EVALUATING BIOSIMILARS UPTAKE AND POLICY IN CANADA

by

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Abstract

BACKGROUND

Despite representing less than 2% of prescriptions, biologics accounted for nearly three of every ten dollars spent on prescribed medicines in Canada in 2018. Similar to generics for small molecule drugs, biologic biosimilars are one potential way in which payers can reduce drug spending. In 2019, the government of British Columbia became the first in North America to mandate switching from reference biologics to biosimilars. While a number of other provinces have followed, the impact of these policies remains unclear. Therefore, this thesis examined the current state of biosimilars use in Canada.

METHODS

This thesis focused on uptake of and spending on infliximab, etanercept, and insulin glargine using two primary data sources: (1) data from the IQVIA Canadian Drugstore and Hospital Purchases Audit representing all Canadian provinces except Newfoundland and Labrador, and (2) British Columbia health administrative data from Population Data BC. Interrupted time series analysis was used to quantify the results of two eras of biosimilars policies in British Columbia, including mandatory biosimilars use for new starters and subsequently mandated switching for all users, among individuals with inflammatory arthritis and psoriasis.

RESULTS

We found that prior to 2019 uptake of biosimilar infliximab, etanercept, and insulin glargine was low across Canada. Coinciding with the introduction of mandatory

switching policies, there was a large increase in utilization thereafter in a number of provinces. In British Columbia, we determined that the introduction of mandatory switching among individuals with inflammatory arthritis and diabetes mellitus resulted in an increase in biosimilars utilization beyond what would have occurred if payers maintained new start policies only.

CONCLUSION

Government-mandated switching policies have the ability to greatly increase use of biosimilars even in the context of a multi-payer system. Although the ability to ascertain savings is limited due to the proprietary nature of drug pricing in Canada, the enhanced use of biosimilars will likely create a more favorable environment for price-based competition among pharmaceutical manufacturers. Future work should continue to examine the impact of mandatory switching on patients and prescribers as well as on the market for biologic drugs on a longer time horizon.

Lay Summary

For every ten dollars the Canadian government spends on drugs, more than four are spent on drugs which cost over $10 000 per year per patient. After the patent expires on the brand name biologic drug, highly similar versions of the medicine, termed ‘biosimilars’, are able to enter the market at a lower cost than the reference drug. Increasing uptake of biosimilar drugs can provide one way in which to save on drug spending. In 2019, the British Columbian government introduced policies to switch patients to biosimilars, and shortly after, a number of other Canadian provinces followed suit. This research evaluated the impact of these biosimilar switching policies on use of biosimilars in Canada. Our findings demonstrate that these policies were successful in greatly enhancing the use of biosimilars. Biosimilar switching policies may have the potential to generate cost-savings to Canadians.

Preface

This thesis was written and performed by the author, Alison McClean, under the co-supervision of Dr Michael R Law and Dr Mark Harrison, and the supervisory committee, Drs Nick Bansback and Fiona Clement. In addition, Drs Mina Tadrous and Tara Gomes (University of Toronto) and Lucy Cheng (University of British Columbia) provided support and feedback throughout the research process.

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of the presented work including revising for critically important intellectual content. All authors gave final approval of the version to be published and agreed to be accountable for all aspects of the work.

Access to data provided by the Data Steward(s) is subject to approval, but can be requested for research projects through the Data Steward(s) or their designated service providers. All inferences, opinions, and conclusions drawn in this publication are those of the author(s), and do not reflect the opinions or policies of the Data Steward(s).

This research was conducted in compliance with the Helsinki Declaration and ethics approval was obtained from the University of British Columbia's Behavioural Research Ethics Board (H20-00252).

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List of Abbreviations

BC	British Columbia
CADTH	Canadian Agency for Drugs and Technologies in Health
DMARD	Disease-modifying antirheumatic drug
FDA	Food and drug administration
HbA1c	Glycated hemoglobin
ITS	Interrupted time series
NIHB	Non-Insured Health Benefits
NSAIDs	Non-steroidal anti-inflammatory drugs
OECD	Organisation for Economic Co-operation and Development
PASI	Psoriasis Area and Severity Index
TNF-α	Tumour necrosis factor-α

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1 Introduction

1.1 Prescribed drug coverage in Canada

In general, Canadians can access prescription drugs through two avenues: in hospital or in community. In hospital, drugs are provided to Canadians free of cost to the individual and instead, this funding comes from the dollars allocated to the hospital purse under the Canada Health Act.[1] However, in the outpatient setting, coverage of prescription drugs is derived from a range of sources which can be primarily broken down to Federal, Provincial/Territorial, and commercial benefits providers, and individual out-of-pocket payments. At present, there is no universal coverage of prescribed medicines in Canada in the community setting.

Certain individuals are eligible for prescription drug coverage from the Federal government, including individuals enrolled in the Indigenous Services Canada, First Nations and Inuit Health Branch, Non-Insured Health Benefits (NIHB) program, the Canadian Forces Drug Benefit Plan, and the Citizenship and Immigration Canada, Federal Health Program, among others.[1] For individuals outside the purview of the federal administration of benefits, provincial and territorial governments allocate funding based on a number of factors such as income, age, and specific diseases status (e.g. cystic fibrosis). Some individuals may receive provincial drug coverage for restricted medicines through a pre-approval process known as 'Special Authority' and others may be eligible for coverage of non-benefit drugs under exceptional funding such as the 'Expensive Drugs for Rare Diseases' program.[2]

The balance of the bill for prescription drugs in Canada not covered by the aforementioned public plans is paid by private payers, including both commercial insurers and individual Canadians. Commercial insurers, such as Pacific Blue Cross and Green Shield Canada, provide private drug benefit plans, which can be paid into by employers or individuals. Lastly, individuals may be responsible for all or a portion of prescribed drug spending via out-of-pocket payments. In 2021, 44.8%, 35.5%, and 19.7% of spending on prescribed medicines in Canada was covered by public, private, and out-of-pocket spending, respectively.[3]

1.2 Canadian prescribed drug spending and biologics

Approximately $32.7 billion was spent on prescription drugs in Canada in 2020. The majority of this expenditure originated in the retail setting ($27.8 billion) compared to in-hospital spending ($4.9 billion).[4] At approximately $15 billion, over half of prescribed drug spending in community was covered by public coverage programs, with the remaining $12.8 billion being covered by private plans and out-of-pocket payments.[5]

Biologic medicines are responsible for a disproportionate impact on Canadian drug spending. In 2018, biologics were responsible for nearly a third of expenditures although they constituted less than 1 in 50 prescriptions dispensed.[6] In the same year, Canadian biologic pricing was second only to the United States among the Organisation for Economic Co-operation and Development (OECD) countries.[7]

As of 2020, the top three drugs in community by spending were biologics: infliximab, adalimumab, and ustekinumab were responsible for $1.2 billion, $970.1 million, and $527.8 million in expenditure, respectively.[4] In addition, there has been an increase in spending of 300% on biologics in Canada in the last ten years and this expenditure is only projected to go up.[8]

1.3 Small molecule drugs and generics versus biologics and biosimilars

Medicines can be divided into two groups: small molecule drugs and biologics. Small molecule drugs have low molecular weights, relatively simple structures, and are derived from more classic chemical reactions. In contrast, biologic drugs are large complex macromolecules isolated from living cells.[9] Because many biologics are proteins, they may have primary, secondary, tertiary, and quaternary molecule structure and they can undergo post-translational modifications after administration. The vast majority of marketed drug products are small molecule drugs, with an estimated 20 000 approved by the US Food and Drug Administration (FDA). In contrast, there are approximately 621 FDA-approved biologic drugs.[10]

Brand name small molecule drugs and biologics can be thought of as the 'innovator' product or the first of its kind authorized to enter the market. As an incentive for innovation, governments often offer market exclusivity or a period of time in which the brand name drug is granted a monopoly (i.e. the brand name drug is the only version permitted in a certain jurisdiction). In Canada, the number of years for which a brand

name manufacturer is provided unfettered access to the market is approximately 8-15 years.[11]

After the exclusivity period expires, generic versions of brand name small molecule drugs and biosimilar versions of brand name biologic drugs are permitted to enter the market by Health Canada. According to Health Canada, approved generic drugs have identical medicinal ingredients in the same amount and are of the same dosage form compared to the innovator.[12] Likewise, biosimilar drugs are very similar to the original brand name drug with no expected clinically meaningful differences in efficacy and safety.[9]

1.4 Regulatory approval of generics versus biosimilars

In order to seek approval from Health Canada, generic drug manufacturers must demonstrate there is no difference in the time it takes for the body to absorb the drug and reach a certain level in the blood when comparing the generic and branded product, termed 'bioequivalence'.[12] Operationally, bioequivalence is determined by healthy individuals taking either the brand or generic drug and then having blood drawn to determine whether the two forms reach the same concentration at the same rate. If approved by Health Canada, a generic drug is considered identical to the brand and may be substituted at the level of the pharmacy without prescriber involvement, as long as the prescriber did not indicate 'no substitution'.

Biosimilars are not the same as generics in that they are not considered identical upon regulatory approval. This owes in part to the structural complexities of biologic drugs compared to small molecule drugs and also because biosimilars may be generated by different cell lines compared to the reference biologic.[9] In order to obtain approval from Health Canada, biosimilar drug manufacturers must submit evidence of drug quality as well as studies demonstrating similarity of the structure, function, efficacy, and safety between the reference and biosimilar product. Similarity of structure and function are determined via comparison of product stability, purity, and biologic, physiochemical, and immunochemical characteristics.[9] Although the biosimilar is not identical to the reference product in the way a generic drug is, biosimilars must have no clinically meaningful difference in efficacy or safety. Compared to generics, biosimilars also have added complexity in that they are not deemed interchangeable upon approval. Instead, interchangeability is up to the provincial and territorial governments to decide.

Health Canada may approve a biosimilar for the same indications as the reference product without evidence for each indication—termed extrapolation of indications— or they may approve for only a subset of the reference product's approved indications. Biosimilar drug makers decide which indications to receive regulatory approval for and some indications may still be under patent protection.[9]

1.5 Approved biosimilars

At present, Canada has 49 biosimilars approved for 15 different active ingredients (Table 1.1).[13] Canada's first biosimilar, Omnitrope (somatropin), was approved in 2009. Shortly

thereafter, Inflectra (infliximab) and Basaglar (insulin glargine) were approved in 2014 and 2015, respectively. Since then, several biosimilars have been approved each year. An uptick in approvals was seen in 2019, with seven approvals, which grew to 13 in 2020 and 12 in 2021. So far in 2022, there have been 8 approvals, including for adalimumab, bevacizumab, etanercept, insulin (human), insulin glargine, ranibizumab, and trastuzumab.

Table 1.1 Reference products and approved biosimilars with list date.[13]

Active ingredient	Biosimilar name	Approval date
Adalimumab	Abrilada	Jun 2021
	Amgevita	Nov 2020
	Hadlima	May 2018
	Hulio	Nov 2020
	Hyrimoz	Nov 2020
	Idacio	Oct 2020
	Simlandi	Jan 2022
	Yuflyma	Dec 2021
Bevacizumab	Abevmy	Apr 2022
	Aybintio	Jun 2022
	Bambevi	Nov 2021
	Mvasi	Aug 2018
	Zirabev	Sep 2019
Enoxaparin sodium	Inclunox	May 2021
	Noromby	Oct 2020
	Redesca	Apr 2021
Etanercept	Brenzys	Sep 2016
	Erelzi	Aug 2017
	Rymti	Aug 2022

Filgrastim	Gastrofil	Mar 2016
	Nivestym	Apr 2020
	Nypozi	Oct 2021
Infliximab	Avsola	Dec 2020
	Inflectra	Sep 2014
	Ixifi	Dec 2021
	Remsima SC	Jan 2021
	Renflexis	Mar 2018
Insulin (Human)	Myxredlin	Aug 2022
Insulin aspart	Kirsty	Oct 2021
	Trurapi	Mar 2021
Insulin glargine	Basaglar	Dec 2015
	Semglee	Apr 2022
Insulin lispro	Admelog	Nov 2019
Pegfilgrastim	Fulphila	Feb 2020
	Lapelga	Feb 2019
	Nyvepria	Jan 2021
	Ziextenzo	May 2020
Ranibizumab	Byooviz	May 2022
	Riabni	Apr 2021
	Riximyo	May 2020
	Ruxience	May 2020
	Truxima	Dec 2019
Somatropin	Omnitrope	Apr 2009
Teriparatide	Osnuvo	Oct 2020
Trastuzumab	Herzuma	Dec 2019
	Kanjinti	Apr 2020
	Ogivri	Jun 2019
	Ontruzant	Jul 2022
	Trazimera	Oct 2019

1.6 Biosimilars policies in British Columbia

Prior to 2019, biosimilars were often included on British Columbia (BC)'s provincial formulary under 'new start' policies. Under these policies, patients who were prescribed a biologic for the first time would be required to initiate therapy with a biosimilar. As an example, individuals initiating infliximab after April 2016 would have been required to initiate therapy with a biosimilar if they wanted to receive provincial drug benefits.[14]

In an effort to further increase biosimilar utilization, In 2019, British Columbia became the first jurisdiction in North America to mandate switching from reference biologics to the biosimilar version in order to maintain provincial drug coverage.[15] Importantly, biosimilars captured under the policy were not deemed interchangeable (i.e. pharmacists were not authorized to switch patients from reference biologics to biosimilars as they would be in the case of generics). Instead, individuals were provided with six months to work with their prescriber in order to make the switch.

The biosimilar switching policy was implemented in a number of phases. This work focuses primarily on Phase One of the initiative where patients living with ankylosing spondylitis, rheumatoid arthritis, plaque psoriasis, and psoriatic arthritis were switched from reference etanercept (Enbrel) to biosimilar etanercept (Brenzys or Erelzi) or reference infliximab (Remicade) to biosimilar infliximab (Inflectra or Renflexis) and individuals living with diabetes mellitus were switched from reference insulin glargine (Lantus) to the biosimilar (Basaglar) (Table 1.2).[15]

Of note, not all individuals in the province receiving infliximab or etanercept were switched under Phase One. Phase Two of the biosimilars switching policy required individuals living with Crohn's disease and ulcerative colitis to switch from reference infliximab to the biosimilar version as of March 2020. Additional switching periods were also implemented for rituximab, adalimumab, insulin lispro, insulin aspart, enoxaparin, and filgrastim.

Table 1.2 Summary of the biosimilar switching policies in British Columbia.[15]

Dates	**Reference product**	**Biosimilar product(s)**	**Indications**
Phase 1 May 27-Nov 25, 2019	Enbrel (etanercept)	Brenzys Erelzi	Rheumatoid arthritis, ankylosing spondylitis, psoriatic arthritis
	Remicade (infliximab)	Inflectra Renflexis	Rheumatoid arthritis, ankylosing spondylitis, psoriatic arthritis, plaque psoriasis
	Lantus (insulin glargine)	Basaglar	Diabetes mellitus
Phase 2 Sep 5, 2019-Mar 5, 2020	Remicade (infliximab)	Inflectra Renflexis	Crohn's disease, ulcerative colitis

1.7 Rheumatoid arthritis

Rheumatoid arthritis is a progressive autoimmune disease characterized by inflammation and swelling in one or more joints which cannot be explained by another cause.[16–18] The prevalence of rheumatoid arthritis is approximately 1% and risk factors include female sex, increasing age, family history, and cigarette smoking. Rheumatoid arthritis is associated with joint damage, deformity, stiffness, and pain and significant morbidity and disability.

The goal of treatment is remission or reduced disease activity where remission is likely not possible. Rheumatoid arthritis medication management includes maintenance with traditional small molecule disease-modifying antirheumatic drugs (DMARDs)—such as methotrexate, sulfasalazine, and/or hydroxychloroquine— and/or biologic or tofacitinib therapy. Monotherapy with methotrexate is typically the preferred first line therapy.[16,19] If significant disease activity remains after monotherapy treatment, combination therapy or treatment with tofacitinib or a biologic may be considered, although special authority is required. Biologics used in rheumatoid arthritis include tumour necrosis factor-α (tumour necrosis factor-α) inhibitors (adalimumab, certolizumab pegol, etanercept, golimumab, or infliximab) and non-TNF-α inhibitors (abatacept, rituximab, or tocilizumab). Glucocorticoids (e.g. prednisone) may be used in individuals with significant disease activity initiating treatment or among those not responding to therapy.

The average work productivity loss associated with rheumatoid arthritis is estimated at $18,242 per patient per year according to a study from Alberta.[18] Healthcare utilization

among individuals living with rheumatoid arthritis is also high: the average total healthcare utilization costs per individual is $5531 per year where individuals with greater disability have greater associated costs ($14 225 versus $4157, respectively).[20]

1.8 Ankylosing spondylitis

Ankylosing spondylitis is an inflammatory arthritis associated with structural damage and inflammation of the sacroiliac joint and inflammation and excess formation of spinal bone.[21–23] Ankylosing spondylitis is relatively rare, with a prevalence of 0.1-0.5%. Risk factors include male sex and genetic predisposition and the majority of individuals present with ankylosing spondylitis before age 30 years. Ankylosing spondylitis is associated with inflammatory back pain, stiffness, reduced range of motion, and disability.

Pharmacological treatment of ankylosing spondylitis includes continuous treatment with non-steroidal anti-inflammatory drugs (NSAIDs).[21,22] Treatment with TNF-α inhibitors —infliximab, etanercept, or adalimumab—are indicated for those who continue to have active disease in spite of continuous NSAID treatment. In general, non-TNF-α inhibitors secukinumab or ixekizumab are recommended when an individual has a contraindication to TNF-α inhibitors. As of 2005, total costs per patient associated with ankylosing spondylitis in Canada were estimated at $9008 per year.[23]

1.9 Psoriatic arthritis

Psoriatic arthritis is a heterogeneous inflammatory musculoskeletal condition impacting as many as 6-40% of individuals with psoriasis or 0.1-0.2% of those in the general population.[24–27] Risk factors for psoriatic arthritis include psoriasis and family history; both males and females are equally likely to develop psoriatic arthritis. Psoriatic arthritis is associated with swelling, pain, and reduced range of motion and potential deformation of the joints. Psoriatic arthritis typically appears after psoriasis has been diagnosed but may present concurrently or psoriasis may develop after psoriatic arthritis.[26] Extra-articular presentations of psoriatic arthritis are also possible, including inflammatory bowel disease.[24–27]

Although the particular treatment strategy is complicated by the variable presentation of psoriatic arthritis, in general, first line therapy for psoriatic arthritis consists of traditional DMARDs (methotrexate, sulfasalazine, leflunomide) or biologic TNF-α inhibitors (etanercept, infliximab, adalimumab, golimumab, certolizumab pegol).[24,25,27] However, treatment with other non-TNF-α inhibitors biologics (ustekinumab, secukinumab, ixekizumab, brodalumab) may also be indicated as first line therapy (e.g. if skin involvement). Persistent psoriatic arthritis symptoms despite maintenance therapy may be managed with NSAIDS and/or glucocorticoid injections. The direct costs of psoriatic arthritis has been estimated at $15 802 per patient per year according to a study from Ontario.[28]

1.10 Plaque psoriasis

Plaque psoriasis is an inflammatory dermatologic condition, impacting roughly 1.4% of the Canadian population or 80-90% of patients with psoriasis.[29,30] Plaque psoriasis is characterized by defined symmetric silvery-scaled erythematous plaques. Family history and age between 15-20 or 55-60 years are risk factors, though both males and females are equally likely to develop plaque psoriasis.[29–31] In addition to the direct dermatologic symptoms, plaque psoriasis may have a negative impact on quality of life and mental health.

Depending on severity, treatment of plaque psoriasis may include topical therapy with corticosteroids, calcipotriol, or a combination product, phototherapy, small molecule methotrexate, and/or biologic TNF-α inhibitors (adalimumab, certolizumab pegol, etanercept, infliximab), brodalumab, guselkumab, ixekizumab, secukinumab, tildrakizumab, or ustekinumab.[32–34] In a study of individuals from British Columbia, Ontario, and Quebec, moderate to severe plaque psoriasis was estimated to cost $4557 per patient per year in direct costs or $7999 per patient per year when including loss of productivity.[30]

1.11 Diabetes mellitus

Diabetes mellitus can be subdivided into two main types: type 1 and type 2. Type 1 diabetes is an unpreventable autoimmune disease characterized by destruction of the insulin-producing pancreatic β cells which leads to a lack of insulin and hyperglycemia. Type 1 diabetes represents roughly 1 in 10 cases of diabetes. Similar to type 1, type 2

diabetes involves insulin deficiency, in addition to insulin resistance, resulting in hyperglycemia. However, the risk of type 2 diabetes can be enhanced by a range of circumstances (e.g. unhealthy diet, a lack of physical activity, obesity) and may be preventable.[35] Type 2 diabetes constitutes about 90% of cases of diabetes in Canada. According to Health Promotion and Chronic Disease Prevention Canada, more than 7% of the Canadian population has diabetes. Complications secondary to diabetes range from cardiovascular disease to nephropathy, retinopathy, neuropathy, and amputations, to lower life expectancy.

The goal of treatment of diabetes is to reduce hyperglycemia while avoiding episodes of hypoglycemia. Glucose control may be estimated via self-monitored blood glucose levels and measurement of glycated hemoglobin (HbA1c). As type 1 diabetics do not create endogenous insulin, treatment generally requires multiple basal and bolus insulin injections per day or a continuous insulin infusion.[36] In comparison, treatment of type 2 diabetes may begin with no pharmacotherapy, metformin only, or a combination of insulin and/or other antihyperglycemic drugs.[37] Depending on a variety of patient-specific factors—e.g. age, cardiovascular disease risk factors, existing comorbidities such as heart failure or chronic kidney disease—other antihyperglycemic agents may be recommended (e.g. dipeptidyl peptidase-4 inhibitors, sodium-glucose cotransporter 2 inhibitors). Estimates suggest that the healthcare related cost of diabetes may reach $15.36 billion this year in Canada.[38]

1.12 Biosimilar infliximab and etanercept: efficacy, safety, and switching

In 2016, an important systematic review examined the bioequivalence of biosimilar TNF-α inhibitors, including infliximab and etanercept.[39] Chingcuanco *et al.* included 21 published articles, the largest proportion of which were randomized controlled trials (n 15). In addition, cross-sectional (n=2), prospective cohort (n=2), and retrospective cohort (n=1) studies were included along with a single case series. Eleven trials examined the pharmacokinetic properties of the biosimilars (e.g. maximum concentration of infliximab in the blood) and all examined potential adverse effects. Seven studies explored efficacy (e.g. improvement in disease activity).

In general, the included pharmacokinetic studies demonstrated equivalence among infliximab (n=8) and etanercept (n=3) with their respective biosimilars.[39] In terms of efficacy, the majority of relevant studies included people living with RA (n=6) and one study included individuals with ankylosing spondylitis. All adequately powered studies of infliximab, etanercept, and adalimumab indicated equivalence in terms of efficacy between the reference product and biosimilar. In general, adverse events and immunogenicity were similar between reference and biosimilar treatments.

In 2017, the first randomized double-blind non-inferiority multicenter trial examining switching from reference to biosimilar infliximab—NOR-SWITCH—was published.[40] NOR-SWITCH included individuals living with rheumatoid arthritis, psoriatic arthritis, spondyloarthritis, plaque psoriasis, Crohn's disease, and ulcerative colitis (n=482). All

study participants began treatment with reference infliximab. In order to examine the non-inferiority of switching to biosimilar infliximab, half of the study participants were randomized to the biosimilar while the other half maintained treatment with the originator. Overall, NOR-SWITCH demonstrated non-inferiority of biosimilar infliximab in terms of disease worsening. Nevertheless, the study was not powered to examine non-inferiority among particular disease states (e.g. specifically among individuals with rheumatoid arthritis). A number of systematic reviews have examined the comparative efficacy and safety of biosimilar infliximab switching and have concluded there is no significant evidence of harm.[41–45] However, ongoing monitoring post-switch has been recommended.

In 2017, a randomized, double-blind, multicenter trial examining the comparative efficacy, safety, and immunogenicity of reference and biosimilar etanercept was published (EGALITY).[46] Individuals living with plaque psoriasis were included (n=531) and half received the biosimilar and half received the reference. After twelve weeks, participants were randomized to either continue their initial therapy or switch treatment arms. The main outcome was ≥75% improvement in disease activity using the psoriasis area and severity index (PASI) although pharmacokinetics, safety, and immunogenicity were also studied. The authors concluded that reference and biosimilar etanercept were similar with respect to efficacy, safety, and immunogenicity. Systematic reviews on examining the comparative efficacy and safety of biosimilar etanercept switching have found similar results although ongoing monitoring post-switch is recommended.[43,45,47,48]

1.13 Biosimilar insulin glargine: efficacy, safety, and switching

The efficacy and safety of biosimilar insulin glargine has been compared to reference insulin glargine in two multicenter, parallel, randomized non-inferiority studies among individuals living with type 1 diabetes (INSTRIDE 1) and type 2 diabetes (INSTRIDE 2).[36,49] In both studies, the main efficacy outcome was change in HbA1c over 24 weeks. Both studies also examined changes in basal insulin requirements and fasting plasma glucose as well as relevant safety endpoints such as hypoglycemia and immunogenicity. Both INSTRIDE 1 and INSTRIDE 2 demonstrated the non-inferiority of biosimilar insulin glargine when compared to the reference product. In addition, there were no significant differences in terms of other efficacy or safety endpoints in either study.

Using study participants from INSTRIDE 1, the INSTRIDE 3 trial was a multicenter parallel randomized study which compared the safety, efficacy, and immunogenicity of reference and biosimilar insulin glargine switching published in 2020.[50] During INSTRIDE 3, there were two parallel groups: those who received reference insulin glargine for the duration of the study (36 weeks) and those who received the biosimilar for 12 weeks, then the reference for 12 weeks, and then the biosimilar again for 12 weeks. As with INSTRIDE 1 and 2, the primary endpoint was change in HbA1c, along with other outcomes such as change in fasting blood glucose, hypoglycemia and immunogenicity. INSTRIDE 3 found no differences in efficacy or safety between treatment with reference and biosimilar insulin glargine.

1.14 Biosimilars policy stakeholders

The available clinical evidence is only one piece of the policy context in which biosimilar switching occurs. It is important to acknowledge that mandated switching policies restrict autonomy of patients and prescribers alike. Therefore, the perspectives of biosimilars policy stakeholders—including patients and prescribers and their associations—should be considered.

Qualitative interviews with people living with rheumatoid arthritis, psoriasis, and inflammatory bowel disease have provided some context regarding how patients perceive biosimilars (n=12). Interviewees noted the need for access to biologic therapy, for autonomy in medical decision-making, the ability to switch back to the reference product if necessary, and for education regarding biosimilars, among other factors.[51] In addition, research has suggested that 1 in 4 individuals may discontinue therapy with a biosimilar due to arthralgia, fatigue, pruritus, and myalgia (termed 'subjective complaints') which renewed calls for increased education and communication between healthcare professionals and individuals receiving biosimilar therapy in order to improve biosimilar switching.[52]

In 2021, a qualitative study on patient perspectives before and after BC's biosimilars switching policy was published. Prior to the switching period, individuals expressed acceptance of the policy although concerns around disease maintenance and quality of life post-switch were noted.[53] After the switch occurred, some individuals interviewed

shared concerns around adverse effects, cost, and the ability to switch back while some noted “it was quite a smooth transition”.

Healthcare professionals have also provided contrasting views on biosimilar switching. For instance, British gastroenterologists were more in favor of switching than their rheumatologist counterparts.[54] However, Canadian rheumatologists surveyed in 2015 noted concerns around biosimilar switching.[55] As evidence on biosimilar switching accrued, recommendations from the Canadian Rheumatology Association became more supportive of biosimilar switching.[56] Today, the Canadian Rheumatology Association suggests biosimilar switching should involve shared decision-making over the course of six months and the ability to switch back if necessary. Conversely, the Joint Canadian Association of Gastroenterology and Crohn’s Colitis Canada Position Statement on Biosimilars for the Treatment of Inflammatory Bowel Disease recommends against biosimilar switching although they acknowledge “this is a weak recommendation based on very low-quality evidence”.[57]

Lastly, as biosimilar competition can disturb the monopoly held by reference biologic manufacturers and potentially drive cost (and profits) down for these drugs, biologic drug manufacturers are another notable stakeholder in the business of biosimilars policies. Although drug pricing information is proprietary in Canada, there is evidence that biologic drug manufacturers have attempted to manipulate pricing in order to avoid biosimilar switching policies. More specifically, when faced with the introduction of biosimilar switching in Ontario, the manufacturers of reference infliximab suggested they

would no longer provide their product for free to over 1800 patients, costing the provincial government an estimated $35 million in 2020-2021 alone.[58] In the US, biologic drug manufacturers have been suspected anticompetitive practices by the FDA and Federal Trade Commission, including potentially "making false or misleading statements comparing biological reference products and biosimilars" and "slowing progress and hampering uptake of these important therapies".[59] The biosimilar switching policies implemented in Canada represent a significant step toward biosimilar competition in North America.

1.15 Research objectives

The objectives of the research presented herein were to:

1. To evaluate biosimilars policies and use related to insulin glargine, infliximab, and etanercept across Canada (Chapter 2)
2. To assess the impact of new start and switching policies on uptake and spending on biosimilar infliximab and etanercept within the province of British Columbia (Chapter 3)

2 Uptake of biosimilar drugs in Canada: An analysis of provincial policies and usage data[14]

2.1 Introduction

Biologics represent a large segment of drug spending in Canada: although they constituted just 1.5% of prescription volumes, biologics accounted for 27.3% of expenditures in 2018.[6] As of 2018, the price of biologics in Canada, including spending per capita, was second only to that in the United States among the OECD countries.[7] For example, Canada has spent more on TNF-α inhibitors, a class of biologic drug, than on any other publicly covered medicine.[5] Over the last 10 years, Canada has seen a threefold increase in spending on biologics, and this spending will continue to grow.[8]

With more than 1000 biologic drugs marketed in Canada and biologics now used in most clinical specialties, the need to achieve cost savings is of critical importance.[13] Biosimilars — agents with similar efficacy and safety to originator drugs — offer an important avenue for cost savings.[6,8,9,60] Yet, presently only 49 biosimilars are approved for use in Canada, roughly half the number available in the European Union, and the use of biosimilars in Canada is relatively low.[13,61]

We evaluated the current state of biosimilar policies and use across Canada, highlighting 3 illustrative cases — insulin glargine, infliximab and etanercept. We briefly discuss interchangeability and indication extrapolation before making suggestions for enhancing

the market through harmonization of biosimilar policies, patient and prescriber education, and manufacturer collaboration.

2.2 Methods

This study can be divided into two parts: (1) understanding the policy context of infliximab, etanercept, and insulin glargine biosimilars in Canada and (2) using real world drug utilization data to examine trends in usage of the aforementioned drugs.

In order to examine relevant biosimilars policies for included provinces, we used publicly available announcements for each province's drug benefits program (Table 2.1). Each repository was searched for keywords 'infliximab', 'etanercept', and 'insulin glargine'. Results were reviewed for relevance. If no keyword search was available, newsletters were manually reviewed beginning one year prior to biosimilar approval until the end of the study period. Drug approval dates were sourced from Health Canada's Drug Product Database online query.[13] Searches were completed via active ingredient (e.g. 'infliximab'). All available product information was reviewed for the original market date for each product.

To explore biosimilar uptake, we used national data from the IQVIA Canadian Drugstore and Hospital Purchases Audit for all provinces except Newfoundland and Labrador from 2017 to the end of 2020. We did not have access to territorial prescription drug utilization data. Usage was quantified in terms of the proportion of total units utilized which were

biosimilar (i.e. total units biosimilar divided by total units of biosimilar plus reference product). Our descriptive results were then presented and analyzed in a narrative style.

Table 2.1 Included provinces and the source and location of information related to their respective drug benefits program.

Province	Source	Location
British Columbia	PharmaCare Newsletter	https://www2.gov.bc.ca/gov/content/health/practitioner-professional-resources/pharmacare/pharmacare-publications/pharmacare-newsletters
Alberta	Alberta Health Care Insurance Plan Bulletins	https://www.alberta.ca/bulletins-for-health-professionals.aspx
Saskatchewan	Saskatchewan Formulary Bulletins	https://formulary.drugplan.ehealthsask.ca/BulletinsInfo
Manitoba	Manitoba Drug Benefits and Interchangeability Formulary	https://www.gov.mb.ca/health/mdbif/bulletins.html
Ontario	Drugs Funded by Ontario Drug Benefit Program: Formulary Downloads	https://www.health.gov.on.ca/en/pro/programs/drugs/edition_43.aspx
Quebec	Quebec: List of medications	https://www.ramq.gouv.qc.ca/en/about-us/list-medications
New Brunswick	New Brunswick Drug Plans Formulary Updates	https://www2.gnb.ca/content/gnb/en/departments/health/MedicarePrescriptionDrugPlan/TheNewBrunswickPrescriptionDrugProgram/NewBrunswickFormularyUpdates.html
Nova Scotia	Nova Scotia Pharmacare News Bulletins	https://novascotia.ca/dhw/pharmacare/pharmacare-news-bulletins.asp
Prince Edward Island	Health PEI: Pharmacare Bulletins	https://src.healthpei.ca/pharmacare-bulletins

2.3.1 What is the policy context of biosimilars in Canada?

Although more than 40 biosimilars have been approved in Canada, uptake has been much lower than that of conventional generics.[6,62] The Canadian policy framework for some of the earliest available biosimilars (i.e., infliximab, etanercept and insulin glargine) provides important insight into the foundation of the marketplace for these products.

2.3.1.1 Biosimilar infliximab and etanercept

The first iteration of the anti-TNF agent infliximab entered the Canadian market in 2001; in 2014, the earliest approved biosimilar infliximab (Inflectra) was marketed.[13] By September 2015, the Canadian Agency for Drugs and Technologies in Health (CADTH)'s Common Drug Review published a review endorsing Inflectra for listing with similar criteria to the innovator.[63] Shortly thereafter, British Columbia and Ontario listed biosimilar infliximab on their formularies for those who were starting infliximab for the first time ('new start policies'; Table 2.2).

Table 2.2 Formulary list date and dates of mandatory biosimilar switching policies (if applicable) for biosimilar insulin glargine, infliximab and etanercept for the included provinces.

	AB	BC	MB	NB	NS	ON	PE	QC	SK
Biosimilar insulin glargine									
List date	10/17	08/18	10/18	10/17[1]	11/17[1]	08/17	09/17[1]	08/17	01/18
Biosimilar switch period	12/19 to 02/21	05/19 to 11/19	N/A	04/21 to 11/21	02/22 to 02/23	N/A	N/A	04/22	N/A
Biosimilar infliximab									
New start	04/16	02/16	04/16	06/16	06/16	02/16	06/16	02/17	05/16[2]
Biosimilar switch period	12/19 to 02/21	05/19 to 11/19	N/A	04/21 to 11/21	02/22 to 02/23	N/A	N/A	04/22	N/A
Biosimilar etanercept									
New start	09/17	07/17	04/18	10/17	11/17	07/17	09/17	08/17	10/17
Biosimilar switch period	12/19 to 02/21	05/19 to 11/19	N/A	04/21 to 11/21	02/22 to 02/23	N/A	N/A	04/22	N/A

1 Special authority was required for originator but not the biosimilar;2 Naïve access to originator permitted

N/A not applicable

AB Alberta; BC British Columbia; MB Manitoba; NB New Brunswick; NS Nova Scotia; ON Ontario; PE Prince Edward Island; QC Quebec; SK Saskatchewan

Another anti-TNF drug (etanercept) had 2 biosimilar products approved in 2016 (Brenzys) and 2017 (Erelzi).[13] As with infliximab, CADTH's report endorsed Erelzi for patients in whom etanercept was considered a necessary therapy under similar

reimbursement criteria to the originator.[63] Under new start policies, biosimilar etanercept was incorporated into provincial formularies beginning in July 2017 with BC and Prince Edward Island. It was not until 2019 that Canadian provinces began implementing policies that required patients receiving treatment to switch to the biosimilar to maintain public drug coverage.

2.3.1.2 Biosimilar insulin glargine

Long-acting insulin glargine was first approved in 2002; in 2015, a single biosimilar was authorized for sale.[13] In the same year, biosimilar insulin glargine was endorsed by the Common Drug Review and was included on all provincial formularies 2 years later (Table 2.2).[63] As with biosimilar infliximab and etanercept, provincially mandated switching was not introduced until 2019.

2.3.2 How has uptake varied across provinces?

At present, all provinces have listed biosimilar insulin glargine, infliximab and etanercept on their formularies. Policies that require replacement of the reference biologic with the biosimilar to maintain coverage have been announced in 5 provinces, although only BC and Alberta had begun implementation as of December 2020 (Table 2.2). Several other provinces and some private insurers have implemented new start policies.

Biosimilar uptake has increased over time, albeit with substantial variation between biosimilars and across jurisdictions (Figure 2.1-2.3). This observed heterogeneity results

in part from the piecemeal nature of Canadian drug coverage. After listing, uptake may be influenced by the availability of alternatives, and its status as a full or restricted benefit.

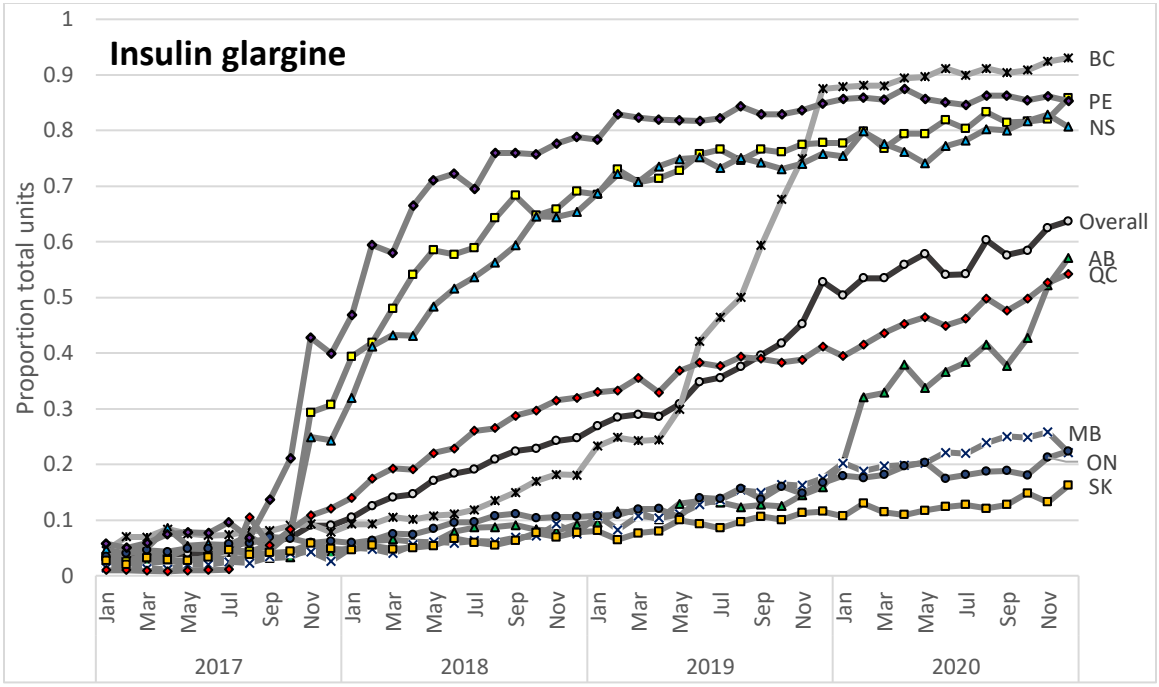


Figure 2.1 The proportion of total units of insulin glargine biosimilar purchased from 2017 to the end of 2020 in drug stores in Alberta (AB), British Columbia (BC), Manitoba (MB), New Brunswick (NB), Nova Scotia (NS), Ontario (ON), Prince Edward Island (PE), Quebec (QC) and Saskatchewan (SK), and overall using data from the IQVIA Canadian Drugstore and Hospital Purchases Audit.

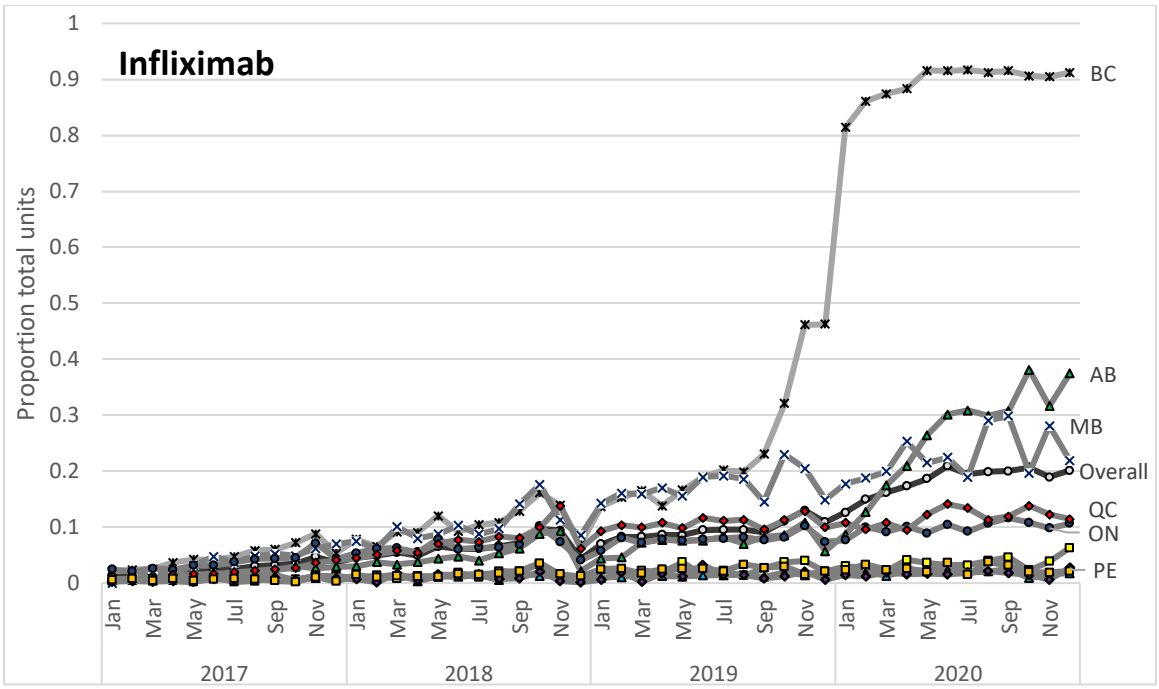


Figure 2.2 The proportion of total units of infliximab biosimilar purchased from 2017 to the end of 2020 in drug stores in Alberta (AB), British Columbia (BC), Manitoba (MB), New Brunswick (NB), Nova Scotia (NS), Ontario (ON), Prince Edward Island (PE), Quebec (QC) and Saskatchewan (SK), and overall using data from the IQVIA Canadian Drugstore and Hospital Purchases Audit.

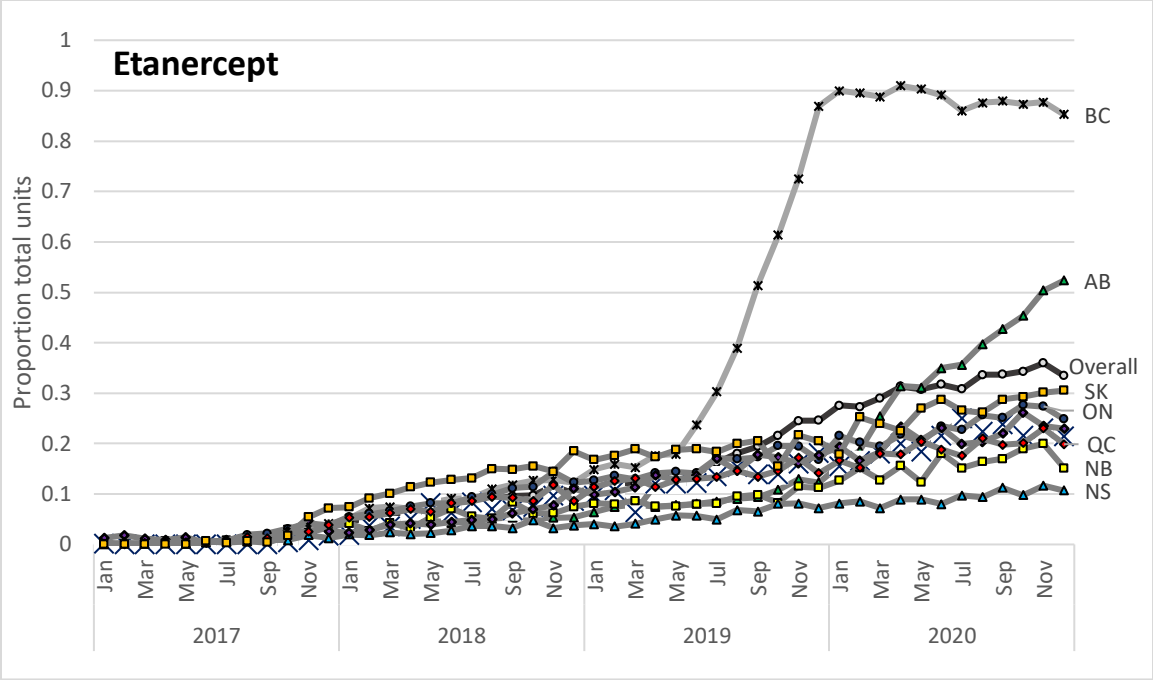


Figure 2.3 The proportion of total units of etanercept biosimilar purchased from 2017 to the end of 2020 in drug stores in Alberta (AB), British Columbia (BC), Manitoba (MB), New Brunswick (NB), Nova Scotia (NS), Ontario (ON), Prince Edward Island (PE), Quebec (QC) and Saskatchewan (SK), and overall using data from the IQVIA Canadian Drugstore and Hospital Purchases Audit.

Perhaps the most dramatic example of how policy can influence uptake of biosimilars is in BC. From May to November 2019, patients receiving insulin glargine or infliximab and etanercept for certain inflammatory conditions were required to switch to the relevant biosimilar to maintain provincial drug coverage. By the end of the phase-in period, uptake of the relevant biosimilars was about 90%. In December 2019, Alberta began implementing a comparable switching policy. The early impacts of this new policy are already discernible for biosimilar insulin glargine, infliximab and etanercept. In contrast,

provinces such as Manitoba, Ontario and Saskatchewan, which listed biosimilar infliximab and etanercept only under new start policies, did not see pronounced increases in uptake (Table 2.2 and Figure 2.2-2.3).

Sales of insulin glargine provide further evidence that simply adding biosimilars to provincial formularies does not ensure market penetration. For example, New Brunswick, Nova Scotia and PEI added insulin glargine as a full benefit in the fall of 2017, and, at the same time, they added a requirement for special authorization to access the originator drug. The result was a marked increase in purchases of biosimilar insulin glargine in drug stores. In contrast, Saskatchewan and Ontario introduced biosimilar insulin glargine as a full benefit around the same time without restricting access to the originator. As shown in Figure 2.1, there was no discernable increase in biosimilar uptake in those provinces.

2.3.3 What about interchangeability and indication extrapolation?

In Canada, after a generic drug receives market approval, it is automatically considered interchangeable with the reference product. This is important, as deeming a drug interchangeable means that a pharmacist can dispense the generic in place of the brand without prescriber involvement, unless the prescriber has indicated no substitutions.[9] In addition, payers can mandate that the generic be dispensed in place of the brand name drug or the patient must pay the difference in price between them. Substituting a generic for the brand at the level of the pharmacy provides a mechanism by which generic uptake and market share are enhanced. Generic drugs are well received in Canada: with an

overall generics market share of 76% in 2018, it is ranked third among the OECD countries in terms of uptake.[62]

Unlike generics, biosimilars are not deemed interchangeable with the reference drug upon approval by Health Canada and, as a result, pharmacists cannot substitute a biosimilar in place of an originator without prescriber involvement. Instead, provincial and territorial governments are responsible for deciding whether to institute policies encouraging biosimilar uptake for patients who are starting biologic therapy or for those who are already receiving originator therapy.[9] However, simply listing a biosimilar does not result in the uptake that would be expected for a generic, even when several formulary strategies have been used. One reason may be clinician and patient reluctance to use biosimilars owing to unease with indication extrapolation.[64]

Indication extrapolation — through which the decision of similarity may be applied to other indications without conducting additional clinical trials — has been a particularly charged issue for clinicians and patients.[55,65] For example, among the biosimilars discussed, studies of originator etanercept and infliximab that involved patients with rheumatoid arthritis were used as evidence for further indications (e.g., Renflexis was deemed similar enough to Remicade for treatment of ankylosing spondylitis).[63] Concerns around using trial data from one indication to substantiate biosimilar use in another may help explain the divergent trends in uptake seen when comparing biosimilar infliximab and etanercept with insulin glargine.

The use of switching policies — when biosimilars are not considered interchangeable or may have garnered additional indications indirectly — is controversial. A joint position statement from the Canadian Association of Gastroenterology and Crohn's and Colitis Canada supported the use of biosimilar infliximab in treatment-naive patients but recommended against switching from treatment with originator drugs among those who were already stable.[57] In contrast, the Canadian Rheumatology Association and Canadian Spondylitis Association generally support biosimilar substitution that involves informed consent and the option to switch back to the reference biologic.[56,66] Physicians and patients have also raised concerns that mental health may be affected if disease remission is not maintained and that biosimilar safety and effectiveness are in doubt.[53,65,67] At least one originator company has provided financial assistance for patients starting treatment to obtain the reference product when faced with biosimilar competition.[58] It is important to emphasize that division remains, concerns regarding biosimilar switching persist, and there are real impacts on patient and provider autonomy as a result of biosimilar switching.

However, if uptake of biosimilars remains low, manufacturers may not take the risks necessary to enter the Canadian market. This could have continued deleterious effects on both cost and access to biologics in the long term. Indeed, with roughly half the number of biosimilars approved compared with the European Union, Canada may already be feeling these effects.

2.3.4 How can we improve uptake of biosimilars in Canada?

In Canada, historical uptake of biosimilars has been lackluster (at about 1.9% of the $7.7 billion biologics industry in 2018).[6] To support a healthy biosimilars market, provincial and territorial policy-makers should consider implementing a united policy front, continue education and supports for patients and providers, and collaborate with manufacturers.

2.3.4.1 Harmonization of policies

At present, Canada has a biosimilars policy salad — many public (and private) plans do not list some biosimilars at all, some list them as the default medicine for new starts only and others mandate biosimilars as the compulsory agent of choice. Provinces and territories should aim for consistency in listing and reimbursement. Policies requiring new users to start a biosimilar version do not appear to have been effective at increasing use on the national scale. Mandated switching has shown the greatest change in uptake; however, any policy that requires switching for those patients already receiving established therapy should be balanced with provider and patient education and support, as well as access to the reference drug when medically justified.

2.3.4.2 Patient and provider support

Warranted concerns around biosimilar safety and effectiveness persist among patients and providers. A systematic review of the literature available on health care providers' beliefs found that, in general, clinicians were reluctant to prescribe biosimilars owing to

safety and efficacy concerns, and concerns about indication extrapolation.[57] Included studies in this review suggested a lack of knowledge of biosimilars and concluded that biosimilar prescribing may be positively affected by time and experience with these drugs. More recent evidence from a payer–provider focus group similarly proposed greater biosimilar education as a means to increase biosimilar use.[68] Patient support programs for certain biologic therapies — including patient education, home delivery and nursing services — typically paid for by manufacturers also contribute to the total value of biologic therapies.[60]

2.3.4.3 Participation from manufacturers

With approximately half the number of biosimilars approved compared with the European Union, improving uptake in Canada may incentivize additional manufacturers to undertake the risks involved in entering the market. In turn, increased competition in the biosimilars space should result theoretically in enhanced bargaining power for public and private payers and lower prices. However, the focus should not be solely on direct cost because value-added services, such as nursing services and other patient supports, are important aspects of the total value of biologic therapies.[60]

2.4 Limitations

Although our study presented robust data for 9 out of 10 Canadian provinces, including representation from 8 of the most populous provinces, we were unable to include data from the province of Newfoundland and Labrador and either of the 3 Canadian territories.

We also only examined the state of biosimilars in Canada in terms of infliximab, etanercept, and insulin glargine, although there are many more currently available in Canada. Our results may not be generalizable to other biosimilar products available in Canada.

In addition, more biosimilar switching policies will likely be rolled out across Canada. It is unclear what the long-term durability of such policies will be. Due to the confidential nature of drug pricing in Canada, we are unable to comment on the cost-savings introduced via biosimilar uptake. Lastly, we were unable to restrict our analysis to only individuals enrolled in their respective provincial drug benefits program and so the presented data likely includes representation of federally-covered individuals.

2.5 Conclusion

Market entry alone is not sufficient to ensure high levels of biosimilar use. The results of new start policies appear lackluster, while mandated switching has resulted in large increases in biosimilar uptake. However, many switching policies were introduced after the period we used for our analysis, and the long-term impacts of these policies remains unknown. Salient concerns among patients and providers persist, and policy-makers should proceed with caution as further evaluation is necessary. With promises of enhanced accessibility, competition and cost savings, now is the time to overcome biosimilars' failure to launch.

3 Uptake and spending on biosimilar infliximab and etanercept after new start and switching policies in Canada: An interrupted time series analysis

3.1 Introduction

Worldwide spending on drugs has been predicted to reach $1.6 trillion by 2026.[69] Specialty drugs, including biologics, have become a major driver of this expenditure, representing roughly 30% of expenditure despite accounting for less than 2% of prescriptions dispensed.[6,70] Two of the costliest biologics in the US, infliximab and etanercept, were responsible for $4.86 and $7.78 billion in spending, respectively, in 2019 alone.[71]

Akin to generics, biosimilars can seek regulatory approval after the patent expires on the innovator product. In order to gain market authorization, the FDA requires biosimilar manufacturers to demonstrate their products are 'highly similar' to the originator biologic with no clinical differences in efficacy, effectiveness, safety, or quality.[72] Biosimilars offer one potential avenue to decrease spending on biologics and projections suggest they could reduce drug expenditures by $215 billion globally between 2022-2026.[69] Despite this potential, biosimilar uptake has been low in some countries, including the United States and Canada.[14,73–76]

The Centers for Medicare and Medicaid Services (CMS) have encouraged uptake of biosimilars through passive approaches, such as through the introduction of unique

billing codes for biosimilars (thereby facilitating unique pricing of biosimilars), providing reimbursement at a rate of the average sales price (ASP) of the biosimilar plus 6% of the reference biologic ASP within Part B, necessitating biosimilar manufacturer discounts in the Part D donut hole for beneficiaries, and requiring biosimilar copayments at a rate similar to generics for those enrolled in the Low-Income Subsidy plan.[77–79]

In Canada, the cost of prescription drugs may be covered by federal payers (e.g. eligible veterans), provincial or territorial governments, private commercial entities, or out-of-pocket payments. All residents are eligible for their respective provincial or territorial plan, although deductible and copayment amounts vary by income and geographic region among other factors. Previous research has suggested that 59.5% residents of British Columbia (BC) have private insurance.[80]

For the most part, Canadian policymakers have encouraged biosimilar uptake through passive 'new start' policies, which require individuals initiating a biologic for the first time to begin treatment with a biosimilar. However, in 2019, the province of British Columbia (BC) became the first region in North America to require individuals established on therapy to switch to a biosimilar in order to maintain provincial drug coverage. Under the first phase of these switching policies, individuals living with inflammatory arthritis and psoriasis and receiving originator etanercept and infliximab were given six months to switch to the relevant biosimilar. Specifically, individuals taking reference etanercept were required to switch to Brenzys (approved in 2016) or Erelzi (2017) whilst individuals receiving reference infliximab switched to Inflectra

(2014) or Renflexis (2018).[13,15] Given the novelty of this policy in North America, we assessed changes in the uptake and spending on biosimilar infliximab and etanercept in BC following these two distinct policy changes.

3.2 Materials and Methods

3.2.1 Study data, sample, and setting

We used linked de-identified province-level outpatient physician billings (Medical Services Plan (MSP) payment information file), hospital discharges and separations (Discharge Abstract Database (DAD)), emergency department visits (National Ambulatory Care Reporting System (NACRS)), outpatient prescription dispensation data (PharmaNet), and the Consolidation file (MSP registration) from Population Data BC from January 2013 to December 2020.[81–85] Individuals were eligible for inclusion if they (1) were ≥18 years, (2) had rheumatoid arthritis, ankylosing spondylitis and/or psoriatic arthritis or plaque psoriasis, and (3) qualified for public drug coverage during the study period.

We identified individuals living with conditions of interest by searching for one or more instance of ICD-9/ICD-10-CA codes 714.X, M05.X, M06.X (rheumatoid arthritis); 720.X, M45.X (ankylosing spondylitis); and/or 696.X, L40.X (psoriatic arthritis/plaque psoriasis) present in the MSP, DAD, and/or NACRS. The aforementioned categories were not mutually exclusive. We used brand names in order to identify dispensations of infliximab (Remicade®, Inflectra®, Renflexis™) or etanercept (Enbrel®, Brenzys®,

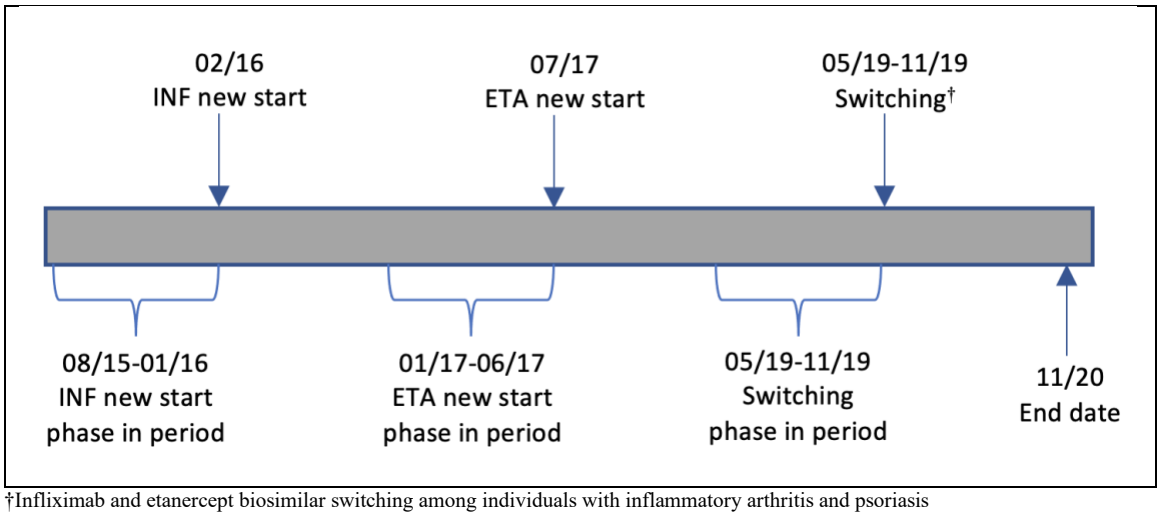
Erelzi™) in PharmaNet. As infliximab is also indicated for the treatment of Crohn's disease and ulcerative colitis but these indications were not subjected to the policies of interest, individuals with instances of these billing codes were excluded from the infliximab cohort (Crohn's disease 555.X, K50.X; ulcerative colitis 556.X, K51.X). Demographic information was derived from the Consolidation file. Age and neighbourhood income quintile were defined at the first instance of an ICD-9/ICD-10-CA code of interest during the study period.

3.2.2 Policies of interest

In BC, access to infliximab and etanercept requires the prescriber to receive prior authorization (termed 'special authority') in order for these medicines to be covered under the provincial drug plan. On 16 February 2016 and 18 July 2017, the BC government required individuals *initiating* infliximab and etanercept, respectively, for certain inflammatory conditions to begin treatment with a biosimilar after receiving special authority approval. From 27 May to 25 November 2019, individuals living with inflammatory arthritis and psoriasis receiving innovator etanercept or infliximab were required to *switch* to a biosimilar version in order to maintain prescription drug coverage offered by the provincial government of BC. As pharmacists were not authorized to switch patients from the reference biologic to the biosimilar medicine without prescriber involvement, the government provided a six-month period for patients and prescribers to work together to make the switch. Large commercial insurers which provide supplementary drug coverage, including Pacific Blue Cross and Green Shield Canada, also introduced biosimilars adjudication rules that mirrored the governments'. Under the

biosimilar switching policies, the provincial government continues to provide exceptional coverage to the reference product if medically needed.[15]

In order to quantify biosimilar uptake prior to the biosimilar new start program, we stipulated a pre-intervention period of six months prior to the introduction of the policy (Figure 3.1). Observation of the new start policy ran from its introduction until the switching policy was implemented. In alignment with the phase in period of the switching policy, we incorporated a phase in period from June and December 2019 in our model. Lastly, our post-intervention period ran from the end of the phase-in period until the end of our data availability in November 2020.



†Infliximab and etanercept biosimilar switching among individuals with inflammatory arthritis and psoriasis

INF infliximab; ETA etanercept

Figure 3.1 Study timeline.

3.2.3 Outcomes of interest

Using PharmaNet, we examined all retail pharmaceutical claims for branded and biosimilar etanercept and infliximab among our cohort members. We examined both public expenditure as well as non-public spending (i.e. patient and/or private insurer) on etanercept and infliximab per month. We studied the proportion of prescriptions dispensed and the proportion of total spending on the biosimilars out of the total amount per agent (i.e. either etanercept and infliximab) during the study period.

3.2.4 Statistical analysis

We used interrupted time series (ITS) analysis, a rigorous quasi-experimental design, to adjust for secular trends in the study data.[86] ITS utilizes repeat measures over time, before and after a program of interest is implemented, in order to estimate the effect of said policy. ITS permits the quantification of both the immediate 'level' change in the outcome of interest as well as the change over time ('trend' change). The sustained change in the proportional uptake or spending on biosimilar etanercept and infliximab was determined from the difference between the pre- and post-intervention level and trend (i.e. the counterfactual).

Using segmented linear regression, we modeled the level and trend change in biosimilar etanercept and infliximab utilization and spending after each of the two policy interventions. We used generalized least squares models and included autoregressive-moving-average (ARMA) with *p* autoregressive and *q* moving-average terms based on standard diagnostic tests.[87] In order to assess sex-based differences and following

Canadian Institutes of Health Research best practices, we also completed a sex-stratified analysis for both biosimilar spending and use.[88] Data were prepared using SAS® 9.4 (Cary, NC, USA) and analyses were conducted with R® 4.0.5 (Vienna, Austria).

3.2.5 Ethics approval

This research was conducted in compliance with the Helsinki Declaration and ethics approval was obtained from the University of British Columbia's Behavioural Research Ethics Board (H20-00252).

3.3 Results

We identified 208,984 individuals, of which 104,796 (50.1%), 99,261 (47.5%), and 23,371 (11.2%) were living with rheumatoid arthritis, plaque psoriasis or psoriatic arthritis, and ankylosing spondylitis, respectively (these groups were not mutually exclusive; Table 3.1). Overall, our study included 123,475 female subjects (59.1%) and individuals were most often aged 50-69 years (92,592, 44.3%).

3.3.1 New start policy

For etanercept, we detected a gradual monthly increase in the proportion of prescriptions dispensed that were biosimilar of 0.65% (95% CI 0.44, 0.85) with no significant level change in utilization (Table 3.2; Figure 3.2). Similar changes were quantified for the change in proportion of total spending on biosimilar etanercept post-new start (Table 3.3; Figure 3.4). No significant changes in utilization or spending were detected for biosimilar

infliximab after the new start policy was introduced (Figure 3.3; Figure 3.5). Comparable results were quantified among our disease-specific cohorts.

Table 3.1 Sociodemographic characteristics of study participants.

	Rheumatoid arthritis[a]	Psoriatic arthritis/plaque psoriasis[a]	Ankylosing spondylitis[a]	Overall
	n (%)			
Sex				
Female	69,823 (66.6)	52,129 (52.5)	12,268 (52.5)	123,475 (59.1)
Male	34,973 (33.4)	47,132 (47.5)	11,103 (47.5)	85,509 (40.9)
Neighbourhood income quintile				
1 - Lowest	21,316 (20.3)	19,102 (19.2)	4,520 (19.3)	41,361 (19.8)
2	21,696 (20.7)	19,848 (20.0)	4,621 (19.8)	42,421 (20.3)
3	21,020 (20.0)	20,033 (20.2)	4,681 (20.0)	42,115 (20.2)
4	20,644 (19.7)	20,438 (20.6)	4,806 (20.6)	42,145 (20.2)
5 - Highest	19,376 (18.5)	19,044 (19.2)	4,512 (19.3)	39,312 (18.8)
Missing	744 (0.7)	796 (0.8)	231 (1.0)	1,630 (0.8)
Age group (years)				
18-29	3,738 (3.6)	9,842 (9.9)	1,904 (8.1)	14,654 (7.0)
30-49	20,484 (19.5)	27,492 (27.7)	7,302 (31.2)	50,707 (24.3)
50-69	49,575 (47.3)	42,432 (42.7)	9,559 (40.9)	92,592 (44.3)
70+	30,999 (29.6)	19,495 (19.6)	4,606 (19.7)	51,031 (24.4)

a Groups based on diagnosis codes were not mutually exclusive

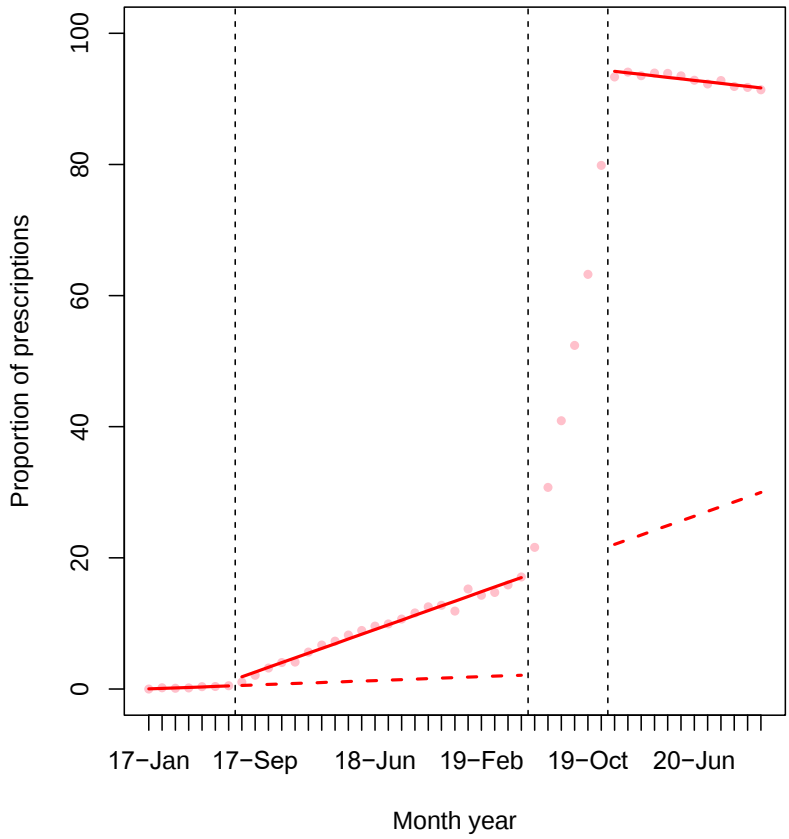


Figure 3.2 Interrupted time series analyses of the overall proportion of prescriptions dispensed that were biosimilar etanercept.

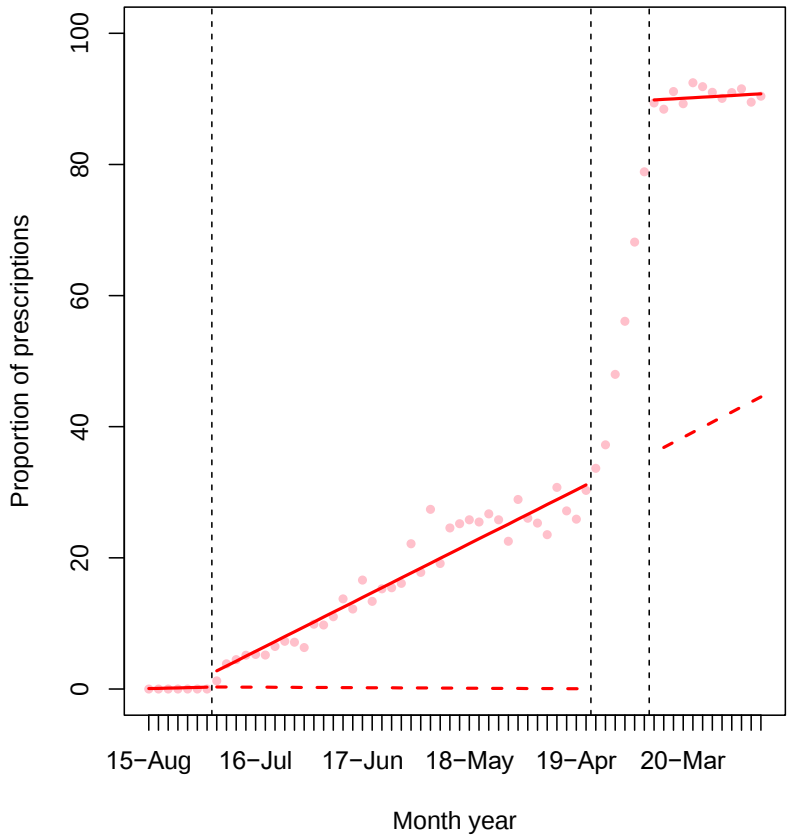


Figure 3.3 Interrupted time series analyses of the overall proportion of prescriptions dispensed that were biosimilar infliximab.

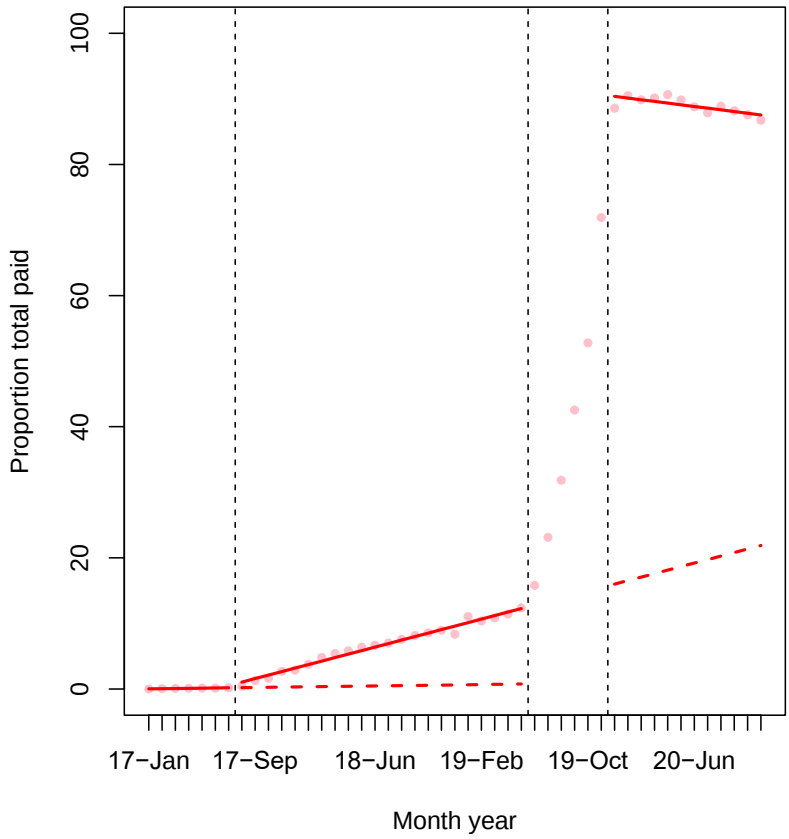


Figure 3.4 Interrupted time series analyses of the overall proportion of total spending on biosimilar etanercept.

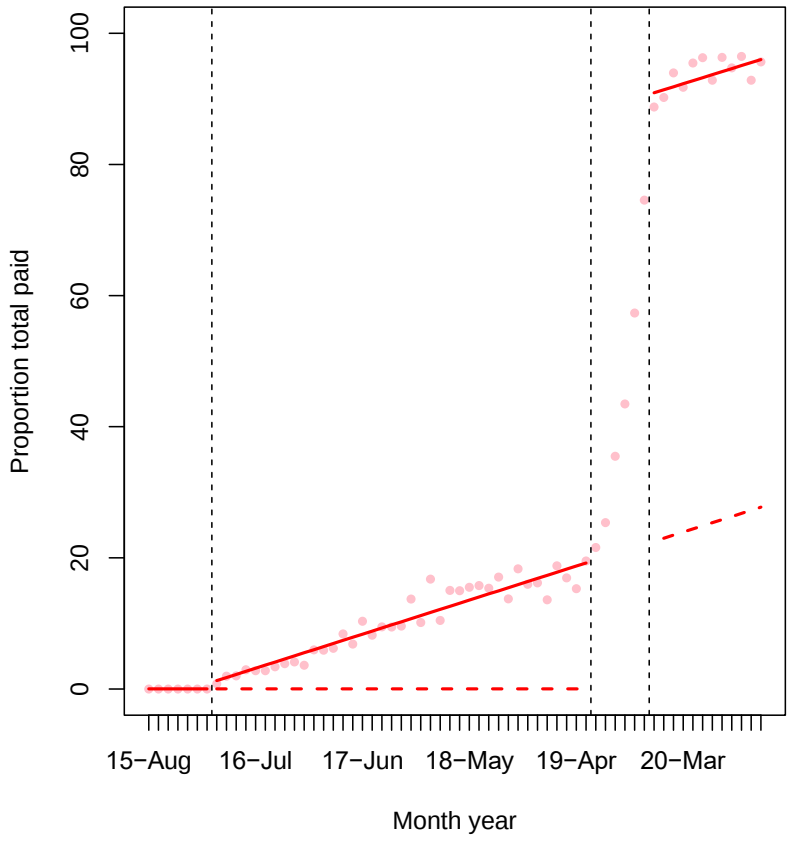


Figure 3.5 Interrupted time series analyses of the overall proportion of total spending on biosimilar infliximab.

3.3.2 Switching policy

In terms of total spending and number of prescriptions dispensed, proportional utilization of biosimilar infliximab increased from 21.6% to 74.6% and 33.7% to 78.9%, respectively, over the pre-intervention period. Similarly, biosimilar etanercept increased from 15.8% to 71.9% and 21.6% to 79.8% in terms of proportion of total spending and prescriptions dispensed, respectively.

After the switching policy was introduced, we observed significant level and trend changes among all study cohorts with respect to the proportion of biosimilar etanercept prescriptions dispensed and total spending (Table 3.2; Table 3.3; Figure 3.2; Figure 3.4). For example, we detected a step change of 76.98% (95% CI 75.56, 78.41) in terms of the proportion of etanercept prescriptions dispensed post-switch, in addition to a persistent gradual decrease of -0.95% per month (95% CI -1.04, -0.85), in our overall cohort in the post-switch period.

We also detected significant level changes in the proportion of biosimilar infliximab prescriptions dispensed and total spending among all cohorts (Table 3.2; Table 3.3; Figure 3.3; Figure 3.5). Among the overall cohort, we found a step change of 58.43% (95% CI 52.11, 64.75) accompanied by a gradual decrease of -0.66% per month (95% CI -1.13, -0.20) in terms of the proportion of biosimilar infliximab prescriptions dispensed after the switch policy. With respect to the proportion of total spending on biosimilar infliximab, we observed non-significant monthly trend changes for all groups.

Table 3.2 Change in the proportion of prescriptions of infliximab and etanercept dispensed that were biosimilar after new start and switching policies were introduced.

	Etanercept			
	New start policy 02/16		Switching policy 05/19-11/19	
	Level (95% CI)	Trend (95% CI)	Level (95% CI)	Trend (95% CI)
Overall	0.68 (-0.18, 1.53)	0.65 (0.44, 0.85)	76.98 (75.56, 78.41)	-0.95 (-1.04, -0.85)
RA	0.64 (-0.23, 1.52)	0.66 (0.45, 0.86)	77.95 (76.49, 79.41)	-0.99 (-1.09, -0.90)
PS	0.20 (-0.81, 1.21)	0.31 (0.07, 0.55)	81.04 (79.34, 82.74)	-0.65 (-0.76, -0.54)
AS	0.93 (-0.53, 2.39)	0.74 (0.27, 1.20)	67.88 (64.70, 71.07)	-1.24 (-1.50, -0.98)
	Infliximab			
	New start policy 07/17		Switching policy 05/19-11/19	
	Level (95% CI)	Trend (95% CI)	Level (95% CI)	Trend (95% CI)
Overall	1.74 (-1.61, 5.09)	0.71 (-0.14, 1.56)	58.43 (52.11, 64.75)	-0.66 (-1.13, -0.20)
RA	0.63 (-2.99, 4.25)	0.74 (-0.18, 1.65)	58.97 (52.13, 65.81)	-0.74 (-1.24, -0.24)
PS	2.33 (-3.15, 7.81)	0.64 (-0.76, 2.04)	53.54 (43.05, 64.02)	-0.37 (-1.15, 0.41)
AS	1.60 (-3.72, 6.91)	0.64 (-0.70, 1.98)	56.13 (46.53, 65.74)	-0.81 (-1.47, -0.15)

RA rheumatoid arthritis; AS ankylosing spondylitis; PS plaque psoriasis and/or psoriatic arthritis; CI confidence interval

95% CIs excluding 1 are indicative of statistical significance at $p < 0.05$

Table 3.3 Change in the proportion of total spending on biosimilar infliximab and etanercept after new start and switching policies were introduced.

	Etanercept			
	New start policy 02/16		Switching policy 05/19-11/19	
	Level (95% CI)	Trend (95% CI)	Level (95% CI)	Trend (95% CI)
Overall	0.34 (-0.60, 1.28)	0.51 (0.28, 0.73)	78.22 (76.65, 79.79)	-0.79 (-0.90, -0.69)
RA	0.32 (-0.55, 1.20)	0.53 (0.33, 0.74)	80.71 (79.25, 82.17)	-0.86 (-0.96, -0.76)
PS	-0.05 (-1.21, 1.10)	0.24 (-0.03, 0.51)	76.55 (74.59, 78.50)	-0.52 (-0.65, -0.40)
AS	1.33 (-0.21, 2.88)	0.76 (0.40, 1.13)	76.39 (73.81, 78.97)	-1.19 (-1.36, -1.02)
	Infliximab			
	New start policy 07/17		Switching policy 05/19-11/19	
	Level (95% CI)	Trend (95% CI)	Level (95% CI)	Trend (95% CI)
Overall	0.77 (-1.65, 3.20)	0.47 (-0.13, 1.07)	71.23 (66.82, 75.65)	-0.01 (-0.33, 0.30)
RA	0.30 (-2.64, 3.23)	0.46 (-0.27, 1.19)	71.55 (66.21, 76.89)	-0.09 (-0.48, 0.29)
PS	1.00 (-2.79, 4.79)	0.45 (-0.49, 1.39)	67.65 (60.78, 74.52)	0.47 (-0.02, 0.95)
AS	0.73 (-2.75, 4.21)	0.43 (-0.45, 1.31)	69.97 (63.50, 76.44)	0.002 (-0.47, 0.47)

RA rheumatoid arthritis; AS ankylosing spondylitis; PS plaque psoriasis and/or psoriatic arthritis; CI confidence interval

95% CIs excluding 1 are indicative of statistical significance at $p < 0.05$

3.3.3 Sex-stratified analysis

When the proportion of biosimilar prescriptions dispensed were stratified by sex, we found similar associations across most groups (Table 3.4). However, a significant level change was detected post-new start among male subjects receiving etanercept—but not among female subjects or overall—in terms of the proportion of biosimilar prescriptions

dispensed and total spending. We also identified unique associations in terms of biosimilar spending among female subjects receiving infliximab after the new start and switch policy: there was a significant positive trend in the post-new start period and a significant downward trend post-switch detected among female subjects and non-significant changes among male subjects.

Table 3.4 Change in the proportion of prescriptions dispensed of biosimilar infliximab and etanercept after new start and switching policies were introduced stratified by sex.

	Proportion prescriptions dispensed			
	Etanercept			
	New start policy 02/16		Switching policy 05/19-11/19	
	Level (95% CI)	Trend (95% CI)	Level (95% CI)	Trend (95% CI)
Female	0.37 (-0.66, 1.40)	0.71 (0.47, 0.96)	76.05 (74.33, 77.76)	-0.97 (-1.08, -0.85)
Male	1.56 (0.64, 2.48)	0.60 (0.36, 0.83)	78.88 (77.29, 80.47)	-0.91 (-1.00, -0.83)
	Infliximab			
	New start policy 07/17		Switching policy 05/19-11/19	
	Level (95% CI)	Trend (95% CI)	Level (95% CI)	Trend (95% CI)
Female	2.56 (-1.44, 6.55)	0.77 (-0.24, 1.77)	52.75 (45.60, 59.90)	-0.70 (-1.19, -0.22)
Male	0.72 (-2.94, 4.39)	0.60 (-0.32, 1.51)	65.32 (58.57, 72.08)	-0.57 (-1.06, -0.09)
	Proportion total spending			
	Etanercept			
	New start policy 02/16		Switching policy 05/19-11/19	
	Level (95% CI)	Trend (95% CI)	Level (95% CI)	Trend (95% CI)
Female	-0.01 (-1.11, 1.09)	0.56 (0.30, 0.82)	77.68 (75.84, 79.51)	-0.79 (-0.91, -0.67)
Male	1.07 (0.24, 1.89)	0.47 (0.27, 0.67)	79.58 (78.18, 80.97)	-0.81 (-0.90, -0.72)
	Infliximab			
	New start policy 07/17		Switching policy 05/19-11/19	
Female	0.91 (-1.27, 3.10)	0.57 (0.03, 1.11)	68.41 (64.36, 72.46)	-0.35 (-0.65, -0.05)
Male	0.54 (-2.10, 3.17)	0.36 (-0.32, 1.03)	75.23 (70.55, 79.91)	0.26 (-0.03, 0.55)

95% CIs excluding 1 are indicative of statistical significance at $p < 0.05$

3.4 Discussion

Our findings suggest mandatory biosimilar switching policies have the potential to greatly increase utilization beyond what was detected for new start programs. While the new start policies may have had a small impact on the monthly trend of biosimilar utilization, introduction of mandatory biosimilar switching resulted in an immediate increase in proportional spending and uptake ranging from 58.43-78.22% among the overall cohort.

We detected sex-based differences in utilization of biosimilars. For instance, male subjects receiving etanercept demonstrated a significant level change post-new start policy whereas female subjects did not. On the other hand, a significant positive trend change post-infliximab new start and a significant negative trend post-infliximab switch was detected among female subjects but not male subjects. Previous research has suggested that there may be differences in medication use by sex; e.g. female subjects may be less adherent to medications and may receive guideline-based care less often compared to male subjects.[89] However, from this work alone, it is unclear whether there are differences in use of biosimilars by sex or whether these findings were due to random chance.

Large increases in biosimilar use are likely in Canada as BC has continued to roll out biosimilar switching programs for patients receiving rituximab, adalimumab, enoxaparin, filgrastim, and a number of insulins and similar policies have now been announced in a number of jurisdictions.[14,15] Greater biosimilar use may make the Canadian market more

appealing for biosimilar manufacturers to enter, having a feedforward effect on biologic competition.

South of the border, biosimilars for the top selling drug in the world, adalimumab, are set to be available for the first time next year in the US.[79] Recent calls from the US Department of Health and Human Services (HHS) for CMS to 'do more' to incentivize biosimilar use could consider mandatory biosimilar switching policies.[77] From our findings, it appears that simply enacting biosimilar new start programs may not be sufficient to greatly enhance use of these medicines.

Notably, we detected a small but significant downward trend in the post-switch period, potentially indicating treatment failure and switches back to the reference product. Studies examining biosimilar infliximab and etanercept switching in BC found no differences in healthcare utilization (e.g. emergency department visits or hospitalizations) post-policy.[90,91] Nevertheless, concerns around the use of biosimilars remain, stemming in part from their regulatory designation as 'similar' but not identical to the reference product in terms of efficacy and safety, their interchangeability and substitutability, and the use of clinical trial data from one disease state to substantiate claims of efficacy and safety in another (i.e. extrapolation of indication), among other factors.[65,79,92,93] However, research examining biosimilar infliximab and etanercept switching in Denmark found no deleterious outcomes associated with the national policies and systematic reviews have also not found evidence of significant safety or efficacy concerns with biosimilar switching.[41,94,95]

Prior to this analysis, it was unclear to what extent a biosimilar switching policy would capture the market for a particular agent. For instance, with less expensive biosimilars (e.g. insulin glargine), one may expect that private insurers and/or individuals would be more likely to pay the difference between the biosimilar and originator in order to maintain treatment with the reference product. In addition, the BC government maintained a system by which patients would be able to receive exceptional coverage for the reference product on a case-by-case basis.[15] Both provide mechanisms by which the impact of biosimilar switching policies may be decreased. Future work should examine the post-switch market structure over a longer time period as it is unclear whether the large increases in uptake of biosimilars will be eroded as the market reaches a new equilibrium. Indeed, we detected a negative gradual trend post-switch that should be monitored. Our sensitivity analysis also detected sex-based differences in utilization of biosimilar infliximab and etanercept which should continue to be tracked. Our findings may be of particular interest to jurisdictions with large public payers considering implementing biosimilar switching policies.

However, rapid biosimilars penetration via switching policies is just one potential policy lever. By combining national drug tendering and procurement with rapid uptake of biosimilars via both switching and new start policies, Denmark saved nearly $2 for every $3 spent on infliximab and tendering provided similar levels of biosimilar infliximab savings in Norway.[96,97] Countries including France and Belgium have combined biosimilars price caps with prescribing quotas aimed to increase use of biosimilars.[98] The

United States recently approved the first interchangeable biosimilars for insulin glargine and adalimumab—which may be automatically substituted at the level of the pharmacy depending on state law—although it is too early to discern the impact of this designation.[99] Interchangeable biosimilars may be particularly compatible with switching policies.

3.5 Limitations

Our study has a number of limitations. We relied on administrative data to identify our cohort which could have inaccuracies related to the diagnoses of interest. This was likely partially mitigated by the fact that etanercept is only indicated for treatment of the conditions of interest in our study and has limited off-label use. Further, any misclassification would likely have persisted over the entire study period, so would not have modified the relative changes we observed.

Our study also required only one instance of a diagnosis code of interest. However, by design, our study only included individuals who also received a prescription for either etanercept or infliximab and who had no previous instance of a diagnosis code for Crohn's disease or ulcerative colitis (in the case of infliximab). Therefore, we believe the potential impact of this less stringent approach on our denominators of interest—namely, total number of prescriptions dispensed or spending *per month* on either etanercept or infliximab—would be at least partially mitigated by design. Of note, individuals with plaque psoriasis and receiving etanercept were not required to switch until 2021. However, it was not possible to exclude individuals with plaque psoriasis from the

etanercept analyses as the relevant diagnosis codes pertain to both plaque psoriasis and psoriatic arthritis.

NACRS does not cover all emergency department visits in BC, although this is unlikely to impact our findings. The generalizability of our results may be limited as the magnitude of impact of biosimilar switching policies may vary by patient, physician, and payer-related factors and may also differ depending on the medication of interest.[100] Due to the nature of our study, we were unable to comment on the impact of these policies at an individual level. In addition to further exploration of the relative factors that may influence biosimilar uptake post-switch, future work should examine the more long-term impacts of these policies. We were unable to comment on cost-savings related to these policies due to the presence of confidential rebates and listing agreement discounts.

Overall, our study clearly shows that a mandatory switching policy was much more effective than a new starter policy at increasing the use of biosimilars. Thus, although new start policies may result in some small gradual increases in biosimilar utilization, payers can substantially influence the use of biosimilars through the implementation of mandatory biosimilar switching policies. Given the clinical similarity in their effect and potential savings, other jurisdictions and payers should seriously consider the use of these policies.

4 Conclusion

4.1 Summary of findings

In general, this thesis examined the current state of biosimilars policy and use in Canada. Specifically, the first research chapter examined provincial payer policies for biosimilar insulin glargine, infliximab, and etanercept from all Canadian provinces except Newfoundland and Labrador and combined this information with retail utilization data from IQVIA. The second research chapter compared biosimilar infliximab and etanercept new start and switching programs—two policy approaches to increasing use of these medicines—among individuals with inflammatory arthritis and psoriasis in the province of BC.

This thesis demonstrates the profound impact that policy interventions can have on the use of biosimilar medicines. Beginning with BC in 2019 with infliximab, etanercept, and insulin glargine, biosimilar switching policies have now been implemented in a number of Canadian provinces and territories and for additional biosimilar agents. As a result of these efforts, we are likely to see large increases in biosimilar use across many indications for which they are prescribed at the national level. However, it is important to note that the actual cost-savings impact of these policies are difficult to assess due to confidential pricing agreements and rebates.

Our results suggest that switching policies have the ability to greatly enhance utilization beyond what would have occurred under new start policies alone. Although this seems obvious, it is important to highlight that the provincial government maintained avenues

for prescribers and patients to access the reference products if deemed necessary. In addition, nearly 3 in 5 individuals in BC have reported having private insurance, which could have provided an alternative means for patients to access reference drugs, potentially reducing the effectiveness of the switching policies of interest. Despite this context, however, the impact of the switching policy remained profound.

Based on our findings, we support the introduction of additional biosimilar switching policies in BC where cost-savings can be achieved. In addition, we encourage the use of biosimilars switching policies among jurisdictions that have not yet introduced them. These switching policies should be combined with consultation of those impacted by the policies directly—including patients and prescribers—as well as education about the available evidence. We also recommend ongoing pharmacovigilance monitoring for safety and effectiveness signals.

4.2 Strengths and limitations

This work has a number of strengths and limitations which can be discussed more cogently by chapter.

4.2.1 Uptake of biosimilar drugs in Canada: An analysis of provincial policies and usage data

This work combined population level purchasing data from all Canadian provinces except Newfoundland and Labrador with a narrative review of the included provinces'

biosimilars policies. This provided a powerful perspective: switching policies were greatly increasing the use of biosimilars in the provinces that had begun implementing them.

However, this study had a number of limitations. Namely, the study was restricted to the first biosimilars switched in Canada (infliximab, etanercept, and insulin glargine) and did not have representation from Newfoundland and Labrador nor the territories. We used wholesale purchasing data, which is not the same as dispensation data. This meant we could not assess the number of users or their switching patterns. We were not able to examine spending by payer type and our study likely included individuals not covered by the provincial plans of interest. Finally, we were also not able to assess biosimilar use by indication which is of particular importance as switching policies for the same biosimilar were implemented over different time periods in some instances (e.g. with infliximab for inflammatory arthritis versus inflammatory bowel disease).

4.2.2 Uptake and spending on biosimilar infliximab and etanercept after new start and switching policies in Canada: An interrupted time series analysis

This chapter combined robust population-level administrative data from the province of BC to identify a cohort of individuals living with inflammatory arthritis and psoriasis and impacted by the policies of interest with quasi-experimental quantitative methodology (i.e. interrupted time series analysis). We were able to compare the two main policy

approaches to increasing use of biosimilars in the province, namely new start and switching policies, using both public and private data.

This work was not without limitations. Identifying cohorts using diagnosis codes can lead to inaccurate inclusion or exclusion of participants. It was important to remove individuals living with inflammatory bowel disease from the infliximab cohort as they were required to switch to a biosimilar under a different phase of the policy. However, it was not possible to remove individuals with plaque psoriasis—due to the disease codes of interest combining psoriatic arthritis and plaque psoriasis—from the etanercept portion of the study even though they were not required to switch to biosimilar etanercept until 2021.

Overall, the generalizability of our findings to other jurisdictions may have limitations. Response to biosimilar switching policies may differ by jurisdiction, reference drug, patient characteristics, provider type, composition of payers, and other policy-relevant characteristics. In addition, we were unable to make conclusions about the cost-savings generated from these policies due to drug pricing information being considered proprietary in Canada. We also did not examine reference to biosimilar switching events, switch-back events, or switching between biosimilars. The long-term effects of these policies are still unknown.

4.3 Recommendations for future work

Future work should continue to build on this analysis, employing robust quantitative methods to examine the use of other biosimilar medicines with switching policies now underway. There may be key differences by jurisdiction that will allow researchers to glean additional insights into the promoters and hindrances to biosimilar switching. In addition, further quantification and characterization of switch-backs and switching between biosimilars is needed.

Post-marketing surveillance for efficacy and safety signals will be critical moving forward. If no concerns are raised post-switch, this will likely bolster the resumé of biosimilars and have a positive impact on policies abroad (e.g. in the US). However, if there are concerns, indicated by mass switch-backs or other safety signals, the government will need to act accordingly.

Market approval and new start policies appear insufficient to ensure rapid uptake of biosimilars. Due to the implementation of provincially-mandated switching policies, biosimilar utilization increased markedly in Canada over our study period. Future work should continue to monitor the long-term impacts of biosimilar switching.

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