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Authors

Bansback, Nick
Curtis, Jeffrey R
Huang, Jie
et al.

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BRIEF REPORT

Patterns of Tumor Necrosis Factor Inhibitor (TNFi) Biosimilar Use Across United States Rheumatology Practices

Nick Bansback,[1] Jeffrey R. Curtis,[2] Jie Huang,[3] Zeling He,[3] Michael Evans,[4] Tracy Johansson,[5] Kaleb Michaud,[6] Gabriela Schmajuk,[7] and Katherine P. Liao[8]

Objective. It is unclear if biosimilars of biologics for inflammatory arthritis are realizing their promise to increase competition and improve accessibility. This study evaluates biosimilar tumor necrosis factor inhibitor (TNFi) utilization across rheumatology practices in the United States and compares whether patients initiating biosimilars remain on these treatments at least as long as new initiators of bio-originators.

Methods. We identified a cohort of patients initiating a TNFi biosimilar between January 2017 and September 2018 from an electronic health record registry containing data from 218 rheumatology practices and over 1 million rheumatology patients in the United States. We also identified a cohort of patients who initiated the bio-originator TNFi during the same period. We calculated the proportion of biosimilar prescriptions compared with other TNFi's and compared persistence on these therapies, adjusting for age, sex, diagnoses codes, and insurance type.

Results. We identified 909 patients prescribed the biosimilar infliximab-dyyb, the only biosimilar prescribed, and 4413 patients with a new prescription for the bio-originator infliximab. Biosimilar patients tended to be older, have a diagnosis code for rheumatoid arthritis, and covered by Medicare insurance. Over the study period, biosimilar prescriptions reached a maximum of 3.5% of all TNFi prescriptions. Patients persisted on the biosimilar at least as long as the bio-originator infliximab (hazard ratio [HR] 0.83, $P = 0.07$).

Conclusion. The uptake of biosimilars in the United States remains low despite persistence on infliximab-dyyb being similar to the infliximab bio-originator. These results add to clinical studies that should provide greater confidence to patients and physicians regarding biosimilar use.

INTRODUCTION

Biosimilars of biologics, specifically tumor necrosis factor inhibitors (TNFis) for inflammatory conditions such as rheumatoid arthritis (RA), psoriasis, psoriatic arthritis (PsA), and ankylosing spondylitis (AS) entered the US market in 2016. Biosimilars are biological products that are "highly similar to the reference product notwithstanding minor differences in clinically inactive components." One hope for biosimilars was that they would lower the cost of TNFi therapy, increase competition, and improve accessibility for patients. Prior to

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[1]Nick Bansback, MSc, PhD: University of British Columbia and Arthritis Research Canada, Vancouver, British Columbia, Canada; [2]Jeffrey R. Curtis, MD, MS, MPH: University of Alabama at Birmingham; [3]Jie Huang, MS, Zeling He, MS: Brigham and Women's Hospital, Boston, Massachusetts; [4]Michael Evans, MS: University of California San Francisco; [5]Tracy Johansson, MS: Practice, Advocacy & Quality, American College of Rheumatology, Atlanta, Georgia; [6]Kaleb Michaud, PhD: University of Nebraska Medical Center, Omaha, Nebraska, and Forward, The National Databank for Rheumatic Diseases, Wichita, Kansas; [7]Gabriela Schmajuk, MD: Rheumatology Division, San Francisco VA Medical Center, San Francisco, CA; [8]Katherine P. Liao, MD, MPH: Brigham and Women's Hospital, Boston, MA and Boston VA Medical Center and Harvard Medical School.

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Address correspondence to Katherine P. Liao, MD, MPH, Brigham and Women's Hospital, Division of Rheumatology, Immunology, and Allergy, 60 Fenwood Road, Boston, MA 02115. Email: kliao@bwh.harvard.edu.

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SIGNIFICANCE & INNOVATIONS

- Among TNFi biosimilar prescriptions, only infliximab-dyyb has been prescribed, comprising of a maximum of 3.5% of all TNFi prescriptions, with the majority of new initiators previously being on the bio-originator infliximab.
- Patients remain on the biosimilar infliximab-dyyb for a similar amount of time as the bio-originator infliximab.
- Merging electronic health record data from hundreds of rheumatology practices into one registry enables early studies of new treatment options in rheumatology, such as biosimilars.

US Federal Drug Administration (FDA) approval, extensive analytical and clinical studies comparing each biosimilar to its bio-originator to confirm "no clinical meaningful differences" were required. Whether they have been widely adopted remains to be seen as there are limited data on biosimilar utilization in the United States.

Because biosimilars for rheumatic conditions are relatively new to the US market, a study population comparing sufficient patients prescribed biosimilars can be difficult to obtain even within a large health care system, as rheumatology patients tend to be a small percentage of any overall patient population. Rheumatology-specific electronic health record (EHR) data registries, such as the American College of Rheumatology (ACR) Rheumatology Informatics System for Effectiveness (RISE) (1), could facilitate the ability to examine the early utilization of new rheumatic disease–specific therapies, such as TNFi biosimilars.

The objective of this study was to evaluate early biosimilar TNFi utilization in the United States and to measure persistence of biosimilars compared with their bio-originator as a proxy for both effectiveness and safety of treatment.

MATERIALS AND METHODS

Data source. The RISE registry contains EHR data from approximately 218 rheumatology practices and over 1 million unique rheumatology patients (1). The EHR data in RISE were collected passively with the primary purpose to assist participating practices with national quality reporting requirements. These data also serve as a platform for studies on quality reporting and health care utilization consisting mainly of group and private practices across the United States.

Study period. To determine the starting month and year for analysis, we searched for the first biosimilar prescription in the RISE data set using medication codes and string searches for the available biosimilars in the US market. These included infliximab-dyyb or "Inflectra" (launched in the United States in November 2016) and infliximab-abda or "Renflexis" (launched in July 2017). We identified that the first biosimilar prescribed for any patient in RISE was infliximab-dyyb in January 2017. There were no data available for other biosimilars during our study period in the RISE data set.

Patients. We identified a cohort of patients who initiated a biosimilar in the time period from January 2017 through September 2018. We also identified a cohort of patients who initiated the bio-originator infliximab or "Remicade" during the same period. New users of infliximab were defined as patients initiating infliximab at or after the date of the first biosimilar prescription in January 2017 and had no biosimilar or bio-originator infliximab prescriptions or infusions in the 3 months prior. Patients who initiated infliximab but switched to the biosimilar during the study period were included only in the biosimilar group, thus their time zero begins at the start of the biosimilar. All subjects were followed until they were either prescribed another biologic disease-modifying antirheumatic drug (DMARD) or to their last follow-up date in the EHR, whichever came first.

Covariates. We extracted information on patient age, sex, race, insurance type (Medicare, Medicaid, commercial), geographic location (region), diagnoses codes (International Classification of Diseases 9th and 10th revision), and prior drug utilization from RISE. Specifically, we examined utilization of either biologic or nonbiologic DMARD use in the 3 months prior to starting the biosimilar or infliximab.

Analysis. To assess biosimilar utilization across RISE practices, we calculated the proportion of biosimilar prescriptions compared with other TNFis each month from January 2017, the month of the first biosimilar prescription, to September 2018, the last month for follow-up in this study.

Among new initiators of the biosimilar and bio-originator infliximab, baseline demographic data were compared between the two groups. Persistence on the biosimilar was compared with new initiators of infliximab and defined as a new prescription for either the biosimilar or infliximab; all patients must have had at least 12 weeks of follow-up time in the RISE data (defined by the last observation available) and no new prescription for another biologic DMARD. Data on persistence between the biosimilar and infliximab were compared using Kaplan-Meier curves. As a sensitivity analysis, we constructed Kaplan-Meier curves for patients with 2 or more consecutive prescriptions of either the biosimilar or infliximab, and persistence was defined as above, with 12 or more weeks of follow-up time after the second prescription. As in the main analysis, patients who filled or received another biologic DMARD in the follow-up period were considered nonpersistent.

Cox proportional hazards regression analysis was conducted to examine the influence of biosimilar versus infliximab utilization on persistence, adjusting for age, sex, and diagnosis codes—factors that differed between those initiating a biosimilar versus infliximab.

Analyses were performed using R (v.3.4.4). The RISE registry was reviewed by the Western Institutional Review Board and has

Table 1. Patient characteristics at baseline, prior to initiating infliximab-dyyb or infliximab

Clinical Characteristics	Infliximab-dyyb, n = 909	Infliximab, n = 4329	*P* Value
Age, mean (yrs)	64.9 (13.4)	57.5 (14.3)	<0.001
Female, %	647 (71.18%)	3361 (73.02%)	0.276
Self-reported race, n (%)[a]			<0.001
White	680 (83.54%)	2475 (75.05%)	
Black	36 (4.42%)	303 (9.19%)	
Other	98 (12.04%)	520 (15.77%)	
Diagnosis codes, n (%)			
Rheumatoid arthritis	536 (58.97%)	2192 (49.67%)	<0.001
Psoriasis or psoriatic arthritis	177 (19.47%)	699 (15.84%)	0.008
Ankylosing spondylitis	51 (5.61%)	341 (7.73%)	0.0031
bDMARDs, n (%)			
Any TNFi	703 (77.34%)	934 (21.16%)	<0.001
Adalimumab	77 (8.47%)	919 (21.23%)	<0.001
Certolizumab	32 (3.52%)	224 (5.17%)	0.042
Etanercept	48 (5.28%)	510 (11.78%)	<0.001
Golimumab	24 (2.64%)	181 (4.1%)	0.047
Infliximab	522 (57.43%)	0	...
Abatacept	30 (3.3%)	181 (4.18%)	0.238
Rituximab	9 (0.99%)	47 (1.09%)	0.841
Tocilizumab	17 (1.87%)	147 (3.4%)	0.018
Tofacitinib	26 (2.86%)	127 (2.93%)	0.975
Nonbiologic DMARD[b]	37 (4.07%)	132 (3.05%)	0.069
No prior DMARD information	124 (13.64%)	1995 (46.08%)	<0.001
Type of insurance, n (%)[c]			<0.001
Medicare	352 (69.84%)	827 (40.96%)	
Medicaid	10 (1.98%)	97 (4.80%)	
Commercial	142 (28.17%)	1095 (54.23%)	
Geographic region[d]			<0.001
New England	3 (0.33%)	93 (2.14%)	
Mid-Atlantic	37 (4.07%)	821 (19.0%)	
East North Central	126 (13.86%)	742 (17.14%)	
West North Central	8 (0.88%)	399 (9.22%)	
South Atlantic	228 (25.8%)	996 (23.01%)	
East South Central	108 (11.88%)	337 (7.78%)	
West South Central	118 (12.98%)	377 (8.71%)	
Mountain	95 (10.45%)	315 (7.28%)	
Pacific	186 (20.46%)	249 (5.75%)	

Abbreviation: bDMARD, biologic disease-modifying antirheumatic drug; TNFi, tumor necrosis factor inhibitor.
[a]Available in n = 822 biosimilar and n = 3298 in infliximab.
[b]Nonbiologic DMARD = methotrexate, hydroxychloroquine, leflunomide, and sulfasalazine.
[c]Available on n = 504 biosimilar and n = 2019 infliximab.
[d]Geographic regions: New England: ME, MA, CT, VT, NH, RI; Mid-Atlantic: MD, PA, VA, NJ, NY, NM, DC, WV; East North Center: KS, IA, MN, MO, NE, ND, SD; South Atlantic: NC, SC, GA, FL; East South Central: AL, KY, MS, TN; West South Central: AK, LA, OK, TX; Mountain: CO, AZ, UT, NM, ID, MT, WY; Pacific: AL, CA, HI, OR, WA.

been designated as a quality improvement registry allowing for studies on health care utilization using a limited data set without individual patient consent.

RESULTS

We identified 909 patients who were prescribed the biosimilar infliximab-dyyb and 4,413 patients with a new prescription for the bio-originator infliximab in the period from January 2017 through September 2018. No other biosimilar prescriptions were identified in the registry during the study period. Overall, biosimilar prescriptions reached a maximum of 3.5% of all TNFi prescriptions during the study period, contributing to 17% of new infliximab-based prescriptions. Patients prescribed biosimilars tended to be older, have a diagnosis code for RA, and were covered by Medicare insurance (Table 1). The region with the most biosimilar prescriptions was the South Atlantic, comprising 25.8% of all biosimilars in RISE, and the region with the fewest prescriptions being New England. Although New England was one of the regions with the least number of practices in the RISE registry—and the South Atlantic had the most—there was no correlation between number of practices per region and biosimilar prescriptions. The Mid-Atlantic region comprised 17.8% of RISE practices, second only to the South Atlantic in the number of practices. However, it was the third lowest

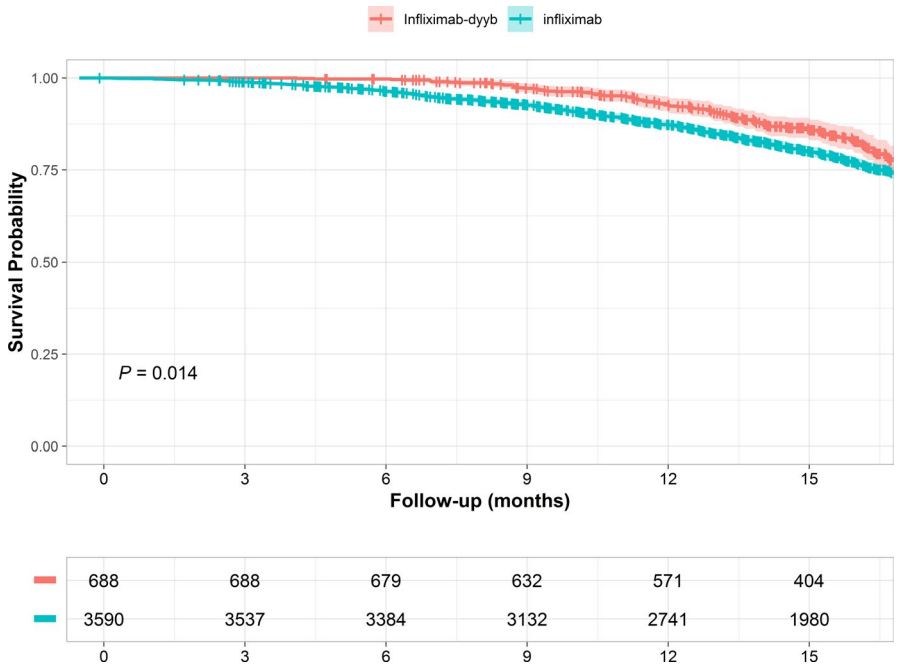

Figure 1. Comparison of persistence on treatment among infliximab-dyyb to infliximab among new initiators.

prescriber of the biosimilar. Nearly 60% of patients on the biosimilar were using infliximab prior to switching to infliximab-dyyb.

Although crude persistence to biosimilar infliximab-dyyb was greater than infliximab (80% vs 75%, $P = 0.02$) at 20 months follow-up (Figure 1), the clinical difference was relatively small. In the sensitivity analysis, which was restricted to patients with at least two consecutive prescriptions for the biosimilar or infliximab, we observed a similar small difference in persistence of 5% with a higher percentage persisting on biosimilars ($P = 0.02$). The results of the multivariate Cox proportional hazards model are shown in Table 2. After adjusting for the potential confounding variables, we observed no statistically significant difference in persistence with treatment between the two groups; the HR for nonpersistence was 0.83 ($P = 0.07$) in biosimilar-dyyb compared with infliximab.

DISCUSSION

This study describes the uptake of biosimilars in patients with inflammatory disease using real-world data from rheumatology practices across the United States. Despite the promise of lower prices and increasing data on the equivalent safety and efficacy from clinical trials (2), the uptake of biosimilars in the United States remains low; nearly 2 years after market entry, only 3.5% among rheumatology practices have participated in the RISE registry. Furthermore, we observed that persistence on infliximab-dyyb was similar to infliximab, further allaying concerns over the use of biosimilars even after adjusting for potential differences between the groups.

The uptake of biosimilars in this study contrasts with that in other countries. In Asia, biosimilar use within the first year was greater than 10% (3). A study in Sweden showed that the uptake of biosimilars was over 30% by the end of 2016 (4). There are various plausible reasons for the low uptake of biosimilars in the United States. Potential causes include mistrust from patients or physicians about the equivalence between biosimilars and their originator (5). Some of this mistrust has been facilitated by unfamiliarity with biosimilars, misinformation, and lobbying (6). Complexities with regard to pricing also mean the savings realized in other countries (7) may not be seen in the United States (8). For

Table 2. Hazard ratio among new initiators of biosimilar or infliximab for nonpersistence (switching to another bDMARD), adjusted for potential confounders

	Base Model			Base Model + Diagnosis		
Clinical Characteristics	HR	95% CI	*P* value	HR	95% CI	*P* value
Age	0.99	0.99, 1.0	0.05	0.99	0.99, 1.0	0.001
Sex	0.99	0.84, 1.2	0.91	0.92	0.78, 1.09	0.35
Race (white vs non-white)	1.18	1.0, 1.4	0.05	1.14	0.97, 1.35	0.11
Diagnoses codes (RA vs other)	...	...	...	1.54	1.32, 1.79	<0.001
Biosimilar	0.84	0.69, 1.0	0.10	0.83	0.68, 1.01	0.07

Abbreviation: bDMARD, biologic disease-modifying antirheumatic drug; HR, hazard ratio; RA, rheumatoid arthritis.

example, the average sales price, according to the Centers for Medicare & Medicaid Services, of a 100-mg vial of infliximab-dyyb was higher than the equivalent vial of infliximab in early 2017—though this had reversed by the end of 2017, with biosimilar products becoming increasingly less expensive over time (9). At least for commercially insured patients, manufacturers have also allegedly offered rebates on originator products to undercut biosimilar competition, increasing the barrier to entry for biosimilars (10). This might explain why, despite three infliximab biosimilars being approved in the US market, uptake has been slow.

The strength of our study is that we are using a large data set from a national US registry. Although trials of biosimilars have typically enrolled fewer than 600 participants, the RISE data has enabled us to compare nearly 1000 patients using a biosimilar to an originator product using real-world data (11). Limitations to this study include the fact that RISE may not reflect a general sampling of US rheumatology practices. Of the RISE practices included in this study, 91% were classified as solo or group practices. The remaining practices were classified as other clinical setting (5%), health system (1%), or unknown (3%). We also adjusted for a limited set of potentially confounding variables and did not include, for example, disease activity or obesity (body mass index). Lastly, we have not been able to study unexpected rare adverse events, though this will become possible over the longer term.

In summary, our study using real-world data suggests no apparent difference in patient's persistence in biosimilar versus bio-originator infliximab, but despite this, it finds low biosimilar utilization. This study also highlights the importance of rheumatology-specific EHR registries that can be used to study early trends for new treatments that may be too uncommon to study in large population registries. Our findings contribute to an evidence base that includes existing clinical trial data, which implies that if price reductions can be realized, biosimilar utilization should be promoted. Further policies are needed to promote fair market competition and ensure accessibility to patients given the issues many patients have with affordability and lack of access to this speciality class of drugs.

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AUTHOR CONTRIBUTIONS

All authors were involved in drafting the article or revising it critically for important intellectual content, and all authors approved the final version to be published and take responsibility for the integrity of the data and the accuracy of the data analysis.

Study conception and design. Bansback, Huang, Liao.

Acquisition of data. Evans, Johansson, Schmajuk.

Analysis and interpretation of data. Bansback, Curtis, Huang, He, Michaud, Schmajuk, Liao.

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