%)	1 (3.0%)	0 (0.0%)
Presence of an ED visit	n (%)	7 (17.9%)	3 (8.1%)	2 (6.1%)	0 (0.0%)
Mean number of gastroenterologist visits	Mean (SD)	0.92 (1.58)	0.73 (0.73)	0.79 (0.82)	0.60 (0.71)
Patients switching from RP infliximab					
Presence of an IBD-related hospitalization	n (%)	0 (0.0%)	3 (5.5%)	0 (0.0%)	0 (0.0%)
Presence of an ED visit	n (%)	2 (3.5%)	4 (7.3%)	1 (1.9%)	1 (2.0%)
Mean number of gastroenterologist visits	Mean (SD)	0.35 (0.69)	0.45 (0.63)	0.31 (0.61)	0.68 (0.82)

P values were obtained from generalized estimating equations (GEEs)

ED emergency department, *IBD* inflammatory bowel disease, *RP* reference product

8 significantly improved from baseline to 12 months' follow-up. In biologic-naïve users, the current study observed a 16-point improvement in SIBDQ score from baseline to 12 months' follow-up. In a randomized phase 3 non-inferiority study, Ye et al. [39] in 2019 observed an 18.6- and a 16.7-point improvement in the 30-week SIBDQ score in biologic-naïve CD patients initiating RP infliximab or CT-P13, respectively. In the present study, biologic-naïve patients initiating infliximab-dyyb also demonstrated significant improvements in scores on the EQ-VAS; the presenteeism, overall work impairment, and daily activity impairment domains of the WPAI; the effectiveness and side effects domains of the TSQM; the GAD-7; and the PHQ-8.

PROs were maintained in users switched from RP infliximab to infliximab-dyyb. Our findings using PROs are novel and valuable, in that there have been few observational studies that have assessed PROs, specifically work productivity, psychological outcomes, and treatment satisfaction in IBD. In this study, SIBDQ,

EQ-VAS, TSQM, GAD-7, and PHQ-8 measures were maintained from baseline to 12-month follow-up in the cohort of patients switching from RP infliximab to infliximab-dyyb. WPAI scores improved significantly in this cohort in the domains of absenteeism and overall work impairment. Our findings are consistent with the randomized, non-inferiority, double-blind NOR-SWITCH study, which assigned patients on stable RP infliximab treatment in a 1:1 ratio to either continue treatment with RP infliximab or be switched to CT-P13, observed that improvements in SF-36, EQ-5D, and WPAI scores were not statistically different between RP infliximab and infliximab-dyyb users [32].

To our knowledge, this is the first study to prospectively evaluate treatment satisfaction in patients switched from RP infliximab to infliximab-dyyb for IBD. Our findings, based on TSQM, suggest that these patients remained satisfied with infliximab-dyyb in terms of its effectiveness, side effects, and convenience.

Our findings as to resource utilization suggest that hospitalization, ED visits, and

outpatient visits decreased over time, which could be due to improvements observed in patients' clinical outcomes and PROs. Regarding AEs, no new safety signals were observed during the conduct of this study. Although the number of patients in this study is small and direct comparisons cannot be made, the AE rates observed in this study are in line with what has previously been reported with RP infliximab [41–44].

This study has several limitations to consider. The study did not collect data on therapeutic drug monitoring. Therefore, any correlations between drug concentrations and outcomes were not examined. The study had a sample size smaller than anticipated. This was likely due in part to the prospective observational nature of the study. One of the main difficulties in patient recruitment was the lack of formulary availability/insurance coverage of infliximab-dyyb during patient enrollment at the time of study initiation. Due to the lack of uptake of infliximab-dyyb at the time of patient enrolment in the US, fewer study sites than planned were able to identify and recruit patients. This was largely because infliximab-dyyb was not on their formulary or because patient insurance would not cover infliximab-dyyb. Additionally, some patients were lost to follow-up. However, nearly 70% of patients completed all four visits. Due to the low sample size for patient subgroups, we did not control for covariates in our MMRM models. However, demographic, and clinical characteristics in our study were not time varying; therefore, we do not anticipate any change in the directionality of our conclusions. Further, due to the overall low sample size ($n < 20$) and multiple patient groups, results from the subgroup of patients switching from other biologics should be interpreted with caution. Future studies with larger sample sizes may confirm the findings from this study.

CONCLUSIONS

In this prospective, observational study, we evaluated real-world clinical outcomes, PROs, and healthcare resource use associated with

infliximab-dyyb for IBD among biologic-naïve patients and patients switching from RP infliximab or other biologics. For biologic-naïve UC patients, clinical outcomes improved significantly, while for biologic-naïve CD patients, they were maintained. Consistent with findings across studies of other immunological diseases, our study found that patients who switched from RP infliximab to infliximab-dyyb maintained clinical outcomes and remission status. The patient-reported quality-of-life and work productivity outcomes improved among biologic-naïve patients and were maintained for patients switched from RP infliximab. AEs occurred at a rate consistent with the known AE profile of RP infliximab, but it must be acknowledged that the number of patients in this study is small and direct comparisons with other studies should be made with caution. To our knowledge, this is the first prospective study of real-world outcomes in IBD patients treated with infliximab-dyyb in North America. The results of this study provide valuable data concerning the use of infliximab-dyyb in clinical practice for patients with IBD.

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Compliance with Ethics Guidelines. The final protocol, any amendments, and informed consent documentation were reviewed and approved by a local data protection agency for each site participating in the study. Informed consent was obtained from all participants included in the study. Full details of institutional review boards that approved the study, along with relevant reference numbers can be found in the Supplementary Material.

Data Availability. Upon request and subject to review, Pfizer will provide the data that support the findings of this study. Subject to certain criteria, conditions, and exceptions, Pfizer may

also provide access to the related individual anonymized participant data. See <https://www.pfizer.com/science/clinical-trials/trial-data-and-results> for more information.

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