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BRIEF REPORT

Characteristics and 6-Month Outcomes in Patients with Rheumatoid Arthritis Initiating Infliximab Biosimilar IFX-dyyb in a Real-World Setting

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ABSTRACT

Introduction: Real-world studies describing biosimilar initiation or switching in patients with rheumatoid arthritis (RA) are limited. The aim of this study was to assess treatment patterns and effectiveness of real-world patients with RA initiating infliximab biosimilar IFX-dyyb (CT-P13; Inflectra®) in the USA.

Methods: This observational study evaluated patients with RA from the CorEvitas RA Registry who initiated IFX-dyyb and had Clinical Disease Activity Index (CDAI) recorded at baseline and 6 months. The primary outcome was reaching low disease activity (LDA; CDAI $\leq$ 10) at 6 months in patients with moderate or high disease activity (CDAI > 10) at baseline. Secondary outcomes were change at 6 months in CDAI and certain patient-reported outcomes (PROs). Patient data were stratified by prior treatment: biologic/targeted synthetic disease-modifying antirheumatic drug (tsDMARD)-naïve, reference infliximab (IFX-REF) or IFX biosimilar, or a non-IFX biologic or tsDMARD.

Results: Of 318 patients initiating IFX-dyyb, 176 had baseline and 6-month CDAI scores; 73 (41%) switched from IFX, 61 (35%) switched from another non-IFX/biologic/tsDMARD, 32 (18%) were naïve to biologics/tsDMARDs, and 10 (6%) switched from an IFX biosimilar. Among patients with moderate or high disease activity at baseline, 32.9% (95% CI 22.9, 42.9) achieved LDA at 6 months. Mean 6-month change from baseline in CDAI was − 1.8 (95% CI − 3.3, − 0.3) overall; − 4.7 (− 7.6, − 1.7) in patients who switched from a non-IFX biologic/tsDMARD, − 4.1 (− 7.8, − 0.3) in biologic/tsDMARD-naïve patients, and 1.1 (− 0.4, 2.6) in patients who switched from IFX-REF/IFX biosimilar. Other clinical outcomes/PROs improved at 6 months. Of the IFX-dyyb initiators, 68% remained on IFX-dyyb at 6 months.

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Conclusion: In this real-world population of patients with RA initiating IFX-dyyb, the majority switched from IFX-REF or a non-IFX biologic/tsDMARD. CDAI remained stable in patients switching from IFX-REF/IFX biosimilar and improved in patients switching from a non-IFX biologic/tsDMARD and in biologic/tsDMARD-naïve patients.

PLAIN LANGUAGE SUMMARY

Infliximab is an effective treatment for rheumatoid arthritis (RA). Biosimilars—biologic drugs designed to be very similar to the originator products—are now available that may be more affordable with matching efficacy and safety. IFX-dyyb is a US Food and Drug Administration-approved infliximab biosimilar but little is known about its use in real-world clinical practice in patients with RA in the USA. This study used data from a large observational registry to look at treatment patterns and effectiveness of IFX-dyyb in adults with RA. One hundred and seventy-six patients were included who had data available at both baseline and at 6 months. Most patients (47%) switched to IFX-dyyb from the originator infliximab or another infliximab biosimilar; 35% switched from another RA treatment, and 18% were new to treatment. Six months after starting IFX-dyyb, 68% of patients were still receiving treatment. A measure of clinical disease activity remained stable in patients who switched from originator infliximab or another biosimilar, while this measure improved in patients switching to IFX-dyyb from other treatments or starting treatment for the first time. Other clinical measures and patient-reported outcomes such as pain and fatigue also improved over 6 months with IFX-dyyb. This real-world study of patients with RA initiating IFX-dyyb in the USA adds to our knowledge of the use of biosimilars in this patient population.

Keywords: Biologic; Biosimilar; CorEvitas Registry; IFX-dyyb; DMARD; Effectiveness; Infliximab; Real-world evidence; Rheumatoid arthritis; TNFα inhibition

Key Summary Points

Why carry out this study?

Real-world data on biosimilar use in patients with rheumatoid arthritis are sparse.

This observational study examined treatment patterns and the effectiveness of IFX-dyyb (CT-P13; Inflectra®) initiation in patients with rheumatoid arthritis.

What was learned from the study?

The majority of patients switched to IFX-dyyb from originator infliximab or a non-infliximab biologic or biological/targeted synthetic disease-modifying antirheumatic drug.

Clinical and patient-reported outcomes improved at 6 months after IFX-dyyb initiation.

Measures of disease activity remained stable at 6 months in patients who switched from originator infliximab or an infliximab biosimilar to IFX-dyyb but improved in patients who switched from a non-infliximab biologic or biological/targeted synthetic disease-modifying antirheumatic drug or initiated biologic treatment.

INTRODUCTION

The anti-tumor necrosis factor alpha (TNFα) antibody infliximab (IFX) is indicated for the treatment of ankylosing spondylitis (AS), adult and pediatric Crohn's disease, plaque psoriasis, psoriatic arthritis (PsA), rheumatoid arthritis (RA) (in combination with methotrexate), and ulcerative colitis (UC) [1–3]. While IFX and other TNFα inhibitors have transformed the

management of chronic immune-mediated inflammatory diseases, they are complex, expensive products, and therefore not easily accessible to all patients.

As the patents of first version (originator) biologics expire, development of biosimilars—biologics designed to be highly similar to originator products—has markedly increased. A biosimilar may have minor structural differences in clinically inactive components compared with its originator reference product but has no clinically meaningful differences in terms of purity and potency from the reference product. Approval of biosimilars by regulatory bodies requires extensive in vitro studies to confirm similarity to the reference product in terms of quality attributes, as well as preclinical and clinical studies to show comparable pharmacokinetics, efficacy, safety, and immunogenicity [4, 5].

Biosimilars offer a more affordable treatment option that may expand access to biologic therapies for patients [4, 6]. IFX-dyyb (CT-P13; Inflectra®) is a biosimilar of Remicade® (IFX-REF) [7]. Randomized controlled trials and studies using real-world data have shown comparable clinical outcomes for IFX-dyyb as for IFX-REF in RA [8–11], AS [12, 13], Crohn's disease [14], and UC [14, 15].

In a recent real-world study of 794 Japanese patients with RA, IFX-dyyb led to clinical improvement when used as the first biological therapy in 318 patients who were naïve to biological disease-modifying antirheumatic drugs (bDMARDs) and maintained effectiveness in the 374 patients who had switched from IFX-REF after 1-year of follow-up [16].

A need exists for better characterization of real-world patients with RA using biosimilars in the USA, and IFX-dyyb in particular [17]. Characterization of patients beginning treatment with IFX-dyyb ("initiators") or switching to IFX-dyyb after starting treatment with IFX-REF ("switchers") is warranted to confirm that clinical trial data may be extrapolated to the real-world setting [18].

This report describes a real-world study that evaluated treatment patterns and effectiveness of IFX-dyyb in adults with RA using data from the CorEvitas RA Registry.

METHODS

DATA SOURCE AND STUDY DESIGN

The CorEvitas RA Registry (formerly CORRONA) is an ongoing, observational clinical registry, established in 2001 in the USA. Longitudinal follow-up data are collected from patients and their rheumatologists during routine clinic visits (approximately every 6 months) using specific CorEvitas RA questionnaires. As of October 31, 2022, more than 200 sites throughout the USA, involving around 1000 physicians, have been involved in data collection. Data from almost 60,000 patients with RA, representing over 225,000 patient years of data, are accessible in the CorEvitas RA database [19–21]. Data include patient visits from April 5, 2016 to October 31, 2022. To be included in the registry, patients of either sex aged 18 years or older had to be diagnosed with RA by a rheumatologist, and be currently receiving a US Food and Drug Administration (FDA)-approved biologic, biosimilar, or Janus kinase (JAK) inhibitor for RA initiated within 365 days of enrollment. Temporary treatment interruptions of less than 180 days were permitted. All patients provided written informed consent.

Patients were excluded from the registry if they had been diagnosed with any other autoimmune inflammatory arthritis; had begun RA treatment with only a non-eligible medication (including conventional synthetic disease-modifying antirheumatic drugs [csDMARDs] and prednisone); or were participating or planned to participate in a clinical trial of another RA therapy.

The study was performed in accordance with the Declaration of Helsinki and the Guidelines for Good Pharmacoepidemiology Practice (GPP). All participating investigators were required to obtain full board approval for conducting noninterventional research involving human subjects with a limited dataset. Sponsor approval and continuing review was obtained through a central institutional review board (IRB), the New England Independent Review Board (NEIRB; no. 120160610). For academic

investigative sites that did not receive authorization to use the central IRB, full board approval was obtained from their respective governing IRBs, and documentation of approval was submitted to CorEvitas, LLC before the site's participation and initiation of any study procedures. All patients in the registry were required to provide written informed consent and authorization before participating.

Study Population

To be included in this study, patients must have initiated IFX-dyyb (defined as first ever use of IFX-dyyb) at the registry enrollment visit or at a follow-up visit from April 2016 onward, have follow-up data for a 6-month clinic visit (3–-9 month window), and have Clinical Disease Activity Index (CDAI) scores recorded at baseline and the 6-month follow-up visit. Baseline was defined as the first visit of IFX-dyyb initiation unless it was initiated between visits, in which case baseline was the visit prior to initiation (within 4 months).

Outcomes

Primary Outcome

The primary outcome was the proportion of patients with moderate or high disease activity (CDAI $>$ 10) at baseline who achieved low disease activity (LDA; CDAI $\leq$ 10) at 6 months following IFX-dyyb initiation.

Secondary Outcomes

Secondary outcomes included the proportion of patients achieving remission (CDAI $\leq$ 2.8) at 6 months in those with LDA, moderate or high disease activity (CDAI $>$ 2.8) at baseline, as well as change from baseline to 6 months in CDAI, Health Assessment Questionnaire (HAQ), and patient-reported outcomes (PROs) of pain and fatigue; achievement of modified American College of Rheumatology (mACR) [22] 20/50/70 response at 6 months ($\geq$ 20%, 50%, and 70% improvement).

Frequencies and counts were used to summarize reasons for initiation of IFX-dyyb. Reasons were categorized as follows: safety (infection, lymphoma/malignancy, toxicity, serious and minor side effect); efficacy (lack of efficacy, disease flare, active disease, primary or secondary loss of efficacy, inadequate initial response, failure to maintain initial response); cost/insurance (lack of insurance); other reason (patient preference, fear of future side effect, frequency of administration, temporary interruption, to improve tolerability, and other).

Statistical Analysis

Patient data were stratified according to RA treatment prior to IFX-dyyb initiation, which included (a) previous biologic/targeted synthetic disease-modifying antirheumatic drug (tsDMARD)-naïve, (b) switched from IFX-REF or IFX biosimilar, or (c) switched from a non-IFX biologic or tsDMARD.

Descriptive statistics were used for demographic, clinical characteristics, medication use, comorbidities, and clinical assessments and outcomes at 6 months. Categorical variables were summarized using frequency and percentages. Continuous variables were summarized by number of observations, mean, standard deviation (SD), or 95% confidence intervals (CI). For patients discontinuing IFX-dyyb before the 6-month visit, outcome data were imputed via last observation carried forward, using only registry visits that occurred before discontinuation.

RESULTS

Baseline: IFX-dyyb Initiation

Of 318 patients who initiated IFX-dyyb, 255 patients had a baseline visit, and 188 patients had a 6-month visit (Fig. 1). Of the 188 patients who had a 6-month visit, 176 (93.6%) had baseline and 6-month CDAI scores and comprised the analysis group. In this analysis group, patients were predominantly White (75.6%) and female (78.4%) with a mean age of 63.6 $\pm$ 13.3 years. The most common comorbidities in this population were hypertension

(33.0%), depression (16.5%), and cardiovascular disease (15.9%).

The distribution of disease characteristics, disease measures, and PROs at the time of initiation was generally similar for IFX-dyyb initiators and those with a 6-month follow-up. At baseline, IFX-REF/IFX biosimilar switchers had a longer RA disease duration than biologic/tsDMARD-naïve patients (Table 1). Prior therapy among IFX-dyyb initiators (n = 176) included 32 (18.2%) of patients who were biologic-naïve or naïve to tsDMARDs, 61 (34.7%) patients who switched from non-IFX biologics/tsDMARDs, and 83 (47.2%) patients who switched from IFX-REF/IFX biosimilar. The mean duration of previous therapy was 3.3 ± 4.2 years.

At initiation, more patients who switched from another IFX (IFX-REF or IFX biosimilar) had controlled disease, as shown by mean CDAI score (8.0 ± 9.1) and remission score (CDAI ≤ 2.8 in 38.6%), compared with those switching from non-IFX biologics/tsDMARDs: mean CDAI 18.8 ± 13.9, remission (CDAI ≤ 2.8 in 11.5%) and biologic/tsDMARD-naïve patients: mean CDAI 15.3 ± 12.4, remission (CDAI ≤ 2.8 in 18.8%) (Table 1). A similar trend was observed across other disease activity measures and PROs (data not shown).

Among the 176 patients initiating IFX-dyyb, 33 patients (18.8%) reported at least one reason for initiating IFX-dyyb. Reasons for initiation included "safety (infection, lymphoma/malignancy, toxicity, serious and minor side effect)" (n = 4), "efficacy (lack of efficacy, disease flare, active disease, primary or secondary loss of efficacy, inadequate initial response, failure to maintain initial response)" (n = 17), "cost/insurance (lack of insurance)" (n = 6), and "other reason" (n = 8).

6 Months Following IFX-dyyb Initiation

At 6 months following IFX-dyyb initiation, 119 (67.6%) patients remained on IFX-dyyb, 35 (19.9%) discontinued IFX-dyyb and did not start other biologic at/before 6 months, and 22 (12.5%) switched to another biologic at/before the 6-month visit. Changes in clinical outcomes

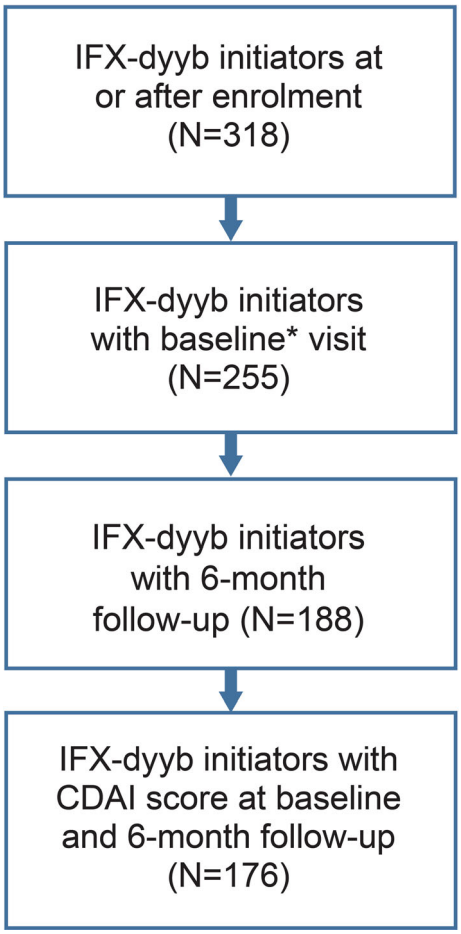

Fig. 1 Patient disposition. *CDAI* Clinical Disease Activity Index. Selection of eligible patients from the CorEvitas RA registry who initiated treatment between April 2016 and October 2022. *Baseline is defined as the first visit of IFX-dyyb initiation. If IFX-dyyb was initiated between visits, baseline was the visit prior to initiation if it was within 4 months of the initiation

for those switching from IFX/IFX biosimilars to IFX-dyyb were small. There was improvement in CDAI in patients switching from a non-IFX biologic/tsDMARD (− 4.7 ± 11.9; 95% CI − 7.6, − 1.7) to IFX-dyyb and biologic/tsDMARD-naïve patients (− 4.1 ± 10.9; 95% CI − 7.8, − 0.3). For those switching from IFX-REF/IFX biosimilars, there was a non-significant increase in CDAI (Table 2). There was a small numerical increase in patient global assessment (PGA) score of 2.1 ± 18.1 (95% CI − 1.8, 6.0) in the IFX-REF/IFX biosimilar switchers, compared with larger decreases of − 3.6 ± 25.9 (95% CI

Table 1 Demographics, comorbidities, treatment history, and disease characteristics at IFX-dyyb initiation (baseline) for all patients with baseline and 6-month CDAI scores and other 6-month follow-up data, stratified by previous RA treatment

Variable	Total (N = 176)	Biologic-naïve	Prior switch	
		Biologic/tsDMARD-naïve (n = 32)	IFX-REF/IFX biosimilar (n = 83)	Non-IFX biologic/ tsDMARD (n = 61)
Mean age, years (± SD)	63.6 ± 13.3	64.8 ± 17.6	65.2 ± 10.7	60.7 ± 13.8
≥ 65 years, n (%)	97 (55.1)	17 (53.1)	47 (56.6)	33 (54.1)
Female, n (%)	138 (78.4)	23 (71.9)	64 (77.1)	51 (83.6)
Race				
White	133 (75.6)	22 (68.8)	66 (79.5)	45 (73.8)
Non-White	43 (24.4)	10 (31.3)	17 (20.5)	16 (26.2)
Comorbid conditions, n (%)				
Cardiovascular disease[a]	28 (15.9)	5 (15.6)	10 (12.0)	13 (21.3)
Malignancy[b]	16 (9.1)	5 (15.6)	5 (6.0)	6 (9.8)
Hypertension	58 (33.0)	14 (43.8)	24 (28.9)	20 (32.8)
Diabetes	21 (11.9)	4 (12.5)	7 (8.4)	10 (16.4)
Osteoporosis	8 (4.5)	2 (6.3)	2 (2.4)	4 (6.6)
Depression	29 (16.5)	4 (12.5)	11 (13.3)	14 (23.0)
Fibromyalgia	11 (6.3)	1 (3.1)	4 (4.8)	6 (9.8)
Disease characteristics				
RA duration, years (mean ± SD)	13.7 ± 11.0	9.7 ± 14.3	15.9 ± 8.7	12.8 ± 11.4
CDAI score (mean ± SD)	13.1 ± 12.6	15.3 ± 12.4	8.0 ± 9.1	18.8 ± 13.9
Remission (CDAI ≤ 2.8)	45 (25.6%)	6 (18.8%)	32 (38.6%)	7 (11.5%)
Patient-reported outcomes				
PGA VAS, 0–100 (mean ± SD)	38.3 ± 28.4	36.9 ± 26.1	32.0 ± 28.4	47.6 ± 27.4
HAQ 0–3 (mean ± SD)	0.9 ± 0.7	0.9 ± 0.8	0.7 ± 0.6	1.0 ± 0.7
Concomitant therapy				
None	52 (29.5)	6 (18.8)	25 (30.1)	21 (34.4)
MTX	76 (43.2)	11 (34.4)	45 (54.2)	20 (32.8)

Table 1 continued

Variable	Total (N = 176)	Biologic-naïve	Prior switch	
		Biologic/tsDMARD-naïve (n = 32)	IFX-REF/IFX biosimilar (n = 83)	Non-IFX biologic/tsDMARD (n = 61)
Non-MTX csDMARD	29 (16.5)	7 (21.9)	7 (8.4)	15 (24.6)
MTX + non-MTX csDMARD	19 (10.8)	8 (25.0)	6 (7.2)	5 (8.2)
Treatment history				
csDMARD				
None	10 (5.7)	1 (3.1)	5 (6.0)	4 (6.6)
1	78 (44.3)	16 (50.0)	39 (47.0)	23 (37.7)
2+	88 (50.0)	15 (46.9)	39 (47.0)	34 (55.7)
Biologics/tsDMARDs				
None	32 (18.2)	32 (100.0)	0 (0.0)	0 (0.0)
1	77 (43.8)	0 (0.0)	51 (61.4)	26 (42.6)
2+	67 (38.1)	0 (0.0)	32 (38.6)	35 (57.4)
Prior prednisone	111 (63.1)	21 (65.6)	51 (61.4)	39 (63.9)
Current prednisone	50 (28.4)	12 (37.5)	18 (21.7)	20 (32.8)

CDAI Clinical Disease Activity Index, *CI* confidence interval, *cs* conventional synthetic, *DMARD* disease-modifying antirheumatic drug, *HAQ* Health Assessment Questionnaire, *IFX* infliximab, *LDA* low disease activity, *mACR* modified American College of Rheumatology, *MTX* methotrexate, *PGA* patient global assessment, *RA* rheumatoid arthritis, *REF* reference, *SD* standard deviation, *ts* targeted synthetic, *VAS* visual analog scale

[a]Myocardial infarction, stroke, transient ischemic attack, acute coronary syndrome, coronary artery disease, congestive heart failure, revascularization procedure including percutaneous coronary intervention, coronary artery bypass grafting or coronary artery stents, ventricular arrhythmia, cardiac arrest, unstable angina, other cardiovascular events, carotid artery disease

[b]History of lung cancer, breast cancer, lymphoma, skin cancer (melanoma and squamous), or other cancer

− 10.2, 2.9) in the non-IFX biologic/tsDMARDs switchers and of − 4.1 ± 23.4 (95% CI − 12.2, 4.0) in biologic/tsDMARD-naïve patients. Changes in HAQ, patient pain, and fatigue by VAS were generally small in all patients after 6 months of IFX-dyyb treatment (Table 2).

Among all patients with moderate or high disease activity (CDAI > 10) at baseline, 32.9% (95% CI 22.9, 42.9) achieved LDA (CDAI ≤ 10) after 6 months of IFX-dyyb treatment. The highest proportion of patients achieving LDA were those who had switched to IFX-dyyb from a non-IFX biologic/tsDMARD (n = 17/61; 37.8%) compared with the IFX-REF/IFX biosimilar (n = 6/83; 26.1%) and biologic/tsDMARD-naïve groups (n = 5/32, 29.4%). However, patients in the non-IFX biologic/tsDMARD group also had the lowest rate of remission (CDAI ≤ 2.8 in 7.4% of patients versus 17.6% and 19.2% for IFX-REF/IFX biosimilar and biologic/tsDMARD-naïve groups, respectively) (Table 2).

Table 2 Clinical outcomes 6 months after IFX-dyyb initiation

Outcome	Total (*N* = 176)		Biologic-naïve		Prior switch			
			Biologic/tsDMARD-naïve (*n* = 32)		IFX-REF/IFX biosimilar (*n* = 83)		Non-IFX biologic/tsDMARD (*n* = 61)	
	n (%)	95% CI	*n* (%)	95% CI	*n* (%)	95% CI	*n* (%)	95% CI
LDA (CDAI ≤ 10)[a]	28/85 (32.9)	22.9, 42.9	5 (29.4)	7.8, 51.1	6 (26.1)	8.1, 44.0	17 (37.8)	23.6, 51.9
Remission (CDAI ≤ 2.8)[b]	18/131 (13.7)	7.8, 19.6	5 (19.2)	4.1, 34.4	9 (17.6)	7.2, 28.1	4 (7.4)	0.4, 14.4
mACR20[c]	21/167 (12.6)	7.5, 17.6	6 (21.4)	6.2, 36.6	4 (4.9)	0.2, 9.7	11 (19.0)	8.9, 29.1
mACR50[c]	14/167 (8.4)	4.2, 12.6	4 (14.3)	1.3, 27.2	3 (3.7)	− 0.4, 7.8	7 (12.1)	3.7, 20.5
mACR70[c]	7/167 (4.2)	1.2, 7.2	3 (10.7)	− 0.7, 22.2	1 (1.2)	− 1.2, 3.6	3 (5.2)	− 0.5, 10.9

Outcome	Total (*N* = 176)		Biologic-naïve		Prior switch			
	Mean (SD)	95% CI	Biologic/tsDMARD-naïve (*n* = 32)		IFX-REF/IFX biosimilar (*n* = 83)		Non-IFX biologic/tsDMARD (*n* = 61)	
			Mean (SD)	95% CI	Mean (SD)	95% CI	Mean (SD)	95% CI
Δ CDAI	− 1.8 (10.0)	− 3.3, − 0.3	− 4.1 (10.9)	− 7.8, − 0.3	1.1 (7.0)	− 0.4, 2.6	− 4.7 (11.9)	− 7.6, − 1.7
Δ PGA (0–100)	− 1.0 (22.1)	− 4.3, 2.3	− 4.1 (23.4)	− 12.2, 4.0	2.1 (18.1)	− 1.8, 6.0	− 3.6 (25.9)	− 10.2, 2.9
Δ HAQ (0–3)	− 0.0 (0.4)	− 0.1, 0.1	− 0.1 (0.5)	− 0.2, 0.1	0.1 (0.3)	− 0.0, 0.1	− 0.0 (0.4)	− 0.2, 0.1
Δ patient pain VAS (0–100)	− 0.5 (22.4)	− 3.9, 2.8	− 2.2 (21.1)	− 9.6, 5.2	2.6 (19.1)	− 1.5, 6.7	− 4.0 (26.4)	− 10.6, 2.7
Δ patient fatigue VAS (0–100)	− 1.4 (24.4)	− 5.0, 2.3	− 1.5 (25.7)	− 10.6, 7.5	0.4 (22.0)	− 4.3, 5.2	− 3.8 (26.9)	− 10.7, 3.1

CDAI Clinical Disease Activity Index, *CI* confidence interval, *DMARD* disease-modifying antirheumatic drug, *HAQ* Health assessment Questionnaire, *IFX* infliximab, *LDA* low disease activity, *mACR* modified American College of Rheumatology, *PGA* patient global assessment, *REF* reference, *SD*, standard deviation, *ts* targeted synthetic, *VAS* visual analog scale

[a]Calculated among those patients with moderate or high disease activity (CDAI > 10) at baseline

[b]Calculated among those patients with LDA, moderate or high disease activity (CDAI > 2.8) at baseline

[c]Calculated among those with complete information for calculation of mACR

DISCUSSION

This is the first real-world analysis of IFX-dyyb initiation in patients with RA in the USA and provides insights into the characteristics of the patients, their treatment patterns, and the effectiveness of IFX-dyyb, particularly in relation to prior therapy. The present study provides data that are reflective of situations in clinical practice, where patients may switch to a biosimilar from the originator or from other biologic DMARDs or tsDMARDs. Our findings suggest that outcomes at 6 months with IFX-dyyb treatment in the real-world setting are comparable with efficacy outcomes in clinical trials [2, 18, 23], with no worsening of disease activity among patients switching therapy from IFX-REF/IFX biosimilar and good response (improvement in CDAI and PROs) among treatment-naïve patients initiating IFX-dyyb.

Clinical outcomes in patients who switched to IFX-dyyb from IFX-REF/IFX biosimilars remained stable over 6 months (mean 6-month change from baseline in CDAI 1.1 [95% CI − 0.4, 2.6]). Greater improvements in CDAI and PGA score were observed in those switching from non-IFX biologics/tsDMARDs and biologic/tsDMARD-naïve patients compared with those who switched from IFX-REF/IFX biosimilars. Both of these findings are expected and are reassuring—stable outcomes in patients switching from IFX-REF demonstrate that IFX-dyyb provides continued efficacy, while patients switching from other treatments may potentially benefit from a therapy with a different mechanism of action.

In our study, there appeared to be a greater response at 6 months in the treatment-naïve group and non-IFX biologic/tsDMARD groups than in the IFX-REF/IFX biosimilar group. This finding is expected since changing from the originator product or other biosimilar product should effectively represent a continuation of therapy. Patients who switched from the originator product (or another biosimilar) also had better disease control at initiation, perhaps because switching occurred for reasons other than inadequate response to the originator product (e.g., cost). In a 5-year retrospective analysis of medical record data of patients with RA in Korea, IFX-dyyb treatment was safe and effective in terms of drug survival, adverse events, and disease activity, with similar findings seen between IFX-naïve patients and switched groups [10]. A Japanese real-world study of 794 patients with RA initiating IFX-dyyb reported that clinical efficacy (evaluated by Disease Activity Score 28-C-reactive protein [DAS28-CRP]) was maintained in patients who switched to IFX-dyyb from IFX-REF and improved in patients who switched from other biologic DMARDs because of lack of response, and in treatment-naïve patients [16]. The improvement in DAS28-CRP was greatest in the IFX-naïve patients, with the smallest improvement seen in patients who switched from IFX-REF who had generally controlled disease activity already [16]. In a large Danish study of patients with RA, PsA, or AS, switching from IFX-dyyb to another IFX biosimilar (GP1111) was well tolerated with no clinically relevant difference in disease activity following the switch [24]. Overall, our observations are consistent with those observed in these prior studies.

Among patients with moderate or high disease activity at baseline, more of those who switched from a non-IFX biologic/tsDMARD achieved LDA than those who switched from IFX-REF/IFX biosimilar. The confidence intervals for these estimates are wide and the values are unadjusted for baseline disease activity. However, this further reinforces the idea that biosimilars should not be expected to provide better efficacy than the originator product.

The patient characteristics observed in the present study are generally consistent with other CorEvitas results in RA [25, 26], and were typical of a general population of US patients with RA. The majority of patients switched to IFX-dyyb from previous IFX (> 40%). Furthermore, 68% of patients remained on IFX-dyyb after 6 months. This 6-month retention rate is similar to previous CorEvitas Registry data reports of a range of 60–77% of patients remaining on first- or second-line etanercept, adalimumab, or JAK inhibitor [27, 28]. The most common reason for initiating IFX-dyyb was to obtain better disease control among only 18.8%

(33/176) of patients who reported a reason. The small proportion of stated reasons for initiations limits the interpretation of the results.

The main strength of the CorEvitas Registry is its size as one of the largest observational longitudinal registry of patients with RA in the world and provides information on a variety of physician and patient-reported disease outcomes, thereby permitting long-term follow-up on the real-world use of biologic treatments in the USA, obtained from a large variety of patients and providers of treatment. The limitations of this study are similar to other observational studies. Although the CorEvitas Registry does not collect data with the robustness of a clinical trial as it relies on information reported on questionnaires from physicians and patients in real practice, it does operate a uniform approach to engagement, training, monitoring, and obtaining feedback for all participating sites. This approach ensures that the same high-quality information is obtained for all patients. The 6-month analyses presented here are descriptive, with no adjustment for potentially confounding variables. Because this study evaluated patients with RA in the USA only, the results may not be representative of all adults with RA who are managed by physicians in other countries or by non-rheumatologists. Also, observations are limited to RA and may not be representative of other indications of IFX-dyyb. Finally, safety outcomes are not covered in this study; future analysis of safety data in the real-world setting may highlight differences from data obtained in clinical trials.

Overall, these data provide insights for clinicians regarding expected disease effectiveness outcomes following switching RA therapy in a real-world setting to IFX-dyyb and potentially alleviate hesitation in its use.

CONCLUSIONS

In this real-world population of patients with RA initiating IFX-dyyb, most patients (81.8%) who initiated IFX-dyyb switched from IFX-REF/IFX-biosimilar or a non-IFX biologic/tsDMARD. Clinical outcomes and evaluated PROs generally remained stable in all patients regardless of prior therapy at 6 months. The greatest improvements were observed in the patients who switched from non-IFX biologic/tsDMARD to IFX-dyyb, while disease activity remained stable in patients who switched from IFX-REF/IFX-biosimilar to IFX-dyyb.

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Data Availability. Access to study data was limited to CorEvitas, LLC. Data are available from CorEvitas, LLC through a commercial subscription agreement and are not publicly available.

Declarations

Conflict of Interest. Joshua Baker has received consulting fees from Bristol Myers Squibb, CorEvitas, Cumberland Pharma, Burns White, and LLC, and has received grant funding from Horizon. Catherine Bakewell is a speaker/consultant for AbbVie, Janssen, Lilly, Novartis, Pfizer, Sanofi/Genzyme, and UCB. Ara Dikranian is a speaker/consultant for AbbVie, Amgen, Eli Lilly, Janssen, Sanofi, Pfizer, and UCB. Gordon Lam is a speaker/consultant for AbbVie, Bristol Myers Squibb, Janssen, Novartis, Pfizer, Sanofi/Genzyme, and UCB. Jacqueline O'Brien, Page C. Moore, and Miao Yu are employees of CorEvitas, LLC, and were contracted by Pfizer to provide data, input into design of data collection and statistical support for the development of the manuscript. Karim R. Masri and Peter Hur are employees and shareholders of Pfizer.

Ethical Approval. The study was performed in accordance with the Declaration of Helsinki and the Guidelines for Good Pharmacoepidemiology Practice (GPP). All participating investigators were required to obtain full board approval for conducting noninterventional research involving human subjects with a limited dataset. Sponsor approval and continuing review was obtained through a central institutional review board (IRB), the New England Independent Review Board (NEIRB; no. 120160610). For academic investigative sites that did not receive authorization to use the central IRB, full board approval was obtained from their respective governing IRBs, and documentation of approval was submitted to CorEvitas, LLC before the site's participation and initiation of any study procedures. All patients in the registry were required to provide written informed consent and authorization before participating.

REFERENCES

1. Lipsky PE, van der Heijde DM, St Clair EW, et al. Infliximab and methotrexate in the treatment of rheumatoid arthritis. Anti-Tumor Necrosis Factor Trial in Rheumatoid Arthritis with Concomitant Therapy Study Group. N Engl J Med. 2000;343:1594–602.

2. Jorgensen KK, Olsen IC, Goll GL, et al. Switching from originator infliximab to biosimilar CT-P13 compared with maintained treatment with originator infliximab (NOR-SWITCH): a 52-week, randomised, double-blind, non-inferiority trial. Lancet. 2017;389:2304–16.

3. Smolen JS, Landewe RBM, Bijlsma JWJ, et al. EULAR recommendations for the management of rheumatoid arthritis with synthetic and biological disease-modifying antirheumatic drugs: 2019 update. Ann Rheum Dis. 2020;79:685–99.

4. Gabbani T, Deiana S, Annese V. CT-P13: design, development, and place in therapy. Drug Des Devel Ther. 2017;11:1653–61.

5. EMA. Committee for Medicinal Products for Human Use (CHMP). Guideline on similar biological medicinal products containing monoclonal antibodies—non-clinical and clinical issues. 2012. http://www.ema.europa.eu/docs/en_GB/document_library/Scientific_guideline/2012/06/WC500128686.pdf. Accessed 26 May 2023.

6. IQVIA. White paper. The impact of biosimilar competition in Europe. 2021. https://www.iqvia.com/-/media/iqvia/pdfs/library/white-papers/the-impact-of-biosimilar-competition-in-europe-2021.pdf. Accessed 10 July 2023.

7. EMA. Committee for Medicinal Products for Human Use (CHMP). Assessment report: Remsima (Infliximab). 2019. https://www.ema.europa.eu/en/documents/assessment-report/remsima-epar-public-assessment-report_en.pdf. Accessed 26 May 2023.

8. Codreanu C, Sirova K, Jarosova K, Batalov A. Assessment of effectiveness and safety of biosimilar infliximab (CT-P13) in a real-life setting for treatment of patients with active rheumatoid arthritis or ankylosing spondylitis. Curr Med Res Opin. 2018;34:1763–9.

9. Kim HA, Lee E, Lee SK, et al. Retention rate and safety of biosimilar CT-P13 in rheumatoid arthritis: data from the Korean College of Rheumatology Biologics Registry. BioDrugs. 2020;34:89–98.

10. Kim TH, Lee SS, Park W, et al. A 5-year retrospective analysis of drug survival, safety, and effectiveness of the infliximab biosimilar CT-P13 in patients with rheumatoid arthritis and ankylosing spondylitis. Clin Drug Investig. 2020;40:541–53.

11. Yoo DH, Racewicz A, Brzezicki J, et al. A phase III randomized study to evaluate the efficacy and safety of CT-P13 compared with reference infliximab in patients with active rheumatoid arthritis: 54-week results from the PLANETRA study. Arthritis Res Ther. 2016;18:82.

12. Park W, Hrycaj P, Jeka S, et al. A randomised, double-blind, multicentre, parallel-group, prospective study comparing the pharmacokinetics, safety, and efficacy of CT-P13 and innovator infliximab in patients with ankylosing spondylitis: the PLANETAS study. Ann Rheum Dis. 2013;72:1605–12.

13. Park W, Yoo DH, Jaworski J, et al. Comparable long-term efficacy, as assessed by patient-reported outcomes, safety and pharmacokinetics, of CT-P13 and reference infliximab in patients with ankylosing spondylitis: 54-week results from the randomized, parallel-group PLANETAS study. Arthritis Res Ther. 2016;18:25.

14. Abraham B, Eksteen B, Nedd K, et al. 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). Adv Ther. 2022;39:2109–27.

15. Kaniewska M, Moniuszko A, Rydzewska G. The efficacy and safety of the biosimilar product (Inflectra(®)) compared to the reference drug (Remicade(®)) in rescue therapy in adult patients with ulcerative colitis. Prz Gastroenterol. 2017;12:169–74.

16. Takeuchi T, Nishikawa K, Yamada F, et al. Real-world safety and efficacy of CT-P13, an infliximab biosimilar, in Japanese rheumatoid arthritis patients naive to or switched from biologics. Mod Rheumatol. 2022;32:718–27.

17. Nikiphorou E, Hannonen P, Asikainen J, et al. Survival and safety of infliximab bio-original and infliximab biosimilar (CT-P13) in usual rheumatology care. Clin Exp Rheumatol. 2019;37:55–9.

18. Goll GL, Haavardsholm EA, Kvien TK. The confidence of rheumatologists about switching to biosimilars for their patients. Joint Bone Spine. 2018;85:507–9.

19. Sebaldt RJ, Kremer JM. CANDOO and CANOAR, CORRONA and more: advancing therapeutics through layered-in clinical data collection and feedback at the point of care. J Rheumatol. 2003;30:2308–11.

20. Kremer JM. The CORRONA database. Autoimmun Rev. 2006;5:46–54.

21. CorEvitas RA Registry. 2023. https://www.corevitas.com/registry/rheumatoid-arthritis. Accessed 26 May 2023.

22. Greenberg JD, Harrold LR, Bentley MJ, Kremer J, Reed G, Strand V. Evaluation of composite measures of treatment response without acute-phase reactants in patients with rheumatoid arthritis. Rheumatology (Oxford). 2009;48:686–90.

23. Yoo DH, Prodanovic N, Jaworski J, et al. Efficacy and safety of CT-P13 (biosimilar infliximab) in patients with rheumatoid arthritis: comparison between switching from reference infliximab to CT-P13 and continuing CT-P13 in the PLANETRA extension study. Ann Rheum Dis. 2017;76:355–63.

24. Nabi H, Hendricks O, Jensen DV, et al. Infliximab biosimilar-to-biosimilar switching in patients with inflammatory rheumatic disease: clinical outcomes in real-world patients from the DANBIO registry. RMD Open. 2022;8:e002560.

25. Harrold LR, Shan Y, Rebello S, et al. Disease activity and patient-reported outcomes in patients with rheumatoid arthritis and Sjogren's syndrome enrolled in a large observational US registry. Rheumatol Int. 2020;40:1239–48.

26. Yoshida K, Harrold LR, Middaugh N, et al. Time-varying association of rheumatoid arthritis disease activity to subsequent cardiovascular risk. ACR Open Rheumatol. 2022;4:587–95.

27. Pappas DA, O'Brien J, Guo L, et al. Treatment patterns and clinical outcomes in patients with rheumatoid arthritis initiating etanercept,

adalimumab, or Janus kinase inhibitor as first-line therapy: results from the real-world CorEvitas RA Registry. Arthritis Res Ther. 2023;25:166.

28. Pappas DA, O'Brien J, Guo L, et al. Outcomes of etanercept and Janus kinase inhibitor treatment after first-line use of adalimumab in patients with rheumatoid arthritis [abstract]. 2022. https://acrabstracts.org/abstract/outcomes-of-etanercept-and-janus-kinase-inhibitor-treatment-after-first-line-use-of-adalimumab-in-patients-with-rheumatoid-arthritis. Accessed 24 Oct 2023.