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UTILIZATION OF BIOLOGICS IN SASKATCHEWAN

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ABSTRACT

Background
Few details are available about the factors driving cost increases of biologic medications.

Objectives
To describe trends in utilization and cost of biologic agents using administrative databases in Saskatchewan, Canada.

Methods
Two analyses were conducted. First, aggregate utilization of biologics based on prescriptions dispensed was measured in each calendar year between 2001 and 2013. Second, a retrospective cohort of new biologic users was created to examine trends in spending between 2001 and 2013. During the first year of biologic therapy, biologic cost was quantified for each specific biologic agent as: (a) total spending; (b) total milligrams dispensed; and (c) estimated unit cost (i.e., total cost in 2013 $CAD divided by total milligrams dispensed during the year). Data analyses were descriptive and all biologic costs were adjusted to 2013 dollars (CAD).

Results
In the first year of biologic availability in Saskatchewan (2001), 133 patients were dispensed at least one biologic agent for a total cost of $0.5 million. In 2013, 2,402 biologic recipients were identified for a total cost of $51.8 million. Almost all of these biologic costs (88.9%) were paid by the provincial government. In 2013, infliximab was the most frequently used agent, accounting for 46.5% of all spending on biologics. Infliximab was also the most expensive agent in 2013 (mean cost $31,340 ±15,307) and showed the highest increase in the mean yearly cost over time due to greater quantities dispensed.

Conclusion
Biologic utilization will require ongoing monitoring to optimize patient-level and societal-level benefits.

Key Words: *biologics, biologic response modifiers, prescription drug utilization, costs*

Biologic response modifier (BRM) medications or "biologics" were introduced to Canadian consumers in 2001. They have proven benefits in patients with inflammatory conditions such as rheumatoid arthritis and Crohn's disease and have become important tools to combat these types of conditions.[1,2] In 2013, Canadian public drug programs spent more on biologic agents than any other medication class ($576.7 million), accounting for 7.4% of total spending.[3] Although the increased spending on BRM in Canada has been reported in aggregate, details about their utilization and cost have not been explored. The aim of this report was to describe changes in utilization and drivers of cost for specific biologic agents (abatacept,

adalimumab, anakinra, etanercept, golimumab, infliximab, rituximab, tocilizumab) using administrative databases in Saskatchewan, Canada. In the province of Saskatchewan, patients can receive coverage for biologic agents if they satisfy certain criteria relating to the disease (e.g., severe rheumatoid arthritis or inflammatory bowel disease), as well as failure or intolerance to traditional medication.[4]

METHODS

Data Source

This study was performed using administrative databases from Saskatchewan's Ministry of Health.[5] Biologic medication utilization was estimated using the prescription drug database. This database captures all dispensations for medications listed in an extensive formulary, including all the specific agents targeted in this study (for patients who are eligible for coverage). It is unlikely patients would obtain these agents without drug coverage considering the annual cost of these agents often exceeds $18,000 CAD. Also, over 90% of the provincial population is eligible for drug plan benefits so the capture of biologic use was likely comprehensive.

The hospital discharge abstract database and the physician fee-for-service claims database were used to establish specific indications for the biologic agents identified. The hospital database contains information for every admission, discharge, transfer, or death of an inpatient. Diagnostic codes (i.e., ICD-9 or ICD-10-CA) corresponding to Saskatchewan's prior-authorization criteria for biologic agents were identified from hospital and physician billing claims databases. Diagnostic information in the physician claims database is limited to three-digit ICD-9 codes listed for every service claim. Information from all databases was linked at the patient level via a unique identifier assigned to every beneficiary.

Aggregate Utilization and Cost

The earliest claims for biologics in Saskatchewan were recorded in 2001. Thus, all individuals receiving at least one dispensation for any of the specified agents between 2001 and 2013 were identified (Table 1). Overall utilization was described for each calendar year using the following measures: (a) annual number of recipients receiving at least one biologic dispensation; (b) total expenditures on biologics (including dispensing fees and markups); and (c) government-specific expenditures. The expenditures were adjusted to 2013 Canadian dollars according to the medicinal and pharmaceutical price index of Saskatchewan reported by Statistics Canada.[6] Utilization was reported in aggregate and also stratified according to individual agents and individual diseases.

Retrospective Cohort

A retrospective cohort study was also conducted to identify the specific drivers of increased biologic spending over time. All individuals with at least one

TABLE 1 Biologic Response Modifiers and Indications Eligible for Reimbursement in Saskatchewan, Canada

Generic Names	Rheumatoid Arthritis and Juvenile Idiopathic Arthritis	Crohn's Disease and Fistulizing Crohn's Disease	Ulcerative Colitis	Psoriatic Arthritis and Plaque Psoriasis	Ankylosing Spondylitis	Wegener's Granulomatosis
abatacept	I					
adalimumab	I			I	I	
anakinra	I					
etanercept	I			I	I	
golimumab	I			I	I	
infliximab	I	I	I	I	I	
rituximab	I					I
tocilizumab	I					

**I = indicated in the exception drug status program with conditional reimbursement. Government of Saskatchewan.*[4]

TABLE 2 International Classification of Diseases (ICD) Diagnosis Codes Used to Identify Specific Conditions Meeting Eligibility Criteria for Biologic Response Modifier Reimbursement in Saskatchewan

Disease Category	ICD-10-CA* Codes	ICD-9* Codes
Ankylosing spondylitis	M45	720
Crohn's Disease and Fistulizing Crohn's Disease	K50, K500, K501, K508, K50813, K509	555, 569
Psoriatic Arthritis and Plaque Psoriasis	L400, M07, M071, M072, M073, M074, M075, M076	696, 696
Rheumatoid Arthritis and Juvenile Idiopathic Arthritis	M05, M051, M052, M053, M058, M059, M06, M061, M062, M063, M068, M069, M08, M080, M081, M082, M083, M084, M088, M089	714, 714
Ulcerative Colitis	K51, K510, K511, K512, K513, K514, K515, K518, K519	556

**ICD-10-CA = Enhanced version (Canada) of International Classification of Diseases, 10th version; ICD-9 = International Classification of Diseases, 9th version.*

biologic dispensation between 2001 and 2012 were eligible, excluding those who were younger than 18 years of age on the date of the first dispensation and those who could not be followed for 365 days due to death, termination of coverage, or reaching the end of the follow-up period (December 31, 2013). For each patient, the specific biologic indication was established if 2 physician claims or one hospital diagnosis was observed within 1 year before or after the date of the first dispensation in each calendar year. Diagnostic codes were selected based on the province's eligibility criteria for reimbursement (Table 2).[4] For those diagnosed with more than one eligible indication, patients were grouped into a multiple-indication group.

All patients were followed for 365 days from the date of the first BRM dispensation. A specific washout period for BRM use was not required because all patients in the cohort were identified on the date of the earliest dispensed biologic agent since 2001 (i.e., the original year of BRM availability). During the 365-day follow-up period, biologic use was quantified at the patient-level using the following endpoints: (a) total spending on each specific biologic agent received (including markup and dispensing fees); (b) total dose (in milligrams) dispensed; (c) estimated unit cost (i.e., total cost in 2013 $CAD divided by total mg dispensed during the year).

A subgroup analysis was conducted on patients initiating a BRM agent between 2008 and 2013. During this period, 5 BRM agents were continuously available in Saskatchewan allowing a parallel comparison of cost between specific agents. Patients were stratified by specific BRM agent and calendar year. Total cost, total dose dispensed, and cost per milligram of BRM dispensed during the 365-day follow-up was averaged for all patients initiating therapy in the same calendar year. Costs were adjusted to 2013 dollars and compared within patients initiating therapy in the 2008 year. All data were reported using descriptive statistics such as means, frequencies, and standard deviations (SD). Data were analyzed using SAS version 9.3 (SAS institute, Cary, NC, USA).

RESULTS

Aggregate Utilization and Cost

The number of patients receiving at least one dispensation for a biologic agent in Saskatchewan increased from 133 in 2001 to 2,402 in 2013, representing 0.02% and 0.35% of all active drug plan beneficiaries in Saskatchewan. Although females were the predominant recipients of biologics, their percentage decreased during the study period, from 69.9% in 2001 to 58.3% in 2013. The mean age of patients receiving a biologic agent remained relatively stable throughout the study period (49.0 ±15.3 in 2001 to 50.7 ±15.7 in 2013).

Total spending on biologics increased from $0.5 million in 2001 to $51.8 million in 2013 (Figure 1). The vast majority of these biologic costs (89.0% or $246.7 million) were paid by the provincial government

FIG. 1 Total annual expenditures and annual percentage increases on biologic medications in Saskatchewan (total spending*) between 2001 and 2013. *Total spending includes dispensing fees and markup on basic drug costs.

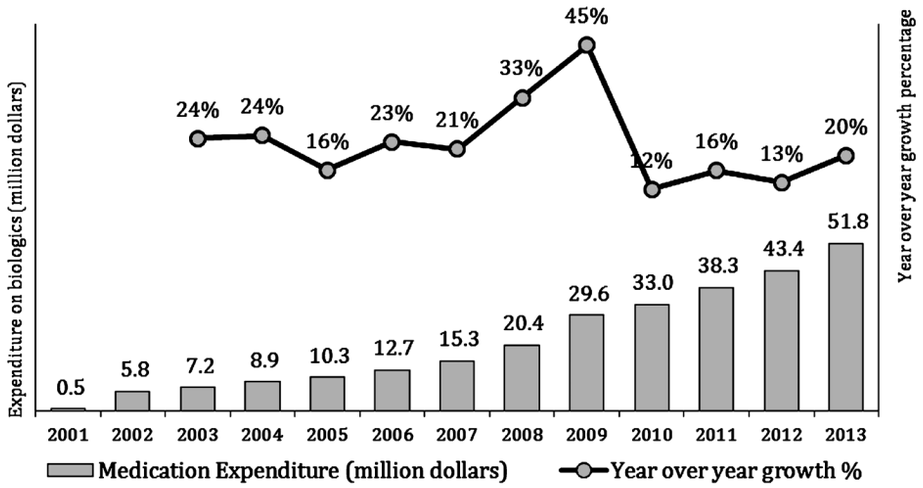
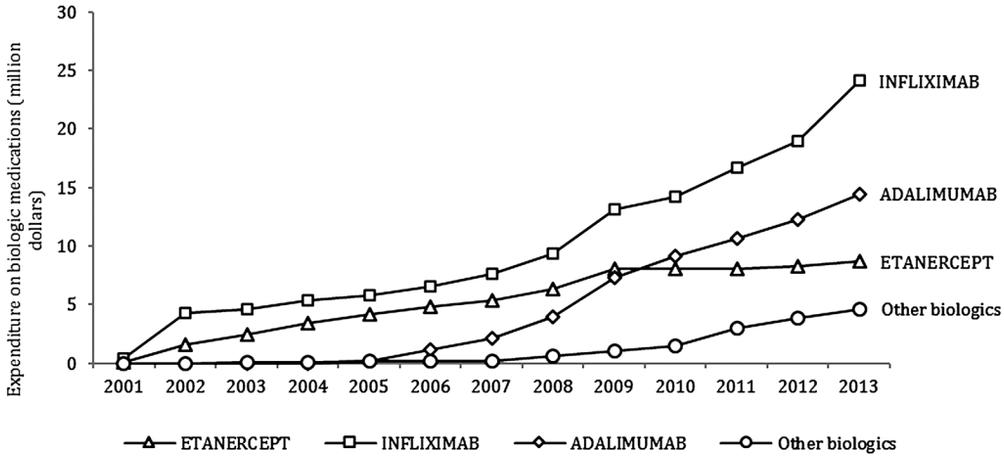


FIG. 2 Annual total expenditure (in 2013 constant dollars) for biologic medications between calendar year 2001 and 2013.



and 3 agents accounted for most of the spending: infliximab, adalimumab, and etanercept (Figure 2). In 2013, infliximab accounted for 46.5% of all biologic spending, followed by adalimumab (27.9%), and etanercept (16.7%). All other biologic agents combined accounted for only 8.9% of the total costs (Figure 2).

Retrospective Cohort

Of 1,195,752 recipients of provincial health insurance between 2001 and 2012 (of which 90% are beneficiaries of drug benefits), 2,881 patients (0.2%) received at least 1 biologic agent. Of these, 2,748 patients (95%) were included in the retrospective cohort study. Eighty-one patients were excluded due to age (i.e., $<$ 18 years or missing age) and 52 were excluded due to inadequate follow-up (i.e., $>$365 days). During the one-year follow-up period, the average cost of biologic therapy increased from $20,925 (SD: 10,269) per patient in 2001 to $24,395 (SD: 13,134) in 2012. In 2012, individuals initiated on infliximab had the highest average biologic costs during follow-up ($31,340, SD: 15,307), followed by

TABLE 3 Comparing patients initiating biologic response modifiers in 2012 versus 2008 with respect to average spending per patient, cumulative dosage, and cost per unit dose of the specific biologic agent within 365 days since the first dispensation*

	Mean (SD) and Percentage Change of Spending in Dollars (CAD) Per Patient (2012 versus 2008)	Percentage Change in the Number of Milligrams** Dispensed Over 1 Year (2012 versus 2008)	Percentage Change in the Cost Per Milligram** Dispensed (2012 versus 2008)
infliximab	31,340 (15,307), +14.7%	+19.7%	−4.2%
adalimumab	21.365 (12,230), +6.0%	+8.0%	−1.9%
abatacept	16.320 (6,641), +0.8%	+0.8%	+0.0%
etanercept	17.423 (9,094), −3.0%	−1.6%	−1.5%
rituximab	12,009 (5,253), −22.8%	−14.1%	−10.2%

**Costs are in 2013 dollars; **Doses in milligrams of the active ingredient of the biologic medications.*

adalimumab ($21,365, SD: 12,230), and etanercept ($17,423, SD: 9,094). Differences in cost persisted when patients were examined within subgroups with the same indication.

During the one-year follow-up period, 245 (8.5%) patients received more than one type of BRM. The highest percentage of "switching" occurred among patients receiving etanercept initially (91 patients or 11.8% within the group), followed by those initiated on adalimumab (53 patients or 9.3% within the group) and those initiated on infliximab (79 patients or 6.5% within the group).

Among agents that were available continuously between 2008 and 2012, infliximab was associated with the highest increase in yearly cost (+14.7%), followed by adalimumab (+6.0%), and abatacept (+0.8%). In contrast, average cost in the first year decreased for rituximab (−22.8%) and etanercept (−3.0%). In general, increased costs in the first year were due to a higher number of milligrams dispensed during the one-year follow up rather than a change in unit cost (Table 3).

DISCUSSION

We conducted a retrospective review of biologic utilization and cost in Saskatchewan, Canada between 2001 and 2013. Total spending on biologic agents increased dramatically over the study period. In 2013 alone, over $50 million (CAD) were spent on 2,403 patients. Although total expenditures were primarily influenced by growth in the number of recipients of biologics, the average cost of these agents in the first year of therapy also increased from $20,925 to $24,395. This growth was primarily due to a higher number of milligrams of infliximab dispensed during the initial year of therapy in more recent years (Table 3). Possible reasons for higher quantities of infliximab such as higher dosages, more frequent infusions, longer persistence on therapy, or other unknown factors were not examined in this study.

Medications are the second leading driver of health care spending in Canada and costs continue to grow.[3] Public and private drug coverage plans are faced with an increasing proportion of expenditures attributed to agents such as BRM and specialty drugs.[7] While these medications may provide significant advancements in treating chronic illnesses,[1,2] their costs are highly disproportionate to the number of patients treated. At a time when payers are "under pressure to control drug expenditures . . . without causing adverse effects on health or shifting costs to other health care services,"[8] the balance between access and spending is becoming a major challenge even for drugs that are considered cost-effective.[9] The costs of biologic agents reported in this study were based on patients meeting specific criteria for coverage. Without this limitation on coverage, the potential financial impact of biologics to the program could be unsustainable. Thus, it is imperative that health care providers, private payers, and governments work together to ensure a maximum return on investment in terms of improved health, quality of life, and functional outcomes.

The information provided in this study is purely descriptive. Thus, increases in utilization and spending were not adjusted for growth in population, or changes in population demographics, disease severity, or the types of diseases eligible for treatment. Also, the total cost of biologic agents may have been influenced by changes in wholesale markups and dispensing fees or markup assigned at community pharmacies during the dispensing process. Although it is possible that these factors impacted the changes reported during the observation period, costs, number of patients receiving therapy, and the indications for therapy are expected to be highly accurate. Granted, individuals could technically obtain biologic medication dispensations without drug plan adjudication if they were covered exclusively by private insurance, or if they paid for the medication independently. The latter situation is unlikely considering the extremely high annual cost of these agents. Moreover, because all claims for biologic agents are adjudicated electronically at the point of sale (assuming prior authorization has already been obtained), total cost estimates are expected to be highly accurate also. That said, the electronic database does not provide information on dosage instructions. Thus, the extent to which higher doses reflect more aggressive prescribing versus longer treatment durations was not established. Finally, limitations exist on the use of physician diagnosis in the physician billing claims database; a physician can only list one diagnosis per claim therefore a patient with more than one medical condition could be mis-represented.

CONCLUSION

Biologic utilization will require ongoing monitoring to optimize patient-level and societal-level benefits. Thus, strong paradigms need to be established to guide decision makers toward consistent and principled regulation of these types of agents.

Conflict of Interest

David Blackburn is the chair in Patient Adherence to Drug Therapy within the College of Pharmacy and Nutrition, University of Saskatchewan. This position was created through unrestricted financial support from AstraZeneca Canada, Merck Canada, Pfizer Canada, and the Province of Saskatchewan's Ministry of Health. A representative of the Ministry of Health (A.C.) was part of the study team.

Disclosure

This study is based in part on de-identified data provided by the Saskatchewan Ministry of Health. The interpretation and conclusions contained herein do not necessarily represent those of the government of Saskatchewan or the Saskatchewan Ministry of Health.

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