Mandatory non-medical switching from originator to biosimilar infliximab in patients with inflammatory arthritis and psoriasis in British Columbia: A cohort study

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ABSTRACT

Background: Spending on biologic medications is increasing and governments are implementing policies which require non-medical switching from originator biologic to biosimilar medications. British Columbia’s (BC) public drug plan program was the first in Canada to implement a switching policy for patients treated with originator infliximab for inflammatory arthritis or psoriasis. Our objective was to monitor the impacts of the BC policy on health services utilization and patient health during the first year of implementation, and provide early data to policymakers.

Methods: In this population-based cohort study, we used administrative data from the BC Ministry of Health to construct 3 historical cohorts and 1 policy cohort of users of originator infliximab. Patients with gastrointestinal conditions and those not covered by the provincial drug plan were excluded. Each cohort included 377 to 520 patients. We examined cumulative incidence of prescription refills for infliximab, switching to other biologic anti-inflammatory medications, and additional health services. Log-likelihood ratios were used to quantify statistical differences between the policy cohort and the historical cohorts.

Results: During months 7 and 8 of follow-up, a temporary but statistically significant decrease (7.2%) in the fourth refills of infliximab was observed in the policy cohort compared with the historical cohorts. An anticipated increase in specialist visits to manage switching to biosimilars was observed from month 4 (15.0%). No increase was observed in the use of other medications or additional health services (log-likelihood ratio < 1.96).

Interpretation: The results of the present study suggest the BC Biosimilars Initiative for non-medical switching to biosimilar infliximab was not associated with negative impacts on health services utilization or patient health. Longer-term detailed cohort studies could provide additional assurance on the safety of the policy.
INTRODUCTION

Worldwide spending on biologic medication is high and increasing,\textsuperscript{1–3} and governments face the challenge of providing these medications and other treatments within limited budgets. The use of biosimilar medications has the potential to reduce costs\textsuperscript{4–6} while providing clinical benefits similar to those of the originator medications.\textsuperscript{7–9} To encourage switching from originator biologics to biosimilar medications, some governments are implementing voluntary\textsuperscript{10} or mandatory\textsuperscript{11–14} non-medical switching policies. Despite evidence that switching is not associated with negative health impacts,\textsuperscript{15,16} many patients and physicians are concerned that switching will reduce the effectiveness of treatment and/or cause adverse effects.\textsuperscript{17,18} Unintended negative effects may be a particular concern when switching is mandatory, regardless of a patient’s clinical presentation or medical history.\textsuperscript{19,20} Close monitoring of the impacts of mandatory switching policies is needed to provide evidence that switching is safe.

On May 27, 2019 British Columbia was the first Canadian province to implement a mandatory non-medical switch from an originator to a biosimilar medication.\textsuperscript{21} Phase 1 of the Biosimilars Initiative targeted patients with rheumatoid arthritis, ankylosing spondylitis, psoriatic arthritis, or plaque psoriasis who had been treated with the originator infliximab and reimbursed by the provincial drug plan, PharmaCare. In British Columbia the costs for infliximab are covered under a PharmaCare Special Authority process.\textsuperscript{22} Since May 27, 2019, new or renewal Special Authority requests for patients with inflammatory arthritis and psoriasis have been approved only for the biosimilar infliximab. Patients with an existing approval were required to switch to the biosimilar infliximab during a 6-month transition period, and on November 27, 2019, PharmaCare no longer covered the originator infliximab.

The launch of the Biosimilars Initiative was followed by real-time monitoring of its impacts.\textsuperscript{23–25} Some impacts were expected such as an increase in visits to specialists during the 6-month
transition period or immediately thereafter; patient-physician consultations would be needed regarding the switch to the biosimilar.\textsuperscript{10,14} Also, a shift in health services utilization was expected beginning March 17, 2020 when the provincial government announced a state of emergency due to the COVID-19 pandemic.\textsuperscript{26} The objective of this study was to monitor the intended and unintended impacts of the Biosimilars Initiative on drug and health services utilization and on patient health during the first year of implementation.

METHODS

Setting and study design

This population-based cohort study used linkable and anonymized administrative data from the British Columbia Ministry of Health databases. The data included prescriptions filled at community pharmacies, information on patient enrolment in the provincial Medical Services Plan, visits to physicians and emergency departments, and hospitalizations. The study protocol\textsuperscript{24} was approved by the University of British Columbia Clinical Research Ethics Board (UBC CREB number H19-02377).

To study health services utilization in patients affected by the Biosimilars Initiative, we created 4 fixed cohorts of users of the originator infliximab: 1 policy cohort and 3 historical control cohorts. We identified patients treated with the originator infliximab based on prescriptions filled at community pharmacies. The policy cohort included patients identified in the 6 months before the initiative was launched (i.e., between November 27, 2018 and May 26, 2019). The 3 historical cohorts included patients identified in the 6 months before May 27 of 2016, 2017, and 2018. Patients not affected by the policy were excluded: those who had a gastrointestinal condition; who had discontinued infliximab; who had switched to another biologic disease modifying
antirheumatic drug (bDMARD), targeted synthetic DMARD (tsDMARD), or the biosimilar
infliximab before cohort entry; or who did not have PharmaCare coverage for infliximab. We
defined switching to another bDMARD or tsDMARD based on filled prescriptions of originator or
biosimilar versions of adalimumab, etanercept, certolizumab, golimumab, abatacept,
tocilizumab, anakinra, tofacitinib, rituximab, ustekinumab, secukinumab, ixekizumab,
brodalumab, and guselkumab after the last infliximab record, and before the cohort entry date
(May 27 each year). We followed patients in the cohorts for 365 days.

Measure of healthcare utilization

We measured the daily cumulative incidence of multiple outcomes. Drug utilization outcomes
included refilling a prescription for infliximab, and switching to another bDMARD or a tsDMARD
(i.e., the first refill of a different bDMARD or a tsDMARD). Health services utilization outcomes
included encounters with physicians (further examining encounters with rheumatologists and
dermatologists), first visit to an emergency department, and first discharge from hospital. For the
policy cohort, hospital data were not available for the last 2 months of the post-policy
intervention period. Secondary outcomes included the average cumulative dose of infliximab
and the average cumulative number of prescriptions filled for anti-inflammatory medications:
conventional synthetic DMARDs (csDMARDs), nonsteroidal anti-inflammatory drugs (NSAID),
or oral steroids. The full list of medications is included in the Supplement, Table S1.

Statistical analysis

Averaged cumulative incidence patterns of outcomes in the historical cohorts represented the
expected patterns for the policy cohort in the absence of a policy impact. We calculated the
daily cumulative incidence difference between the policy cohort and the average of the 3
historical cohorts. Statistical significance after each daily update was determined using log-likelihood ratios. Log-likelihood ratios were used instead of test statistics because interpretation of the former remained the same regardless of how many times the data analysis was updated. A cumulative incidence difference between the policy and historical cohorts was considered statistically significant if the log-likelihood ratio was sustained above 1.96.24

RESULTS

The source population included 5,431,788 individuals who had been enrolled in the provincial Medical Services Plan between November 2015 and May 2019. Each of the 4 infliximab cohorts included 377 to 520 patients (Figure 1). Patients with Crohn’s disease or ulcerative colitis accounted for 82.4% of the patients treated with the originator infliximab; those patients were not targeted by the first phase of the initiative and therefore excluded from the analysis. The median age in the 4 cohorts ranged between 57.5 and 60.0 years, and most patients were female (53.1% to 55.6%) (Table 1). Rheumatoid arthritis was the most common diagnosis (50.4% to 53.5% of patients in the different cohorts), and psoriasis was the least common (3.3% to 4.0%). Compared with the average of the 3 historical cohorts, patients in the policy cohort received originator infliximab longer and used fewer conventional synthetic anti-inflammatory medications (Table 1). No other statistically significant differences in baseline characteristics were observed between the cohorts. By the end of the 6-month transition period, 62.8% of patients in the policy cohort had switched to biosimilar infliximab, and by the end of the 1-year follow-up, 87.3% had switched (Figure 2).

Most patients refilled their infliximab prescriptions at least 4 times by the end of the follow-up period (Figure 3A-D). The cumulative incidence for the first 3 infliximab refills were similar in the policy and the historical cohorts (log-likelihood ratios of less than 1.96). We observed a small
but statistically significant decline (7.2%) in the fourth refills of infliximab in patients from the policy cohort during days 223 to 275 (months 7 and 8, January 14 to February 26) (Figure 3D and Supplement, Figure S1). In the following days, the incidence of the fourth refills of infliximab increased, and the log-likelihood ratios decreased below the 1.96 threshold for the remaining follow-up duration. This pattern was not associated with a significant change in the average cumulative dose of infliximab (Supplement, Figure S2). Otherwise, we observed no statistically significant difference between the policy cohort and the average of the historical cohorts in relation to switching to a different biologic anti-inflammatory medication (Figure 3E).

Trends in visits to any physician by patients from the policy cohort were similar to the historical trends, and nearly all patients had 4 visits (Figure 4A–D). Approximately 90% of patients from the historical cohorts had a first visit to a specialist (Figure 4E); and 67% to 74% had a second visit to a specialist (Figure 4F). Patients in the policy cohort made a first visit to a specialist earlier than patients in the historical cohorts (Figure 4E and Supplement, Figure S3), but by the end of the 1-year follow-up period, the differences were no longer statistically significant. In addition, more patients in the policy cohort visited a specialist twice compared with patients in the historical cohorts, and the log-likelihood ratios remained above the 1.96 threshold from day 155 (month 6) onward (Figure 4F and Supplement, Figure S3).

Patients’ first visits to an emergency department and first discharges from hospital in the policy cohorts were similar to the average of the historical cohorts (Figure 5, log-likelihood ratios < 1.96). The cumulative incidence of the first visit to an emergency department ranged between 21% and 23% by the end of the 1-year follow-up period, and the cumulative incidence of the first discharge from hospital ranged between 7.8% and 10% by the end of 10 months of follow-up. Finally, compared with the historical cohorts, we found no increase in the utilization of other anti-inflammatory medications in the policy cohort. The policy cohort received fewer refills of csDMARDs and NSAIDs compared with the average of the historical cohorts, but all cohorts
had similar patterns of oral steroid use (Supplement, Figure S4). Similar patterns in the use of csDMARDs and NSAIDs were also observed in a subgroup analysis of patients with rheumatoid arthritis (Supplement, Figure S5).

INTERPRETATION

This monitoring of infliximab users targeted by Phase 1 of the British Columbia Biosimilars Initiative provided data early after policy implementation and allowed continuous assessment of the impact of the policy. We observed no negative impact of the policy on health services utilization during the first year of follow-up; i.e., we found no increase in switching to another biologic/biosimilar anti-inflammatory medication, no increase in the use of other anti-inflammatory medications, and no increase in visits to emergency departments or in hospitalizations. We did, however, detect a temporary decrease in refills of infliximab and an expected increase in visits to specialists.

Seasonal trends do not explain the small temporary decrease in the number of patients receiving a fourth refill of their infliximab prescriptions because we compared utilization during the same calendar months for the 4 cohorts. The decrease could reflect an increase in the number of attempts to discontinue or taper treatment following remission, followed by re-initiation of treatment after a flare-up of symptoms (e.g., due to the nocebo effect). In the absence of clinical data, we are unable to confirm this explanation. Overall, we did not observe an increase in switching to a different biologic anti-inflammatory drug in January and February 2020, and the decline in infliximab refills was temporary; both are encouraging signs.

The increase in visits to specialists in rheumatology and dermatology for patients in the policy cohort was expected as patients were likely to want to discuss switching with their specialists; similar increases have been observed previously. While the use of conventional synthetic
anti-inflammatory medications and NSAIDs was lower than in previous years, we consider this a positive effect, i.e., fewer patients from the policy cohort experienced symptoms while on biosimilars treatment. We confirmed that this effect was not the result of differences in disease mix by showing that patients with rheumatoid arthritis had the same patterns of use of conventional synthetic anti-inflammatory medications and NSAIDs as the full cohorts.

While the findings of our study provide evidence on the safety of the Biosimilars Initiative, further research is warranted to explore the potential longer-term impacts of a non-medical switch to biosimilars. Indeed, the British Columbia Ministry of Health has decided to extend the monitoring plan to a second year. In the absence of clinical data, we interpreted drug and health services utilization outcomes as proxies for patient health; more clinical research is needed to confirm our interpretation. Finally, this study focused on the use of infliximab in patients with inflammatory arthritis and psoriasis; monitoring switches involving other medications and other diseases is also important, as the impact of switching in these populations may be different.

This study had several limitations. First, no adjustment for patient characteristics were made, and different patient characteristics may lead to changes in clinical practice and health services utilization. Another limitation is that we did not study the impact of the policy on individual patients but rather focused on populations. In the case of the Biosimilars Initiative, focusing on populations (i.e., cohorts) allowed for signal detection that can be useful in for planning further assessments of the policy. Finally, the follow-up was limited to 1 year after the initiative was launched and 6 months after all targeted patients were affected. This duration may be too short to detect delayed effects.
CONCLUSIONS

We observed no negative impact of the British Columbia Biosimilars Initiative, a policy that targeted users of infliximab for inflammatory arthritis and psoriasis. Despite the switch to a biosimilar being mandatory, there was no unexpected increase in health services utilization or in switching to different biologic anti-inflammatory medications. This suggests that switching to the biosimilar infliximab had negligible or minimal impacts on patients' health. Our monitoring provided data early after policy implementation. Longer-term detailed cohort studies could provide additional assurance on the safety of the policy.

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- British Columbia Ministry of Health [creator] (2020): Medical Services Plan (MSP) Payment Information File. BC Ministry of Health [publisher]. MOH (2019);
- British Columbia Ministry of Health [creator] (2020): PharmaNet. BC Ministry of Health [publisher]. Data Stewardship Committee (2019);
- Canadian Institute for Health Information [creator] (2020): National Ambulatory Care Reporting System. BC Ministry of Health [publisher]. MOH (2019);
- Canadian Institute for Health Information [creator] (2020): Discharge Abstract Database (Hospital Separations). BC Ministry of Health [publisher]. MOH (2019);
• British Columbia Ministry of Health [creator] (2020): Consolidation File (MSP Registration & Premium Billing). BC Ministry of Health [publisher]. MOH (2019)

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### Table 1: Cohorts of users of the originator infliximab

|                      | Infliximab cohorts |  |  |  |  |
|----------------------|--------------------|---|---|---|---|
|                      | Historical cohort | Historical cohort | Historical cohort | Policy cohort |
|                      | 2016 (N = 520)    | 2017 (N = 461)    | 2018 (N = 423)    | 2019 (N = 377) |
| Age (years)          |                    |                |                |               |
| Mean (standard deviation) | 56.4 (15.7)     | 57.4 (16.0)     | 58.3 (15.6)     | 58.6 (15.7)    |
| Median (min, max)    | 57.5 (6.0, 91.0)  | 58.0 (4.0, 90.0) | 59.0 (7.0, 91.0) | 60.0 (8.0, 91.0) |
| Females N (%)        | 289 (55.6)        | 247 (53.6)      | 228 (53.9)      | 200 (53.1)     |
| Most likely diagnosis: N (%) |                    |                |                |               |
| Any rheumatologic diagnosis | 480 (92.3) | 422 (91.5) | 387 (91.5) | 345 (91.5) |
| Rheumatoid arthritis | 278 (53.5) | 242 (52.5) | 218 (51.5) | 190 (50.4) |
| Ankylosing spondylisis | 115 (22.1) | 109 (23.6) | 101 (23.9) | 90 (23.9) |
| Psoriatic arthritis | 45 (8.7) | 41 (8.9) | 38 (9.0) | 30 (8.0) |
| Psoriasis | 19 (3.7) | 15 (3.3) | 17 (4.0) | 15 (4.0) |
| Undetermined | 21 (4.0) | 24 (5.2) | 19 (4.5) | 17 (4.5) |
| Time from first infliximab use (years): mean (standard deviation) | 7.2 (4.5) | 8.5 (4.4) | 9.6 (4.3) | 10.6 (4.3)* |
| Health services utilization in the previous year: mean (standard deviation) |               |                |                |               |
| Number of different medications | 9.3 (6.0) | 9.3 (6.2) | 8.7 (5.4) | 8.7 (5.6) |
| Biologic anti-inflammatory medications | 1.1 (0.3) | 1.0 (0.1) | 1.0 (0.0) | 1.0 (0.0) |
| Conventional synthetic anti-inflammatory medications | 0.8 (0.8) | 0.8 (0.8) | 0.8 (0.8) | 0.7 (0.7)* |
| Number of visits to physicians | 23.2 (16.7) | 23.1 (17.9) | 21.7 (14.6) | 20.9 (15.0) |
| Numbers of nights in hospital | 1.0 (5.2) | 0.8 (3.9) | 0.6 (3.6) | 0.5 (2.6) |

* Statistically significant difference between the policy cohort and the weighted average of the historical cohorts, defined as $p$ value < 0.05 in a Chi-square test or non-parametric ANOVA. $P$ values were corrected for multiple comparisons.
FIGURES
Figure 1: Flow chart of cohort creation – users of the originator infliximab.

GI – gastrointestinal. Gastrointestinal conditions include ulcerative colitis and Crohn’s disease.

Low compliance/infliximab discontinuation was defined as no medication supply on May 27 + no refill in the 84 days before (excluding) May 27. Switching was defined as a refill of a different biologic anti-inflammatory medication or the biosimilar version of infliximab. Short follow-up was defined as less than 1 month of medical plan enrolment starting on the cohort entry date (May 27). PharmaCare coverage was determined based on all infliximab refills during the 6-month period before May 27.

a The number of patients who switched was less than 6.

b The number of patients with follow-up duration shorter than 1 month was less than 6.
Figure 2 – Cumulative incidence of switching to the biosimilar infliximab, policy cohort (n = 377).
Figure 3: Cumulative incidence of filling the first (A), second (B), third (C), and fourth (D) prescriptions of infliximab and another biologic disease modifying antirheumatic drug (E) during the 1-year follow-up period, by cohort.

Cumulative incidence is expressed as the percentage of patients in each cohort who experienced the outcome by day of follow-up. The 6-month transition period of the policy is shaded in grey. Periods of statistically significant difference between the policy cohort and the average of the historical cohorts are marked by a red block.
Figure 4: Cumulative incidence of the first (A), second (B), third (C), and fourth (D) visits to a physician and first (E) and second (F) visits to a specialist during the 1-year follow-up period, by cohort.

Cumulative incidence is expressed as the percentage of patients in each cohort who experienced the outcome by day of follow-up. The 6-month transition period of the policy is shaded in grey. Periods of statistically significant difference between the policy cohort and the average of the historical cohorts are marked by a red block.
Figure 5: Cumulative incidence of first visit to an emergency department (A) and first discharge from hospital (B) during the 1-year follow-up period, by cohort.

Cumulative incidence is expressed as the percentage of patients in each cohort who experienced the outcome by day of follow-up. The 6-month transition period of the policy is shaded in grey. Hospital data were available until March 26, 2020.
STROBE Statement—Checklist of items that should be included in reports of *cohort studies*

| Item No | Recommendation | Page(s) |
|---------|----------------|---------|
| **Title and abstract** | 1  
  *(a)* Indicate the study’s design with a commonly used term in the title or the abstract  
  *(b)* Provide in the abstract an informative and balanced summary of what was done and what was found | 1,2 |
| **Introduction** | 2  
  Explain the scientific background and rationale for the investigation being reported | 3-4 |
| **Objectives** | 3  
  State specific objectives, including any prespecified hypotheses | 3-4 |
| **Methods** |  
  **Study design** | 4  
  Present key elements of study design early in the paper | 4 |
| **Setting** | 5  
  Describe the setting, locations, and relevant dates, including periods of recruitment, exposure, follow-up, and data collection | 4-5 |
| **Participants** | 6  
  *(a)* Give the eligibility criteria, and the sources and methods of selection of participants. Describe methods of follow-up | 4-5 |
|  | *(b)* For matched studies, give matching criteria and number of exposed and unexposed | n/a |
| **Variables** | 7  
  Clearly define all outcomes, exposures, predictors, potential confounders, and effect modifiers. Give diagnostic criteria, if applicable | 5 |
| **Data sources/measurement** | 8*  
  For each variable of interest, give sources of data and details of methods of assessment (measurement). Describe comparability of assessment methods if there is more than one group | 5 + supplement |
| **Bias** | 9  
  Describe any efforts to address potential sources of bias | n/a |
| **Study size** | 10  
  Explain how the study size was arrived at | n/a (all eligible patients were used) |
| **Quantitative variables** | 11  
  Explain how quantitative variables were handled in the analyses. If applicable, describe which groupings were chosen and why | n/a |
| **Statistical methods** | 12  
  *(a)* Describe all statistical methods, including those used to control for confounding  
  *(b)* Describe any methods used to examine subgroups and interactions  
  *(c)* Explain how missing data were addressed  
  *(d)* If applicable, explain how loss to follow-up was addressed  
  *(e)* Describe any sensitivity analyses | 5-6, n/a, n/a, n/a, n/a |
| **Results** |  
  **Participants** | 13*  
  *(a)* Report numbers of individuals at each stage of study—eg numbers potentially eligible, examined for eligibility, confirmed eligible, included in the study, completing follow-up, and analysed | 6 + Figure 1 |
(b) Give reasons for non-participation at each stage

(c) Consider use of a flow diagram

Descriptive data

14*  (a) Give characteristics of study participants (eg demographic, clinical, social) and information on exposures and potential confounders

6 + Table 1

(b) Indicate number of participants with missing data for each variable of interest

n/a

(c) Summarise follow-up time (eg, average and total amount)

n/a

Outcome data

15*  Report numbers of outcome events or summary measures over time

6-8 Figures 2-5

Main results

16  (a) Give unadjusted estimates and, if applicable, confounder-adjusted estimates and their precision (eg, 95% confidence interval). Make clear which confounders were adjusted for and why they were included

6-8, Figures 2-5, supplement Figures S1, S3

(b) Report category boundaries when continuous variables were categorized

n/a

(c) If relevant, consider translating estimates of relative risk into absolute risk for a meaningful time period

n/a

Other analyses

17  Report other analyses done—eg analyses of subgroups and interactions, and sensitivity analyses

8 + supplement Figure S5

Discussion

Key results

18  Summarise key results with reference to study objectives

8

Limitations

19  Discuss limitations of the study, taking into account sources of potential bias or imprecision. Discuss both direction and magnitude of any potential bias

9-10

Interpretation

20  Give a cautious overall interpretation of results considering objectives, limitations, multiplicity of analyses, results from similar studies, and other relevant evidence

10

Generalisability

21  Discuss the generalisability (external validity) of the study results

10

Other information

Funding

22  Give the source of funding and the role of the funders for the present study and, if applicable, for the original study on which the present article is based

11

*Give information separately for exposed and unexposed groups.

Note: An Explanation and Elaboration article discusses each checklist item and gives methodological background and published examples of transparent reporting. The STROBE checklist is best used in conjunction with this article (freely available on the Web sites of PLoS Medicine at http://www.plosmedicine.org/, Annals of Internal Medicine at http://www.annals.org/, and Epidemiology at http://www.epidem.com/). Information on the STROBE Initiative is available at http://www.strobe-statement.org.
Mandatory non-medical switching from originator to biosimilar infliximab in patients with inflammatory arthritis and psoriasis in British Columbia: A cohort study

On-line supplement
Table S1 – Drug utilization outcomes: list of medications

| Therapeutic group                                      | Generic drugs                                                                                                                                 |
|--------------------------------------------------------|---------------------------------------------------------------------------------------------------------------------------------------------|
| Biologic and targeted synthetic disease-modifying antirheumatic drugs (bDMARDs and stDMARDs) | Adalimumab, etanercept, certolizumab, golimumab, abatacept, tocilizumab, anakinra, tofacitinib, rituximab, ustekinumab, secukinumab, ixekizumab, brodalumab, and guselkumab |
| Conventional synthetic disease-modifying antirheumatic drugs (csDMARDs) | Methotrexate, hydroxychloroquine, leflunomide, sulfasalazine, minocycline, azathioprine, auranofin, chloroquine, cyclophosphamide, cyclosporine, gold sodium thiomalate, mycophenolate, and penicillamine |
| Oral steroids                                           | Cortisone, dexamethasone, hydrocortisone, ethamethasoneb, fludrocortisone, methylprednisolone, prednisone, prednisolone, and triamcinolone |
| Nonsteroidal anti-inflammatory drugs (NSAIDs)            | Aspirin, celecoxib, diclofenac, diflunisal, etodolac, ibuprofen, indomethacin, ketoprofen, nabumetone, naproxen, oxaprozin, piroxicam, salsalate, sulindac, and tolmetin |
Figure S1 – Fourth infliximab refill: log-likelihood ratios in comparisons between the infliximab policy cohort and the average of the three historical cohorts.
Figure S2 – Average cumulative dose of infliximab, by cohort.
Figure S3 – First and second visits to a specialist: log-likelihood ratios in comparisons between the infliximab policy cohort and the average of the three historical cohorts.
Figure S4 – Average cumulative number of refills for conventional synthetic disease-modifying antirheumatic drugs (csDMARDs) (A), nonsteroidal anti-inflammatory drugs (NSAIDs) (B), and oral steroids (C) during the 1-year follow-up period, by cohort.
Figure S5 – Average cumulative number of refills for conventional synthetic disease-modifying antirheumatic drugs (csDMARDs) (A) and nonsteroidal anti-inflammatory drugs (NSAIDs) (B) in patients with rheumatoid arthritis during the 1-year follow-up period, by cohort.