No Change in Surgical and Hospitalization Trends Despite Higher Exposure to Anti-Tumor Necrosis Factor in Inflammatory Bowel Disease in the Québec Provincial Database From 1996 to 2015

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Background: Crohn disease (CD) and ulcerative colitis (UC) have high health care expenditures because of medications, hospitalizations, and surgeries. We evaluated disease outcomes and treatment algorithms of patients with inflammatory bowel disease (IBD) in Québec, comparing periods before and after 2010.

Methods: The province of Québec's public health administrative database was used to identify newly diagnosed patients with IBD between 1996 and 2015. The primary and secondary outcomes included time to and probability of first and second IBD-related hospitalizations, first and second major surgery, and medication exposures. Medication prescriptions were collected from the public prescription database.

Results: We identified 34,644 newly diagnosed patients with IBD (CD = 59.5%). The probability of the first major surgery increased after 2010 in patients with CD (5 years postdiagnosis before and after 2010: 8% [SD = 0.2%] vs 15% [SD = 0.6%]; $P < 0.0001$) and patients with UC (6% [SD = 0.2%] vs 10% [SD = 0.6%] ; $P < 0.0001$). The probability of the second major surgery was unchanged in patients with CD. Hospitalization rates remained unchanged. Patients on anti-tumor necrosis factor (anti-TNF) medications had the lowest probability of hospitalizations (overall 5-year probability in patients with IBD stratified by maximal therapeutic step: 5-aminosalicylic acids 37% [SD = 0.6%]; anti-TNFs 31% [SD = 1.8%]; $P < 0.0001$). Anti-TNFs were more commonly prescribed for patients with CD after 2010 (4% [SD = 0.2%] vs 16% [SD = 0.6%]; $P < 0.0001$) in the public health insurance plan, especially younger patients. Corticosteroid exposure was unchanged before and after 2010. Immunosuppressant use was low but increased after 2010. The use of 5-ASAs was stable in patients with UC but decreased in patients with CD.

Conclusions: The probability of first and second hospitalizations remained unchanged in Québec and the probability of major surgery was low overall but did increase despite the higher and earlier use of anti-TNFs.

Key Words: epidemiology, administrative database, surgery, hospitalization, biological therapy

INTRODUCTION

Inflammatory bowel diseases (IBD) are chronic progressive and disabling conditions affecting mainly young adults with a substantial impact on patient physical health, social functioning, and quality of life. With the advent of the Selecting Therapeutic Targets in Inflammatory Bowel Disease[1] guidelines, symptomatic improvement has been replaced by more objective treatment targets and monitoring including

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clinical response, biochemical targets, and endoscopic healing. Emerging data suggest that accelerated treatment strategies and earlier introduction of immunosuppressants and biologics may be associated with improved outcomes, including a lower risk for surgery and hospitalization.[2-6]

The recent ECCO-EpiCom inception cohort studies provided European data about up-to-date IBD incidences, treatment strategy, and disease outcomes.[7-9] Data on the natural history and therapeutic strategies of Crohn disease (CD) has also been reported in population-based studies from North America, including data from the Mayo Clinic in Minnesota and from Manitoba, Canada.[5, 10, 11] Of note, direct comparison of the above studies is limited by the differences in health care insurance systems and hence data acquisition.

A recent publication from Europe showed that the maximal treatment step could be regarded as a proxy severity marker in administrative databases for patients with IBD.[12] There are no such data available for the Province of Québec because of the implementation of routine reimbursement of biologics. Québec is known to be an area of high incidence and prevalence of IBD.[13] The primary aim of the present study was to evaluate the recent trends in therapeutic strategy (accelerated access to advanced medical therapies) and to assess disease outcomes in a population-based IBD cohort.

METHODS

Administrative Database and Case Definition

The Régie de l'Assurance Maladie du Québec, a population-based health insurance database for the Province of Québec, was used. Patients were selected using *ICD-9* and *ICD-10* definitions for ulcerative colitis (UC) and CD (indeterminate IBD was excluded) in inpatient and outpatient settings and using drug prescriptions from January 1996 to December 2015, using a previously described methodology.[13-15] Cohort entry corresponded to the IBD diagnosis. Time-to-event was defined as being from the diagnosis of IBD to the minimum date between patients' first (or second) event, the administrative end of the study (December 2015), or death, whichever occurred first.

Primary and Secondary Outcomes

Events included first and second major surgeries, first and second IBD-related hospitalizations, and initiation of IBD-related drugs. Major surgeries were defined using Canadian Classification of Health Interventions and Canadian Classification of Diagnostic, Therapeutic, and Surgical Procedures codes for any major surgeries related to IBD diagnosis (including small and large bowel resection, colectomy, stricturoplasty, and ostomy). Minor surgeries (eg, fistulotomy, abscess drainage, seton placement or removal) were excluded.

Medical therapies

For the drug outcomes, we looked at initiation of 5-aminosalicylic acids (5-ASAs), thiopurines, methotrexate, biologics, and corticosteroids (excluding budesonide). Patient groups were stratified according to maximal therapeutic step[12] into 3 groups: 5-ASA therapy, immunosuppressant therapy (including steroids, azathioprine, 6-mercaptopurine, methotrexate), and biologics therapy (infliximab, adalimumab).

Infliximab was approved for use in IBD in 2005-2006 by Health Canada. Adalimumab qualified for reimbursement in 2012. However, the uptake of biologics in clinical practice became more widespread after 2010 following landmark trials (SONIC[16]) highlighting the benefit of biologics in early disease. Other biologics (ie, vedolizumab, ustekinumab, tofacitinib) became available post-2015. A limitation of the data capture was that the public plan covers approximatively 41.8% of biologics prescriptions across Canada, the remainder being covered by private funds, which consequently excluded them from this analysis.[17]

Statistical Analysis

SAS version 9.4 was used for all analyses. For each time-to-event analysis, Kaplan-Meier curves stratified by IBD type (CD or UC) were drawn. These were further stratified by year of cohort entry (≤2010, >2010), age group (aged ≤40 years, >40 years), and sex. For all Kaplan-Meier plots, we tested whether the hazard functions in time were different across all groups and within each stratum of CD and UC groups using a log-rank test. We also reported for each plot the probability of survival without the event along with its standard error at 0, 3, 5, and 10 years of follow-up.

In a second analysis, we looked at time to second event, starting from the time of the first event. Kaplan-Meier curves were drawn for time to second event and the analyses were further stratified by year of cohort entry (≤2010, >2010), age group (aged ≤40 years, >40 years), sex, and the last drug used before the second event (eg, 5-ASAs, biologics, other drugs, and no treatment). The analyses stratified by the last drug used were further stratified by year of cohort entry (≤2010, >2010). A P value of <0.05 was deemed statistically significant.

RESULTS

Patient Characteristics

Overall, 34,644 newly diagnosed patients with IBD were identified from the population-based health insurance database of Québec from 1996 to 2015. We identified CD as the diagnosis in 20,644 patients (or 59.5%), and the remainder had UC. The male-to-female ratio for CD was 3:4 and for UC it was 1:1. The CD cohort was younger than the UC cohort (patients with CD aged <40 years = 46% vs patients with UC aged <40 years = 35%).

Hospitalization Rates

The rates of first hospitalization remained essentially unchanged between the 2 periods (Fig. 1A) but were more

common in patients with CD vs patients with UC (5-year overall probability: CD 43% [SD = 0.4%] vs UC 35% [SD = 0.4%]; $P < 0.0001$). Women with CD had higher rates of first hospitalization (5-year probability: 45% [SD = 0.5%]) vs men with CD (41% [SD = 0.6%]; $P < 0.0001$); this trend did not persist for second hospitalizations. Meanwhile, the probability of a second hospitalization was also essentially unchanged between the 2 periods (Fig. 1B).

In a sensitivity analysis, patients with IBD on biologics had an overall lower probability of first hospitalizations compared with other drug types (overall 5-year probability for all patients with IBD using 5-ASAs: 37% [SD = 0.6%]; biologics: 31% [SD = 1.8%]; $P < 0.0001$; especially for patients with CD [Figs. 2A, B]). Higher rates of hospitalization occurred in the population receiving no therapy (41% [SD =0.4%]). This result was also true with regard to second hospitalization rates (overall 5-year probability for all patients with IBD using biologics: 44% [SD = 2.5%]; 5-ASAs: 56%[SD = 1.0%]; for patients not using biologics: 62% [SD = 0.6%]).

In biologics users (Fig. 3), a significant increase in rates of first hospitalization after 2010 were observed compared with the rates before 2010 (in patients with CD, 5-year probability before 2010: 19% [SD = 2.4%] vs after 2010: 45% [SD = 3.5%]; $P < 0.0001$; in patients with UC: 21% [SD = 4.5%] vs 44% [SD = 8.3%]; $P < 0.0178$). Rates of second hospitalization in biologics users followed the same trend as first hospitalization rates for patients with CD (3-year probability: 16% [SD = 3.2%] vs 47% [SD = 3.5%]; $P < 0.0001$) but were unchanged for patients with UC (3-year probability of second hospitalization, before 2010 vs after 2010: 32% [SD = 8%] vs 33% [SD = 5.2%]; $P = 0.641$).

Major Surgery Rates

The probability of major surgery was overall low but was increased after 2010 in patients with CD (at 5 years after diagnosis, before and after 2010: 8% [SD = 0.2%] vs 15% [SD = 0.6%]; $P < 0.0001$) and patients with UC (6% [SD = 0.2%] vs 10% [SD = 0.6%]; $P < 0.0001$) (Fig. 4A). In patients with both UC and CD, men had higher rates of major surgery than women (for CD patients, 5-year probability for men: 10% [SD = 0.4%] vs 9% for women [SD = 0.3%]; in UC patients, the 5-year probability for men was 8%[SD = 0.3%] vs 6% for women [SD = 0.3%] ;$P < 0.0001$).

The rates of second surgeries in CD were unchanged during the observational period (5-year probability, before and after 2010: 18% [SD = 1.2%] vs 21% [SD = 1.3%]; $P = 0.4116$) (Fig. 4B). Older patients (those aged >40 years: 22% [SD = 1.2%] vs those aged <40 years: 16% [SD = 1.2%]; $P = 0.0087$) and men with CD had higher rates of second surgery rates (5-year probability for men: 23% [SD = 1.4%) vs 17% for women [SD = 1.1%]; $P < 0.0001$). Patients taking biologics (10% [SD = 2.3%]) had a lower probability of second surgery than did patients who did not take biologics (24% [SD = 1.2%]; $P < 0.0001$).

A sensitivity analysis with patients stratified by the maximal therapeutic step confirmed the increase in surgical rates in patients with CD after 2010 regardless of therapeutic step (Fig. 5; $P < 0.0001$). In patients with UC, the same analysis showed increased surgery rates in patients treated using 5-ASAs ($P < 0.0001$) and immunosuppressants ($P < 0.0001$) but not in patients treated using biologics (Fig. 5; $P = 0.152$).

Therapeutic Strategy in the Québec Public Plan

Biologics were used more commonly and prescribed earlier in the disease course after 2010. The 5-year probability pre-/post-2010 for patients with CD pre-2010 was 4% (SD = 0.2%) vs 16% post-2010 (SD = 0.6%); for patients with UC pre-2010 it was 2% (SD = 0.2%) vs 13% post-2010 (SD = 0.7%); $P < 0.0001$, especially patients aged <40 years at diagnosis (Fig. 6).

Initiation of 5-ASAs in the public plan was high and stable in patients with UC (40% [SD = 0.4%]; $P = 0.087$), but

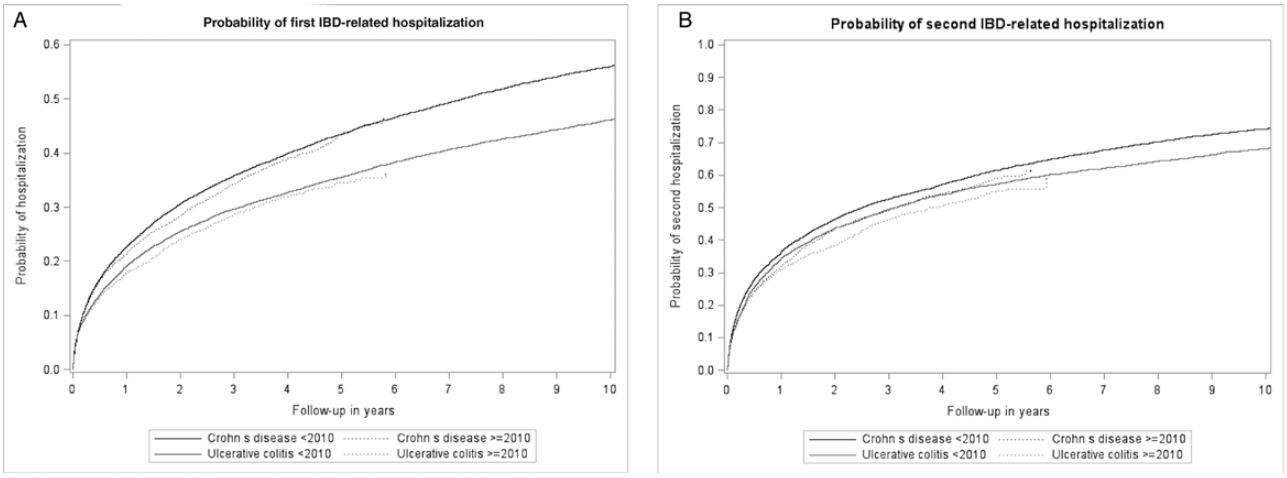

FIGURE 1. Probability of hospitalization in patients with CD and UC before and after 2010. A, First hospitalization. B, Second hospitalization.

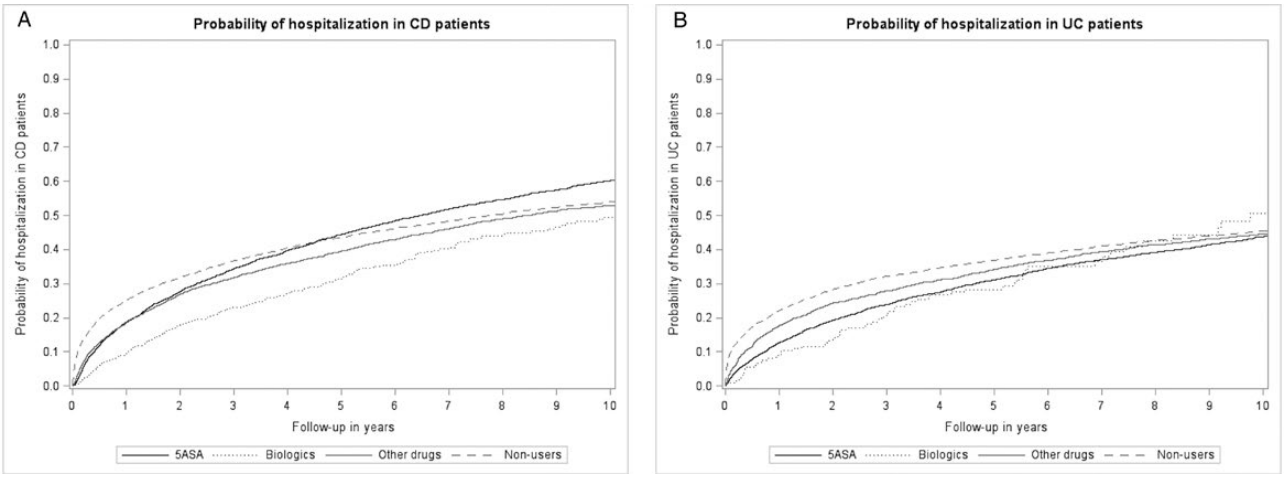

FIGURE 2. Probability of first hospitalization. A, Probability of first hospitalization in patients with CD by last drug used (5-ASAs vs biologics vs other drugs, eg, immunosuppressants, steroids) vs nonusers (ie, patients with no drug treatment). B, Probability of first hospitalization in patients with UC by last drug used (5-ASAs vs biologics vs other drugs, eg, immunosuppressants, steroids) vs nonusers (ie, patients with no drug treatment).

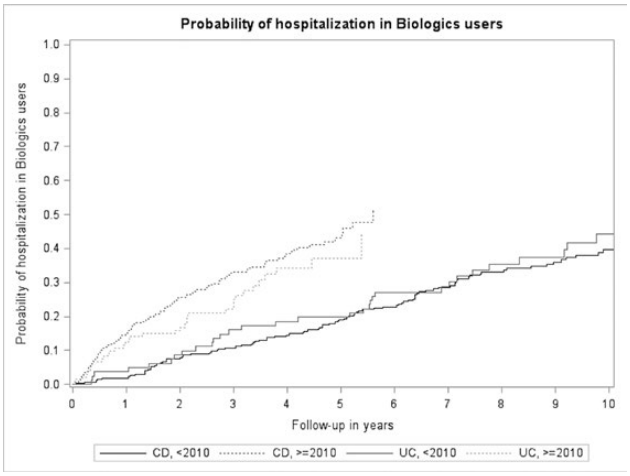

FIGURE 3. Probability of hospitalization in patients with CD and UC on biologics before and after 2010.

their use decreased in patients with CD after 2010 (5-year probability pre-/post-2010: 33% [SD = 0.4%] vs 21% [SD = 0.6%]; $P < 0.0001$). In all patients with IBD, 5-ASA use was favored in the older cohort (aged >40 years at diagnosis; $P < 0.0001$). There were no sex differences. The use of topical 5-ASA therapy in patients with UC overall was 29.9%.

Corticosteroids were prescribed equally between patients with CD and patients with UC, with no change in prescription practices in patients diagnosed pre- or post-2010 (CD: 31% [SD = 0.4%] vs 30% [SD = 0.7%]; $P = 0.46$; UC: 31% [SD = 0.5%] vs 34% [SD = 0.9%]; $P = 0.03$), and they were more commonly prescribed in older patients with IBD (aged >40 years; $P < 0.0001$).

Thiopurine exposure increased after 2010 (patients with CD pre-2010: 21% [SD = 0.4%] vs 24% post-2010 [SD = 0.6%]; $P < 0.0001$; patients with UC pre-2010: 13% [SD = 0.4%] vs 16% post-2010 [SD = 0.7%]; $P < 0.0001$), mainly in the younger patient cohort (aged <40 years). Methotrexate was used in only a fraction of patients with IBD overall; nevertheless, its use was increased in patients with CD (5-year probability pre-/post-2010: CD: 2%-7% [SD = 0.1%-0.4%) and UC: 1%-4% [SD = 0.1%-0.4%]; $P < 0.0001$), with no sex differences.

DISCUSSION

Overall, this large population-based inception cohort from Québec showed that whereas the probability of first and second hospitalization remained unchanged, the probability of first major surgery, though low, was increased despite the higher and earlier use of biologics and immunosuppressant therapies.

The efficacy of anti-TNF therapies has been established in randomized clinical trials. Studies for infliximab (ACCENT,[18] ACT[19]) and adalimumab (CHARM,[20] ULTRA[21]) reported a reduction in rates of hospitalizations and surgeries in cohorts of patients with both moderate and severe CD and UC. However, patient cohorts in clinical trials are substantially different from those seen in everyday practice,[22] so outcomes from clinical trials cannot be directly extrapolated to everyday clinical practice.

Few data are available on recent trends in hospitalization rates from population-based cohorts. Recently, the EpiCom cohort reported that 23% of patients with CD were hospitalized during the first year after diagnosis and the 5-year hospitalization rate reached 36% (23% in the first year).[23] For patients with UC, the 5-year hospitalization rate was 23%, with the majority of patients hospitalized within 10 months from diagnosis.[24] Moreover, the EpiCom studies[23] showed similar hospitalization rates in Western Europe compared with Eastern Europe in patients with CD despite a higher number of patients in Western Europe who received biologic therapy (33%) and immunomodulators (66%)

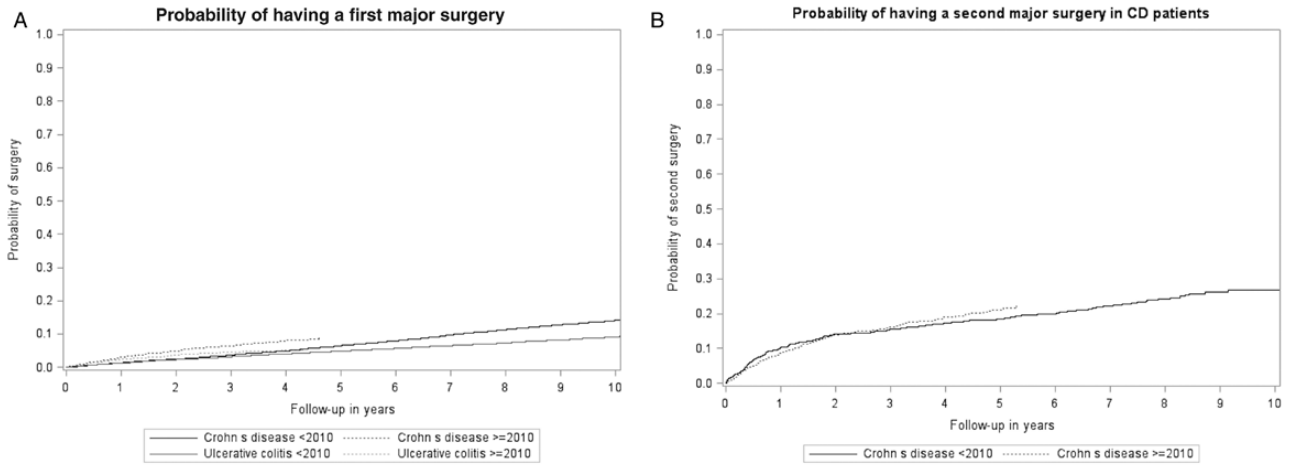

FIGURE 4. Probability of major surgery before and after 2010. A, Probability of first major surgery in patients with CD and UC. B, Probability of second major surgery in patients with CD.

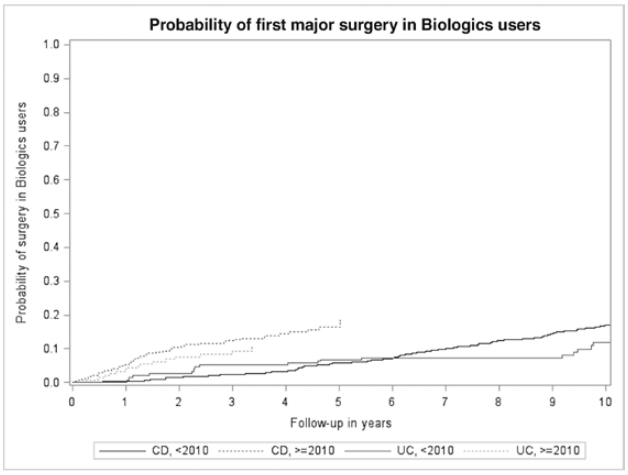

FIGURE 5. Probability of first major surgery in patients with UC and CD on biologics before and after 2010.

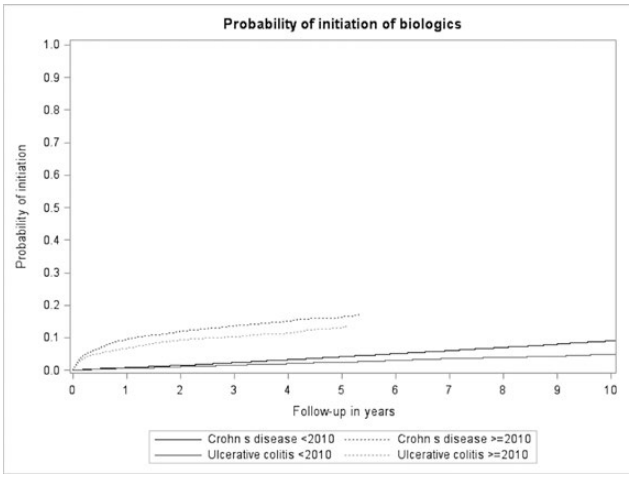

FIGURE 6. Probability of initiation of biologics in patients with UC and CD before and after 2010.

compared with patients in Eastern Europe (14% and 54%, respectively; $P < 0.01$). Our cohort showed higher 5-year hospitalization rates, with 43% in patients with CD and 35% in patients with UC with no change in the first and second hospitalization rates over the observation period. Furthermore, in biologics users there was a significant increase in the rate of first (CD: $P < 0.0001$; UC: $P < 0.0178$; Fig. 3) and second hospitalizations in patients with CD after 2010. This trend may more likely reflect more a severe disease phenotype or practice changes but less likely disease complications or adverse events, although these hypotheses cannot be directly assessed in an administrative database.

A meta-analysis of population-based cohorts in the pre-biologics era by Bernstein et al[3] showed that surgical rates in patients with CD in Canada were already declining before the availability of biologics. Based on a meta-analysis of 30 population-based studies by Frolkis et al,[25] the pooled 5-year risk of surgery in patients wtih CD decreased from 27.7% in patients diagnosed after 1990, to 24.2% in patients diagnosed after 2000 when anti-TNFs were introduced. A similar trend was seen in patients with UC, with the 5-year risk of surgery dropping from 9.9% to 7.6%. Meanwhile, the recent EpiCom inception cohort study reported a 5-year surgery rate in patients with CD of 24% overall[22] and 6% in patients with UC.[23, 25] In addition, recent data from Murthy et al,[26] who evaluated the Ontario health database to determine the effect of infliximab on hospitalization and surgical rates in patients with UC and CD and showed that the introduction of anti-TNF medications failed to modify the trend of CD-related hospitalizations (odds ratio [OR], 1.06; 95% confidence interval [CI], 0.81-1.39), intestinal resections (OR, 1.10; 95% CI, 0.81-1.50), UC-related hospitalizations (OR, 1.22; 95% CI, 1.07-1.39), or colectomies (OR, 0.93; 95% CI, 0.54-1.61).

Our data show low rates of surgery in patients with CD overall and equivalent rates in patients with UC. Nevertheless, despite the low rates, we do report an increase in the surgical rates that may be related to more proactive referrals for elective surgery. Notably, a previous work by Ma et al[27] suggested that emergent surgeries are decreasing and elective surgeries are increasing in patients with IBD in Canada.

Rates of second major surgeries at 5 years postdiagnosis were approximately 20% in our CD cohort and were unchanged over time. Limited data are available on the risk of second surgeries in the literature. Nguyen et al[5] reported rates of recurrent surgeries in patients with CD at 1, 5, and 10 years after the first surgery to be 11%, 23%, and 34%, respectively.

We also assessed the trends of therapeutic algorithms and medication uses in the Province of Québec. Biologics were prescribed more often, mostly in younger patients, and earlier in the disease course. Private prescriptions for biologics were not accounted for, so a higher percentage should be expected. The use of 5-ASAs remained stable and high in patients with UC at 40%. Their use was high but decreasing in patients with CD. Immunosuppressant use was also noted to be increased, possibly because of prescription regulations. Interestingly, prescriptions for steroids remained unchanged at around 30% despite an increase in biologics uptake. In comparison, during the same period in Europe, the Epi-IBD Study in patients with CD from Western Europe vs Eastern Europe reported a higher exposure to biologics (after 5 years from diagnosis: 14% vs 33%; $P < 0.01$) and immunomodulators (54% vs 66%; $P < 0.01$) but a lower exposure to 5-ASAs (90% vs 56%; $P < 0.05$)[23]; meanwhile, no disparity in treatment use between Eastern and Western Europe was noted in patients with UC, with biologics exposure of 11% and immunomodulator exposure of 29% in total.[24] In the present study, biologics use under the public reimbursement plan was 13% in patients with UC and 16% in patients with CD, which is more similar to the trends seen in Western Europe.

In addition, although some recent population-based studies[4, 12, 23, 24] reported that surgery rates did not decrease (eg, in Ontario and in the present study from Québec), the association with drug exposure and comparing exposed and nonexposed populations remains controversial, subject to multiple possible confounders such as selection bias, differences in patient characteristics, differences in prescription regulations, delay in start of biological therapy, and differences in patient monitoring.

The strengths of this study include the large, well-characterized, population-based IBD cohort and methodology. Our study provides full coverage of hospitalization and surgical data from the provincial administrative database for the Province of Québec. However, limitations of the administrative databases include the lack of disease phenotype or possible disease modifiers such as smoking or pharmaceutical compliance. In addition, the Québec drug plan for biologics therapy is 2-fold, with public Régie de l'Assurance Maladie du Québec or private insurance coverage; the latter was not captured in our dataset. Notably, 41.8% of prescribed drug spending is paid for by provincial health care plans across Canada.[17] Subsequently, biologic exposure may have occurred within the immunosuppressant group (steroids-immunosuppressants) without being captured in the data as it may have originated from the private insurance coverage. Nevertheless, we believe that exposures to 5-ASAs and biologics are reliable markers for patient characterization and can be regarded as a proxy of disease severity in the context of an administrative database analysis.[12]

CONCLUSIONS

In patients with CD, biologics and immunosuppressant use increased and 5-ASA use was reduced. Interestingly, steroid use remained unchanged. Despite these changes in therapeutic practice, the overall rates of IBD-related hospitalizations remained unchanged. The probability of first major surgery was low overall but with an increasing trend, despite the earlier and more frequent use of biologics. However, we believe that this latter increasing trend may at least partly reflect proactive medical decisions, supported by the more balanced surgery rates observed after the first year after diagnosis.

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