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# Incidence of serious infection among etanercept and infliximab initiators: safety comparison between biosimilars and bio-originators with Canadian population-based data

Marina G. Birck[1,2], Luck Lukusa[1], Denis Choquette[3], Gilles Boire[4,7], Walter P. Maksymowych[5], Harminder Singh[6], Waqqas Afif[2] and Sasha Bernatsky[1,2*]

## Abstract

**Background** Safety remains a significant concern for biologic drugs, and studies are needed to ensure a comparable safety profile for biosimilars and their legacy treatments. Using Canadian administrative health data from 2015–2019, we compared the incidence of serious infection between biosimilars and bio-originators initiators for etanercept and infliximab, two of the most commonly used biologics during this time.

**Methods** We performed a retrospective cohort study using pan-Canadian data (except Quebec) from the National Prescription Drug Utilization Information System linked to hospitalization data. We studied new users of infliximab or etanercept (January/2015-December/2019) and compared incidence rates of serious infection, defined as those which required hospitalization, by using Cox regression models adjusted by biological sex, age at treatment initiation, prior corticosteroid or biologic, province, and calendar year.

**Results** We studied 6,583 etanercept users (mean age 62) and 7,202 infliximab users (mean age 45). Hospitalization with infections occurred in 7% of infliximab and 2% of etanercept users. Comparing the risk of infection between biosimilar to bio-originator, the adjusted hazard ratio (95% confidence interval) was 1.33 (0.77, 2.30) for etanercept and 0.93 (0.72, 1.18) for infliximab.

**Conclusions** Our study found no clear difference between etanercept and infliximab biosimilars and their bio-originators for infection incidence, suggesting a similar safety profile.

**Keywords** Biosimilar pharmaceuticals, Infections, Safety, Observational study

*Correspondence:
Sasha Bernatsky
sasha.bernatsky@mcgill.ca
Full list of author information is available at the end of the article

## Background

Biologic drugs are a rapidly expanding class of medications that have revolutionized the management of autoimmune diseases, such as inflammatory arthritis (IA) and inflammatory bowel disease (IBD). Given the complexity of biological molecules, safety remains a paramount concern. As IA and IBD biologic drugs downregulate the immune system, these individuals are prone to serious infection [1, 2].

As patent protection for bio-originators expires, biosimilars are constantly being introduced into the market as cost-effective alternatives [3]. Biosimilars are highly similar versions of their bio-originators, but structural and potential immunogenicity differences among originators and biosimilars warrant investigation to ensure a comparable safety profile [3]. Rigorous comparative studies, mainly randomized clinical trials, have demonstrated similar safety events between bio-originators and biosimilars [3–5]. However, although some real-world comparative studies have been conducted [1, 6–9], additional investigations are imperative to comprehensively assess the long-term and comparable effects of both biosimilars and bio-originators, including more recent biosimilar entrants to the market, in diverse populations [10].

Healthcare providers' reimbursement claims and administrative databases are widely used as real-world data with the advantage of capturing data from very large and diverse populations, reflecting routine clinical practice from various healthcare settings [11, 12]. These databases enable long-term safety assessments in populations not eligible for clinical trials but at higher risk of serious infection and may capture missed rare adverse events.

In this study, we compared serious infection occurrence, one of the most common safety events, of biosimilars and their corresponding legacy (bio-originator) drugs for etanercept and infliximab, the two most prescribed biosimilars for autoimmune disease in Canada during 2015–2019 [13, 14].

## Methods

This retrospective cohort study used administrative health data from January 2014 to December 2019 to conduct a comparative analysis of infliximab and etanercept biosimilars and their respective legacy drugs. The longitudinal dataset includes the National Prescription Drug Utilization Information System (NPDUIS) linked to the hospital Discharge Abstract Database (DAD).

The study period spans from January 2014 to December 2019. Data from 2014 was used to ascertain baseline characteristics and certain selection criteria (e.g. new users defined as one year with no claims of the respective drug). We selected this study period to ensure that the use of originators was captured, as mandatory switch policies result in fewer prescriptions of originators over time. Bio-originators have been used for a long time in Canada, and biosimilar policies have been implemented since 2016. The mandatory use of biosimilars for people initiating infliximab was established around mid-2016 for most provinces and mid-end 2017 for etanercept. People already on infliximab or etanercept were not mandated to switch to the biosimilar before 2020, except for British Columbia (mandatory switch from 05 to 11/2019) [15].

### Data sources

The two linked databases used for the analysis are held by the Canadian Institute for Health Information (CIHI) [16]. NPDUIS [17] contains claims-level data on prescription dispensations paid from public drug programs from all provinces (except Quebec) and the territory of Yukon. It has information on age, sex, province, and dispensed drugs (identified using Health Canada's Drug Identification Number, DIN), including dose and amount of drug supplied, but not specifically the indication.

CIHI also has access to the Discharge Abstracts Database (DAD) [18], which captures information on hospital discharges from facilities in all provinces and territories except Quebec. It includes demographic, administrative and clinical data for each hospital admission. Since 2004–2005, discharge diagnosis has been coded as International Statistical Classification of Diseases and Related Health Problems, 10th Revision, Canada (ICD-10-CA), and procedures as Canadian Classification of Health Interventions (CCI).

### Population

We studied all adults (≥ 18 years) in the database initiating infliximab or etanercept during the study period (2015–2019). Cohort entry was established as the date of the first prescription of one of the drugs, regardless of indication. Individuals were allowed to have used other biologics (not naïve) except infliximab or etanercept: (a) for the infliximab analysis, we specifically studied infliximab-naïve individuals (meaning those who had not received infliximab in the year prior to cohort entry) with at least one infliximab infusion during the study period; and (b) for the etanercept analysis, etanercept-naïve individuals (also one year) with at least one etanercept dispensation were included. We excluded individuals with a history of malignancy (except non-melanoma skin cancer), HIV or organ transplant in the year prior to cohort entry. Although we could not identify the indication of use unless an individual was hospitalized due to the condition (database limitation later described), we excluded those taking etanercept and with hospitalization due to IBD as etanercept is not currently indicated or effective for this condition.

### Exposure

Etanercept originator (ETA-O) and biosimilar (ETA-B), as well as infliximab originator (INF-O) and biosimilar (INF-B), were defined using DINs. (see Additional File 1—A).

As NPDUIS lacks information on indication, the primary analysis was done for all exposed individuals regardless of indication. In an attempt to stratify per indication, sensitivity analyses were done for IA and IBD; however, only hospital discharge codes were used as proxies to identify these underlying conditions. Therefore, in sensitivity analyses of etanercept, we restricted its use for IA, defined as individuals hospitalized with rheumatoid arthritis, ankylosing spondylitis, or psoriatic arthritis (ICD-10 codes M05-06, M45, M070-M073, L40). In sensitivity analyses of infliximab, we restricted to IA (defined before) and IBD, defined as individuals hospitalized with Crohn's disease (ICD10 K50) or ulcerative colitis (K51).

### Outcomes of interest

Serious infection was defined as the first hospitalization with a record of infectious-related ICD-10 codes (see Additional file 1) identified in any position (primary cause or others) [1, 19]. For infection, follow-up starts at treatment initiation and ends at the occurrence of the event, treatment discontinuation plus 90 days, or end of study period (whichever came first). See additional file 1 (supplemental Fig. 1) for the follow-up schema.

### Covariates

Covariates were assessed at baseline, up to one year prior to cohort entrance. Variables of interest (as potential effect modifiers or confounders) included age, sex, prior biologics, prior systemic corticosteroids, province (Ontario versus others as Ontario accounts for more than one-third of the cohort and was the last province to adopt biosimilar policies), and underlying diagnosis (IA and IBD).

### Statistical analysis

Cohort characteristics were summarized as absolute numbers with percentages for categorical variables and median with interquartile range (IQR) for continuous variables. The incidence rate of serious infection was estimated per 1,000 person-year (PY), with 95% confidence intervals (CI).

We compared originator and biosimilar (ETA-O vs ETA-B, and INF-O vs INF-B) by using Cox regression models, adjusting for potential confounders and effect modifiers, including sex, age at ETA/INF initiation, prior corticosteroids or other biologics, region (Ontario versus other), and calendar year. We further performed sensitivity analyses by restricting cohorts by indication (etanercept users with inpatient claims of IA and infliximab users with inpatient claims of IBD and IA). We used Cox regression models to compare biosimilar and bio-originator for each indication.

All analyses were conducted using SAS version 9.4 software (SAS Institute, Cary, NC, USA).

## Results

From the entire NPDUIS population (2015–2019), we identified 6,583 and 7,202 individuals who initiated etanercept and infliximab, respectively. Details of subjects excluded due to age < 18 or past malignancy can be seen in Fig. 1. Median follow-up (IQR) for infliximab users was 2.2 (1.1–3.7) years and for etanercept 2.2 (1.1–3.5) years. Most individuals in the etanercept cohort were women, median age was 62 years (IQR 50–69), and at least 10% had a diagnosis of IA (90% could not be ascertained due to lack of hospitalization caused by IA). For the infliximab cohort, half were women, younger (median age was 45 years, IQR 28–61), and only 2% were identified with IA and 35% with IBD. Table 1 describes the studied population in more detail.

Approximately 7% of those under infliximab had a hospitalization due to infection, in contrast to 2% of those taking etanercept. The incidence rate was higher for serious infection among infliximab users (30 cases per 1000 PY) than for etanercept use (9 cases per 1000 PY) (Table 2).

In the time to first event analysis, we also did not observe a clear difference in the risk of incidence of serious infection between biosimilar and bio-originator for both infliximab and etanercept when adjusted for confounders (Table 3). Prior corticosteroid use was independently associated with higher infection risk for both etanercept and infliximab, while older age was a risk factor for infection in etanercept initiators.

Similar results were found when restricting the analysis to IA (supplementary Table 1) and IBD (supplementary Table 2). For individuals with IA treated with etanercept ($n = 695$; 44% on biosimilar) or with infliximab ($n = 154$; 45%), we were unable to establish a clear difference between biosimilar and bio-originator use in terms of first serious infection (aHR 1.69, 95% CI 0.64–4.49; and aHR 1.74, 95% CI 0.51–5.89, respectively). In the case of individuals with IBD diagnostic codes treated with infliximab ($n = 2{,}506$; 25% on biosimilar), we also could not establish a clear difference between biosimilar versus bio-originator in terms of serious infection (aHR 1.19; 95% CI 0.86–1.64).

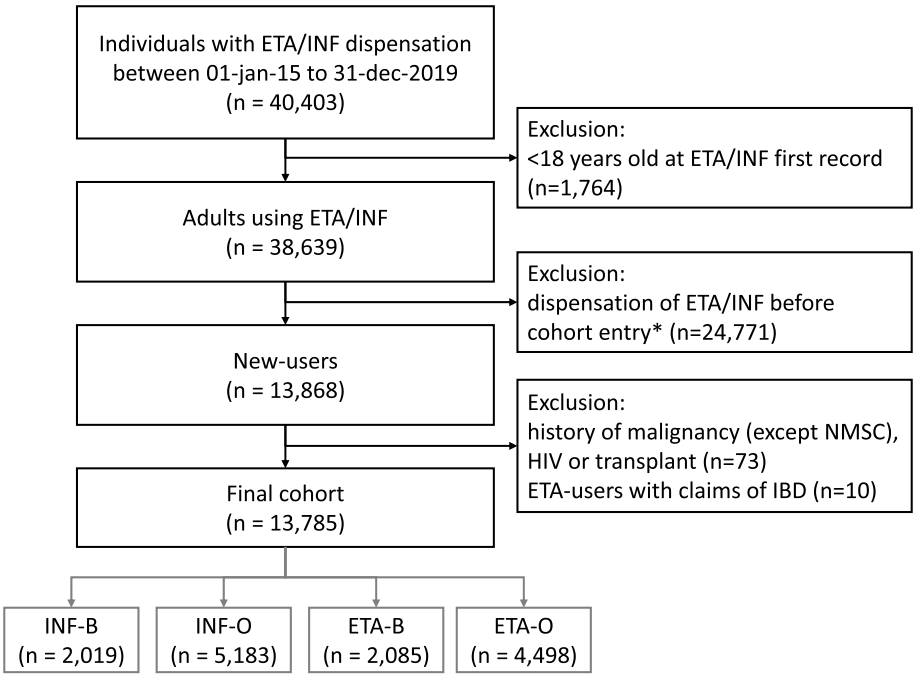


**Fig. 1** Cohort selection

**Table 1** Cohort description

| Characteristics | Infliximab | | | Etanercept | | |
|---|---|---|---|---|---|---|
| | Overall | Biosimilar | Originator | Overall | Biosimilar | Originator |
| | *N* = 7202 | *N* = 2019 | *N* = 5183 | *N* = 6583 | *N* = 2085 | *N* = 4498 |
| Female sex, N (%) | 3736 (51.9) | 1109 (54.9) | 2627 (50.7) | 4243 (64.5) | 1408 (67.0) | 2835 (63.0) |
| Median age in years, IQR | 45 (28–61) | 51 (34–66) | 42 (27–60) | 62 (50–69) | 64 (51–71) | 61 (49–67) |
| Age ≥ 65 years, N (%) | 1513 (21.0) | 552 (27.4) | 961 (18.5) | 2866 (43.5) | 1009 (48.4) | 1857 (41.3) |
| Year of cohort entry ≥ 2018, N (%) | 2753 (38.2) | 1414 (70.0) | 1339 (25.8) | 2642 (40.1) | 1822 (87.4) | 820 (18.2) |
| Ontario province, N (%) | 2450 (34.0) | 737 (36.5) | 1713 (33.1) | 2697 (41.0) | 958 (45.6) | 1739 (38.7) |
| Prior biologic use, N (%) | 608 (8.4) | 278 (13.8) | 330 (6.4) | 790 (12.0) | 412 (19.8) | 378 (8.4) |
| Prior steroid use, N (%) | 2904 (40.3) | 762 (37.7) | 2142 (41.3) | 2247 (34.1) | 846 (40.6) | 1401 (31.1) |
| Underlying condition, N (%) | | | | | | |
| IA | 154 (2.1) | 69 (3.4) | 85 (1.6) | 695 (10.6) | 305 (14.6) | 390 (8.7) |
| IBD | 2506 (34.8) | 635 (31.5) | 1871 (36.1) | - | - | - |
| Others/Not defined | 4542 (63.1) | 1315 (65.1) | 3227 (62.3) | 5888 (89.4) | 1780 (85.4) | 4108 (91.3) |

**Table 2** Incidence rate of serious infection (first episode)

| Serious infection | Number of cases (%) | Incidence rate per 1,000 PY (95%CI) | | |
|---|---|---|---|---|
| | | Overall | Biosimilar | Originator |
| Etanercept | 138 (2.1) | 8.90 (7.50, 10.6) | 11.8 (7.9, 16.8) | 8.4 (6.9, 10.1) |
| Infliximab | 510 (7.1) | 30.1 (27.5, 32.8) | 33.4 (27.2, 40.1) | 29.3 (26.6, 32.3) |

**Table 3** Comparative risk of serious infection (first episode) between biosimilar and bio-originator (HR, 95%CI)

| Variables | Etanercept | | Infliximab | |
|---|---|---|---|---|
| | Unadjusted | Adjusted* | Unadjusted | Adjusted* |
| **Biosimilar** | **1.60 (1.06, 2.43)** | **1.33 (0.77, 2.30)** | **1.00 (0.86, 1.35)** | **0.93 (0.72, 1.18)** |
| Female (biological sex) | 1.21 (0.86, 1.71) | 1.14 (0.80, 1.62) | 0.94 (0.79, 1.12) | 0.93 (0.78, 1.10) |
| Age ≥ 65 years | 1.03 (1.02, 1.05) | 1.03 (1.01, 1.04) | 1.00 (0.99, 1.01) | 1.00 (0.99, 1.01) |
| Prior corticosteroids use | 1.95 (1.41, 2.70) | 1.75 (1.25, 2.44) | 1.56 (1.32, 1.88) | 1.76 (1.47, 2.11) |
| Prior biologic use | 0.92 (0.52, 1.64) | 0.83 (0.46, 1.50) | 1.01 (0.80, 1.58) | 0.97 (0.68, 1.37) |
| Ontario province | 2.15 (1.56, 2.98) | 1.78 (1.28, 2.49) | 1.41 (1.18, 1.69) | 1.58 (1.31, 1.90) |
| Treatment initiation ≥ 2018 | 1.37 (0.90, 2.10) | 1.05 (0.61, 1.83) | 1.30 (1.04, 1.62) | 1.34 (1.06, 1.71) |

* adjusted for biological sex, age (≥ 65 years), prior corticoid or biologic use, province (Ontario) and treatment initiation (calendar year)

## Discussion

In this Canadian real-world study, we did not observe a clear difference between infliximab and etanercept biosimilars and their bio-originators with respect to the risk of serious infections, one of the most expected safety events. Our findings, combined with results from clinical trials and other observational studies, provide reassuring evidence of a comparable safety profile for biosimilars. Notably, there have been few real-world studies that have comprehensively addressed the safety of etanercept and infliximab in large populations, and most of these have focused on comparing the first biosimilar (CT-P13 or SB4) to its corresponding bio-originator, overlooking other biosimilars in the market [1, 8, 9, 20–23].

Most studies examining the safety of tumour necrosis factor inhibitors (TNFi) biosimilars have primarily focused on early infliximab biosimilars, particularly CT-P13, and are based on randomized controlled trials (RCT) with limited follow-up periods and restricted populations. Two meta-analyses of RCT showed no difference in adverse drug events between infliximab bio-originator and biosimilar among individuals with ankylosing spondylitis [5] and people with rheumatoid arthritis (RA) [4]; however, it only included results from the PLANETAS and PLANETRA studies, respectively, which studied CT-P13 only [20, 21]. Another meta-analysis of RCT involving individuals with RA treated with infliximab in combination with methotrexate (a common practice) suggested a comparable safety profile between infliximab-biosimilar and originator, or placebo as well [24]. The NOR-SWITCH RCT [25] and its extension [26] indicated that switching to an infliximab-biosimilar and maintaining therapy with an infliximab-originator had a similar safety profile. The incidence of infection reported in those studies (~ 1%) was lower than our estimates (8.3% for infliximab), likely due to differences in population characteristics (RCT with restricted patient selection) and follow-up duration (1.5 years for NOR-SWITCH vs > 2 years in ours).

Ongoing registries and post-marketing studies have consistently demonstrated no major safety concerns regarding infliximab biosimilars [22, 27]. Two claims database studies in France compared one infliximab-biosimilar with its originator among people with ulcerative colitis (UC) [8] ($n = 3{,}112$) and Crohn's Disease (CD) [1] ($n = 5{,}050$). Overall, the authors did not observe a clear difference between treatment groups regarding serious infection. They found, among UC [8] and CD [1] biosimilar users, a higher incidence rate of serious infection (40–52 vs 30 cases per 1,000 PY) than our study. Differences in population might explain our differences with the French database, which only included IBD and mostly French population, vs. all indications and mixed population in our study, as well as shorter study periods in the French studies, and potential differences in identifying serious infection. In a Japanese cohort of individuals with psoriasis, researchers observed a similar safety profile of one infliximab-biosimilar compared to its originator in a post-marketing evaluation. They did not detect any new safety signals [23]. They found a 0.6% incidence of serious infection, much lower than in our study—the small sample size and limited follow-up period might have been insufficient to provide a more precise estimate in their cohort.

As for etanercept-biosimilar, few published studies regarding serious infection comparison in real-world settings exist. A post-marketing surveillance study followed 583 individuals with autoimmune arthritis using etanercept-biosimilar for up to 12 months and reported an incidence of 4% of infection, but that included both hospitalized and non-hospitalized cases [28]. In a real-world national cohort of 242 people with active rheumatoid arthritis, authors found around 3% of infection (regardless of severity) among bio-originator and 4% among biosimilar users within 6 months of treatment (no formal comparison was made) [9]. In a Korean cohort of 314 individuals with rheumatic diseases, only 0.3%

cases of infection (pneumonia) were observed among etanercept-biosimilar [29]. In the German JuMBO registry, the incidence of infection (regardless of severity) among etanercept-biosimilar users was 1.2% among 83 individuals with juvenile inflammatory arthritis, totalling 8.28 events (95% CI 4.28–14.46) per 100 PY, but no description and comparison with the originator was made [30]. The variability of the incidence rate of infection among studies, including ours, can be explained by the differences in population, study design, outcomes definitions and follow-up time. The lack of robust comparison between etanercept biosimilar and bio-originator regarding serious infection warrants studies like ours. Hopefully, more real-world, long-term, and robust studies will be conducted to demonstrate the safety of etanercept biosimilars.

In our multivariate analysis, we observed a few covariates associated with increased risk of serious infection: previous corticosteroid use, Ontario province, age for etanercept and calendar year for infliximab. Corticosteroids are known to increase susceptibility to infection; moreover, people needing corticosteroids might present more severe or inadequate control of the disease and could potentially be at increased risk of infection. Age is another well-known risk factor for infection, and individuals with IA (particularly RA) are normally older than individuals with IBD. In the case of Ontario and calendar year, both were used to adjust our analysis as uptake of biosimilars differs according to province, with Ontario being one of the last provinces to implement biosimilar mandatory policies; moreover, Ontario public drug insurance covers only older adults (65 + years), differing from other provinces.

Administrative health care databases, like NPDUIS and DAD, are valuable tools for investigating drug safety, but limitations must be carefully considered in study design and interpretation to help mitigate challenges and ensure meaningful safety evidence. CIHI databases [17] are comprehensive databases that can be used in post-marketing drug surveillance studies. NPDUIS linked to DAD enables long-term safety assessments by providing longitudinal data on a broad population, allowing for the monitoring of rare adverse events and capturing real-world outcomes over extended periods while capturing all molecules used routinely in clinical practice, ultimately generating results more generalizable to the target population [31]. However, data limitations might have prevented the widespread use of CIHI databases in comparative safety studies. First, selection bias is likely present. Though we identified all etanercept and infliximab initiators acquiring drugs from the public drug insurance, we were unable to identify most indications (IBD, IA), and we potentially identified more severe cases—as NPDUIS lacks information on drug indications, DAD was used as proxies to define presumable indications. For example, as hospitalizations due to IA may not occur often, it is harder to identify people with IA, imposing a selection bias in the subgroup analysis restricted to IA. Individuals with IBD are more likely to be hospitalized due to IBD, but selection bias might still occur as severe cases are more likely to be hospitalized due to IBD than mild cases. However, this bias is probably equally distributed between biosimilar and bio-originators; hence, our comparison should not be highly affected by this bias. Similarly, the lack of outpatient and other medication data limited our ability to capture baseline characteristics, potentially resulting in residual confounding.

Second, while NPDUIS covers a significant portion of the Canadian population, it does not capture data from all private drug plans or non-insured individuals, potentially introducing selection bias; e.g. in Ontario, only seniors (65 + years) are covered by public insurance. Although we could have introduced selection bias by excluding individuals using etanercept who had an IBD-related hospitalization, it is very minimal as it represents about 0.07% of the cohort. Third, the availability and consistency of data elements across different jurisdictions may vary, requiring careful consideration during data analysis and interpretation. Fourth, similar to other claims databases, CIHI databases lack clinical and laboratory details, limiting the ability to fully assess disease severity and treatment response. Coding error, inability to control for other residual confounders (such as disease severity and race), potential outcome misclassification, and selection bias should be acknowledged as possible limitations of these databases.

## Conclusions

Using real-world administrative health care data, focussing on etanercept and infliximab, we were unable to demonstrate a clear difference regarding hospitalized infection risk when comparing biosimilars and their corresponding bio-originators, corroborating previous findings of RCT and RWE. With ongoing safety surveillance, we can enhance our understanding of the safety profiles of biosimilars and foster evidence-based decision-making in managing chronic inflammatory diseases.

## Data Declarations

Parts of this material are based on data and information provided by the Canadian Institute for Health Information. However, the analyses, conclusions, opinions, and statements expressed herein are those of the authors and not necessarily those of the Canadian Institute for Health Information.

**Abbreviations**

| | |
|---|---|
| aHR | Adjusted hazard ratio |
| CCI | Canadian Classification of Health Interventions |
| CD | Crohn's Disease |
| CI | Confidence interval |
| CIHI | Canadian Institute for Health Information |
| DAD | Discharge Abstract Database |
| DIN | Health Canada's Drug Identification Number |
| ETA-B | Etanercept biosimilar |
| ETA-O | Etanercept originator |
| IA | Inflammatory arthritis |
| IBD | Inflammatory bowel disease |
| ICD-10-CA | International Statistical Classification of Diseases and Related Health Problems, 10th Revision, Canada |
| INF-B | Infliximab biosimilar |
| INF-O | Infliximab originator |
| IQR | Interquartile range |
| NPDUIS | National Prescription Drug Utilization Information System |
| PY | Person-year |
| RA | Rheumatoid arthritis |
| RCT | Randomized controlled trial |
| RWE | Real-world evidence |
| TNFi | Tumor Necrosis Factor Inhibitors |
| UC | Ulcerative colitis |

## Supplementary Information

The online version contains supplementary material available at https://doi.org/10.1186/s41927-024-00415-5.

Supplementary Materials 1.

Supplementary Materials 2.

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**Authors' contributions**
Substantial contributions to the conception: MGB, SB. Design of the work: MGB, SB. Data acquisition, analysis: LL. Interpretation of data: MGB, LL, DC, GB, WM, HS, WA, SB. Drafted the work: MGB. Substantively revised: DC, GB, WM, HS, WA, SB.

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**Availability of data and materials**
The data that support the findings of this study are not openly available due to sensitivity reasons and are available from the corresponding author upon reasonable request.

## Declarations

**Ethics approval and consent to participate**
The study received approval from the McGill University Health Centre Research Ethics Board (MP-37–2019) and complies with the Declaration of Helsinki. The study used pan-Canadian claims and formulary administrative health data from the Canadian Institute for Health Information (CIHI). CIHI is a secondary data collector of health information providing researchers with third-party access to de-identified record-level data. No human participants were directly involved as the data disclosed to the authors was de-identified record-level data; therefore, obtaining individual consent is unnecessary.

**Consent for publication**
Not applicable.

**Competing interests**
MGB, LL, and SB declare that they have no competing interests.
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**Author details**
[1]Research Institute of the McGill University Health Centre, Montreal, QC, Canada. [2]McGill University, Montreal, QC, Canada. [3]Centre Hospitalier de Université de Montréal, Institut de Rhumatologie de Montréal, Montreal, QC, Canada. [4]Université de Sherbrooke, Sherbrooke, QC, Canada. [5]University of Alberta, Edmonton, AB, Canada. [6]Max Rady College of Medicine, University of Manitoba, Winnipeg, MB, Canada. [7]Centre hospitalier de Sherbrooke (CIUSSS de l'Estrie-CHUS), Centre intégré universitaire de santé et de services sociaux de l'Estrie, Sherbrooke, Canada.

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