Switch from Infliximab to Infliximab-dyyb for Rheumatology Indications

Alexi Spoto, PharmD, BCPS; Katie Pitcher, PharmD, APh, BCGP; Rita Hui, PharmD, MS; Aeris Lautchang

Abstract

Introduction
Multiple expert panels at Kaiser Permanente approved infliximab-dyyb (Inflectra®, a biosimilar to the reference product infliximab (Remicade®), to be the preferred infliximab agent for therapeutic substitution from infliximab for adult patients with dermatologic, rheumatologic, and/or gastroenterologic diagnoses. The objective of this study was to assess the safety and effectiveness of infliximab-dyyb for Kaiser Permanente Northern California patients with psoriatic and rheumatoid arthritis who switched from infliximab to infliximab-dyyb.

Methods
This was an observational, data-only, non-inferiority study assessing adult patients with a rheumatologic condition of psoriatic arthritis (PsA) or rheumatoid arthritis (RA) who were switched from infliximab to infliximab-dyyb or used infliximab continuously in the Northern California region of Kaiser Permanente from May 2017 through May 2018. Both groups were followed for 12 months. The primary effectiveness outcome was disease worsening requiring acute care defined as emergency room visit or hospitalization related to the rheumatologic condition or orthopedic surgery intervention. Non-inferiority was set at an upper limit of 4%.

Results
A total of 70 individuals were identified as continuing infliximab and 727 individuals were switched to infliximab-dyyb. There were 2 patients (2.9%) in the infliximab group and 22 patients (3.0%) in the infliximab-dyyb group who experienced disease worsening requiring acute care (P = 0.03 for non-inferiority).

Conclusion
There was no increased risk of disease worsening requiring acute care in patients with RA or PsA who switched from infliximab to infliximab-dyyb when compared to patients who remained on infliximab in this population.

Introduction
It was estimated that between 1.28 to 1.36 million Americans suffered from rheumatoid arthritis (RA) in 2014.(1) As of 2020, psoriatic arthritis (PsA) was estimated to affect nearly 1 million Americans and nearly 30% of those suffering from psoriasis.(2)

Patients with RA and PsA are typically managed with medication therapy. The American College of Rheumatology Guideline for Treatment of Rheumatoid Arthritis (2015) lists methotrexate as first line therapy.(3) It is a cost-effective option compared to biologics. Methotrexate therapy, however, has been estimated to fail in approximately 25% of patients within 12 months.(4) Failure is attributed to adverse effects or lack of efficacy. The major adverse effects of methotrexate include stomatitis and mucositis, bone marrow suppression, liver toxicity, and pulmonary toxicity. Second line treatment choices include a tumor necrosis factor-α (TNF-α) inhibitor, such as infliximab (Remicade®, Janssen Biotech, Horsham, PA, USA) with or without methotrexate. For PsA, initial treatment for active disease includes TNF-α inhibitors.(5)

Treatment with a biologic such as infliximab for RA and PsA includes induction and maintenance therapy. Use of biologic products may last years or decades, depending on efficacy and tolerability. This may impose a heavy cost burden on the patient. In 2017, the FDA approved the biosimilar infliximab-dyyb (Inflectra®, Pfizer, New York, NY).(6) Infliximab-dyyb is a less costly alternative to infliximab and may help more patients access long-term treatment. It is estimated that the use of biosimilars will reduce direct spending on biologics by $54 billion from 2017 to 2026.(7)

Biosimilars are biologics that are highly similar to and have no clinically meaningful difference from the existing FDA-approved biologic, according to the FDA.(8)

Infliximab-dyyb was FDA-approved in the United States(6) for all the same adult treatment indications as the reference (originator) product infliximab(9,10) based on the results of the NOR-SWITCH trial.(11) The NOR-SWITCH trial was a randomized, non-inferiority, double-blind phase 4 trial with 52 weeks of follow up.(11) Patients who were stable on infliximab and treated in the hospital for at least 6 months of therapy were eligible to take part in the trial. Patients were randomized to either continue on infliximab or switched to infliximab-dyyb and the dosing regimen was unchanged. The non-inferiority margin was set at 15%, assuming 30% disease worsening in each arm. The study evaluated patients with each infliximab indication, including Crohn’s disease (CD), ulcerative colitis (UC), spondyloarthritis, RA, PsA, and chronic plaque psoriasis. For those with a diagnosis of RA receiving infliximab, 11 patients (36.7%) experienced disease worsening compared to 9 patients (30%) in the infliximab-dyyb group (RR 4.5%, 95% CI -20.3 to 29.3). Meanwhile 7 patients (53.8%) with PsA who received infliximab experienced disease worsening compared to 8 patients (61.5%) receiving infliximab-dyyb (RR -8.8%, 95% CI -45.4 to 28.1). Overall, disease worsening occurred in 53 patients (26%) continued on infliximab, and in 61 (30%) of patients transitioned to infliximab-dyyb with an adjusted treatment difference -4.4% (95% CI -12.6 to 3.9). Adverse events occurred at a similar rate, with 24 serious adverse events (10%) for infliximab and 21 (9%) for infliximab-dyyb. The authors of this study concluded that infliximab-dyyb was non-inferior to infliximab.(11) However, only 22% of all patients in the study had RA or PsA, leaving the question as to whether
the results of the NOR-SWITCH trial are applicable on a larger scale to patients with rheumatology diagnoses. The aim of the current study was to compare the real-world effectiveness of switching from infliximab to infliximab-dyyb compared to continuing on infliximab in patients with RA or PsA in Kaiser Permanente Northern California.

Methods

Study Design
This was a retrospective, data-only non-inferiority cohort study conducted within the Kaiser Permanente Northern California (KPNC) region. Kaiser Permanente is a national integrated healthcare system serving over 12 million members nationally and 4.4 million members in northern California. Electronic data are captured for all services provided within the network. This study was approved by the KPNC institutional review board and a waiver of informed consent was received.

Study Population
Electronic databases and health records were used to identify patients with RA and PsA in KPNC who received infliximab or infliximab-dyyb between May 1, 2017 through May 31, 2018, the cohort identification period. While the switch was offered, it was not mandatory, and patients could continue treatment with infliximab. The index date was defined as the first infliximab-dyyb administration for those who switched from infliximab to infliximab-dyyb, or the first infliximab administration within the cohort identification period for those continued on infliximab. Patients were included if they were 18 years or older and had a documented negative tuberculosis test. Patients were excluded if they were nursing or pregnant females, they had not used infliximab at a stable dose for at least 6 months prior to the index date, or the dose of the infliximab product was changed on the index date. The follow-up period was 12 months after the index date.

Outcome Measures and Definitions
The primary outcome was a composite endpoint of disease worsening requiring acute care, which was defined as an emergency room visit, hospitalization, or orthopedic surgery intervention related to the rheumatologic condition. Secondary outcomes included disease worsening requiring acute care or switch to an alternative biologic or tofacitinib, average change in CRP, average change in ESR, and incidence of provider-reported adverse reactions.

Statistical Analysis
Intent-to-treat analysis was used. Based on the results of the NOR-SWITCH trial\(^\text{(11)}\), disease worsening was assumed in 30% of patients in each arm. In order to detect a 4% relative non-inferiority upper-limit margin, 1624 individuals would be required in each study arm. The authors of the NOR-SWITCH trial used a 15% margin but based on the retrospective nature of this study and a low event rate for rheumatologic conditions requiring acute care, this study set the non-inferiority upper-limit margin at 4%. To compare baseline characteristics, Chi-square tests were used for categorical variables, and t tests were used for continuous variables. Statistical analyses were performed using SAS statistical software version 9.4 (SAS Institute, Cary, NC). For this study, \(\alpha\) was set at 0.05.

Results

Cohort
A total of 1405 patients were identified with diagnoses of RA or PsA within KPNC. After applying exclusion criteria, 797 individuals were included in the study cohort (Figure 1). There were 70 individuals who continued on infliximab and 727 who switched to infliximab-dyyb. The two study groups were very different in size because of the clinical practice within Kaiser Permanente. Kaiser Permanente embraces biosimilars and use of infliximab-dyyb was quickly implemented across medical centers, explaining why the infliximab-dyyb group was over 10 times larger than the infliximab continue group.

Figure 1. Cohort flow diagram

Baseline Characteristics
Baseline characteristics were shown in Table 1. Patients in the infliximab-dyyb switch group were older, with a mean age (± standard deviation) of 65.9 ± 13.9 years old versus the infliximab continue group of 59.8 ± 14.8 years old (\(P < 0.01\)). In both study arms, females comprised 77.1% and 72.4% of the infliximab and infliximab-dyyb arms, respectively (\(P = 0.39\)). Rheumatoid arthritis made up the majority of diagnoses in both arms with 57.1% of patients in the infliximab continue arm and 67.5% in the infliximab-dyyb switch arm (\(P = 0.08\)). More patients in the infliximab arm (28.6%) had diagnoses of inflammatory polyarthritis versus the infliximab-dyyb arm (9.4%), \(P < 0.01\). The mean number of infliximab product administrations during the study period was similar between the two groups, with 6.8 ± 3.4 administrations in the infliximab group and 6.4 ± 2.6 administrations in the infliximab-dyyb group (\(P = 0.23\)). This corresponds with approximately one administration of an infliximab product every 2 months.

Primary Outcome
There were 2 patients (2.9%) in the infliximab continue group versus 22 patients (3.0%) in the infliximab-dyyb switch group who experienced disease worsening requiring acute care (\(P = 0.03\) for non-inferiority) (Table 2). Non-inferiority was met as the difference in the proportion of patients with a composite end point for disease worsening requiring acute care was -0.17%, falling within the prespecified upper-limit relative non-inferiority margin of +4%.
Table 1. Baseline characteristics

| Characteristic                        | Infliximab (n = 70) | Infliximab-dyyb (n = 727) | p value |
|---------------------------------------|---------------------|---------------------------|---------|
| Age, mean ± SD                        | 59.8 ± 14.8         | 65.9 ± 13.9               | <0.01   |
| Female, n (%)                         | 54 (77.1)           | 526 (72.4)                | 0.39    |
| Rheumatoid arthritis, n (%)           | 40 (57.1)           | 491 (67.5)                | 0.08    |
| Psoriatic arthritis, n (%)            | 10 (14.3)           | 168 (23.1)                | 0.10    |
| Inflammatory polyarthritis, n (%)     | 20 (28.6)           | 68 (9.4)                  | <0.01   |
| Number of infliximab administrations, mean ± SD | 6.8 ± 3.4 | 6.4 ± 2.6 | 0.23 |
| Mean ESR at baseline, mg/L            | 29.55 ± 15.41 (n = 22) | 28.08 ± 19.72 (n = 244) | 0.73 |
| Mean CRP at baseline, mg/L            | 2.04 ± 5.69 (n = 23) | 0.85 ± 2.20 (n = 135)    | 0.08 |

Table 2. Primary outcome: composite of disease worsening requiring acute care

| Characteristic                        | Infliximab (n = 70) | Infliximab-dyyb (n = 727) | p value |
|---------------------------------------|---------------------|---------------------------|---------|
| Overall incidence, n (%)              | 2 (2.9)             | 22 (3.0)                  | 0.03    |
| Emergency room visit, n (%)           | 1 (1.4)             | 16 (2.2)                  | -       |
| Hospitalization, n (%)                | 0                   | 1 (0.1)                   | -       |
| Orthopedic surgery, n (%)             | 1 (1.4)             | 5 (0.7)                   | -       |

Secondary Outcomes

Table 3 shows that there were 9 patients (12.9%) in the infliximab continue group compared to 159 patients (21.9%) in the infliximab-dyyb group who experienced disease worsening requiring acute care or switched to an alternative biologic or tofacitinib (P = 0.88 for non-inferiority). Non-inferiority was not demonstrated for this secondary outcome. A sub-analysis was performed to evaluate patients who switched to an alternative biologic or tofacitinib. Seven patients (10%) in the infliximab group compared to 10 patients (1.4%) in the infliximab-dyyb group switched to an alternative non-infliximab biologic. Meanwhile, no individuals in the infliximab continue group and 130 individuals (17.9%) in the infliximab-dyyb group switched back to infliximab. Individuals who switched from infliximab-dyyb back to infliximab did so after receiving a mean of 2.77 doses of infliximab-dyyb (SD 1.99; range 1 to 12 doses). This outcome was not applicable for the infliximab continue group.

Table 3. Secondary outcome: composite of disease worsening requiring acute care or switch to an alternative biologic or tofacitinib

| Characteristic                        | Infliximab (n = 70) | Infliximab-dyyb (n = 727) | p value (for noninferiority) |
|---------------------------------------|---------------------|---------------------------|-------------------------------|
| Overall incidence, n (%)              | 9 (12.9)            | 159 (21.9)                | 0.88                          |
| Emergency room visit, n (%)           | 1 (1.4)             | 13 (1.8)                  | -                             |
| Hospitalization, n (%)                | 0                   | 1 (0.1)                   | -                             |
| Orthopedic surgery, n (%)             | 1 (1.4)             | 5 (0.7)                   | -                             |
| Switch to alternative biologic or tofacitinib, n (%) | 7 (10) | 140 (19.3) | - |
| Non-infliximab biologic or tofacitinib, n (%) | 7 (10) | 10 (1.4) | - |
| Infliximab, n (%)                     | N/A                 | 130 (17.9)                | -                             |

Table 4. Secondary outcome: provider-reported adverse reactions

| Characteristic                        | Infliximab (n = 70) | Infliximab-dyyb (n = 727) | p value |
|---------------------------------------|---------------------|---------------------------|---------|
| Overall Adverse Reactions, n (%)      | 2 (2.9)             | 11 (1.5)                  | 0.40    |
| Infusion reaction, n (%)              | 1 (1.4)             | 1 (0.1)                   | 0.10    |
| Rash, n (%)                           | 1 (1.4)             | 1 (0.1)                   | 0.10    |
| Drug-induced lupus, n (%)             | 0                   | 2 (0.3)                   | 0.64    |
| Joint pain, n (%)                     | 0                   | 2 (0.3)                   | 0.64    |
| Elevated LFTs, n (%)                  | 0                   | 1 (0.1)                   | 0.45    |
| GL side effects, n (%)                | 0                   | 1 (0.1)                   | 0.45    |
| Headache, n (%)                       | 0                   | 1 (0.1)                   | 0.45    |
| Itching, n (%)                        | 0                   | 1 (0.1)                   | 0.45    |
| Anti-NMDA receptor antibody-mediated encephalopathy, n (%) | 0 | 1 (0.1) | 0.45 |
Patients used a variety of alternative biologics after failing infliximab products, however a large number of individuals in the infliximab-dyyb group switched back to infliximab (n = 130). The biologic products to which patients switched after use of infliximab products included abatacept, adalimumab, etanercept, golimumab, tocilizumab, and tofacitinib.

Changes in ESR and CRP were also evaluated. ESR and CRP are both non-specific markers for inflammation but may be elevated in other unrelated conditions such as infection or trauma. For both CRP and ESR, the higher the number, in theory, the more inflammation is present when evaluated in the context of rheumatologic diseases. A positive change over time indicates an increase in inflammatory plasma markers and a negative change indicates a reduction. For those with baseline and follow-up CRP labs within the study period, those continuing on infliximab had an average change (= standard deviation) in CRP of -0.52 ± 2.34 mg/L compared to those who switched to infliximab-dyyb who had an average change in CRP of -0.16 ± 2.15 mg/L (two-tailed P = 0.46). For patients with baseline and follow-up ESR labs during the study period, those continuing on infliximab had an average change (= standard deviation) in ESR of 2.86 ± 21.86 mm/hr and those who switched to infliximab-dyyb had an average change in ESR of 1.14 ± 14.62 mm/hr (two-tailed P = 0.61).

There were a total of 13 patients who experienced adverse reactions, 2 patients (2.9%) in the infliximab arm and 11 patients (1.5%) in the infliximab-dyyb arm (two-tailed P = 0.40). A breakdown of adverse reactions by type were shown in Table 4. All adverse reactions that occurred are documented in the package insert except for anti-NMDA receptor antibody-mediated encephalopathy.(10) This adverse event occurred in one patient and was confirmed by cerebrospinal fluid (CSF) testing and imaging. Case studies report TNF-α inhibitors and other biologic products as being associated with leptomeningeal enhancement and anti-NMDA receptor encephalopathy.(10,14) Overall, there was no statistically significant difference between study arms for overall adverse reactions or for any single adverse reaction.

**Discussion**

This retrospective non-inferiority study evaluated the effectiveness of switching from infliximab to infliximab-dyyb compared to continuing infliximab for patients with RA, PsA, or inflammatory polyarthritis. In the process of identifying patients with RA or PsA using diagnostic coding (ICD-10), patients were also identified with inflammatory polyarthritis which may have introduced bias. Non-inferiority was demonstrated in patients who switched from infliximab to infliximab-dyyb compared to those remaining on infliximab for the primary outcome of disease worsening requiring acute care. Non-inferiority was not met for the secondary outcome of disease worsening requiring acute care or switch to an alternative biologic or tofacitinib. A possible explanation is that if patients did not appear to be doing as well on infliximab-dyyb after the switch, providers commonly switched patients back to infliximab. For the individuals who switched back to infliximab, over 63% of those were switched back after 1 or 2 doses of infliximab-dyyb. While accounting for switching back from infliximab-dyyb to infliximab is a concern, the authors chose to use intent-to-treat analysis. Rather than exclude patients who switched back from infliximab-dyyb to infliximab, the authors felt it was important to describe the number of patients who elected to switch back to infliximab, as well as define it as a treatment failure, seeing as patients may have been switched off their treatment due to real or perceived disease worsening. There was no difference in changes in ESR, CRP, or provider-reported adverse reactions between the two groups. This study reflects real-world practice within an integrated healthcare system in the United States and these results are in accordance with the NOR-SWITCH trial and other studies.(11,15,16) This study, while not adequately powered, represented a large group of patients in the United States with rheumatologic indications for infliximab or infliximab-dyyb. It adds to the growing pool of data available regarding switching to biosimilar products.

There were some key limitations. There was selection bias due to the retrospective nature of the study. The small cohort of patients continuing on infliximab and lack of historic control are additional limitations of this study. Patients with psoriasis and no diagnosis of psoriatic arthritis were excluded. However, if an individual had both psoriasis and psoriatic arthritis, a psoriasis flare could lead to changes in disease management, including changes to the biologic product. Per protocol analysis would not have allowed for a switch back to be considered treatment failure. A 2019 study(17) evaluated patient perspectives on switching from infliximab to infliximab-dyyb and found that while patients were generally satisfied, many expressed concern that there was not enough information to switch, that switching would lead to a loss of disease activity control, and that infliximab-dyyb has potential side effects. Patient concerns and provider skepticism of biosimilar products could influence a switch back from infliximab-dyyb to infliximab. This may be explained by the nocebo effect, a phenomenon that occurs when negative expectations from a patient or provider surrounding a particular treatment cause that treatment to have an emphasized negative effect.(16) The nocebo effect may be a critical determinant in patient acceptance of new treatment alternatives such as biosimilars. The true impact of the nocebo effect on patient and provider decisions is unknown and is outside the scope of this study. In addition, detection of adverse reactions required clear documentation, so mild reactions may not have been captured. Literature shows a higher incidence of adverse reactions than found in this study.(10,11,16) Of the side effects observed in this study, the package insert for infliximab describes the incidence as follows: 18% experienced infusion related reactions, 10% experienced skin rash, fewer than 1% experienced drug-induced lupus, 8% experienced arthralgia, 34-50% with RA or PsA experienced increased alanine aminotransferase (ALT) less than 3 times the upper limit of normal, 21% experienced nausea, 12% of those with RA experienced abdominal pain, 18% experienced headache, 7% experienced itching, and fewer than 1% experienced NMDA receptor antibody-mediated encephalopathy.(10) Chart review was not performed, and disease worsening was not confirmed, so the outcomes assessed were surrogate markers for disease worsening. The study may also not be generalizable to all patients as it took place within an integrated health care system.

There is also a potential for inherent bias for individuals who remained on infliximab. Kaiser Permanente membership status was not evaluated throughout the study period for each individual, though active membership was likely as infusion clinic visits are limited to Kaiser Permanente members. Finally, this study was underpowered as a total of 1,624 individuals per arm were needed to provide 80% power with a relative non-inferiority upper-limit margin set at 4%.
Conclusion
There was no increased risk of disease worsening requiring acute care in patients with RA or PsA who switched from infliximab to infliximab-dyyb when compared to patients who remained on infliximab in this population. Non-inferiority was not demonstrated for disease worsening requiring acute care or switch to an alternative biologic or tofacitinib, largely driven by individuals switching back from infliximab-dyyb to infliximab. There was no difference between the two study arms based on changes in ESR, CRP, or incidence of documented adverse reactions. While the study was underpowered, it contributes additional data points to a small pool of existing literature and shows that infliximab-dyyb may be an equally effective and safe option compared to infliximab.

About the Authors
Alexi Spoto, PharmD, BCPS, is an ambulatory care pharmacist specializing in chronic pain management at Kaiser Permanente South Sacramento. Dr. Spoto completed her PGY1 residency in 2020 at Kaiser Permanente South Sacramento and is active in precepting and mentoring future pharmacists. She has no conflicts of interest to report.

Katie Pitcher, PharmD, APh, BCGP, is a Drug Education Coordinator at Kaiser Permanente South Sacramento. Dr. Pitcher has no conflicts of interest to report.

Rita Hui, PharmD, MS, is a Clinical Pharmacy Research Scientist in the Pharmacy Outcomes Research Group for Kaiser Permanente National Pharmacy. Dr. Hui has no conflicts of interest to report.

Aeris Lautchang is a 2021 PharmD Candidate at University of the Pacific in Stockton, California and pharmacist intern at Kaiser Permanente South Sacramento. She is active in her school chapter of CSHP and a founder of the interprofessional organization Pride Health Alliance. Ms. Lautchang has no conflicts of interest to report.

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