Research Report

Impact of Nonmedical Switches From Reference Infliximab to Biosimilars on Disease Control Within a Rheumatology Practice

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Marta Jankowska, PharmD[1], Krista Dessureault, PharmD, BCPS[1], Julie MacDougall, PharmD, MBA, BCPS[1], Matthew Sowers, PharmD[1], Morgan Merchand, NP[2], and Amanda G. Kennedy, PharmD, BCPS[3]

Abstract

Background: Infliximab is an anti–tumor necrosis factor agent used to treat rheumatologic disease. Evidence on the safety of switching to biosimilars and the associated risk factors for flares/loss of disease control within rheumatology is limited. **Objective:** The primary objective is to evaluate nonmedical switches from reference infliximab to biosimilars in rheumatology on risks and level of disease control. **Methods:** This retrospective analysis of data was conducted on all adult patients at our institution's rheumatology clinics with a rheumatologic diagnosis who were stable on reference infliximab and switched to the formulary biosimilars infliximab-dyyb or infliximab-abda, during the study period. Patient demographics as well as concomitant rheumatologic medications, markers of disease control, and hospitalization data were collected. **Results:** Of the 317 patients screened, 48 patients met inclusion criteria. A total of 29 patients (60.4%) were on reference infliximab and 19 patients (39.6%) were switched to biosimilar. Eight patients (42.1%) flared after a switch to biosimilar. Of the biosimilar patients, all patients were on infliximab-dyyb and were mandated to switch by insurance. Two patients who flared after switch to biosimilar (25%) had a delay in treatment due to attempts to receive prior authorization for reference infliximab. **Conclusions:** In the patients who switched to biosimilar, almost half experienced a flare. Two of these eight patients (25%) had a delay in treatment after the switch, which may be a risk factor for flaring/loss of disease control. Pharmacists should be following patients who switch to biosimilar closely during the transition period, to monitor for signs of flares/loss of disease control.

Keywords

rheumatology, clinical decision-making, clinical pharmacy, adult medicine, ambulatory care

Introduction

Infliximab is an anti–tumor necrosis factor agent used to treat rheumatologic disease, including ankylosing spondylitis, psoriatic arthritis, rheumatoid arthritis, and uveitis.[1] The use of infliximab within these disease states is well studied, though there has been an increase in use of the 4 U.S. Food and Drug Administration (FDA)–approved infliximab biosimilars in recent years, infliximab-abda, infliximab-axxq, infliximab-dyyb, and infliximab-qbtx, due to their associated reduction in cost. The FDA defines biosimilars as a, "biological product that is highly similar and has no clinically meaningful differences from an existing FDA-approved reference product."[2] Manufacturers must demonstrate that the suggested biosimilar product has no clinically meaningful differences in safety, purity, and efficacy from the reference product through extensive pharmacokinetic and pharmacodynamic studies.[2] A biosimilar product that undergoes additional requirements may

[1]Specialty Pharmacy Services, The University of Vermont Medical Center, Burlington, VT, USA
[2]Division of Rheumatology, The University of Vermont Medical Center, Burlington, VT, USA
[3]Department of Medicine, Larner College of Medicine, The University of Vermont, Burlington, VT, USA

Corresponding Author:
Marta Jankowska, Specialty Pharmacy Services, The University of Vermont Medical Center, 111 Colchester Avenue, Burlington, VT 05405, USA.
Email: marta.jankowska@uvmhealth.org

be named an interchangeable product under the Biologics Price Competition and Innovation Act. An interchangeable product is a biosimilar product that is expected to produce the same clinical result as the reference product in any given patient and may be substituted for the reference product without prescriber input.[2] Switching studies are conducted for products pursing interchangeable designation.[2] Infliximab currently does not have any interchangeable data.[3]

Risk factors for flares in rheumatology include higher baseline disease activity, poor adherence to therapy, stress, or active infection.[4,5] Evidence on the safety of switching to biosimilars and the associated risk factors for flares/loss of disease control within rheumatology is limited. The NOR-SWITCH trial evaluated maintaining originator infliximab or switching to biosimilar CT-P13 (now infliximab-dyyb) and showed that switching products was noninferior to continued treatment, establishing the safety and efficacy of switching to biosimilar product.[6,7] The trial evaluated patients with various diagnoses, though only rheumatoid arthritis, psoriatic arthritis, and spondylarthritis represented rheumatologic diagnoses.[6] A retrospective case series, which evaluated the recurrence rates of inflammation after switching from originator infliximab to biosimilar infliximab-abda for noninfectious uveitis, found that patients who switched to biosimilar product experienced more flares than when previously treated with the originator infliximab.[8] These conflicting results highlight the need for additional studies that evaluate various rheumatologic diagnoses, along with several biosimilar products.

The purpose of this pilot study was to evaluate the level of disease control after nonmedical switches from reference infliximab to biosimilars in rheumatology patients. Nonmedical switches are defined as a change in a patient's treatment regimen for reasons other than efficacy, safety, or adherence, and may often be required by insurance companies as a means of reducing medication costs.[9]

Methods

This was a secondary data analysis of electronic health record data (EPIC) at the University of Vermont Health Network (UVMHN). The (UVMHN) is a 6-hospital network serving patients in (Vermont) and (northern New York). Two of the network hospitals have dedicated rheumatology clinics. Eligible patients included adults 18 years and older at either the University of (Vermont) Medical Center (UVMMC) in (Burlington), (Vermont), or Central (Vermont) Medical Center (CVMC) in (Berlin), (Vermont), with a rheumatologic diagnosis, who were clinically stable on reference infliximab or switched from reference product to the formulary biosimilars infliximab-abda or infliximab-dyyb, between January 1, 2018 and August 31, 2023. Patients were excluded if they were initially started on a biosimilar, started reference infliximab prior to January 1, 2018, or if they received the infusions outside of (UVMMC) or (CVMC).

Demographic data included date of birth, gender identity, race, ethnicity, insurance, height, weight, and smoking status. Rheumatology data included rheumatologic diagnoses, diagnosis year, age at disease diagnosis, and hospitalizations with a rheumatology flare as the primary problem during the study interval, and length of hospitalization stay. Medication-related data included concomitant disease-modifying antirheumatic drug (DMARD) use, time on medication (reference infliximab and/or biosimilar), use of acute prednisone prescriptions, indications for switching, and dosing of medication postswitch. Laboratory data consisted of Routine Assessment of Patient Index Data 3 (RAPID-3) scores, c-reactive protein (CRP), and erythrocyte-sedimentation rate (ESR). Data were collected using manual chart review and managed using REDCap electronic data capture tools hosted at the University of (Vermont).[10] This study was approved as exempt research by the University of (Vermont) Committees on Human Research (STUDY00002725).

Data were analyzed descriptively in REDCap software. The primary outcome of this study was to determine the incidence of flares or loss of disease control after a nonmedical switch to biosimilar compared with continuation of infliximab reference product. Flares/loss of disease control were defined as either provider documentation of this terminology, any numerical worsening in RAPID-3 scoring, increased ESR or CRP, the need for acute prednisone prescriptions, or dose increases while on biosimilar.

Results

A total of 317 patients were screened for eligibility. Of the 317 patients, 48 patients met study criteria. Of the 269 exclusions, 87 patients started reference infliximab over 5 years ago, 61 patients were not seen at (UVMMC) or (CVMC) Rheumatology, 43 patients were deemed unstable on reference infliximab at baseline, 51 patients were initially started on biosimilar, 48 patients received infusions at an outside infusion center, and 113 were otherwise excluded. Many patients had more than one reason for exclusion. The majority of patients on reference infliximab products were white females, with a mean age of 59 years and a diagnosis of psoriatic arthritis (Table 1). Several patients who remained on reference infliximab were treated with a concomitant DMARD, the most common being methotrexate (55.2%). The majority of patients who switched to biosimilar product were of a parallel demographic, white females with a mean age of 50 years. Similarly, several patients who switched to biosimilar product were also on a concomitant DMARD, methotrexate also being the most common (63.2%). The primary diagnosis differed in the switch to biosimilar group, as

Table 1. Baseline Characteristics.

Characteristic	Reference infliximab		Infliximab biosimilar	
	N = 29	(%)	*N* = 19	(%)
Age, mean (SD)	59	(13.9)	50	(12.1)
Female	17	(58.6)	11	(57.9)
White race	28	(96.6)	18	(94.7)
Insurance				
Commercial	14	(48.3)	7	(36.8)
Medicaid	1	(3.4)	7	(36.8)
Medicare	13	(44.8)	5	(26.3)
Dual Medicare/Medicaid	1	(3.4)	0	(0)
Smoking				
Current	5	(17.2)	3	(15.8)
Former	8	(27.6)	7	(36.8)
Never	16	(55.2)	9	(47.4)
Rheumatologic diagnosis				
Rheumatoid arthritis	5	(17.2)	3	(15.8)
Psoriatic arthritis	10	(34.5)	4	(21.1)
Ankylosing spondylitis	4	(13.8)	3	(15.8)
Inflammatory arthritis	1	(3.4)	1	(5.3)
Other	9	(31.0)	8	(42.1)
Hospitalization for flare during study interval	2	(6.9)	2	(10.5)
Concomitant DMARDs				
Hydroxychloroquine	1	(3.4)	2	(10.5)
Methotrexate	16	(55.2)	12	(63.2)
Sulfasalazine	1	(3.4)	0	(0)
Leflunomide	1	(3.4)	0	(0)
On chronic prednisone	3	(10.3)	4	(21.1)
Baseline labs, if available, mean (SD)				
RAPID-3 score	9.9	(7.1)	12.4	(4.9)
CRP	7.4	(21.5)	3.6	(5.2)
ESR	17.8	(14.7)	8.9	(9.5)

it was an "other" diagnosis, which was commonly a subset of sarcoid. Primary insurance coverage differed among the two groups, as there was an almost even split between commercial and Medicare coverage for the patients in the infliximab reference group, while the biosimilar group has commercial and Medicaid as the primary coverages.

A total of 29 patients (60.4%) were on infliximab reference only during the study timeframe, with 19 patients (39.6%) who switched to biosimilar product. Of the biosimilar patients, all the patients were on infliximab-dyyb, and 17 patients (89.5%) were a result of an insurance mandate to switch to biosimilar. The other two biosimilar patients did not have clear documentation of the reason for the product switch.

Table 2 describes the flares/loss of disease control after a switch to biosimilar. There were 8 out of the 19 patients (42.1%) who flared/experienced a loss of disease control after switching products. The majority of patients who flared are no longer on biosimilar product (75%), with 5 of these patients switching back to reference infliximab and 1 patient changing therapy to a medication of a different class. Half of these patients had a documented increase in their RAPID-3 scoring, with the other half of patients either having no recorded RAPID-3 score prior to switch or score after the switch. Two patients who flared after the switch to biosimilar (25%) had a delay in treatment due to attempts to receive prior authorization for reference infliximab. Six of the 8 patients (75%) reported the flare/loss of disease control within the first 4 months following the switch.

Discussion

The results of the study suggest that switching to biosimilar infliximab-dyyb from reference infliximab may be associated with an increased risk of flares or loss of disease control for rheumatology patients. Eight out of 19 patients (42.1%) flared or experienced a loss of disease control after a switch to biosimilar product. Two of these patients (25%)

Table 2. Description of Flares/Loss of Disease Control After Switch to Biosimilar.[a]

Length of time on reference infliximab prior to switch	RAPID-3 prior to switch	RAPID-3 post switch	Time to flare post switch to biosimilar	Description	Is the patient currently on biosimilar?	Was there a delay in treatment after switch?
7 years	2.0	3.8	Reported ~2-3 months after first dose of biosimilar	36-year-old patient with inflammatory arthritis initiated on reference infliximab in March 2014 and switched to biosimilar in July 2021. A gastroenterologist note from December 2021 notes that the patient believes she had a flare up in August and September. Patient described a rash and itchy skin associated with her infusion, but symptoms improved with adding diphenhydramine.	Yes, patient stable on biosimilar at initiated dose.	Unclear, as patient received reference infliximab infusions at an outside infusion center.
~1 year	5.3	15.3	Reported 2 months after first dose of biosimilar	38-year-old patient with RA reported worsening fatigue, pruritic rash on palms, and mild, intermittent arthralgia involving hands and feet. Provider noted change in RAPID-3 score.	No, patient switched back to reference infliximab after 3 doses of infliximab biosimilar due to flaring/worsening of disease.	Yes, the patient preferred to remain on reference product and requested appeal for continued use 4 days prior to infusion due date. Appeal was denied as there was no medical indication for reference over biosimilar, resulting in a delay in treatment.
~1 year	Not reported	14.5	Reported 1 month after first dose of biosimilar	62-year-old patient with sarcoid arthritis reported that when she switched to biosimilar, she had increased symptoms, including pain in hands, wrists, ankles, and toes. She reports that after receiving an infusion of biosimilar, her face became red/hot and that she had a "blotchy redness" on her hands. Pain was more cutaneous than joints.	No, patient switched back to reference product after one dose of infliximab biosimilar due to side effects and lack of effect from biosimilar product.	No, patient received biosimilar on time.
~5.5 years	10.7	17.3	Evaluated 3 months after first dose of biosimilar	37-year-old patient with sarcoidosis. Provider notes, "unclear if [biosimilar] is less effective than brand name, as patient has bilateral trochanteric bursitis R>L." Patient reports an increase in pain, stiffness, and muscle cramps after the switch. The provider will revisit plan if cortisone injections improve bursitis, but the patient continues to feel that the biosimilar is not as effective as reference.	Yes, patient continued with the biosimilar product.	Yes, patient due for infliximab infusion every 7 weeks and received the biosimilar ~12 weeks after the last infusion, due to attempts to receive prior authorization for reference product.

(continued)

Table 2. (continued)

Length of time on reference infliximab prior to switch	RAPID-3 prior to switch	RAPID-3 post switch	Time to flare post switch to biosimilar	Description	Is the patient currently on biosimilar?	Was there a delay in treatment after switch?
8 years	14.0	15.3	Patient first reported flares 6 months after first dose, though evaluated ~9 months after first dose.	51-year-old patient with reactive arthritis. Patient reports that the biosimilar is not working as well as the reference product. Reports fewer side effects and improved symptom control with reference product. Patient reports getting flares to her hands, though prior to switch she only had flares to her feet and ankles.	No, patient switched back to and remains on reference product.	No, patient received biosimilar on time.
1.5 years	Not reported	Not reported	Reported 1 month after first dose of biosimilar	57-year-old patient with PsA. Patient only received one dose of biosimilar product, as they reported seeing no benefit, to either the reference or biosimilar product. Patient reports having breakthrough skin disease and persistent enthesitis.	No, patient switched to ustekinumab.	No, patient received biosimilar on time.
~5 years	Not reported	Not reported	Reported 4 months after first dose of biosimilar	74-year-old patient with RA. Patient reports an increase in joint pain over the first few months following the switch to biosimilar and reports thinking that "she has gone backwards since switching [to biosimilar] infusions." The provider notes an increase in joint aches and morning stiffness, which they attribute to be consistent with the switch.	No, patient switched back to and remains on reference product.	No, patient received biosimilar on time.
~12 years	Not reported	7.0	Reported 8 months after first dose of biosimilar	50-year-old patient with reactive SpA. Patient reports that the biosimilar lasts about 10 weeks and then he gets left third toe swelling that gets uncomfortable to walk on. Patient feels that brand product lasted the full 12 weeks, so they would prefer reference product.	No, patient switched back to and remains on reference product.	No, patient due for infliximab infusion every 12 weeks and received the biosimilar ~13 weeks after the last infusion, due to delaying infusion due to illness.

Abbreviations: PsA, psoriatic arthritis; RA, rheumatoid arthritis; SpA, spondyloarthropathy.
[a]All switches were required by insurance and all switches were to infliximab-dyyb.

flared or experienced a loss of disease control after a delay in treatment due to attempts to receive prior authorization for reference infliximab, which may provide reasoning for this occurrence. This leaves many patients (75%) who flared without a documented suspected reason for the flares. Of note, infliximab-dyyb is not an interchangeable product for reference infliximab, which may also provide reasoning for the observed flares/loss of disease control after switching to the product.[3]

Pharmacists have important roles in the multidisciplinary team approach to the management of chronic inflammatory disease.[11,12] The addition of a pharmacist to a patient care team can have many benefits, including medication education, improvement of patient adherence, and improved access to care through management of prior authorization requests.[11,12] Required switches to biosimilar by insurance companies will continue as new products are developed and enter the market. Many of the instances of flares/loss of disease control in the patients who switched to biosimilar occurred within the first few months after the switch, which may highlight the need for additional monitoring of patients during this time. Pharmacist education surrounding the new biosimilar product and close monitoring during the transition period may prove to be beneficial and may aid in the minimization for risk of flares or loss of disease control for patients during this time.

Our study included patients that were stable on reference infliximab, so we did not evaluate the occurrence of flares/loss of disease control in patients who did not switch to biosimilar. Future studies directly comparing the rate of flares/loss of disease control in rheumatology patients who remain on reference product to patients who switch to biosimilar are needed. Additionally, our study excluded patients who were initially started on biosimilar products. The incidence of flares/loss of disease control in this patient population would also be worth exploring. The results of this study demonstrate the further need for exploration of risk factors for flares when switching therapies. We were able to identify two patients (25%) who flared due to a delay in treatment, though noticed no other trends among the eight patients who flared.

Limitations

There are several limitations to note. This was a retrospective study, limited by a small sample size from a single health network that included a primarily white population. Our sample size did not permit more rigorous statistical comparisons; therefore, this study should be considered a pilot and would need more data to draw meaningful conclusions. We considered any numeric worsening in RAPID-3, ESR, or CRP as a flare. This may have indicated more flares than were clinically relevant; however, we wanted to be more conservative in our assessment of flares, in order to capture any patient that was affected by the change in medication. Our chart review excluded some patients on reference infliximab or biosimilar product if there was missing documentation of the medications or a lack of follow-up after the switch to biosimilar product. Additionally, the data collection was reliant on the detail of documentation within provider visit notes, which may be subject to documentation errors or omissions. The performance of RAPID-3 scoring and frequency of lab test (ESR, CRP) ordering are not standardized within the health network, which made it difficult to consistently collect information on these findings for every patient. Finally, our health network's formulary does not include every available infliximab biosimilar, which limits the findings of the study only to infliximab-abda and infliximab-dyyb.

Conclusion

In the patients who switched to biosimilar, 8 out of the 19 patients (42.1%) experienced a flare/loss of disease control. Two of these eight patients (25%) had a delay in treatment after the switch, which may be a risk factor for flaring/loss of disease control. Pharmacists should follow patients who switch to biosimilar closely during the transition period, to provide education on biosimilars and to monitor for signs of flares/loss of disease control.

Authors' Note

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Declaration of Conflicting Interests

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ORCID iDs

Marta Jankowska https://orcid.org/0009-0008-7512-2375

Julie MacDougall https://orcid.org/0000-0002-4087-2853

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