CoLab Network

Utilization Study

Utilization Analysis of Tofacitinib and Other Drugs Among Individuals With Ulcerative Colitis: Feasibility Analysis

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Key Messages

Tofacitinib is a drug approved for use in Canada to treat moderate to severe ulcerative colitis and other inflammatory diseases in adults.

Safety concerns with tofacitinib have emerged from studies in older patients with rheumatoid arthritis, but these concerns may not be generalizable to people treated for ulcerative colitis.

A retrospective cohort study was conducted to describe the use of tofacitinib and other therapies in ulcerative colitis and to determine the feasibility of a comparative safety study of major adverse cardiac events, thrombotic events, and cancer.

This cohort study used administrative health databases from 3 Canadian provinces (Manitoba, Ontario, and Saskatchewan) and the US.

The study identified 401,651 adults diagnosed with ulcerative colitis between 2010 and 2023. Of these, 399 initiated tofacitinib between January 1, 2018, and March 31, 2023. A limited number of safety events were identified among those taking tofacitinib.

Tofacitinib is currently rarely used for ulcerative colitis, and when it is, it is mostly used as a third-line or fourth-line treatment.

It is not possible to draw conclusions about associations between the use of tofacitinib in ulcerative colitis and safety events due to the limited number of events observed. These findings suggest that detailed safety studies of tofacitinib in ulcerative colitis are currently not feasible in our data holdings.

Table of Contents

List of Tables

List of Figures

Abbreviations

CNODES	Canadian Network for Observational Drug Effect Studies
IBD	inflammatory bowel disease
JAK	Janus kinase
MACE	major adverse cardiovascular events
TNF	tumour necrosis factor
UC	ulcerative colitis

Background

Inflammatory bowel disease (IBD) is an important chronic autoimmune condition that includes Crohn disease and ulcerative colitis (UC). Canada is among the countries with the highest prevalence and incidence of IBD in the world.[1] The prevalence of IBD in 2023 is estimated at 825 per 100,000 individuals (approximately 0.8% of the population), corresponding to 410 per 100,000 for Crohn disease and 414 per 100,000 for UC and unclassified IBD together.[2] In the majority of patients, UC develops around 30 to 40 years of age, with periods of remission and relapse throughout life.[3]

Tofacitinib, a Janus kinase (JAK) inhibitor, was approved by Health Canada on October 28, 2018, for moderate to severe UC in adult patients. The recommended dosage for individuals with UC is 10 mg orally twice daily for at least 8 weeks, and then 5 mg twice daily for maintenance therapy.[4] The 10 mg twice daily dose may also be used for maintenance in some patients. However, it is recommended to use the lowest effective dose for the shortest duration needed.[4] The 2019 CADTH Reimbursement Review recommended that tofacitinib be reimbursed in individuals with moderate to severe UC with "an inadequate response, loss of response or intolerance to either conventional UC therapy or a tumour necrosis factor alpha inhibitor," dependent on additional conditions.[5] Conventional UC therapy includes 5-aminosalicylates, corticosteroids, and conventional immunosuppressants, such as azathioprine and 6-mercaptopurine. Other advanced UC therapies include biologics, such as tumour necrosis factor alpha (TNF alpha) inhibitors, a selective alpha 4 beta 7 integrin inhibitor (vedolizumab), and an interleukin-12/23 inhibitor (ustekinumab).

Safety concerns with tofacitinib have emerged from studies that have reported increased risks of major adverse cardiovascular events (MACE), thrombotic events, and cancer.[6-9] As a result, in 2022, Health Canada issued a health professional risk communication for tofacitinib, and updated the product monograph labelling for tofacitinib and other JAK inhibitor products sold in Canada. Updated labelling included a "Serious Warning and Precautions" box.[10,11] Similar recommendations were issued by the US FDA and the European Medicines Agency (EMA).[12,13] However, the safety signals in question were detected in older patients who were treated with tofacitinib for rheumatoid arthritis and may not be generalizable to individuals treated for UC, who tend to be a younger population with fewer comorbidities. There are limited data available regarding the safety of tofacitinib in individuals with UC, especially from Canadian studies.[14-18] Most studies have been limited by relatively small sample sizes and short durations of follow-up. In addition, the patent for tofacitinib expired in November 2022, generic versions are entering the market, and new and emerging drugs are currently under development, including other JAK inhibitors. Given the expanded treatment options for UC and increasing public drug plan spending on biologics, there is a need for real-world data to inform on the safety of tofacitinib in UC and the optimal sequencing of advanced therapies.

Purpose of this Report

The purpose of this report was to determine the feasibility of conducting a detailed analysis evaluating the safety of tofacitinib among a patient population with UC. Further consideration will then be given about

whether a CADTH Therapeutic Review should be undertaken regarding how tofacitinib should be used relative to other advanced therapies in patients with UC.

Main Take-Away

Tofacitinib is a drug used to treat moderate to severe UC and other inflammatory diseases in adults. Some safety concerns have arisen from studies reporting an increased risk of MACE, thrombotic events, and cancer in older patients with rheumatoid arthritis treated with tofacitinib. It is unknown if these safety concerns apply to individuals treated for UC, and existing safety data from studies with Canadian population are limited. This study aims to determine the feasibility of conducting a detailed analysis to evaluate the safety of tofacitinib in UC.

Policy Issue

Although tofacitinib has demonstrated efficacy in patients with moderate to severe UC, new safety signals in patients with rheumatoid arthritis have emerged resulting in regulatory agencies issuing warnings and labelling recommendations. The safety data for patients with rheumatoid arthritis may not be generalizable to patients with UC therefore further analyses in patients with UC are needed. Findings from such investigations could have an impact on formulary management in the future.

Policy and Research Questions

1. What is the utilization of tofacitinib in UC?
2. What is the feasibility of conducting a safety study of tofacitinib among individuals with UC using the adverse outcomes of MACE, hospitalized thrombotic events, and cancer identified in populations of patients with rheumatoid arthritis?

Research Objective

The objective of this analysis was to conduct a feasibility study of MACE, hospitalized thrombotic events, and cancer in patients with UC who are treated with tofacitinib using the data holdings available to the Canadian Network for Observational Drug Effect Studies (CNODES). This objective required analysis of other drugs used in UC, to place tofacitinib safety in context with other treatments, and to determine the potential of using patients with UC who are on other treatments as controls for patients treated with tofacitinib in a full safety study.

In each of 4 UC drug treatment cohorts (a tofacitinib cohort, an TNF alpha cohort, a vedolizumab or ustekinumab cohort, and a conventional therapy cohort), the following measures were estimated to meet the objective:

- crude incidence rate of MACE
- crude incidence rate of hospitalized thrombotic events

- crude incidence rate of cancer
- prevalence of use of other treatments for UC before and after starting treatment.

Methods

Study Design and Data Sources

This feasibility study was conducted by CNODES.[19,20] We conducted a retrospective cohort study using administrative health databases from 3 Canadian provinces (Manitoba, Ontario, and Saskatchewan), and the US Merative MarketScan database. Results are limited to these 4 databases due to availability at the time of reporting (inclusion of the British Columbia and the UK Clinical Practice Research Datalink [CPRD] databases were not feasible given the timelines). Details of the databases included in the analysis are provided in Appendix 1, Table 1. Briefly, the analyses used data on prescription drug claims, physician service claims, hospital records, emergency department records (where available), and health insurance plan registration. The US MarketScan database included more than 70 million individuals covered by large US employer health insurance plans, governments, and other public organizations.

Study Population

The study design diagram is depicted in Appendix 1, Figure 1. In each participating database, we established a base cohort of individuals with a UC diagnosis (International Classification of Diseases Ninth Revision [ICD-9]: 556; Tenth Revision [ICD-10]: K51) between January 1, 2010, and March 31, 2023 (or the latest date for which data were available in each database; refer to Appendix 1, Table 2). This cohort was based on at least 1 record of a hospitalization or a visit to a physician, emergency department, or ambulatory care provider. The earliest date of a diagnosis during this period was defined as the UC index date. We excluded individuals who were missing data on sex or date of birth, were enrolled in their health plan for less than 2 years before their index date (1 year in MarketScan, gaps of up to 90 days permitted), were younger than 18 years of age at their UC index date, or had a history of other diseases treated with advanced therapies used in UC. These included a diagnosis at any time on or after January 1, 2010 (or before if data were available), and before or on the UC index date, of 1 or more of the following diseases: Crohn disease, rheumatoid arthritis or polyarticular juvenile idiopathic arthritis, ankylosing spondylitis or nonradiographic axial spondylarthritis, psoriasis, or psoriatic arthritis (refer to Appendix 1, Table 3). In Ontario, due to prescription drug data availability, our analysis was limited to those aged 67 years and older and those younger than 67 years who received social assistance.

Four UC treatment cohorts were then created from the base UC cohort in each participating database, where we defined individuals with an index prescription for the following 4 therapy categories between January 1, 2018, and March 31, 2023 (or the latest date of data available in each database): new users of tofacitinib, new users of a TNF alpha inhibitor, new users of vedolizumab or ustekinumab, and new users of a conventional therapy. New use was defined as a minimum of 2 years without a prior prescription for a drug in the same category and the date of the new prescription was on or after the UC base cohort index date.

The date of the new prescription defined the treatment cohort entry date. This 2-year period was used to distinguish between new and subsequent use of study medications at the start of each patient's data history. A shorter duration of this requirement would not lead to appreciably more patients on tofacitinib because the drug started being used for UC in 2018–2019, and nearly all patients with UC in the base cohort had at least 2 years of data history by this time. Individuals could enter more than 1 treatment cohort, but those starting therapies from multiple treatment categories on the same date were excluded from the analysis. We further excluded patients who were no longer enrolled in their health plan for any reason or had a diagnosis for another disease also treated with advance UC therapies before their treatment cohort entry date (refer to Appendix 2, Figures 2 to 5). Loss of enrolment in a health plan was defined as a 90-day gap or longer in the 2 years before starting treatment.

In each UC treatment cohort, individuals were followed until earliest occurrence of a study outcome (defined subsequently), loss of enrolment in their health plan, death, discontinuation of the study cohort entry drug, a switch to or between advanced treatments for UC (tofacitinib, TNF alpha inhibitors, or vedolizumab or ustekinumab), or the end of the study period in each database. Separate follow-up times were determined for each outcome. For nonmelanoma skin cancer and other cancer outcomes, individuals were followed starting 180 days and 90 days after treatment cohort entry, respectively. This was done to allow for a minimum biologically plausible duration of time for induction to cancer, latency for its detection, and to minimize detection bias around the time of treatment initiation.[21] Individuals with occurrence of a study outcome or a censoring event during this 90-day or 180-day period were excluded from the analyses of the cancers or nonmelanoma skin cancer outcomes.

Exposure

Individuals were classified into 1 of the 4 UC treatment categories at study cohort entry: tofacitinib; TNF alpha inhibitors (infliximab, adalimumab, or golimumab); vedolizumab or ustekinumab, either alone or in combination with each other; or conventional therapy (5-aminosalicylates, corticosteroids, or immunosuppressants [including azathioprine, methotrexate, 6-mercaptopurine, or cyclosporine]). A detailed list of the medications included in each category is presented in Appendix 1, Table 4. Exposure was defined using an as-treated approach, in which individuals were followed while continuously exposed to the cohort entry drug until death, loss of insurance coverage, or treatment discontinuation, defined as a 60-day gap or longer between consecutive dispensations or switching to or between advanced UC treatments.

Outcome Measures

The outcomes of interest were MACE, hospitalized thrombotic events, and cancer. A detailed list of the outcome definitions is included in Appendix 1, Table 5. MACE was defined as a composite outcome of myocardial infarction, ischemic stroke, or cardiovascular death.[22] Myocardial infarction and ischemic stroke were defined as a hospitalization with a relevant diagnosis code. Cardiovascular death was defined using the following algorithm previously validated by CNODES: in-hospital death with a cardiovascular diagnosis or out-of-hospital death without documentation of cancer in the prior year or trauma in the preceding month.[23] Hospitalization for a thrombotic event was defined as a composite outcome of arterial thrombotic events[24] or venous thrombotic events, including deep vein thrombosis and pulmonary embolism. Cancer was defined

as any cancer (excluding nonmelanoma skin cancer), nonmelanoma skin cancer, lymphoma, and lung cancer. Nonmelanoma skin cancer was defined using an adapted validated algorithm based on the presence of a diagnosis code plus a related surgical procedure code within 180 days using inpatient or outpatient physician service claims.[25]

Baseline Characteristics

We selected characteristics of the individuals included in each UC treatment cohort that would aid in the determination of whether a safety study would be feasible. Baseline characteristics included age, biological sex, calendar year of treatment cohort entry, UC duration (the time between the UC diagnosis index date and the treatment cohort entry date), previous use of other study drugs (assessed from January 1, 2015, onward to the treatment cohort entry date), and subsequent use of other study drugs (assessed after treatment cohort entry until the end of follow-up). We also assessed the occurrence of the study outcomes during the 5 years before study cohort entry. In many drug safety studies, evidence of past events may be used to exclude individuals with such events so that only incident events, such as new cancers, are counted during follow-up. However, because this was a feasibility analysis, we identified prior events rather than exclude on the basis of them. Finally, as a general measure of comorbidity, we used the Deyo-Charlson Comorbidity Index derived from physician claims and hospital records for up to 5 years before cohort entry.[26,27] This is a weighted index originally developed to predict mortality that takes into account the number and seriousness of the comorbid conditions of an individual.

Data Analysis

Descriptive statistics were used to summarize baseline covariates of individuals in each of the UC treatment cohorts. Continuous variables were described using the median and interquartile range. Categorical covariates were provided using frequencies, along with the percentage of the cohort with the covariate. Crude incidence rates within each treatment group were obtained using the number of events for a given outcome divided by the total number of person-years of follow-up, and expressed per 100 person-years of follow-up with a 95% confidence interval. Incidence rates were stratified by age (18 to 49 years, ≥ 50 years) and sex (females, males).

Findings

Main Take-Aways

We identified 401,651 adults who were diagnosed with UC between 2010 and 2023.

A total of 399 adults in this cohort initiated tofacitinib between January 1, 2018, and March 31, 2023.

Tofacitinib is currently rarely used for UC. When it is used, it is mostly used as a third-line or fourth-line treatment.

The overall duration of follow-up was brief, with the median durations ranging from less than 0.5 years to approximately 1.5 years.

There were no MACE and either zero or less than 6 thrombotic events among individuals taking tofacitinib.

Cancer rates could not be estimated for individuals taking tofacitinib.

Overall, we identified 401,651 individuals who were diagnosed with UC between January 1, 2010, and March 31, 2023. From the Canadian databases, there were 13,389 in Manitoba, 115,847 in Ontario, and 8,335 in Saskatchewan, and there were 264,080 from MarketScan. From this base cohort of individuals with a recorded UC diagnosis, there were a total of 399 new users of tofacitinib (131 in the Canadian databases), 2,463 new users of TNF alpha inhibitors (796 in the Canadian databases), 1,279 new users of vedolizumab or ustekinumab (927 in the Canadian databases), and 51,052 users of a new conventional therapy (12,656 in the Canadian databases) between January 1, 2018, and March 31, 2023. The construction of the study cohorts in each database is depicted in Appendix 2, Figures 2 to 5.

Baseline Characteristics

Baseline characteristics of individuals in the 4 UC treatment cohorts are summarized by database in Appendix 2, Tables 6 to 9. In general, the proportion of individuals initiating a TNF alpha inhibitor, vedolizumab or ustekinumab, or a conventional therapy was similar across databases between 2018 and 2023, with more individuals initiating tofacitinib in recent years. There were differences in age distribution across databases and treatment cohorts. Overall, new users of conventional therapy were older compared with individuals in other treatment cohorts, with the median age ranging from 50 years in Manitoba to 65 years in Ontario. The median age ranged from 27 years in Manitoba to 59 years in Ontario for new users of tofacitinib, and from 37 years in Manitoba to 44 years in Ontario for new users of TNF alpha inhibitors, with a higher proportion of individuals aged 18 to 49 years in Manitoba in both cohorts compared with other databases. Among users of vedolizumab or ustekinumab, the median age ranged from 41 years in Manitoba to 58 years in Ontario. In all 4 UC treatment cohorts, sex was distributed similarly across databases, except in Manitoba, where a greater percentage of new users of tofacitinib were male. There were only 399 new users of tofacitinib during the study period (Table 6), which indicates use of this drug in UC was rare compared with the other treatment categories. Previous use of other drug categories suggests that tofacitinib therapy, when used in UC, is typically as a third- or fourth-line treatment (Table 6).

Variations in duration of UC were observed across treatment groups. Among new users of tofacitinib, median durations were 1.8 years in MarketScan, 3.2 years in Ontario, 6.0 years in Saskatchewan, and 7.4

years in Manitoba. In Canadian provinces, the duration of UC was similar between databases among users of TNF alpha inhibitors (median durations, 2.1 to 2.7 years), vedolizumab or ustekinumab (median durations, 3.3 to 3.6 years), and conventional therapies (median durations, 1.6 to 3.7 years). In the MarketScan database, median durations were 0.5 years, 1.7 years, and 0.4 years for TNF alpha inhibitors, vedolizumab or ustekinumab, and conventional therapies, respectively. Prior use of other study drugs was similar across databases in the conventional therapy cohort, whereas differences between databases were noted among the 3 other UC treatment cohorts. There was limited prior use of tofacitinib among initiators of TNF alpha inhibitors or of vedolizumab or ustekinumab. The proportion of prior use of TNF alpha inhibitors was greater among users of tofacitinib (range, 25.7% to 66.7%) than among users of vedolizumab or ustekinumab (range, 14.0% to 39.8%). There were differences in the prior use of vedolizumab or ustekinumab among users of tofacitinib (range, 9.0% to 44.4%) and TNF alpha inhibitors (range, 0.6% to 28.2%). Conventional therapies were almost universally used before initiation of advanced therapies in all databases except the Ontario database, for which this proportion ranged from 60.4% to 70.8% compared with 92.0% to 100% in the other databases. Subsequent use of other study drugs was similar across databases in the 4 UC treatment cohorts.

In all databases and UC treatment cohorts, a small percentage of patients had evidence of prior MACE (< 3%) or thrombotic events (≤ 2%) in the 5 years preceding cohort entry. In general, across all 4 cohorts, a greater percentage of Ontarians had evidence of cancer in the 5 years preceding UC treatment. We observed differences in the Deyo-Charlson Comorbidity Index score between databases and UC treatment cohorts. Among new users of tofacitinib, fewer patients had a score greater than or equal to 2 in Manitoba and Saskatchewan compared to Ontario (27.1%) and MarketScan (18.7%). This proportion was similar across databases among users of TNF alpha inhibitors (range, 9.8% to 23.0%), vedolizumab or ustekinumab (range, 13.9% to 31.6%), and conventional therapies (range, 27.1% to 46.1%).

Incidence of Outcomes

The number of events and crude incidence rates are presented by outcome and database in Appendix 2, Tables 10 to 15. The overall duration of follow-up was relatively brief in all databases, with median follow-up durations ranging from less than 0.5 years to approximately 1.5 years. Events for most outcomes were sparse in all databases. There were zero MACE events, and either zero or less than 6 thrombotic events among users of tofacitinib. MACE and thrombotic events were also either zero or less than 6 for the other advanced treatment cohorts. Rates for these 2 outcomes were only estimable in the conventional therapy cohorts, which were substantially larger than the advanced therapy cohorts. Incidence rates for MACE in the conventional therapy cohort were 2.1 events per 100 person-years in Manitoba, 2.2 events per 100 person-years in Ontario, 0.4 events per 100 person-years in Saskatchewan, and 0.1 events per 100 person-years of follow-up in MarketScan. In the same order, incidence rates for thrombotic events for Manitoba, Ontario, Saskatchewan, and MarketScan were 0.5 per 100 person-years, 0.6 per 100 person-years, 0.3 per 100 person-years, and 0.4 per 100 person-years of follow-up, respectively. Cancer rates could not be estimated for tofacitinib patients in any database. For overall cancers (excluding nonmelanoma skin cancer), incidence rates were estimable for the other 3 treatment cohorts, but there was only 1 instance in the Canadian results

in which 95% confidence intervals did not overlap across databases. This was an incidence rate of 8.6 per 100 person-years in Ontario, which might best be explained by the older age of that cohort. Similar trends were observed for lymphoma and lung cancer. There were a limited number of events for all outcomes when stratified by age and sex, and incidence rates could not be estimated (data not reported).

Strengths and Limitations

To our knowledge, our study is 1 of few observational studies of the utilization of tofacitinib and other advanced therapies in patients with UC in everyday clinical practice using a large source population from several jurisdictions. Our study has important limitations. Our UC definition was based on 1 record of a health care encounter; therefore, it is sensitive rather than specific. This approach was taken to increase sample size, with the understanding that the main intent of the query was to conduct a feasibility analysis to estimate risk of the identified outcome in a population with UC in contrast to a population with rheumatological disease. There was a limited number of events across the databases and UC treatment cohorts, especially in the analyses stratified by age and sex. Follow-up in the study population was limited for all outcomes, which also contributes to the limited number of events observed. The analyses are crude, without adjustment for individual characteristics that may confound the association between study therapies and the safety outcomes. The lag period used for the cancer outcomes was shorter than typically used in observational studies of drug and cancer outcomes because a more ideal, longer lag period was not feasible given the timing of coverage of tofacitinib for UC and the limited follow-up time available to us.[21] In addition, our case definition for cancer for this feasibility analysis was imprecise, which very likely served to overestimate the number of events. The actual number of incident cancer events captured in provincial cancer registries would have been fewer. Moreover, drugs in the conventional therapy cohorts were combined into a single group, and no analyses were conducted by molecule given their different safety profiles. Finally, our study is limited to data from 3 Canadian provinces and the US, and the findings may not be generalizable to other jurisdictions. These limitations suggest our findings should be interpreted with caution.

Conclusions and Implications for Decision- or Policy-Making

Main Take-Aways

Due to the lack of events observed in our study, it is not possible to draw conclusions regarding associations between use of tofacitinib in UC and the safety events that we studied.

Safety studies of tofacitinib in UC are not currently feasible given the limited amount of data available.

Summary

We analyzed the use of tofacitinib and other therapies in individuals diagnosed with UC to determine if a safety study of MACE, thrombotic events, or cancer would be feasible using the data holdings available to CNODES. Patients with UC in Ontario were older compared to those in Manitoba, Saskatchewan, and the US, and would be expected to have greater prevalence of both prior events and comorbidities. There was a lower prevalence of prior conventional therapy in the advanced treatment cohorts in Ontario, which was likely the result of patients with UC in Ontario being relatively older than in other databases and because some UC treatments may have been missed for patients on social assistance who received drugs before obtaining their social assistance drug coverage. Although we observed other differences in baseline characteristics of new users of tofacitinib compared to new users of other UC therapies across the databases and between treatment cohorts, there were zero or a limited number of outcome events among new users of tofacitinib in all databases. Similar findings were observed for new users of TNF alpha inhibitors and vedolizumab or ustekinumab. A higher number of outcome events were observed among users of new conventional therapies. However, these were substantially larger cohorts than the advanced therapy cohorts, and it is to be expected that the number of events would be nominally greater and therefore the incidence rates would be more likely to be estimable. Importantly, the outcome incidence rates we computed are crude and should be interpreted with caution given the paucity of events and lack of stratification by characteristics that are potentially associated with adverse treatment effects. In addition, the duration of the follow-up period was short for all outcomes, especially for cancer. The short duration of follow-up time can be explained by a high proportion of censoring due to treatment discontinuation and switching to or between advanced UC treatments, and by a short period of tofacitinib data availability at all sites (refer to Appendix 1, Table 2). Due to the lack of events observed in our study, it is not possible to draw conclusions regarding associations between use of tofacitinib in UC and the safety events that we studied. There remains limited data on the risk of MACE, thrombotic events, and cancer with use of tofacitinib in individuals with UC.[14-18,28]

Conclusion

We conducted a utilization analysis to determine the feasibility of a safety study of tofacitinib among individuals with UC in the data holdings available to CNODES and observed a limited number of MACE, thrombotic events, and cancer events among new users of tofacitinib and other UC therapies. Tofacitinib is currently rarely used for UC; when it is used, it is mostly as a third-line or fourth-line treatment. Targeted safety studies of these outcomes in this setting are not currently feasible in our data holdings.

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Authors

CNODES Disclaimer: The opinions, results, and conclusions contained in this report are those of the authors. No endorsement by CADTH, the provinces, data stewards, the participating research centres, or the Canadian Institute for Health Information (CIHI) is intended or should be inferred.

Clinical Review

Colin Dormuth, as the project lead and US MarketScan site investigator, drafted the scientific protocol and statistical analysis plan, oversaw submission and approval of data access and ethics approval, conducted quality checks of results, and drafted the final report.

Silvia Alessi-Severini, as the Manitoba site investigator, reviewed the protocol, submitted ethics and data use agreement with data owner, approved conducted analyses, contributed to draft report, and approved final version.

Alain Bitton, as the content expert, reviewed and provided feedback on the scientific protocol, interpreted results, and reviewed and approved final draft of the report.

Kristian B. Fillion, as the UK Clinical Practice Research Datalink site investigator, reviewed and provided feedback on the scientific protocol and statistical analysis plan, contributed to the interpretation of data, reviewed the final draft of report, and reviewed and approved final draft of report.

Donica Janzen, as the Saskatchewan site investigator, reviewed and provided feedback on scientific protocol and statistical analysis plan, particularly with respect to Saskatchewan context, conducted quality checks of results, and reviewed and approved final draft of report.

Lisa M. Lix, as the methods lead, drafted the scientific protocol, drafted the statistical analysis plan, conducted quality checks of results, and reviewed and approved final draft of report.

Michael Paterson, as the Ontario site investigator, reviewed and contributed to the scientific protocol and statistical analysis plan; oversaw preparation of the site's application for project approval; oversaw, reviewed, and approved the site data analyses; reviewed and contributed to the preparation of the study report; and reviewed and approved the final version of the report to be published.

Matt Dahl, as the lead analyst and Manitoba site analyst, reviewed and provided feedback on the scientific and analytical protocols, contributed to the analysis at Manitoba site, and reviewed and provided feedback on manuscripts.

Xinya Lu, as the Saskatchewan site analyst, conducted data analysis and reviewed the draft report.

Audray St-Jean, as the research assistant, participated in drafting the scientific protocol and statistical analysis plan; review and interpretation of the study results; and drafting and revising the report.

Fangyun Wu, as the Ontario site analyst, reviewed and provided feedback on scientific protocol and statistical analysis plan, particularly with respect to Ontario context; conducted analysis; conducted quality checks of results; and reviewed final draft of report.

Contributors

Anat Fisher, as the previous project lead, contributed to conception and study design.

Ayodele Ajayi, as the US MarketScan site analyst, conducted analyses.

Xue Feng, as the Saskatchewan site analyst, was part of the analysis team.

Jason Kim, as the US MarketScan site analyst, conducted analyses and quality checks of results.

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Louis de Léséleuc and **David Stock** reviewed the drafts and final report. **Emily Farrell** provided knowledge mobilization support. **Brandy Appleby** provided project management support.

Conflicts of Interest

Silvia Alessi-Severini disclosed the following:
Jupiter LSC — Consulting on new therapies 2022; 1 ad hoc consultation

Payment as advisor or consultant:
- Ad hoc advisory committee — Leo Pharma, consulting on new product, 2020

Alain Bitton disclosed the following:
Speaking engagements:
- Educational programs: Janssen, Fresenius Kabi, Amgen
- Educational needs assessment: Takeda
- AbbVie

Educational lectures: Viatris

Payments as advisor or consultant:
- Advisory boards: Janssen, Takeda, AbbVie, Bristol Myers Squibb, Pfizer, BIOJAMP, Amgen, McKesson, Viatris, Hoffman LaRoche

Kristian B. Fillion disclosed the following:
INESSS — Member of the CSEMI of INESSS. Received honorariums for serving as a committee member and for serving as a member of a consultation committee regarding guidelines for the treatment of menopause.

CNODES — Honorariums received as CPRD team lead
- Boehringer Ingelheim — Authored an article in 2019 for a study funded by Boehringer Ingelheim

Donica Janzen disclosed the following:
Travel funding or payment:
- CNODES — ICPE conference travel August 2022, analyst training program honorarium March 2021
- Received an honorarium for work as a peer reviewer for analyst training program in March 2021

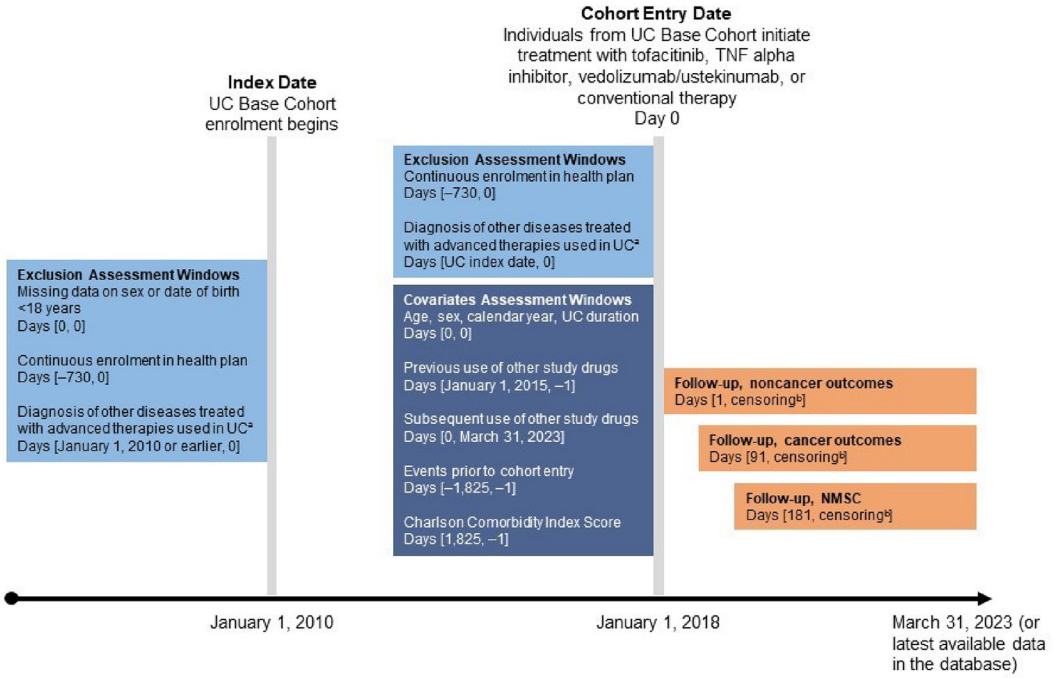
Michael Paterson disclosed the following:
Employee of the Institute for Clinical Evaluative Sciences (ICES), which is funded by the Ontario Ministry of Health

No other conflicts of interest were declared.

Appendix 1: Additional Information on Methods

Note that this appendix has not been copy-edited.

Figure 1: Study Design Diagram



NMSC = nonmelanoma skin cancer; TNF = tumour necrosis factor; UC = ulcerative colitis.

Note: Graphical depiction of the study design as proposed by Schneeweiss and colleagues (Schneeweiss et al. Ann Intern Med. 2019; doi: 10.7326/M18-3079).

[a] Diagnosis of 1 or more of the following diseases: Crohn disease, rheumatoid arthritis and polyarticular juvenile idiopathic arthritis, ankylosing spondylitis and nonradiographic axial spondyloarthritis, psoriasis, or psoriatic arthritis.

[b] Patients followed until earliest occurrence of the study outcome, loss of enrolment, death, discontinuation of the study cohort entry drug, switch to or between advanced treatments for UC, or end of the study period. Minimum follow-up time of 180 days for nonmelanoma and 90 days for other cancer outcomes.

Table 1: List of Databases Used in Each Participating CNODES Site

CNODES site	Databases				
	Prescription drug claims (and dispensing captured)	Physician service claims	Hospital records	Emergency department records	Health insurance registry
Manitoba	Drug Program Information Network (all)	Medical Claims/ Medical Services	CIHI Discharge Abstract/ Manitoba Hospital Abstracts	Not available	Manitoba Health Insurance Registry
Ontario	ODB Program (covers those ≥ 65 years and social assistance recipients)	OHIP Claims History Database	CIHI Discharge Abstract Database	NACRS	OHIP Registered Person's Database
Saskatchewan	Prescription Drug Plan Historical Claims (all)	Medical Services Branch	CIHI Discharge Abstract Database	NACRS	Person Health Registration System
US MarketScan[a]	Outpatient prescription drug claims (all)	Outpatient services	Inpatient admissions and inpatient services	Outpatient services (where place of service is emergency department)	Enrolment

CIHI = Canadian Institute for Health Information; CNODES = Canadian Network for Observational Drug Effect Studies; NACRS = National Ambulatory Care Reporting System; ODB = Ontario Drug Benefit; OHIP = Ontario Health Insurance Plan.

[a]The Merative MarketScan Research Databases includes the Commercial Claims and Encounters database and Supplemental and Coordination of Benefits (COB) database.

Table 2: Dates of the Accrual Period in Each Participating CNODES Site

CNODES site	Beginning date of data availability[a]	End date of data availability
Manitoba	January 1, 2010	March 31, 2022
Ontario	January 1, 2010	December 31, 2022
Saskatchewan	January 1, 2010	March 31, 2023
US MarketScan	January 1, 2010	December 31, 2021

CNODES = Canadian Network for Observational Drug Effect Studies; UC = ulcerative colitis.

[a]Use of data back until January 1, 2002, in Manitoba, April 1, 1997, in Ontario, and January 1, 2006, in the US MarketScan for the exclusion of individuals with a diagnosis of other diseases treated with the advanced therapies used in UC in the base cohort.

Table 3: Other Diseases Treated With Advanced Therapies for UC

Disease[a]	ICD-9 codes	ICD-10 codes
Crohn disease	555	K50

Disease[a]	ICD-9 codes	ICD-10 codes
Rheumatoid arthritis and polyarticular juvenile idiopathic arthritis	714	M05 M06 M08 (excluding M08.1)
Ankylosing spondylitis and nonradiographic axial spondyloarthritis	720	M45
Psoriasis	696	L40 (excluding L40.5)
Psoriatic arthritis	696.0	L40.5

ICD = International Classification of Diseases Ninth or Tenth Revision; UC = ulcerative colitis.

[a]Defined as 1 health encounter (outpatient, hospitalization [any diagnostic position], emergency department).

Table 4: List of Medications for the 4 UC Treatment Cohorts

Category of therapy	UC treatment cohort	Generic name	ATC codes
Advanced therapies	JAK inhibitor	Tofacitinib	L04AA29
	TNF alpha inhibitors	Adalimumab	L04AB04
		Infliximab	L04AB02
		Golimumab	L04AB06
	Interleukin-12/13 inhibitor or selective alpha 4 beta 7 integrin inhibitor	Ustekinumab	L04AC05
		Vedolizumab	L04AA33
Conventional therapies	5-aminosalicylates	Sulfasalazine	A07EC01
		Mesalazine	A07EC02
		Olsalazine	A07EC03
		Balsalazide	A07EC04
	Corticosteroids	Prednisone	A07EA03, H02AB07
		Prednisolone	A07EA01, H02AB06
		Hydrocortisone	A07EA02, H02AB09
		Methylprednisolone	H02AB04
		Budesonide	A07EA06
	Immunosuppressants	Azathioprine	L04AX01
		Methotrexate	L01BA01, L04AX03
		6-Mercaptopurine	L01BB02
		Cyclosporine (ciclosporin)	L04AD01

ATC = Anatomic Therapeutic Chemical; JAK = Janus kinase; TNF = tumour necrosis factor; UC = ulcerative colitis.

Table 5: Study Outcomes Definitions

Condition	Diagnosis or procedure codes	Data source and definition	Comment
MACE			
Myocardial infarction[a]	ICD-10 code: I21	Hospitalization (outcome date is admission date)	Primary position/most responsible diagnosis (type M) in diagnosis position 1
Ischemic stroke[a]	ICD-10 codes: I63, I64	Hospitalization (outcome date is admission date)	Primary position/most responsible diagnosis (type M) in diagnosis position 1
Cardiovascular mortality[a,b]	In-hospital death with a cardiovascular diagnosis [ICD-10 codes: I00-I77 (except I46.9)] recorded as primary position/most responsible diagnosis (type M) in diagnosis position 1; OR Out-of-hospital death (including death in the emergency department if data available) without: • Documentation of cancer (ICD-9 codes: 140-172, 174-209; ICD-10-CA: C00-C43, C45-C97) in hospital, emergency department or physician claims data in the prior year; or • Documentation of trauma (ICD-9 codes: 800-999, E000-E999; ICD-10-CA: S00-T98, V01-Y98) in hospital, emergency department or physician claims data in the preceding month.		
Thrombotic events			
Arterial thromboembolism[c] (including ischemic stroke or systemic embolization)	ICD-10 codes: I63, I64, I74	Hospitalization (outcome date is admission date)	Primary position/most responsible diagnosis (type M) in diagnosis position 1
Venous thromboembolism (including deep vein thrombosis and pulmonary embolism)	ICD-10 codes: I26, I80, I81, I82	Hospitalization (outcome date is admission date)	Primary position/most responsible diagnosis (type M) in diagnosis position 1
Cancer			
Cancer (excluding nonmelanoma skin cancer)	**Diagnosis codes:** ICD-9 codes: 140-172, 174-209 ICD-10 codes: C00-C43, C45-C97 **Procedure codes:** 1. Ambulatory codes for radiotherapy and chemotherapy (as applicable in each database) 2. CCI codes in hospital records: 1.xx.35.xx (chemotherapy); 1.xx.27.xx (radiotherapy) 3. Hospital or emergency department types or MRDx/ main problem: Z51.0, Z51.1	One hospitalization with a diagnosis code (outcome date is admission date) OR 2 visits to physicians/nurse practitioners within 3 months with diagnosis codes (outcome date is second diagnosis date) OR One record (outpatient or in hospital) with a procedure code (outcome date is admission date)	Any diagnostic position

Condition	Diagnosis or procedure codes	Data source and definition	Comment
Nonmelanoma skin cancer[d]	**Diagnosis codes:** ICD-9 codes: 173 ICD-10 codes: C44 AND **procedure codes** on diagnosis date or the 180 days before/after the diagnosis	Hospitalization (outcome date is admission date) Visits to physicians/nurse practitioners (outcome date is the latest among diagnosis/ procedure date)	Refer to Azoulay et al. (2023)[25] for list of procedure codes
Lymphoma	Diagnosis codes: ICD-9: 200, 202, 204 ICD-10: C81-C86	Has the cancer outcome plus at least 1 lymphoma diagnosis code in hospitalization, emergency department, or a visit to physicians/nurse practitioners, on or after the first cancer encounter (outcome date is the lymphoma diagnosis date)	Any diagnostic position: hospitalization, emergency department, visits to physicians/ nurse practitioners
Lung cancer	ICD-9 codes: 162 ICD-10 codes: C34	Meets the definition for the "Cancer (excluding nonmelanoma skin cancer)" **plus** at least 1 diagnosis code for lung cancer in hospitalization, emergency department, or a visit to physicians/nurse practitioners, on or after the first cancer encounter (outcome date is the lung cancer diagnosis date)	Any diagnostic position: hospitalization, emergency department, visits to physicians/ nurse practitioners

CCI = Canadian Classification of Health Interventions; ICD = International Classification of Diseases Ninth or Tenth Revision; MRDx = most responsible diagnosis (for the individual's stay in hospital).

[a]Definition from: Filion KB, Lix LM, Yu OHY, et al. Sodium glucose cotransporter 2 inhibitors and risk of major adverse cardiovascular events: multi-database retrospective cohort study. BMJ. 2020;370:m3342.

[b]Definition from: Lix LM, Sobhan S, St-Jean A, et al. Validity of an algorithm to identify cardiovascular deaths from administrative health records: a multi-database population-based cohort study. BMC Health Serv Res. 2021;21(1):758.

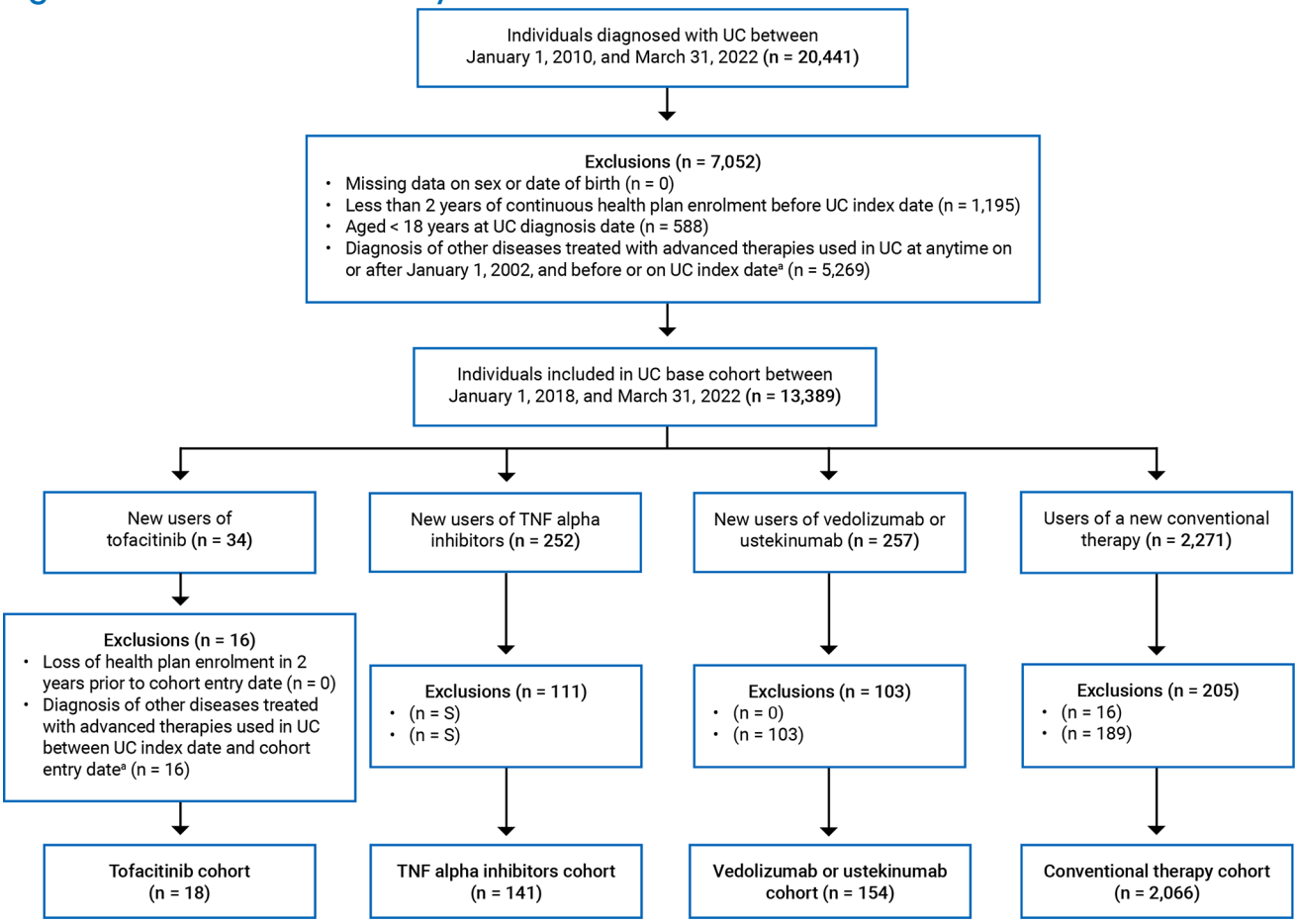
[c]Definition from: Durand M, Schnitzer ME, Pang M, et al. Effectiveness and safety among direct oral anticoagulants in nonvalvular atrial fibrillation: A multi-database cohort study with meta-analysis. Br J Clin Pharmacol. 2021;87(6):2589-2601.

[d]Definition from: Azoulay L, St-Jean A, Dahl M, et al. Hydrochlorothiazide use and risk of keratinocyte carcinoma and melanoma: A multi-site population-based cohort study. J Am Acad Dermatol. 2023;89(2):243-253.

Appendix 2: Main Findings

Note that this appendix has not been copy-edited.

Figure 2: Flow Chart of Study Cohort Construction in Manitoba

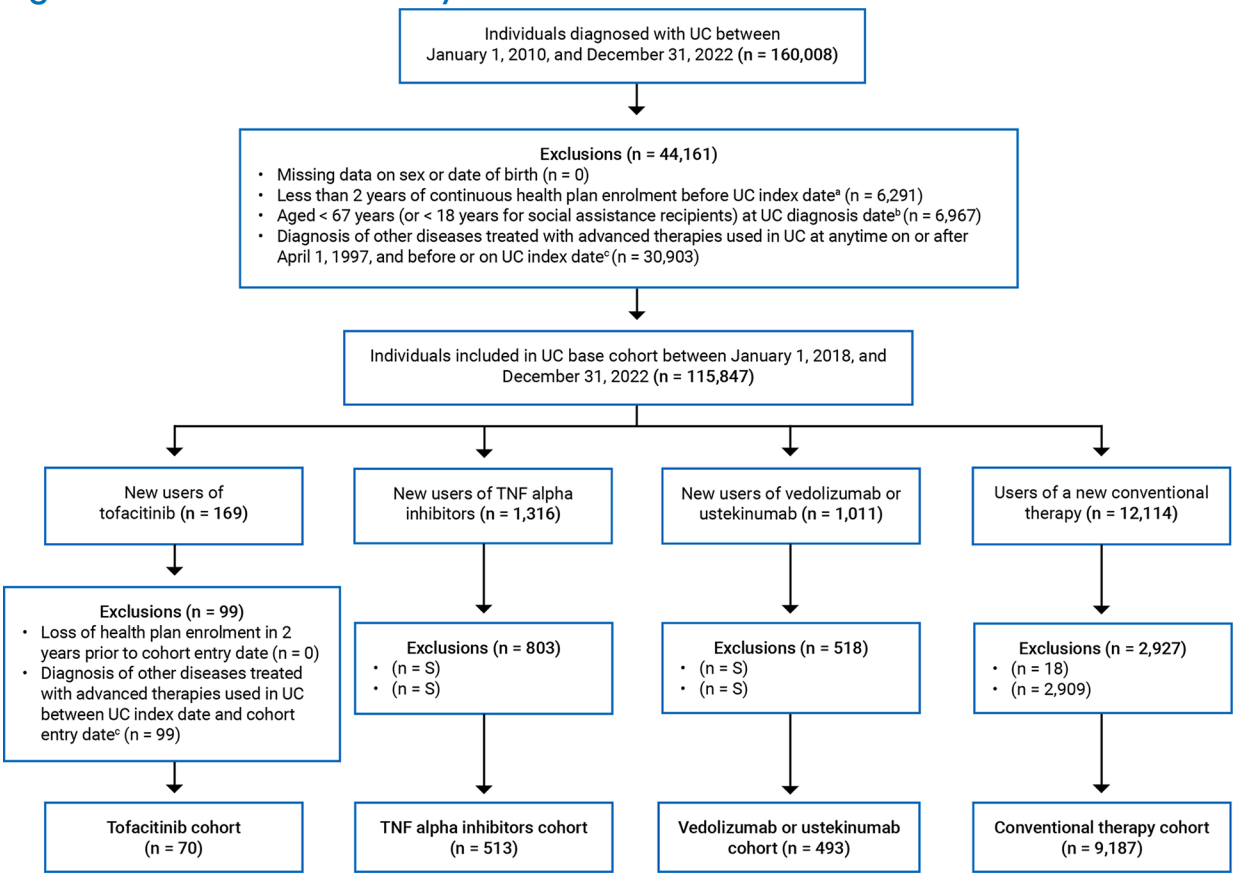


S = value suppressed; TNF = tumour factor necrosis; UC = ulcerative colitis.

Note: Values between 1 and 5 inclusively were suppressed due to privacy restrictions.

[a] Diagnosis of 1 or more of the following diseases: Crohn disease, rheumatoid arthritis and polyarticular juvenile idiopathic arthritis, ankylosing spondylitis and nonradiographic axial spondyloarthritis, psoriasis, or psoriatic arthritis.

Figure 3: Flow Chart of Study Cohort Construction in Ontario



S = value suppressed; TNF = tumour necrosis factor; UC = ulcerative colitis.

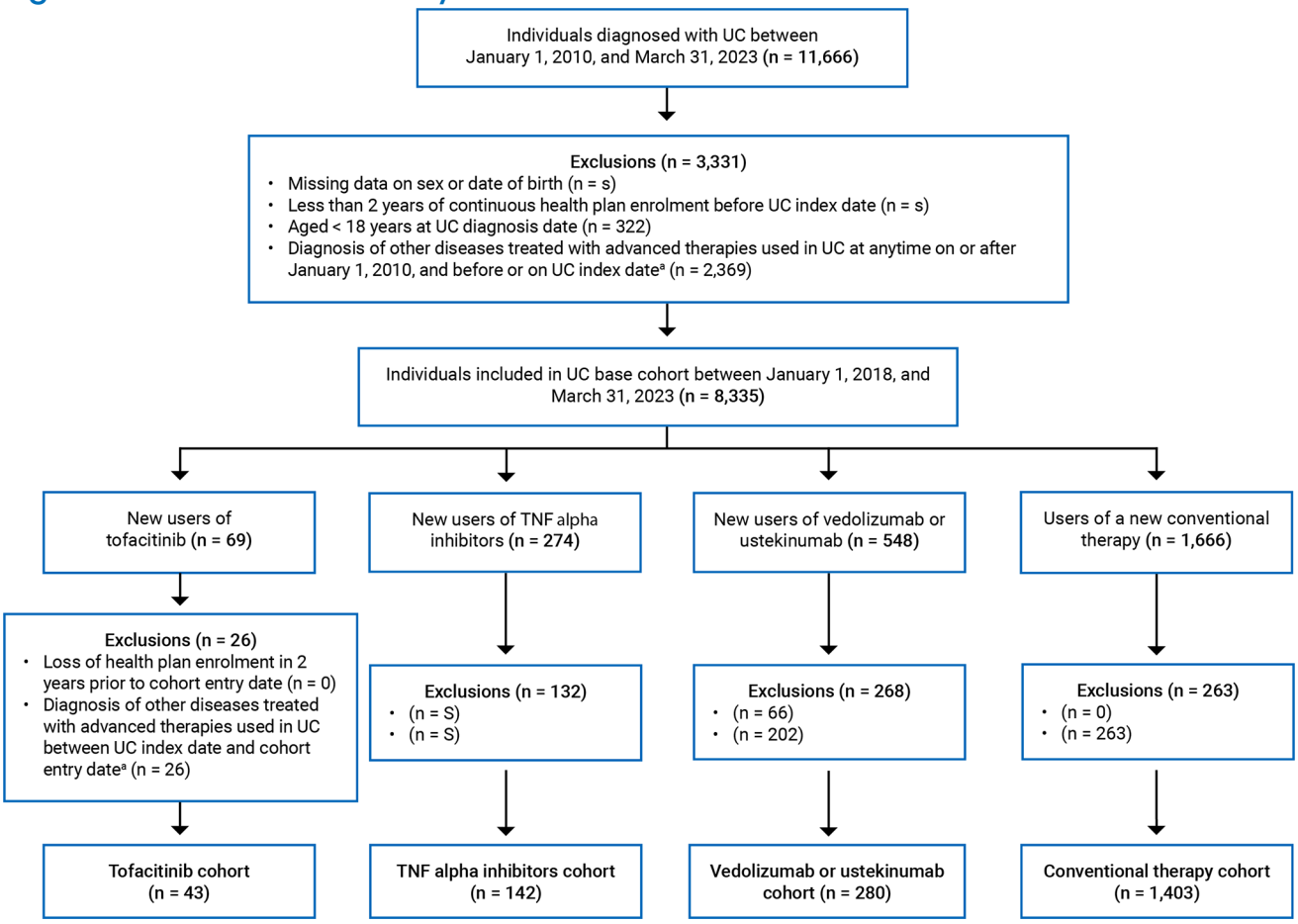
Note: Values between 1 and 5 inclusively were suppressed due to privacy restrictions.

[a] Continuous drug coverage not required for those aged < 65 years.

[b] Due to prescription drug claims data availability, the study population was limited to those aged 67 years and older and those < 67 years who are social assistance recipients in Ontario.

[c] Diagnosis of 1 or more of the following diseases: Crohn disease, rheumatoid arthritis and polyarticular juvenile idiopathic arthritis, ankylosing spondylitis and nonradiographic axial spondyloarthritis, psoriasis, or psoriatic arthritis.

Figure 4: Flow Chart of Study Cohort Construction in Saskatchewan

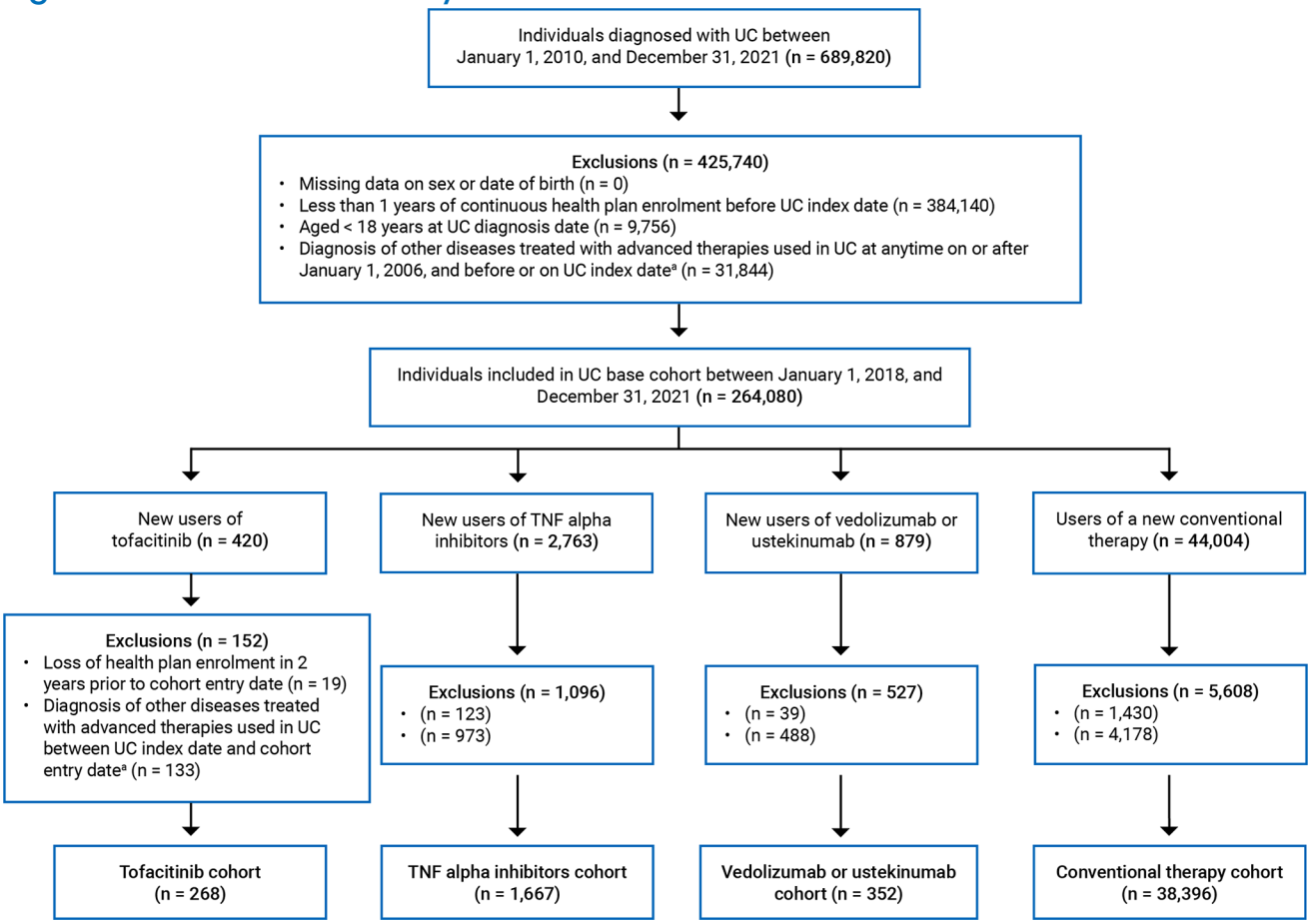


S = value suppressed; TNF = tumour necrosis factor ; UC = ulcerative colitis.

Note: Values between 1 and 5 inclusively were suppressed due to privacy restrictions.

[a] Diagnosis of 1 or more of the following diseases: Crohn disease, rheumatoid arthritis and polyarticular juvenile idiopathic arthritis, ankylosing spondylitis and nonradiographic axial spondyloarthritis, psoriasis, or psoriatic arthritis.

Figure 5: Flow Chart of Study Cohort Construction in MarketScan



TNF = tumour necrosis factor; UC = ulcerative colitis.

[a] Diagnosis of 1 or more of the following diseases: Crohn disease, rheumatoid arthritis and polyarticular juvenile idiopathic arthritis, ankylosing spondylitis and nonradiographic axial spondyloarthritis, psoriasis, or psoriatic arthritis.

Table 6: Baseline Characteristics of New Users of Tofacitinib by Database

Characteristics	Manitoba (n = 18)	Ontario (n = 70)[a]	Saskatchewan (n = 43)	MarketScan (n = 268)
Age (years)				
Median (IQR)	27 (22 to 39)	58.5 (39 to 67)	40 (32 to 53)	45 (32 to 58)
< 50 years, n (%)	17 (94.4)	26 (37.1)	30 (69.8)	154 (57.5)
Females, n (%)	6 (33.3)	29 (41.4)	20 (46.5)	112 (41.8)
Calendar year of study cohort entry, n (%)				
2018	S	S	0 (0)	45 (16.8)
2019	8 (44.4)	S	11 (25.6)	113 (42.2)

Characteristics	Manitoba (n = 18)	Ontario (n = 70)[a]	Saskatchewan (n = 43)	MarketScan (n = 268)
2020	S	S	18 (41.9)	64 (23.9)
2021	6 (33.3)	37 (52.9)	S	46 (17.2)
2022	0 (0)	23 (32.9)	7 (16.3)	—
2023	—	—	S	—
Years between UC diagnosis and cohort entry, median (IQR)	7.4 (3.4 to 9.1)	3.2 (1.4 to 7.4)	6.0 (2.8 to 9.2)	1.8 (0.8 to 3.9)
Previous use of other study drugs, n (%)				
Adalimumab, infliximab or golimumab	12 (66.7)	18 (25.7)	18 (41.9)	125 (46.6)
Vedolizumab or ustekinumab	8 (44.4)	8 (11.4)	15 (34.9)	24 (9.0)
5-ASA, corticosteroids or immunosuppressants	18 (100)	48 (68.6)	42 (97.7)	259 (96.6)
Concurrent/subsequent use of other study drugs, n (%)				
Adalimumab, infliximab or golimumab	S	S	S	14 (5.2)
Vedolizumab or ustekinumab	S	S	14 (32.6)	25 (9.3)
5-ASA, corticosteroids or immunosuppressants	11 (61.1)	37 (52.9)	33 (76.7)	195 (72.8)
Individuals captured in another cohort, n (%)				
TNF alpha inhibitor cohort	6 (33.3)	17 (24.3)	15 (34.9)	88 (32.8)
Vedolizumab or ustekinumab cohort	7 (38.9)	10 (14.3)	21 (48.8)	34 (12.7)
Conventional therapy cohort	7 (38.9)	32 (45.7)	10 (23.3)	130 (48.5)
Events in the 5 years before cohort entry, n (%)				
MACE (myocardial infarction or ischemic stroke)	0 (0)	S	0 (0)	0 (0)
Hospitalization for thrombotic events	0 (0)	0 (0)	0 (0)	S
Cancer (excluding nonmelanoma skin cancer)	S	33 (47.1)	S	94 (35.1)
Charlson Comorbidity Index Score, n (%)				
0	11 (61.1)	31 (44.3)	32 (74.4)	155 (57.8)
1	S	20 (28.6)	S	63 (23.5)
2	S	8 (11.4)	S	26 (9.7)
3+	0 (0)	11 (15.7)	S	24 (9.0)

5-ASA = 5-aminosalicylates compounds; IQR = interquartile range; S = value suppressed; TNF = tumour necrosis factor; UC = ulcerative colitis.

Note: Values between 1 and 5 inclusively were suppressed due to privacy restrictions.

[a]Due to prescription drug claims data availability, our analysis was limited to those aged 67 years and older and those < 67 years who are social assistance recipients in Ontario.

Table 7: Baseline Characteristics of New Users of TNF Alpha Inhibitors by Database

Characteristics	Manitoba (n = 141)	Ontario (n = 513)[a]	Saskatchewan (n = 142)	MarketScan (n = 1,667)
Age (years)				
Median (IQR)	37 (27 to 54)	43 (26 to 65)	44 (30 to 58)	41 (29 to 53)
< 50 years, n (%)	99 (70.2)	288 (56.1)	84 (59.2)	1,116 (66.9)
Females, n (%)	70 (49.6)	223 (43.5)	66 (46.5)	806 (48.4)
Calendar year of study cohort entry, n (%)				
2018	35 (24.8)	167 (32.6)	44 (31.0)	442 (26.5)
2019	27 (19.1)	87 (17.0)	19 (13.4)	453 (27.2)
2020	S	66 (12.9)	28 (19.7)	364 (21.8)
2021	49 (34.8)	89 (17.3)	30 (21.1)	408 (24.5)
2022	S	104 (20.3)	15 (10.6)	–
2023	–	–	6 (4.2)	–
Years between UC diagnosis and cohort entry, median (IQR)	2.2 (0.7 to 5.9)	2.7 (0.8 to 6.6)	2.1 (0.6 to 5.8)	0.5 (0.1 to 2.1)
Previous use of other study drugs, n (%)				
Tofacitinib	S	S	S	9 (0.5)
Vedolizumab or ustekinumab	23 (16.3)	22 (4.3)	40 (28.2)	10 (0.6)
5-ASA, corticosteroids or immunosuppressants	139 (98.6)	310 (60.4)	138 (97.2)	1,534 (92.0)
Concurrent/subsequent use of other study drugs, n (%)				
Tofacitinib	7 (5.0)	20 (3.9)	16 (11.3)	90 (5.4)
Vedolizumab or ustekinumab	31 (22.0)	47 (9.2)	36 (25.4)	113 (6.8)
5-ASA, corticosteroids or immunosuppressants	110 (78.0)	315 (61.4)	113 (79.6)	1,198 (71.9)
Individuals captured in another cohort, n (%)				
Tofacitinib cohort	6 (4.3)	17 (3.3)	15 (10.6)	88 (5.3)
Vedolizumab or ustekinumab cohort	38 (27.0)	62 (12.1)	58 (40.9)	90 (5.4)
Conventional therapy cohort	59 (41.8)	218 (42.5)	60 (42.3)	1,026 (61.5)
Events in the 5 years before cohort entry, n (%)				
MACE (myocardial infarction or ischemic stroke)	S	6 (1.2)	S	6 (0.4)
Hospitalization for thrombotic events	S	7 (1.4)	S	22 (1.3)
Cancer (excluding nonmelanoma skin cancer)	13 (9.2)	136 (26.5)	23 (16.2)	158 (9.5)
Charlson Comorbidity Index Score, n (%)				
0	88 (62.4)	289 (56.3)	89 (62.7)	1,031 (61.8)

Characteristics	Manitoba (n = 141)	Ontario (n = 513)[a]	Saskatchewan (n = 142)	MarketScan (n = 1,667)
1	34 (24.1)	106 (20.7)	39 (27.5)	385 (23.1)
2	13 (9.2)	57 (11.1)	7 (4.9)	126 (7.6)
3+	6 (4.3)	61 (11.9)	7 (4.9)	125 (7.5)

5-ASA = 5-aminosalicylates compounds; IQR = interquartile range; S = value suppressed; TNF = tumour necrosis factor; UC = ulcerative colitis.

Note: Values between 1 and 5 inclusively were suppressed due to privacy restrictions.

[a]Due to prescription drug claims data availability, our analysis was limited to those aged 67 years and older and those < 67 years who are social assistance recipients in Ontario.

Table 8: Baseline Characteristics of New Users of Vedolizumab or Ustekinumab by Database

Characteristics	Manitoba (n = 154)	Ontario (n = 493)[a]	Saskatchewan (n = 280)	MarketScan (n = 352)
Age (years)				
Median (IQR)	41 (28 to 57)	58 (30 to 70)	43 (31 to 59)	44 (32 to 55)
< 50 years, n (%)	96 (62.3)	203 (41.2)	172 (61.4)	219 (62.2)
Females, n (%)	71 (46.1)	211 (42.8)	140 (50.0)	171 (48.6)
Calendar year of study cohort entry, n (%)				
2018	34 (22.1)	116 (23.5)	40 (14.3)	34 (9.7)
2019	19 (12.3)	97 (19.7)	66 (23.6)	61 (17.3)
2020	30 (19.5)	61 (12.4)	59 (21.1)	105 (29.8)
2021	62 (40.3)	80 (16.2)	58 (20.7)	152 (43.2)
2022	9 (5.8)	139 (28.2)	48 (17.1)	–
2023	–	–	9 (3.2)	–
Years between UC diagnosis and cohort entry, median (IQR)	3.3 (1.3 to 7.6)	3.6 (1.4 to 7.7)	3.4 (0.8 to 6.5)	1.7 (0.4 to 3.7)
Previous use of other study drugs, n (%)				
Tofacitinib	0 (0.0)	S	8 (2.9)	21 (6.0)
Adalimumab, infliximab or golimumab	35 (22.7)	69 (14.0)	41 (14.6)	140 (39.8)
5-ASA, corticosteroids or immunosuppressants	153 (99.4)	349 (70.8)	277 (98.9)	336 (95.5)
Concurrent/subsequent use of other study drugs, n (%)				
Tofacitinib	8 (5.2)	10 (2.0)	16 (5.7)	18 (5.1)
Adalimumab, infliximab or golimumab	25 (16.2)	28 (5.7)	44 (15.7)	18 (5.1)
5-ASA, corticosteroids or immunosuppressants	109 (70.8)	234 (47.5)	201 (71.8)	230 (65.3)
Individuals captured in another cohort, n (%)				
Tofacitinib cohort	7 (4.5)	10 (2.0)	21 (7.5)	34 (9.7)

Characteristics	Manitoba (n = 154)	Ontario (n = 493)[a]	Saskatchewan (n = 280)	MarketScan (n = 352)
TNF alpha inhibitor cohort	38 (24.7)	62 (12.6)	58 (20.7)	90 (25.6)
Conventional therapy cohort	54 (35.1)	155 (31.4)	87 (31.1)	210 (59.7)
Events in the 5 years before cohort entry, n (%)				
MACE (myocardial infarction or ischemic stroke)	0	7 (1.4)	S	S
Hospitalization for thrombotic events	S	6 (1.2)	S	6 (1.7)
Cancer (excluding nonmelanoma skin cancer)	23 (14.9)	153 (31.0)	24 (8.6)	158 (44.9)
Charlson Comorbidity Index Score, n (%)				
0	77 (50.0)	236 (47.9)	172 (61.4)	200 (56.8)
1	44 (28.6)	101 (20.5)	69 (24.6)	75 (21.3)
2	18 (11.7)	72 (14.6)	20 (7.1)	39 (11.1)
3+	15 (9.7)	84 (17.0)	19 (6.8)	38 (10.8)

5-ASA = 5-aminosalicylates compounds; IQR = interquartile range; S = value suppressed; TNF = tumour necrosis factor; UC = ulcerative colitis.

Note: Values between 1 and 5 inclusively were suppressed due to privacy restrictions.

[a]Due to prescription drug claims data availability, our analysis was limited to those aged 67 years and older and those < 67 years who are social assistance recipients in Ontario.

Table 9: Baseline Characteristics of Users of a New Conventional Therapy by Database

Characteristics	Manitoba (n = 2,066)	Ontario (n = 9,187)[a]	Saskatchewan (n = 1,403)	MarketScan (n = 38,396)
Age (years)				
Median (IQR)	50 (35 to 64)	65 (57 to 74)	54 (38 to 67)	53 (40 to 61)
< 50 years, n (%)	997 (48.3)	1,903 (20.7)	602 (42.9)	15,952 (41.5)
Females, n (%)	1,193 (57.7)	5,094 (55.4)	725 (51.7)	21,407 (55.8)
Calendar year of study cohort entry, n (%)				
2018	499 (24.2)	2,348 (25.6)	316 (22.5)	10,590 (27.6)
2019	544 (26.3)	1,919 (20.9)	304 (21.7)	10,385 (27.0)
2020	474 (22.9)	1,628 (17.7)	239 (17.0)	8,542 (22.2)
2021	463 (22.4)	1,572 (17.1)	223 (15.9)	8,879 (23.1)
2022	86 (4.2)	1,720 (18.7)	258 (18.4)	–
2023	–	–	63 (4.5)	–
Years between UC diagnosis and cohort entry, median (IQR)	2.0 (0 to 6.1)	3.7 (0.5 to 7.7)	1.6 (0 to 5.6)	0.4 (0 to 2.6)
Previous use of other study drugs, n (%)				
Tofacitinib	S	9 (0.1)	0 (0.0)	15 (0.0)
Adalimumab, infliximab or golimumab	29 (1.4)	112 (1.2)	23 (1.6)	357 (0.9)

Characteristics	Manitoba (n = 2,066)	Ontario (n = 9,187)[a]	Saskatchewan (n = 1,403)	MarketScan (n = 38,396)
Vedolizumab or ustekinumab	7 (0.3)	29 (0.3)	6 (0.4)	40 (0.1)
Concurrent/subsequent use of other study drugs, n (%)				
Tofacitinib	11 (0.5)	39 (0.4)	15 (1.1)	159 (0.4)
Adalimumab, infliximab or golimumab	103 (5.0)	284 (3.1)	101 (7.2)	1,280 (3.3)
Vedolizumab or ustekinumab	81 (3.9)	188 (2.0)	117 (8.3)	309 (0.8)
Individuals captured in another cohort, n (%)				
Tofacitinib cohort	7 (0.3)	32 (0.3)	10 (0.7)	130 (0.3)
TNF alpha inhibitor cohort	59 (2.9)	218 (2.4)	60 (4.3)	1,026 (2.7)
Vedolizumab or ustekinumab cohort	54 (2.6)	155 (1.7)	87 (6.2)	210 (0.5)
Events in the 5 years before cohort entry, n (%)				
MACE (myocardial infarction or ischemic stroke)	43 (2.1)	267 (2.9)	24 (1.7)	267 (0.7)
Hospitalization for thrombotic events	20 (1.0)	180 (2.0)	14 (1.0)	581 (1.5)
Cancer (excluding nonmelanoma skin cancer)	247 (12.0)	2,251 (24.5)	161 (11.5)	3,541 (9.2)
Charlson Comorbidity Index Score, n (%)				
0	978 (47.3)	3,112 (33.9)	715 (51.0)	18,384 (47.9)
1	530 (25.7)	1,840 (20.0)	302 (21.5)	8,373 (21.8)
2	249 (12.1)	1,433 (15.6)	161 (11.5)	4,031 (10.5)
3+	309 (15.0)	2,802 (30.5)	225 (16.0)	7,608 (19.8)

5-ASA = 5-aminosalicylates compounds; IQR = interquartile range; S = value suppressed; TNF = tumour necrosis factor; UC = ulcerative colitis.

Note: Values between 1 and 5 inclusively were suppressed due to privacy restrictions.

[a]Due to prescription drug claims data availability, our analysis was limited to those aged 67 years and older and those < 67 years who are social assistance recipients in Ontario.

Table 10: Crude Incidence Rate of MACE by Database and UC Treatment Cohort

Database	No. of patients	Median follow-up (years)	Total follow-up (years)	No. of events	Crude incidence rate (per 100 person-years) (95% CI)
Manitoba					
Tofacitinib	18	0.6	16	0	0
TNF alpha inhibitors	141	1.0	202	0	0
Vedolizumab/ustekinumab	154	0.9	187	S	S
Conventional therapy	2,066	0.2	1,097	23	2.1 (1.2 to 3.0)
Ontario[a]					
Tofacitinib	70	0.2	34	0	0

Database	No. of patients	Median follow-up (years)	Total follow-up (years)	No. of events	Crude incidence rate (per 100 person-years) (95% CI)
TNF alpha inhibitors	513	0.2	361	S	S
Vedolizumab/ustekinumab	493	0.4	367	S	S
Conventional therapy	9,187	0.3	6,484	142	2.2 (1.8 to 2.6)
Saskatchewan					
Tofacitinib	43	1.4	74	0	0
TNF alpha inhibitors	142	1.7	285	S	S
Vedolizumab/ustekinumab	280	1.5	547	S	S
Conventional therapy	1,402	1.2	2,507	9	0.4 (0.2 to 0.6)
MarketScan					
Tofacitinib	268	0.2	96	0	0
TNF alpha inhibitors	1,667	0.1	612	0	0
Vedolizumab/ustekinumab	352	0.2	127	0	0
Conventional therapy	38,396	0.2	15,185	22	0.1 (0.0 to 0.2)

CI = confidence interval; MACE = major adverse cardiovascular events; S = value suppressed; TNF = tumour necrosis factor.

Note: Values between 1 and 5 inclusively were suppressed due to privacy restrictions.

[a]Due to prescription drug claims data availability, our analysis was limited to those aged 67 years and older and those < 67 years who are social assistance recipients in Ontario.

Table 11: Crude Incidence Rate of Hospitalized Thrombotic Events by Database and UC Treatment Cohort

Database	No. of patients	Median follow-up (years)	Total follow-up (years)	No. of events	Crude incidence rate (per 100 person-years) (95% CI)
Manitoba					
Tofacitinib	18	0.6	16	0	0
TNF alpha inhibitors	141	1.0	201	S	S
Vedolizumab/ustekinumab	154	0.9	188	0	0
Conventional therapy	2,066	0.2	1,097	6	0.5 (0.1 to 0.9)
Ontario[a]					
Tofacitinib	70	0.2	34	0	0
TNF alpha inhibitors	513	0.2	362	0	0
Vedolizumab/ustekinumab	493	0.4	367	S	S
Conventional therapy	9,187	0.3	6,487	42	0.6 (0.4 to 0.8)

Database	No. of patients	Median follow-up (years)	Total follow-up (years)	No. of events	Crude incidence rate (per 100 person-years) (95% CI)
Saskatchewan					
Tofacitinib	43	1.4	74	0	0
TNF alpha inhibitors	142	1.7	283	S	S
Vedolizumab/ustekinumab	280	1.5	550	S	S
Conventional therapy	1,402	1.2	2,513	8	0.3 (0.1 to 0.5)
MarketScan					
Tofacitinib	268	0.2	95	S	S
TNF alpha inhibitors	1,667	0.1	612	S	S
Vedolizumab/ustekinumab	352	0.2	127	S	S
Conventional therapy	38,396	0.2	15,164	62	0.4 (0.3 to 0.5)

CI = confidence interval; S = value suppressed; TNF = tumour necrosis factor.

Note: Values between 1 and 5 inclusively were suppressed due to privacy restrictions.

[a]Due to prescription drug claims data availability, our analysis was limited to those aged 67 years and older and those < 67 years who are social assistance recipients in Ontario.

Table 12: Crude Incidence Rate of Cancer (Excluding Nonmelanoma Skin Cancer) by Database and UC Treatment Cohort

Database	No. of patients	Median follow-up (years)	Total follow-up (years)	No. of events	Crude incidence rate (per 100 person-years) (95% CI)
Manitoba					
Tofacitinib	17	0.3	11	S	S
TNF alpha inhibitors	106	0.9	129	8	6.2 (1.9 to 10.5)
Vedolizumab/ustekinumab	137	0.7	141	7	5.0 (1.3 to 8.7)
Conventional therapy	896	0.3	629	18	2.9 (1.6 to 4.2)
Ontario[a]					
Tofacitinib	35	0.5	22	S	S
TNF alpha inhibitors	221	0.5	227	18	7.9 (4.2 to 11.6)
Vedolizumab/ustekinumab	249	0.6	241	17	7.1 (3.7 to 10.5)
Conventional therapy	4,952	0.4	3,934	337	8.6 (7.7 to 9.5)
Saskatchewan					
Tofacitinib	40	1.2	63	S	S
TNF alpha inhibitors	132	1.4	235	9	3.8 (1.3 to 6.3)

Database	No. of patients	Median follow-up (years)	Total follow-up (years)	No. of events	Crude incidence rate (per 100 person-years) (95% CI)
Vedolizumab/ustekinumab	263	1.3	462	13	2.8 (1.3 to 4.3)
Conventional therapy	1,228	1.2	2,084	83	4.0 (3.1 to 4.9)
MarketScan					
Tofacitinib	105	0.3	54	S	S
TNF alpha inhibitors	518	0.4	360	13	3.6 (1.6 to 5.6)
Vedolizumab/ustekinumab	110	0.3	50	7	14.0 (3.6 to 24.4)
Conventional therapy	12,685	0.3	6,793	542	8.0 (7.3 to 8.7)

CI = confidence interval; S = value suppressed; TNF = tumour necrosis factor.

Note: Values between 1 and 5 inclusively were suppressed due to privacy restrictions.

[a]Due to prescription drug claims data availability, our analysis was limited to those aged 67 years and older and those < 67 years who are social assistance recipients in Ontario.

Table 13: Crude Incidence Rate of Nonmelanoma Skin Cancer by Database and UC Treatment Cohort

Database	No. of patients	Median follow-up (years)	Total follow-up (years)	No. of events	Crude incidence rate (per 100 person-years) (95% CI)
Manitoba					
Tofacitinib	11	0.3	8	0	0
TNF alpha inhibitors	110	0.8	130	S	S
Vedolizumab/ustekinumab	114	0.6	120	S	S
Conventional therapy	507	0.6	481	S	S
Ontario[a]					
Tofacitinib	26	0.5	14	0	0
TNF alpha inhibitors	183	0.7	214	6	2.8 (0.6 to 5.0)
Vedolizumab/ustekinumab	214	0.6	204	0	0
Conventional therapy	3,057	0.7	3,417	75	2.2 (1.7 to 2.7)
Saskatchewan					
Tofacitinib	34	1.6	53	0	0
TNF alpha inhibitors	119	1.6	225	S	S
Vedolizumab/ustekinumab	232	1.4	412	S	S
Conventional therapy	1,039	1.5	1,879	19	1.0 (0.5 to 1.5)

Database	No. of patients	Median follow-up (years)	Total follow-up (years)	No. of events	Crude incidence rate (per 100 person-years) (95% CI)
MarketScan					
Tofacitinib	54	0.5	35	S	S
TNF alpha inhibitors	375	0.4	276	S	S
Vedolizumab/ustekinumab	87	0.4	46	0	0
Conventional therapy	7,095	0.4	4,917	70	1.4 (1.1 to 1.7)

CI = confidence interval; S = value suppressed; TNF = tumour necrosis factor.

Note: Values between 1 and 5 inclusively were suppressed due to privacy restrictions.

[a]Due to prescription drug claims data availability, our analysis was limited to those aged 67 years and older and those < 67 years who are social assistance recipients in Ontario.

Table 14: Crude Incidence Rate of Lymphoma by Database and UC Treatment Cohort

Database	No. of patients	Median follow-up (years)	Total follow-up (years)	No. of events	Crude incidence rate (per 100 person-years) (95% CI)
Manitoba					
Tofacitinib	17	0.3	12	0	0
TNF alpha inhibitors	106	0.9	133	0	0
Vedolizumab/ustekinumab	137	0.7	149	0	0
Conventional therapy	896	0.3	642	S	S
Ontario[a]					
Tofacitinib	38	0.5	23	0	0
TNF alpha inhibitors	255	0.6	277	0	0
Vedolizumab/ustekinumab	292	0.5	280	S	S
Conventional therapy	5,348	0.4	4,482	23	0.5 (0.3 to 0.7)
Saskatchewan					
Tofacitinib	40	1.2	64	0	0
TNF alpha inhibitors	132	1.6	258	0	0
Vedolizumab/ustekinumab	264	1.4	482	0	0
Conventional therapy	1,243	1.3	2,195	S	S
MarketScan					
Tofacitinib	108	0.3	56	0	0
TNF alpha inhibitors	551	0.4	392	0	0
Vedolizumab/ustekinumab	139	0.4	76	0	0

Database	No. of patients	Median follow-up (years)	Total follow-up (years)	No. of events	Crude incidence rate (per 100 person-years) (95% CI)
Conventional therapy	13,442	0.3	7,436	10	0.1 (0.0 to 0.2)

CI = confidence interval; S = value suppressed; TNF = tumour necrosis factor.

Note: Values between 1 and 5 inclusively were suppressed due to privacy restrictions.

[a]Due to prescription drug claims data availability, our analysis was limited to those aged 67 years and older and those < 67 years who are social assistance recipients in Ontario.

Table 15: Crude Incidence Rate of Lung Cancer by Database and UC Treatment Cohort

Database	No. of patients	Median follow-up (years)	Total follow-up (years)	No. of events	Crude incidence rate (per 100 person-years) (95% CI)
Manitoba					
Tofacitinib	17	0.3	12	0	0
TNF alpha inhibitors	106	0.9	133	0	0
Vedolizumab/ustekinumab	137	0.7	149	0	0
Conventional therapy	896	0.3	641	S	S
Ontario[a]					
Tofacitinib	38	0.5	23	0	0
TNF alpha inhibitors	254	0.6	277	S	S
Vedolizumab/ustekinumab	291	0.5	278	S	S
Conventional therapy	5,372	0.4	4,498	23	0.5 (0.3 to 0.7)
Saskatchewan					
Tofacitinib	40	1.2	64	0	0
TNF alpha inhibitors	132	1.6	258	0	0
Vedolizumab/ustekinumab	264	1.4	481	S	S
Conventional therapy	1,243	1.3	2,187	13	0.6 (0.3 to 0.9)
MarketScan					
Tofacitinib	108	0.3	56	0	0.0
TNF alpha inhibitors	551	0.4	391	S	S
Vedolizumab/ustekinumab	138	0.4	76	0	0.0
Conventional therapy	13,445	0.3	7,443	20	0.3 (0.2 to 2.4)

CI = confidence interval; S = value suppressed; TNF = tumour necrosis factor.

Note: Values between 1 and 5 inclusively were suppressed due to privacy restrictions.

[a]Due to prescription drug claims data availability, our analysis was limited to those aged 67 years and older and those < 67 years who are social assistance recipients in Ontario.

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