Original Article

Cost of Refractory Crohn’s Disease Before and After Ustekinumab Utilization

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Abstract

Background: Crohn’s disease (CD) is associated with major health services utilization and costs. Between 2012 and 2015, ustekinumab was used off-label in Quebec, Canada for treatment of refractory CD.

Aims: We assessed the direct medical cost of adult CD patients in the 1-year pre- and 1-year postustekinumab initiation.

Methods: Data were obtained from the provincial administrative databases. CD patients dispensed subcutaneous ustekinumab in 2012 to 2014 were followed for 1 year from the date of initiation (index-date). Kaplan Meier plots were used to display time to ustekinumab discontinuation and factors associated with discontinuation were identified using multivariate Cox regression models. Direct medical costs and 95% confidence interval (CI) of gastrointestinal-related health services were calculated for the 1-year pre- and 1-year post-index-date.

Results: Thirty-four CD patients (mean age ± standard deviation, 44 ± 14 years, 59% women and 41% with low income) were included. Of these, 14 (41%) discontinued ustekinumab during the postperiod. Discontinuation was less likely among older patients: hazard ratio (95% CI) per 5-year age increase, 0.77 (0.61 to 0.96). The total $CAN direct medical cost (mean, 95% CI) was higher in the post- versus preperiod: $1,681,239 ($49,448; $42,265 to $57,160) versus $880,060 ($25,884; $20,391 to $31,596), while the total costs of GI-related health services were similar: $250,206 ($7359, $3536 to $11,674), versus $213,446 ($6278, $3609 to $9423).

Conclusion: In patients with severe refractory CD on off-label ustekinumab, approximately 60% remained on treatment beyond 1 year. The cost of gastrointestinal services did not increase during that year as compared to that of the year preceding ustekinumab use.

Keywords: Administrative data; Chron’s disease; Direct medical cost; Health services utilization; Refractory; Ustekinumab

Background

Crohn’s disease (CD) is a chronic immunological disorder that affects individuals at all ages with incidence peaking in early adulthood (1–4). Rectal bleeding, impaired bowel function, and abdominal pain are among the challenges of living with CD (5–8). Expressed per 100,000 persons, CD prevalence in 2008 was 319 in Canada (9,10) and 277 in the province of Quebec (3).

Patients with CD experience relapsing and remitting episodes, with progression over time to complications including stricture, fistulas and abscesses (11). Conventional pharmacotherapy
for mild-to-moderate CD includes mesalamine substances, corticosteroids and immunosuppressive agents (12). Treatment with tumour necrosis factor inhibitors (TNFi) alone or in combination with an immunomodulator is provided to patients with moderate-to-severe CD who are intolerant or do not respond to conventional pharmacotherapy (12). TNFi treatment is effective in these patients (13–15), but not all respond to initial treatment and there is a loss of response over time (13,16–20).

Ustekinumab, a biologic agent that blocks the activity of interleukin-12 and interleukin-23 (21), was approved by Health Canada in December 2016 for the treatment of moderate-to-severe CD patients who have had an inadequate response or were intolerant to either conventional or TNFi treatments (22). Studies have shown better overall response to ustekinumab compared to placebo in these patients (23–30); although about one-third of ustekinumab responders lost response within 1 year (27), dose increase may improve ustekinumab response maintenance (30).

Health services utilization and direct medical cost of CD are substantial; lifelong pharmacotherapy treatment and high acquisition costs of biologic agents, in addition to frequent outpatient physician visits, emergency department (ED) visits and hospitalizations are all contributors (31–33). In 2005/2006, the mean annual direct cost of CD in Canada was Canadian (CAN)$42,322 overall and CAN$31,440 in patients using infliximab (the only TNFi available at that time) (32). The change in health resource utilization and the direct medical costs of TNFi refractory patients who are started on ustekinumab has not been assessed.

In Quebec, infliximab, adalimumab and vedolizumab are listed on the public drug formulary for the treatment of moderate-to-severe CD when conventional pharmacotherapy has failed (34). Ustekinumab is listed for moderate-to-severe plaque psoriasis and for psoriatic arthritis, but not yet for CD. As such, during our study period, ustekinumab was available for CD patients for off-label use (exceptional patient) which requires approval by the public drug insurance agency, the Régie de l’assurance maladie du Québec (RAMQ), before prescription. Also, at that time, the intravenous induction dose was not available and only subcutaneous ustekinumab was used. Vedolizumab was listed in Quebec for CD treatment in 2017 and will not be discussed in this study.

We assessed the direct medical cost (medication, physician billings, ED visits and hospitalizations) of CD patients (≥20 years of age) in Quebec, Canada from the perspective of the provincial health care system in the 1-year pre- versus 1-year postustekinumab initiation, in 2012 to 2015.

Approval to conduct the study was obtained from the Quebec Ethics Review Agency, the Commission d’accès à l’information, and the McGill University Health Centre Ethics Review Board (IRB Number: 12-056GEN(#2563)).

Methods

Data Sources and Study Population

We used demographic, physician claims, pharmacy claims and hospital abstract records obtained from the RAMQ databases on all individuals 20 years of age and older who received an outpatient diagnosis code (International classification of disease-9th revision, ICD-9 code: 556.x) or a primary or secondary inpatient diagnosis code (ICD-9 until March 2006: 556.x and ICD-10 since April 2006: K51.x) in 1997–2015. Hospitalization cost data were obtained from the Ministère de la santé et services sociaux (MSSS)—the All Patient Refined Diagnosis Related Groups (APR-DRGs) database (35). In Quebec, all residents are covered by RAMQ for outpatient and inpatient physician services. In addition, drug insurance is mandatory for all residents. All residents 65 years of age or older (1,232,985 individuals in 2012), all those who receive social assistance (476,535 individuals in 2012) and those under the age of 65 who do not have private drug insurance through their employer or a family member’s plan (1,777,754 individuals in 2012) are eligible for the public drug plan coverage (34).

Study Patients

A validated algorithm (sensitivity 78% and specificity 99.8%) was used to identify patients with CD (36). A CD diagnosis was defined by at least one hospitalization or four physician claims for CD within a 2-year period (36); the date of CD diagnosis was the first date of such claim or hospitalization. Among CD patients, those who used ustekinumab and had 1 year of RAMQ drug coverage before and after the first ustekinumab dispensed prescription (index-date) were included.

Ustekinumab Utilization in 1-Year Follow-up

Ustekinumab dose and duration were assessed at index-date and overall over the study period. Ustekinumab discontinuation in the postyear was defined by a 90-day period where ustekinumab was not supplied.

Direct Medical Costs

CD total direct medical cost was the primary outcome and was calculated separately for the pre- and postyear.

For each patient, the total direct medical cost was the sum of the costs of gastrointestinal (GI)-related hospitalizations, ED visits, pharmacological treatment and outpatient physician services. The predetermined GI events considered in this study are listed in Supplementary Table 1. The pharmacological treatment costs included the costs of the 5-aminosalicylic acid (5-ASA) (mesalamine, olsalazine and sulfasalazine), immunomodulators (mercaptopurine, azathioprine and methotrexate), TNFi (infliximab, adalimumab, golimumab and certolizumab), other biologic agents (natalizumab) and corticosteroids (prednisone, hydrocortisone, budesonide, ...
Ustekinumab Utilization

The first ustekinumab prescription was dispensed for an average of 27 days (SD 21 days) with an average induction dose of 295 mg and median (quartiles) monthly dose of ustekinumab first prescription and overall, time to ustekinumab discontinuation and rate of discontinuation were reported. Kaplan Meier plots were used to display time to ustekinumab discontinuation. Factors associated with ustekinumab discontinuation were identified using a multivariate Cox proportional hazard model. Mean (SD) and 95% confidence intervals (CI) and median (quartiles) of total direct medical cost of study patients and total direct medical costs of GI-related health services received were calculated for the pre- and postperiods. The bootstrap method was used to calculate the 95% CI.

Two sensitivity analyses were conducted. First, all analyses described above were repeated separating patients into those with versus without CD complications (fistula of intestine, stricture or abscess of intestine, rectum or anus) to examine the effect of these complications on ustekinumab utilization and costs; second, intravenous (IV) ustekinumab, currently used for induction, was not available during our study period. The IV induction cost is $2,079.84 per each 130 mg vial. The average patient weighing 55 to 90 kg receives 390 mg; so, the IV induction costs approximately $6,239.52. The cost of a subcutaneous induction of 90 mg x 3 that was used during the study period was $4,593.14 x 3 = $13,779.42. We recalculated the total cost of ustekinumab and the total cost of medications for the postyear assuming the induction cost was $6,239.52 during the first 8 weeks of treatment.

Statistical analyses were performed using SAS version 9.3 for UNIX (SAS Institute Inc., Cary, NC).

Results

Description of Cohorts

Among the 17,877 CD patients identified in 1997 to 2015, 69 were dispensed ustekinumab, of whom, 34 met the inclusion criteria (index-date ≤ 31 December 2014 to insure a full year of data post-index-date, and drug plan coverage 1-year pre- and 1-year post-index-date) and were studied.

Table 1 describes the patients’ baseline characteristics. Patients were on average 44 years old (SD 14 years), 59% were women, 41% had low income and the majority used GPA (65%) in the preperiod. Eleven patients (32%) had CD complications including fistula of intestine and stricture or abscess of intestine, anal and rectal regions (Supplementary Table 1), comorbidity assessed in the prior year (cancer, peptic ulcer disease and anemia/blood disease), and medications used in the prior year (corticosteroids, gastroprotective agents [GPAs], antidepressants, antidiabetics and antihypertensives)]. SES with subindices of social and material deprivation is available from RAMQ data. SES was developed on the basis of census enumeration area data on education level, employment/population ratio and average income (37).

Statistical Analyses

Descriptive analyses (means [standard deviations, SD], medians [quartile or proportions) were used as appropriate to report patient baseline characteristics and GI-related health services utilization by study period. Mean (SD) and median (quartiles) monthly dose of ustekinumab first prescription and prednisolone, methylprednisolone). The GI-related outpatient and ED physician visits costs included the reimbursement cost for all gastroenterologist outpatient and ED encounters and all other physicians (e.g., general practitioner, internist, surgeon) outpatient and ED encounters where the diagnosis (ICD-9 code) was for a pertinent GI disorder (Supplementary Table 1). The total hospitalization costs included those for small bowel surgery and those where the primary or secondary diagnosis was for a pertinent GI disorder (Supplementary Table 1).

The prescribed medication costs were available from the RAMQ data. They included the pharmacist fee, RAMQ reimbursement and the patient out-of-pocket contribution. The physician visit costs were the RAMQ reimbursements for the fee-for-service claims. The hospitalization costs were the sum of the physician claims costs for services that occurred during that hospitalization plus the product of the NIRRUs (niveau d’intensité relative des ressources utilisées) associated to that hospitalization times the unit cost per NIRRUs (physician claims + NIRRUs x unit cost per NIRRUs). The NIRRUs and unit cost per NIRRUs were provided in the APR-DRG data. The NIRRU is an indicator of the level of health services utilization intensity and is provided for all hospitalizations and ED visits; unit costs per NIRRUs are provided per year (35). The ED visit cost was the sum of the physician claims for that visit plus the cost associated with 1 NIRRU (as provided by the APR-DRG data).

Patient Baseline Characteristics

Patient characteristics assessed at index-date included age, sex, type of insurance plan (based on patient eligibility for premium subsidies; Guaranteed Income Supplement (GIS), partial premium subsidies (partial-GIS) and no premium subsidies (no-GIS). GIS and partial GIS were grouped in one category labelled ‘low income’), residency (urban or rural), socioeconomic status (SES), visits to gastroenterologists in the prior year, CD complications including fistula of intestine and stricture or abscess of intestine, anal and rectal regions (Supplementary Table 1), comorbidity assessed in the prior year (cancer, peptic ulcer disease and anemia/blood disease), and medications used in the prior year (corticosteroids, gastroprotective agents [GPAs], antidepressants, antidiabetics and antihypertensives]). SES with subindices of social and material deprivation is available from RAMQ data. SES was developed on the basis of census enumeration area data on education level, employment/population ratio and average income (37).
Table 1. Patient characteristics at the first ustekinumab prescription date (index-date)

| Characteristic                                    | N of patients | Percentage |
|--------------------------------------------------|---------------|------------|
| N of patients                                    | 34            |            |
| Age, mean (standard deviation)                   | 43.76 (13.96) |            |
| Women, N (%)                                     | 20 (58.8)     |            |
| Total or partial subsidies, N (%)                | 14 (41.2)     |            |
| SES quintile, N (%)                              | 2 (5.9)       |            |
| Complications (fistula, stricture or abscess)    | 11 (32.3)     |            |
| Medication use in the prior year, N (%)          |               |            |
| Antidepressants                                  | 19 (55.9)     |            |
| Antidiabetics                                    | 1 (2.9)       |            |
| Gastroprotective agents                          | 22 (64.7)     |            |
| Antihypertensives                                | 9 (26.5)      |            |
| Comorbidity assessed in the prior year, N (%)    |               |            |
| Anemia/blood disease*                            | 9 (26.5)      |            |
| Cancer                                           | 3 (8.8)       |            |

SES, socioeconomic status.
*Eight patients had anemia and one patient eosinophilia.

90 mg × 2, quartiles: 90 mg × 1 and 90 mg × 4. The median maintenance dose (overall prescriptions beyond the first 4 weeks) was 90 mg per 4 weeks; quartiles 90 mg per 8 weeks and 90 mg per 3 weeks. Of study patients, 14 (41%) discontinued ustekinumab during the postyear with most discontinuing it in the first 3 months (Figure 1). The total number of days on ustekinumab in the postyear was 9,161, mean 269 days (SD 131 days) and median 365 days (quartiles 106, 365 days). In multivariable cox regression model, older patients were less likely to discontinue ustekinumab in the postyear: hazard ratio (95% CI) per 5-year increase in age, 0.77 (0.61 to 0.96) (Table 3).

Health Services Utilization in the Pre- and Postperiods
Among the 34 study patients, 28 (82%) used a biologic agent in the preperiod (Table 4), with most using adalimumab (13 patients) (Supplementary Table 2). Other medication uses, and GI-related health service utilizations did not seem to differ between the two periods, although the number of patients using immunomodulators dropped from 16 (47%) in the preperiod to 12 (35%) in the postperiod and 2 patients used other biologics in the postperiod (infliximab and certolizumab).

Clinical Events and Direct Medical Costs
There were no deaths following index-date (Table 2). The total number of patients with the events of interest and the mean (SD) and median (quartiles) of the direct medical costs of these events in the years pre- and post-index-date are given in Tables 3–4. The total direct medical cost (SCAN) in the postperiod was $1,681,239 (median $49,064 [quartiles $34,054 to $59,405]) and in the preperiod $880,060 (median $24,698 [quartiles $16,039 to $36,711]). The higher cost in the postperiod was mainly due to the increase in the medications cost largely driven by the ustekinumab cost. The total costs of GI-related health services were similar between the two periods (postperiod: total: $250,206; median $836, quartiles $574 to $9645); and preperiod: total: $213,446, median $1398, quartiles $798 to $7813). While the total cost of medications in the postperiod was $1,431,033 (median $40,093, quartiles $30,831 to $53,759), and in the preperiod $666,614 (median $17,532, quartiles $7839 to $25,928)). The costs of the specific GI services are given in Table 5 and the costs of the specific pharmacological treatments are given in Table 6. Multivariate models did not identify any patient characteristic that were associated with nonmedication GI-related cost change in the post- versus preperiod and therefore are not presented.

Sensitivity Analyses
Among the 34 CD patients included, 11 had complications (fistula of intestine, stricture or abscess of intestine, rectum or anus). The characteristics of these patients are presented in Supplementary Table 3. Their direct medical costs (median $43,821, quartiles $36,732 to $68,646) were not higher than those for patients without these complications (median $49,184, quartiles $31,464 to $59,127) (Supplementary Table 5).

Cost analyses, assuming that all patients were given IV induction dose for the first 8 weeks of treatment with ustekinumab, showed lower total ustekinumab and total medication costs in the postperiod: $1,031,648 (median $28,882, quartiles $17,439 to $43,963) and $1,065,540 (median $29,881, quartiles $17,659 to $44,340), respectively. However, these costs remained higher than those of the preperiod.

Discussion
Our study assessed ustekinumab utilization and direct medical costs in severe, TNFi refractory CD patients at a time when no other biologic therapy was available for them and surgical management would have been their most likely alternative treatment. Our results showed that about 60% of the patients remained on ustekinumab beyond 1 year reflecting perhaps clinical response as physicians are required to present evidence of clinical improvement to renew the authorization for ustekinumab prescription (34). In another study conducted in Quebec, 81% of refractory CD patients had a clinical response and 66% were in clinical remission at 26 weeks following ustekinumab initiation (25).
As expected, an increase in the total medical cost in the post-versus preperiod was observed in our study and was mainly driven by the acquisition cost of ustekinumab; the GI-related services cost and the costs of other CD medications were generally similar between the pre- and postperiods. Of note, ustekinumab induction during the study period was accomplished through subcutaneous injections, likely leading to a suboptimal efficacy and increased costs as compared to the now available intravenous injection (29). Nonetheless, our sensitivity analyses assuming that patients were given IV induction doses in the first 8 weeks of treatment showed lower medication costs, although these remained higher in the post-versus the preperiod.

Ustekinumab is not listed for CD on the provincial drug formulary; therefore, an official reimbursement pattern regarding induction and maintenance doses and the duration of use has not been issued by RAMQ for this indication. Our study patients received a median induction dose of 90 mg × 2 in the first 4 weeks and a median maintenance dose of 90 mg per 4 weeks thereafter (quartiles 90 mg per 8 weeks and 90 mg per 3 weeks). These induction and maintenance doses were higher than those used in RCTs of CD patients (23), but somewhat similar to those reported by Canadian observational studies (24,38).

In our study, the average cost found in the preperiod ($25,884) was substantial. In that period, most patients (82%) used TNFi. TNFi treatment is expensive compared to conventional treatment with immunomodulators and corticosteroids (32). Spanish studies have reported 2.4- and 3.7-fold higher direct medical costs in CD patients in the year postinfliximab use and the year postadalimumab use as compared to the year before the use of these treatments, respectively with the increase in cost due to the high acquisition costs of the TNFi treatments (39,40). A study conducted in Manitoba also found a threefold increase in the mean direct medical cost of inflammatory bowel disease (IBD) in the year post- ($31,440) versus pre- ($9683) infliximab use with the increase in cost due to the high cost of infliximab (32). The cost of ustekinumab is higher than those of infliximab and adalimumab (34); therefore, the higher mean cost in the post- ($49,448) versus preperiod ($25,884) found in our study was expected.

Few therapeutic options exist for the treatment of TNFi refractory CD patients (12). These include the biologic agents, vedolizumab and ustekinumab (12). A review conducted by the Institut national d’excellence en santé et en services sociaux (INESSS), that provides recommendations to the Quebec Government regarding drug listing, found ustekinumab cost-effective relative to conventional treatment in TNFi refractory CD.

In Figure 1, Kaplan Meier curve displaying time to first ustekinumab discontinuation in the postperiod.
patients with an incremental cost-effectiveness ratio (ICER) of around $46,000 by one quality-adjusted life year (QALY) (41). The cost increase in our study reflects a real-life situation and is important to further inform budget allocation and treatment decision making.

The total number of ustekinumab users included in our study was low. During the study period, ustekinumab was listed on the drug formulary only for psoriasis and psoriatic arthritis treatment and, as such RAMQ preapproval was required for ustekinumab cost reimbursement in CD patients. The alternative treatment for these patients would have been surgery or additional complications for those in whom surgery was not indicated as reflected by the significantly higher direct medical cost of GI services incurred by patients who discontinued ustekinumab (14 patients, mean cost $13,541; 95% CI $5274 to $22,789) and those who did not (20 patients; mean cost $3032; 95% CI $1263 to $5192). Of note, the mean costs in the preperiod were not different ($5510; 95% CI $2041 to $10,948 and $3032; 95% CI $1263 to $5192). The population-based approach using provincial administrative databases that we adopted allowed complete tracking of the health resource utilization of interest. We were able to show a cost breakdown by medication and health services use, which allows better generalizability and comparison with similar studies conducted elsewhere.

Our study has also some limitations. First, treatment adverse events or complications were not assessed (32). Ustekinumab adverse events have not been well examined in CD patients. However, evidence derived from studies conducted in patients with psoriasis (42–44), randomized controlled trials (RCTs) and open-label observational studies in CD patients point to a safety profile of ustekinumab similar to that of placebo (24,27,28). Second, indirect CD costs could not be assessed in our study. Some authors have reported higher indirect costs of CD compared to direct medical costs (45,46); however, no study assessed indirect cost in CD refractory patients; indirect medical costs are better estimated prospectively. Third, the use of a suboptimal subcutaneous induction protocol (unavailability of intravenous induction dosing during the study period) may have led to increased ustekinumab dosing during maintenance treatment and increased cost. With the availability of intravenous ustekinumab for induction, the frequency of subcutaneous ustekinumab maintenance is likely lower than reported. Finally, our study included only very refractory CD patients registered with the provincial drug plan during a time period when ustekinumab was not yet listed for CD. Therefore, generalizability to TNFi naive individuals, those who have private drug insurance or to a more recent era should be done with care. In a U.S. study, publicly insured CD patients incurred a higher cost compared to those privately insured.

The codes used to identify CD patients from our study database do not allow identification of CD phenotype. Therefore, our study did not assess ustekinumab utilization and costs by CD phenotype. Nonetheless, patients with CD complications during the study period (pre- or postperiod ICD-9 or ICD-10 codes for fistula of intestine, stricture or abscess of intestine, rectum or anus) were identified. Our results did not show differences in ustekinumab utilization and costs between patients with complications versus those without complications, perhaps because of the small number of patients in each group.

Our study is the first to assess the CD direct medical cost from the perspective of a single payer system in TNFi refractory patients before and after ustekinumab utilization. We used a pre and postdesign to limit the possibility of indication bias. The population-based approach using provincial administrative databases that we adopted allowed complete tracking of the health resource utilization of interest. We were able to show a cost breakdown by medication and health services use, which allows better generalizability and comparison with similar studies conducted elsewhere.

Table 2. Ustekinumab use and mortality in the postperiod

| Variable                              | Value                              |
|---------------------------------------|------------------------------------|
| Number of patients                    | 34                                 |
| Number of patients who died           | 0                                  |
| Number of days of first prescription  | 26.79 (21.04)                      |
| Mean, SD                              | 269.44 (130.63)                    |
| Median (quartiles) in days            | 25.5 (8, 43)                       |
| Range in days                         | 2–71                               |
| Total number of days on ustekinumab   | 9161                               |
| Mean, SD                              | 365.00 (106.00, 365.00)            |
| Median (quartiles)                    | 294.79 (369.99)                    |
| Monthly dose over all, but the first  | 168.75 (87.10, 337.50)             |
| ustekinumab prescriptions, mean, SD   | 180.03 (329.50)                    |
| Median (quartiles)                    | 96.43 (55.10, 128.57)              |
| Patients who discontinued ustekinumab  | 14                                 |
| Crude rate of ustekinumab discontinuation per 100 person-years | 55.78 |

The variables: sex, low income, region of residency (urban or rural), socioeconomic status, complications (fistula, stricture or abscess), cancer, anemia/blood disease, corticosteroids, gastroprotective agents, antidepressants, antidiabetics and antihypertensives were not significant.

Table 3. Patients characteristics associated with ustekinumab discontinuation at 1 year: Cox regression model

| Variable                              | Hazard ratio (95% confidence interval) |
|---------------------------------------|---------------------------------------|
| Age per 5-year increase               | 0.77 (0.61, 0.96)                     |

The variables: sex, low income, region of residency (urban or rural), socioeconomic status, complications (fistula, stricture or abscess), cancer, anemia/blood disease, corticosteroids, gastroprotective agents, antidepressants, antidiabetics and antihypertensives were not significant.
However, this may not be the case in Quebec where all citizens are publicly insured for their physician visits and hospitalizations and private insurance companies have to cover at least the medications covered by RAMQ with similar reimbursement conditions (34). With the availability of both ustekinumab (intravenous induction) and vedolizumab, studies in a broader CD population are warranted to better assess health services utilization and costs.

### Table 4. Health services utilization in the pre- and postperiods

#### Medication use in the preperiod

| Medication Type                      | N (%) | N of prescriptions |
|--------------------------------------|-------|--------------------|
| 5-aminosalicylic acid                | 3 (9) | 14                 |
| Corticosteroids                      | 25 (74) | 138               |
| Immunomodulators                     | 16 (47) | 147               |
| Nonustekinumab biologic agents       | 28 (82) | 269               |

#### Outpatient physician encounters for a gastrointestinal event

| Encounter Type                          | N (%) | N of visits |
|-----------------------------------------|-------|-------------|
| Gastroenterologists                     | 31 (91) | 188         |
| Nongastroenterologist physicians        | 15 (44) | 48          |
| Emergency Department                     | 14 (41) | 48          |

#### Hospitalizations for a gastrointestinal event

| Encounter Type                          | N (%) | N of hospitalizations |
|-----------------------------------------|-------|-----------------------|
| Hospitalization for any noncolectomy GI event | 15 (44) | 26 (182 days) |
| Hospitalization for colectomy           | 0     | 0                     |

#### Medication use in the postperiod

| Medication Type                      | N (%) | N of prescriptions |
|--------------------------------------|-------|--------------------|
| 5-aminosalicylic acid                | 3 (9) | 5                  |
| Corticosteroids                      | 22 (65) | 270               |
| Immunomodulators                     | 12 (35) | 126               |
| Nonustekinumab biologic agents       | 2 (6)  | 9                  |
| Ustekinumab                           | 34 (100) | 261              |

#### Outpatient physician encounters for a gastrointestinal event

| Encounter Type                          | N (%) | N of visits |
|-----------------------------------------|-------|-------------|
| Gastroenterologists                     | 31 (91) | 141         |
| Nongastroenterologist physicians        | 16 (47) | 43          |
| Emergency Department                     | 10 (29) | 33          |

#### Hospitalizations for a gastrointestinal event

| Encounter Type                          | N (%) | N of hospitalizations |
|-----------------------------------------|-------|-----------------------|
| Hospitalization for any noncolectomy GI event | 11 (32) | 24 (247 days) |
| Hospitalization for colectomy           | 1 (3)  | 1 (29 days)          |

5-aminosalicylic acid (5-ASA): mesalamine, olsalazine and sulfasalazine.
Immunomodulators: mercaptopurine, azathioprine and methotrexate.
Biologics: TNFi (infliximab, adalimumab, golimumab and certolizumab) and natalizumab.
Corticosteroids: prednisone, hydrocortisone, budesonide, prednisolone, methylprednisolone.

(47). However, this may not be the case in Quebec where all citizens are publicly insured for their physician visits and hospitalizations and private insurance companies have to cover at least the medications covered by RAMQ with similar reimbursement conditions (34). With the availability of both ustekinumab (intravenous induction) and vedolizumab, studies in a broader CD population are warranted to better assess health services utilization and costs.
In conclusion, in severe CD patients who failed TNFi, the cost of GI services remained stable following ustekinumab use and approximately 60% of patients remained on ustekinumab treatment for greater than 1 year, suggesting its efficacy in this refractory group of patients.

**SUPPLEMENTARY DATA**

Supplementary data are available at *Journal of the Canadian Association of Gastroenterology* online.

**Supplementary Table 1.** Gastrointestinal events considered in the cost analysis

**Supplementary Table 2.** Biologic agents used by the 34 study patients

**Supplementary Table 3.** Patient characteristics at the first ustekinumab prescription date (index-date) by CD complications (fistula, strictureing or abscess)

**Supplementary Table 4.** Ustekinumab use and mortality in the postperiod by CD complications

**Supplementary Table 5.** Direct medical cost in Canadian dollars by CD complications

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Author Contributions
E.R. and W.A. contributed to all aspects of the study. They developed the study protocol and obtained financial support to conduct the analyses. E.R. acquired the data, supervised the statistical analyses and wrote the first draft of the manuscript. W.A. provided clinical expertise with respect to Crohn’s disease management and the utilization of ustekinumab in Quebec. H.N. conducted all the statistical analyses and assisted with the interpretation of data. All authors reviewed and approved the final draft of the manuscript.

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