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Isotretinoin Use and the Risk of Inflammatory Bowel Disease: A Population-Based Cohort Study

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Abstract

Limited evidence suggests that isotretinoin may be associated with inflammatory bowel disease (IBD). To explore this association, we conducted a retrospective population-based cohort study in British Columbia, Canada, among participants who were newly treated with isotretinoin or topical

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CONFLICT OF INTEREST

All authors have completed and submitted the ICMJE Form for Disclosure of Potential Conflicts of Interest. Dr Alhusayen reports receiving travel grants from the European Society for Dermatological Research (ESDR). Dr Mamdani reports receiving consultancy fees from Hoffman LaRoche Advisory Boards, GSK, Pfizer, Novartis, and EIi Lilly. Dr Shear reports receiving consultancy fees from Galderma, as well as payment for lectures and the development of educational materials from Galderma. Dr Shear also works with Roche (one of the several manufacturers of isotretinoin) regarding the use of rituximab to treat pemphigus. Advisory board activities may exist in the next year. The remaining authors state no conflict of interest.

Author contributions

All the authors contributed to the conception and the design of the study. RA drafted the study protocol. RM and CD collected the data and performed the analyses, whereas all authors contributed to the interpretation of the data. RA and DJ drafted the article. All the authors critically revised it for intellectual content and approved the final version. DJ is the guarantor and accepts responsibility for the study in its entirety.

acne medications. The entire population of untreated provincial residents aged 12–29 years served as the reference group. During the 12-year study period, we identified 46,922 participants treated with isotretinoin, 184,824 treated with a topical acne medication, and 1,526,946 untreated individuals. Compared with untreated individuals, we observed no significant association between isotretinoin use and IBD (rate ratio (RR) 1.14; 95% confidence interval (CI) 0.92–1.41). As expected, we found no association with topical acne medications (RR 1.11; 95% CI 0.99–1.24). In prespecified secondary analyses, isotretinoin was associated with IBD among individuals aged 12–19 years (RR 1.39; 95% CI 1.03–1.87) and topical acne medications were associated with ulcerative colitis (RR 1.19; 95% CI 1.00–1.42). Our primary analyses found no association between isotretinoin and IBD. In prespecified secondary analyses, some evidence was found of associations with isotretinoin as well as topical acne medications, suggesting a possible association between IBD and acne itself. Additional research is needed to explore this possibility.

INTRODUCTION

Isotretinoin is a synthetic retinoid widely used for the treatment of severe nodulocystic acne. It is considerably more effective than other therapies and can produce long-term remission (Chen *et al.*, 2002). However, isotretinoin therapy is associated with significant adverse effects including hypertriglyceridemia, xerostomia, intracranial hypertension, and severe teratogenicity (Brelsford and Beute, 2008). The association with depression and suicidal ideation remains controversial, with a recent study suggesting that the association could be with acne rather than isotretinoin (Hull and D'Arcy, 2003; Sundstrom *et al.*, 2010). More recently, some reports linked isotretinoin to inflammatory bowel disease (IBD) (Reniers and Howard, 2001).

IBD is a debilitating disease affecting young adults worldwide (Hanauer, 2006). A suspected association between isotretinoin and IBD has prompted numerous lawsuits, some of them culminating in substantial awards (Voreacos and Martin, 2010). A review of 85 cases reported to the US Food and Drug Administration determined, using the Naranjo probability scale, that in 73% of instances, the association between isotretinoin use and IBD was either probable or highly probable (Naranjo *et al.*, 1981; Reddy *et al.*, 2006). However, uncertainty remains about the association between isotretinoin and IBD. Two observational studies have offered conflicting conclusions, with one showing no association and the other showing a strong association with ulcerative colitis (UC) but not Crohn's disease (Bernstein *et al.*, 2009; Crockett *et al.*, 2010). These studies had a small number of events and failed to adjust for the use of other medications.

Several mechanisms may underlie an association between isotretinoin and IBD (Shale *et al.*, 2009). Retinoids inhibit neutrophil chemotaxis, and impaired neutrophil activity has been implicated in the pathogenesis of Crohn's disease (Norris *et al.*, 1987; Marks *et al.*, 2006). Furthermore, isotretinoin increases the expression of gut homing markers, which may promote T-cell-mediated intestinal inflammation (Kang *et al.*, 2007).

It remains unclear whether isotretinoin therapy is associated with IBD. Because case reports are rarely definitive proof of causation, and because a randomized controlled trial exploring drug-related harm is unlikely, observational studies are the best means of exploring the

potential association between isotretinoin therapy and IBD. We used the comprehensive population-based health care records of approximately 4.5 million residents of British Columbia, Canada to examine the association between isotretinoin use and the risk of developing IBD.

RESULTS

During the 12-year study period, we identified 46,922 patients treated with isotretinoin, 184,824 patients treated with a topical acne medication, and 1,526,946 untreated individuals. Because the study design allowed individuals in any group to reenter the analysis, the untreated group contributed a total of more than 9 million observations. The baseline characteristics for all groups are shown in Table 1. Compared with untreated patients, those treated with isotretinoin were less likely to have a low-income status and, as expected, were more likely to have been previously exposed to tetracyclines and erythromycin. They were also more likely to be male compared with those who received topical acne medication (54% vs. 38%, respectively), an expected finding in light of the drug's teratogenicity.

Acne therapy and incident IBD

Among patients with no history of IBD in the 5 years before index date, we identified 11,408 first medical encounters for IBD during follow-up, including 87 patients in the isotretinoin-treated cohort, 316 in the topical acne medication cohort, and 11,005 in the reference group (Tables 2 and 3). In the primary adjusted analysis, compared with untreated participants, we found no association between IBD and the use of isotretinoin (rate ratio 1.14; 95% confidence interval (CI) 0.92–1.41) or topical acne medications (rate ratio 1.11; 95% CI 0.99–1.24).

We tested the robustness of our findings in prespecified analyses according to age and disease type. Among patients aged 12–19 years, isotretinoin use was associated with a significant risk of IBD compared with no treatment (rate ratio 1.39; 95% CI 1.03–1.87), but no such association was evident in patients aged 20–29 years (rate ratio 0.93; 95% CI 0.67–1.29). A similar but nonsignificant trend was evident among young patients using topical acne medications (rate ratio 1.15; 95% CI 0.98–1.36) but not older patients (rate ratio 1.07; 95% CI 0.91–1.25). In an analysis of IBD subtype, we found no significant association between isotretinoin therapy and IBD among patients with UC (rate ratio 1.31; 95% CI 0.96–1.80) or Crohn's disease (rate ratio 1.17; 95% CI 0.90–1.52). We did find a modest but statistically significant association between topical acne medications and UC (rate ratio 1.19; 95% CI 1.00–1.42) but not Crohn's disease (rate ratio 1.07; 95% CI 0.93–1.23).

When we used a stricter definition of IBD requiring two clinical encounters or one encounter with the subsequent prescription of medications used to treat IBD, we again found no significant association between isotretinoin and IBD (rate ratio 1.14; 95% CI 0.92–1.41). However, the previously observed association between isotretinoin and IBD in younger patients was again documented in this analysis (rate ratio 1.39; 95% CI 1.03–1.87).

Hospitalization for exacerbations of IBD

Patients with a history of IBD may be particularly prone to disease exacerbations following exposure to potential triggers. Among patients with IBD, we found that those treated with isotretinoin were not at an increased risk of subsequent hospital admission for IBD (rate ratio 0.75; 95% CI 0.44–1.27) relative to untreated patients, whereas treatment with topical acne medications was associated with a significantly higher risk (rate ratio 1.38; 95% CI 1.16–1.63; Table 4).

DISCUSSION

In this population-based cohort study of nearly 50,000 isotretinoin-treated patients, we found that the isotretinoin therapy was not associated with physician visits or hospital admissions for IBD, although a weak but significant association was apparent in a prespecified analysis among subjects aged 12–19 years. However, we also found an association between topical acne medications and UC, suggesting that IBD may be associated with acne itself, rather than its treatment.

Previous research on the potential association between isotretinoin and IBD has yielded conflicting results. One negative study was limited by relatively few events, whereas a positive study did not account for medications and conditions that might be associated with IBD (Bernstein *et al.*, 2009; Crockett *et al.*, 2010). Importantly, our analysis adjusted for previous use of oral tetracyclines, which have been linked to increased risk of IBD (Margolis *et al.*, 2010). No previous study has examined the association between topical acne medications and IBD. We planned this analysis to contextualize any observed association between isotretinoin and IBD. We found that the risk of IBD during isotretinoin therapy was very similar to that seen with topical acne medications. Overall, our findings offer reassurance that isotretinoin does not confer a major increase in the risk of IBD.

We speculate that a previously unrecognized association exists between IBD and acne itself, rather than its treatment. In this context, acne could be viewed as a systemic inflammatory condition rather than an exclusively cutaneous disease. This is not an entirely novel concept —systemic involvement is well documented in acne fulminans, and case reports describe acne fulminans in the setting of IBD (McAuley and Miller, 1985; Wakabayashi *et al.*, 2011; Zaba *et al.*, 2011). Acne has also been described as an element of other systemic inflammatory syndromes (Kahn and Chamot, 1992; Lindor *et al.*, 1997). Moreover, an association between hidradenitis suppurativa and IBD has recently been suggested; and misdiagnosis of the two conditions is a possibility (van der Zee *et al.*, 2010).

In patients with a previous history of IBD, we speculate that the paradoxically lower risk of exacerbations with isotretinoin reflects the selective avoidance of isotretinoin and the preferential use of topical medications in these patients. Conversely, it may represent a genuine protective effect, perhaps on the basis of retinoid-mediated attenuation of intestinal inflammation through the activation of peroxisome proliferator-activated receptor-γ, the primary site of action of amino-salicylate drugs used for IBD (Dubuquoy *et al.*, 2002, 2006; Zouboulis, 2006).

Some limitations of our study merit emphasis. We had incomplete information regarding patient-level characteristics including family history of IBD, ethnicity, and smoking status. However, this limitation applies equally to all study groups. We used a single code for IBD as the outcome measure. Although sensitive, the specificity and positive predictive value of a single code may be low. However, our findings were replicated in a secondary analysis using a stricter definition of IBD.

In summary, we found that neither isotretinoin nor topical acne medications were associated with a statistically significant increase in the risk of IBD. However, supplementary analyses suggested associations in certain subsets of patients. In general, our findings argue against an association between isotretinoin and IBD but do suggest a possible association between IBD and acne itself, rather than its treatment. Further research is necessary to explore this possibility.

MATERIALS AND METHODS

Setting and source population

We conducted a population-based retrospective cohort study among residents of British Columbia, Canada, aged 12–29 years, between 1 January 1997 and 31 December 2008. British Columbia is Canada's third most populous province, with a population of approximately 4.5 million. This study was approved by the Clinical Research Ethics Board of the University of British Columbia, and data access was provided by the British Columbia Ministry of Health. Because we used deidentified data from existing administrative databases, individual patient consent was not required.

Data sources

We obtained prescription drug data from the British Columbia PharmaNet database, which contains a record of all outpatient prescriptions dispensed to British Columbia residents. Using encrypted unique personal health numbers, we linked these records with other comprehensive provincial physician billing claim records and hospital visits. We used the British Columbia Medical Services Plan database to extract physician billing records and the Canadian Institute for Health Information Discharge Abstract Database to identify diagnostic information regarding all acute care hospital admissions in the province. The British Columbia Medical Services Plan covers all residents of the province with the exclusion of approximately 4% of residents who are federally insured (e.g., aboriginal people, prisoners, and military).

The PharmaNet system includes all prescriptions dispensed at community pharmacies. The system performs data quality checks, and prescriptions are linked by unique personal health numbers to province-wide databases for hospitalizations and physician visits. Data on hospitalizations were obtained from the Canadian Institute for Health Information, which collects hospital data for all Canadian provinces, including Ontario where the data have been evaluated for accuracy (Williams and Young, 1996).

Study design

We conducted a retrospective cohort study involving two groups of patients treated with acne medications. The first group included participants who commenced treatment with oral isotretinoin; in this group, we anticipated an association between drug therapy and incident IBD. The second group consisted of patients who commenced a topical acne preparation (benzoyl peroxide, erythromycin, clindamycin, retinoic acid, or adapalene). We included this group of patients to contextualize any positive association between isotretinoin and IBD, anticipating no association between topical acne preparations and IBD. Treatment initiation was defined as a new prescription for a study drug with no prescriptions for the same drug in the preceding 365 days, and we defined the index date as the date on which the prescription was dispensed. As previous reports suggest that some cases of IBD could develop within days from starting isotretinoin, a minimum exposure period for inclusion in the study was not imposed (Shale *et al.*, 2009).

We restricted the analysis to patients aged 12–29 years because they represent the majority of isotretinoin recipients (Chen *et al.*, 2002). To eliminate the possibility of residual isotretinoin effect, patients were excluded from the topical acne medication group if they had received a prescription for isotretinoin in the 365 days before index date. Because a large number of patients prescribed isotretinoin also have antecedent use of topical medications, the corresponding restriction was not applied. We required that all study participants be residents of British Columbia for at least 5 years before entering the study, as determined by enrollment in the provincial Medical Services Plan.

For all analyses, the entire population of untreated British Columbia residents aged 12–29 years served as the reference group. Patients were evaluated for enrollment in the reference group on a randomly assigned calendar date for each individual. On the anniversary of this date each year, each patient was enrolled in the reference group with their anniversary date as a new index date, provided they still met the inclusion criteria at that time. Patients were excluded from the reference group if they had received a prescription for isotretinoin or a topical acne medication in the 365 days before each index date.

We observed each study participant for up to 1 year following the index date to identify outcomes of interest. We selected this approach because a review of the existing literature suggested that all cases of IBD associated with isotretinoin developed within 1 year of starting the drug (Shale *et al.*, 2009). Moreover, a course of treatment with isotretinoin typically lasts 16 weeks (Shalita *et al.*, 1983; Layton *et al.*, 1993). Therefore, this design allowed treated and untreated patients to enter the analysis more than once, either in the same cohort (as might occur with successive prescriptions for topical acne medications at intervals >1 year) or in another cohort (as might occur when untreated patients later progress to treatment, for example) with different index dates each time. Each entry was considered a discrete observation. Patients in the topical acne medication group were censored if they switched to isotretinoin (a common clinical occurrence), and patients in the reference group were censored if they commenced any acne therapy. We also censored at time of death, the end of medical services coverage, or the end of study period (31 December 2008), whichever occurred first.

Statistical analysis

The primary analysis examined the time to any clinical encounter (physician visit or hospital admission) for IBD among patients with no diagnosis of either UC or Crohn's disease (International Classification of Disease-9: 555 and 556, and International Classification of Disease-10: K50 and K51) in the 5 years before the index date. Using the Poisson regression, we adjusted for potential confounders including age, gender, and socioeconomic status (patients receiving a public subsidy for BC Medical Services Plan premiums were considered to have low-income status). We also adjusted for various aspects of medical care before cohort entry including prescriptions in the year before the index date (tetracyclines, erythromycin, oral contraceptives, or nonsteroidal antiinflammatory drugs), and any physician visit or hospital admission in 1 year before the index date for any gastrointestinal diagnosis, because these may have presaged the development of IBD. Finally, to address any potential discrepancy in access to health care, we adjusted for any physician visits in 1 year before the index date.

We conducted several prespecified secondary analyses to test the robustness of our conclusions. We first stratified by age (12–19 years and 20–29 years), reasoning that younger patients would be more likely to receive isotretinoin for acne, whereas older patients sometimes receive the drug for rosacea. We also conducted separate analyses of Crohn's disease and UC, because the diseases have different pathogeneses. Patients coded as having both diagnoses were included in both of these analyses. Finally, given the possibility that isotretinoin may exacerbate preexisting IBD, we conducted a secondary analysis of the risk of hospital admission (as opposed to any medical encounter) for IBD among patients with a history of IBD in the 5 years before the index date.

Finally, because a single encounter for IBD may not be specific, we conducted a sensitivity analysis using a stricter definition of IBD. In this analysis, we required two clinical encounters (physician claims or hospital admissions) for IBD, or one such encounter along with subsequent prescription of a drug used to treat IBD (including systemic corticosteroids, sulfasalazine and related drugs, methotrexate, azathioprine, or 6-mercaptopurine). For all analyses we used a two-tailed type 1 error rate of 0.05 as the threshold for statistical significance. All analyses were performed using SAS version 9.1.2 (SAS Institute, Cary NC).

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Abbreviations

CI	confidence interval
IBD	inflammatory bowel disease

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Table 1

Patient characteristics

	Isotretinoin	Topical acne medications	Unexposed group
Patients with no history of IBD			
Number of patients[1]	46,922	184,824	1,526,946
Number of observations	54,614	239,144	9,533,230
Age, mean (SD)	19 (4)	18 (5)	20 (5)
Female, %	46	62	48
Low-income status, %	23	25	31
Medication use, %			
Contraceptives[2]	23	20	24
Tetracyclines	48	13	2
Erythromycin	11	6	3
NSAIDs	8	8	7
Previous GI visits, %[3]	3	4	1
Previous non-GI visits, %[3]	98	94	25
Patients with history of IBD			
Number of patients[1]	326	1,518	18,088
Number of observations	349	1,791	60,454
Age, mean (SD)	21 (4)	21 (5)	23 (5)
Female, %	51	64	54
Low-income status, %	30	33	38
Medication use, %			
Contraceptives[2]	33	35	35
Tetracyclines	47	12	4
Erythromycin	10	6	5
NSAIDs	14	14	12
Previous GI visits, %[3]	46	49	44
Previous non-GI visits, %[3]	99	98	92
IBD hospitalization, %[3]	11	16	11

Abbreviations: GI, gastrointestinal; IBD, inflammatory bowel disease; NSAIDs, nonsteroidal antiinflammatory drugs.

[1]The design allowed patients to enter different cohorts at different times after lapses of at least 365 days with no relevant medications, allowing some patients to represent multiple observations. Patient characteristics in the table reflect average characteristics across all observations, including multiple observations for some patients.

[2]Among females.

[3]In 365 days before index date.

Table 2

Association between isotretinoin and IBD

	Events among isotretinoin group (*n* = 54,614)[1]	Events among unexposed group (*n* = 9,533,230)[1]	Unadjusted rate ratio (95% confidence interval)	Adjusted rate ratio (95% confidence interval)[2]
Primary outcome				
IBD	87	11,005	1.34 (1.09–1.66)	1.14 (0.92–1.41)
Subgroup analyses				
12–19 Years	50	3,318	1.80 (1.36–2.39)	1.39 (1.03–1.87)
20–29 Years	37	7,687	1.24 (0.90–1.72)	0.93 (0.67–1.29)
UC	41	4,612	1.51 (1.11–2.05)	1.31 (0.96–1.80)
Crohn's disease	60	7,263	1.40 (1.09–1.81)	1.17 (0.90–1.52)

Abbreviations: IBD, inflammatory bowel disease; UC, ulcerative colitis.

[1]The number of observations (*n*) in each group includes multiple observations for some patients, because patients were allowed to enter different cohorts at different times, or reenter the same cohort, following a period of no prescription of relevant medications for ≥365 days. There were 46,922 unique patients in the isotretinoin group and 1,526,946 in the unexposed group.

[2]Poisson regression model estimates adjusted for age; sex; socioeconomic status; receipt in the year preceding cohort entry of tetracyclines, erythromycin, oral contraceptives, or nonsteroidal antiinflammatory drugs; any physician visit or hospital admission; and any gastrointestinal diagnosis in the year preceding cohort entry.

Table 3

Association between topical acne medications and IBD

	Events among topical acne group (*n* = 239,144)[1]	Events among unexposed group (*n* = 9,533,230)[1]	Unadjusted rate ratio (95% confidence interval)	Adjusted rate ratio (95% confidence interval)[2]
Primary outcome				
IBD	316	11,005	1.14 (1.02–1.28)	1.11 (0.99–1.24)
Subgroup analyses				
12–19 Years	152	3,318	1.26 (1.07–1.48)	1.15 (0.98–1.36)
20–29 Years	164	7,687	1.35 (1.16–1.58)	1.07 (0.91–1.25)
UC	139	4,612	1.20 (1.02–1.42)	1.19 (1.00–1.42)
Crohn's disease	205	7,263	1.13 (0.98–1.29)	1.07 (0.93–1.23)

Abbreviations: IBD, inflammatory bowel disease; UC, ulcerative colitis.

[1]The number of observations (*n*) in each group includes multiple observations for some patients, because patients were allowed to enter different cohorts at different times, or reenter the same cohort, following a period of no prescription of relevant medications for ≥365 days. There were 184,824 unique patients in the topical acne medication group and 1,526,946 in the unexposed group.

[2]Poisson regression model estimates adjusted for age; sex; socioeconomic status; receipt in the year preceding cohort entry of tetracyclines, erythromycin, oral contraceptives, or nonsteroidal antiinflammatory drugs; any physician visit or hospital admission; and any gastrointestinal diagnosis in the year preceding cohort entry.

Table 4

Acne therapies and risk of hospital admission for inflammatory bowel disease in patients with a history of disease

	Events among isotretinoin group (n = 349)[1]	Events among topical acne group (n = 1,791)[1]	Events among unexposed group (n = 60,454)[1]	Unadjusted rate ratio (95% confidence interval)	Adjusted rate ratio (95% confidence interval)[2]
Isotretinoin versus unexposed	14	—	3,582	0.64 (0.38–1.09)	0.75 (0.43–1.27)
Topical acne medications versus unexposed	—	144	3,582	1.37 (1.16–1.62)	1.38 (1.16–1.63)

[1]The number of observations (n) in each group includes multiple observations for some patients, because patients were allowed to enter different cohorts at different times, or reenter the same cohort, following a period of no prescriptions for relevant medications for ≥365 days. There were 326 unique patients in the isotretinoin group, 1,518 in the topical acne medication group, and 18,088 in the unexposed group.

[2]Poisson regression model estimates adjusted for age; sex; socioeconomic status; receipt in the year preceding cohort entry of tetracyclines, erythromycin, oral contraceptives, or nonsteroidal antiinflammatory drugs; any physician visit or hospital admission; and any gastrointestinal diagnosis in the year preceding cohort entry.