

# Isotretinoin Is Not Associated With Inflammatory Bowel Disease: A Population-Based Case–Control Study

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**OBJECTIVES:** There is anecdotal evidence that isotretinoin use is associated with development of colitis. We aimed at determining whether there is an association between isotretinoin use and development of inflammatory bowel disease (IBD).

**METHODS:** The population-based University of Manitoba IBD Epidemiology Database and a control group matched by age, sex, and geographical residence were linked to the provincial prescription drug registry, a registry that was initiated in 1995. The number of users and duration of isotretinoin use were identified in both IBD cases and controls.

**RESULTS:** We found that 1.2% of IBD cases used isotretinoin before IBD diagnosis, which was statistically similar to controls (1.1% users). This was also similar to the number of IBD patients who used isotretinoin after a diagnosis of IBD (1.1%). There was no difference between isotretinoin use before Crohn's disease compared with its use before ulcerative colitis.

**CONCLUSIONS:** Patients with IBD were no more likely to have used isotretinoin before diagnosis than were sex-, age-, and geography-matched controls. Although there may be anecdotes of isotretinoin causing acute colitis, our data suggest that isotretinoin is not likely to cause chronic IBD.

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## INTRODUCTION

Inflammatory bowel disease (IBD) refers to ulcerative colitis and Crohn's disease. The etiologies of these diseases remain unknown. It is considered that persons with genetic susceptibility experience an environmental trigger that stimulates an injurious immunoinflammatory response of the gastrointestinal tract, which ultimately leads to the development of IBD. To date, progress has been made in defining certain predisposing gene mutations, but we have little more than hypotheses as to what the environmental triggers might be (1). Although some drugs may cause acute colitis, few if any have been shown to cause what is classically defined as IBD (2). IBD is thought to affect approximately 1–1.5 million Americans, and in both the United States and in Canada, the peak age of incidence is the third decade with a steady rise in incidence seen through the second decade of life (3–5).

Acne has a prevalence of 80–85% among adolescents. It persists throughout adulthood in 12% of women older than 25 years and in 3% of persons aged 35–44 years (6,7). Up to

15–30% of patients with acne need intense medical treatment, thus representing the largest patient group seen by dermatologists worldwide (6,8). Isotretinoin (13-*cis*-retinoic acid, Accutane, Hoffman La-Roche, Mississauga, Ontario) was approved in the United States in 1982 as treatment for severe recalcitrant nodulocystic acne that is unresponsive to conventional therapy including systemic antibiotics (6,9).

The most severe safety issue with regard to oral isotretinoin is teratogenicity because it is highly potent in inducing fetal abortions and malformations (6,10). Treatment with oral isotretinoin has also been associated with suicidal ideation, mood alterations, and depression. Although case reports suggested such an association, current literature has questioned whether a causative link between isotretinoin and depression exists (6,11–15). Although mucocutaneous complications are also cited as potential side effects, IBD as a toxicity has not routinely been cited by recent expert reviews (6,16). However, the package insert suggests the possibility of IBD occurring in users.

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Sporadic case reports of mostly colitis occurring during or after isotretinoin therapy have been reported (17–21). Some convincingly show an exacerbation of enteritis or colitis during isotretinoin therapy, remission of the enteritis or colitis on drug withdrawal, and relapse of enteritis or colitis on isotretinoin reintroduction (17–19). Other case reports of what seems to be definite IBD occurring during or after isotretinoin use have further raised the question as to whether these associations are coincidental or are providing an actual cause of the ensuing IBD (20,21). Another paper reported on the use of isotretinoin in four patients upon diagnosis of IBD, and only one had a flare of disease (22).

Recently, a review was compiled of the cases filed with the Food and Drug Administration through the MedWatch system between 1997 and 2002 of isotretinoin use in relation to development of colitis (23). The extent or duration of follow-up of all patients who were diagnosed with colitis during or just after isotretinoin use was not defined for most of these patients. Within this report, there were three patients who developed colitis during therapy, remitted off therapy, and relapsed with colitis with the reintroduction of isotretinoin. These are fairly convincing examples of a colitis arising from isotretinoin use. An additional 15 patients were reported to have symptom resolution with a decrease or cessation of isotretinoin therapy. The descriptions do not present any evidence that these 18 patients had developed true IBD but certainly suggest the emergence of colitis (possibly self-limited). Two other patients had IBD before using isotretinoin. This left 65 patients who were diagnosed with IBD at some time after isotretinoin use. The median age of presentation in the report of the 85 patients was 18–19 years. Although there is likely to be an underreporting of adverse events in relation to most prescription drug use, this report combined with existing case reports likely represents cumulatively < 100 patients out of the several million isotretinoin users and the 1–1.5 million patients with IBD in the United States (3,9).

We undertook a population-based case-control study to assess the likelihood that incident cases of IBD are more likely than controls to be treated with isotretinoin.

## METHODS

### Data sources

Data for this study were derived from the Manitoba Health Administrative Databases. Manitoba Health provides universal health insurance for Manitoba residents, which includes coverage for physician and hospital services. Manitoba Health maintains computerized records that are based on the use of health-care services by individuals in the province, including admissions to hospital and physician visits. For each physician service, patient's identification, date of service, diagnosis (three digit, International Classification of Diseases, 9th revision, Clinical Modification, ICD-9-CM code), and service tariff code are entered into a "physician claims" database. Similarly,

after each hospitalization, Manitoba hospitals submit an abstract to Manitoba Health, which includes patient's identification, dates of admission and discharge, details of attending physicians, and up to 16 ICD-9-CM diagnoses. These hospital separation records constitute the "hospital file". The accuracy of these administrative health data has been demonstrated for a number of medical conditions (24).

Manitoba Health also maintains a population registry that contains dates of insurance coverage, family information, and details of residence for Manitoba residents. Death reports from Manitoba Vital Statistics are routinely reviewed and used to update the population registry. Since 1984, the Manitoba Health population registry has maintained a unique personal health identification number, which is included with each physician claim record and each hospital separation record.

Earlier, we used the Manitoba Health Databases to create the University of Manitoba IBD Epidemiology Database (UMIBDED) (4). This database includes all persons with a physician claim or hospitalization for a diagnosis of Crohn's disease (ICD-9-CM code 555.xx) or ulcerative colitis (ICD-9-CM code 556.xx) since 1984. To improve the accuracy of case definition, persons resident in the province for at least 2 years were designated as having IBD only if they had at least five separate physician claims and/or hospitalizations. Persons resident in the province for less than 2 years were included in the IBD cohort if they had at least three separate physician claims and/or records. The accuracy of this case definition is high (sensitivity and specificity of approximately 90%) in comparison with both self-report and chart review (4). The specificity of 90% refers to the specificity among those with at least one physician or hospital claim for a diagnosis of Crohn's disease or ulcerative colitis. As the vast majority of the population of Manitoba (>1,000,000) has no claims for either IBD diagnosis, the specificity of our definition is actually much closer to 100% in the general population.

### Manitoba health's drug program information network

We have recently linked our University of Manitoba IBD Epidemiology Database with drug program information network to study pharmaceutical usage by IBD patients (25,26). The drug program information network Database is a population-based database that records all drugs prescribed for each resident of Manitoba registered with the provincial health-care system and has been in effect since 1995. The linkage was deterministic, using a scrambling algorithm to create a unique individual identifier on the basis of personal health identification number. Thus, for all database usage, no nominal patient information is used. Earlier, we used this linkage to produce unique and important data regarding prescription drug utilization by patients with IBD, and have assessed trends in the use of certain IBD-specific drugs as well as the relationship between 5-ASA use and the development of colorectal cancer (25,26).

### Comparison with the general population

A case-control analysis was performed, nested within an existing cohort of persons with IBD and matched population controls. All persons with IBD in the Manitoba IBD Database (see above) have been matched to 10 randomly selected population controls by age, gender, and postal area of residence. This control cohort was extracted from the population registry of Manitoba Health. Controls were also matched to cases on the basis of IBD diagnosis date in such a manner that the controls were registered and living in Manitoba on the date of the IBD diagnosis of their index IBD case. Cases and controls had equivalent Manitoba Health coverage time before that date. In previous case-control studies, using our University of Manitoba IBD Epidemiology Database, we found that person-time of coverage was not different between cases and controls going back to the mid-1980s (27). Therefore, analysis of medication use for controls was for the same time period as that for IBD cases. Data on health system contacts were obtained throughout the patients' medical histories dating back to 1984 (the time at which personal health identification numbers were in use in the Manitoba Health system) and forward to 2008 for as long as the patients (case or control) remained alive and were a resident of Manitoba.

### Study design and analysis

Only IBD cases and their controls with a case date for IBD after 1 April 1995 and who were under the age of 40 years when diagnosed were included. We chose age less than 40 years, as this would capture a substantive number of IBD patients and cover the majority of isotretinoin users. We aimed to avoid diluting the potential effect of isotretinoin use and IBD onset by excluding patients who were at a very low likelihood of using isotretinoin (those over the age of 40 years).

To assess exposure, we searched the drug program information network Database for all prescriptions for any form of oral isotretinoin, identified by DIN number, among IBD cases and controls, and assessed whether isotretinoin was used before the date of first IBD diagnosis or after. The isotretinoin compounds assessed included Accutane Roche (DIN: 00582344, 00582352), and Clarus (Mylan Pharmaceuticals ULC, Etobicoke, Ontario) (DIN: 02257955, 02257963). These correspond to ATC code D10BA01 for isotretinoin.

Odds ratios and their 95% confidence intervals were calculated for the following two situations: drug use before the diagnosis of IBD and (only for patients who were not given prescriptions before diagnosis) drug use after diagnosis. For controls, diagnosis date was the date of diagnosis for their associated case. Proportions were compared using the  $\chi^2$ -test. SAS version 9.1 (Cary, NC) function phreg was used to perform proportional hazard analysis. Predictor IBD disease conformed to the proportional assumption required by the model.

The construction of the University of Manitoba IBD Epidemiology Database and the use of it for clinical studies including this study were approved by the University of

Manitoba Research Ethics Board and by the Health Information Privacy Committee of Manitoba Health.

## RESULTS

There were 25 patients (1.2%) who received isotretinoin before their first diagnosis of IBD, and 23 patients (1.1%) who used isotretinoin after IBD diagnosis. There was a comparable number of controls who used isotretinoin (1.1 and 0.9%, respectively). There was no statistical difference in isotretinoin usage before or after IBD diagnosis between IBD cases and controls (Table 1). Only 3 of the 25 IBD patients who had prescriptions before diagnosis had prescriptions after diagnosis.

The mean number of days between the first isotretinoin prescription and initial IBD diagnosis for the 25 IBD cases who were prescribed the drug before diagnosis was 1,102.4 (s.d. 655.3) and the median number of days was 906 (range, 88–2,339). Of the 3 of the 25 patients who had prescriptions before diagnosis and also after diagnosis, their last prescriptions of isotretinoin were 41, 806, and 1,107 days after their IBD diagnosis, for each of the three cases, respectively. The time between the last prescription and diagnosis for the other 22 patients was 1,048.0 days (s.d. 632.1) and the median number of days was 1,043.5 (range, 133–2,114). Three of these patients had only one prescription for isotretinoin. Table 2 shows the number of days between the first and last prescription of isotretinoin for IBD patients.

**Table 1.** Association between the use of isotretinoin and inflammatory bowel disease (IBD) in a population-based case-control study in Manitoba, Canada, 1995–2007

Isotretinoin usage	Number (%) of cases	Number (%) of controls	Odds ratio (95% CI)
<i>Crohn's disease (n=1,118)</i>			
Before diagnosis <sup>a</sup>	14 (1.3)	120 (1.1)	1.15 (0.61–2.02)
After diagnosis	14 (1.3)	115 (1.0)	1.21 (0.64–2.12)
No use	1,090	10,801	
<i>Ulcerative colitis (n=890)</i>			
Before diagnosis <sup>a</sup>	11 (1.2)	93 (1.1)	1.16 (0.56–2.20)
After diagnosis	9 (1.0)	67 (0.8)	1.33 (0.58–2.69)
No use	870 (97.8)	8,618	
<i>All IBD (n=2,008)</i>			
Before diagnosis <sup>a</sup>	25 (1.2)	213 (1.1)	1.16 (0.73–1.77)
After diagnosis	23 (1.2)	182 (0.9)	1.25 (0.77–1.94)
No use	1,960 (97.6)	19,419 (98.0)	

<sup>a</sup>For controls, the timing of isotretinoin usage is determined by the date of diagnosis of the index IBD case. CI, confidence interval.

**Table 2.** Days between the first and last prescriptions of isotretinoin in IBD patients who used it before diagnosis

	Mean $\pm$ s.d. (days)	Median (days)	Range (days)
Crohn's disease ( $n=14$ )	276 $\pm$ 410	107.5	0–1366
Ulcerative colitis ( $n=11$ )	235 $\pm$ 334	100	10–1195

IBD, inflammatory bowel disease.

## DISCUSSION

In assessing the potential of a link between isotretinoin use and IBD, the main confounding issues are the comparable ages of onset of acne and of IBD, and hence the possibility that IBD occurring during or after isotretinoin therapy is coincidental. Furthermore, the beginning of microcomedone formation is also associated with vascular endothelial cell activation and inflammatory events, which support the hypothesis that acne may represent a genuine inflammatory disease (28). Could acne be increased in IBD as other inflammatory diseases are (29)? As acne is so common, this association would be difficult to prove (6).

If the occurrence of IBD after isotretinoin use is a coincidence, then more coincidental events might emerge, as an analysis of acne treatment over a period of 1990–2002 using the National Ambulatory Medical Care Survey found significant increases in the likelihood of treating acne with agents that do not rely on antimicrobial mechanisms such as topical retinoids and oral isotretinoin (9).

Even for mood disorders in which there is more familiarity with a possible association with isotretinoin, there is a lack of definite evidence for an association. One conclusion of a systematic review of psychiatric toxicity was that there was an overall lack of concrete scientific data on the relationship between drug and psychiatric side effects, and hence the ability to draw a conclusion regarding a causal relationship between isotretinoin and psychiatric adverse events was limited (30). When depression, a more widely accepted toxicity of isotretinoin is subject to closer scrutiny, there are greater doubts of a true association. This type of closer scrutiny with regard to isotretinoin and enterocolitis is warranted, as to date, any association has been based on sporadic case reports. In fact, even while NSAIDs have been one category of drugs that has been reportedly highly associated with IBD (3), a recent review examining the association has concluded that, although NSAIDs may cause acute colitis and may even trigger a flare of IBD, there is little evidence that NSAIDs can cause true IBD (31).

Our study is the first study to analyze the association between isotretinoin and IBD beyond a case series. We have shown that there is no greater likelihood for isotretinoin use to be followed by a diagnosis of IBD than for isotretinoin to be used after IBD is diagnosed, or in a group of matched con-

trols. Furthermore, we found that when IBD did follow after a course of isotretinoin, it occurred during the ongoing drug use in only three patients, and among the remaining 22 patients, there was a median of approximately 3 years between the last drug prescription and the first IBD diagnosis. If isotretinoin has adverse biological effects on intestinal mucosa, it is unknown what the potential lag time would be before frank colitis would manifest. It should be noted that we were not studying whether isotretinoin could cause a self-limited enterocolitis, nor were we evaluating whether it could trigger a flare of IBD once IBD is diagnosed. That isotretinoin could have an adverse effect on gastrointestinal mucosa remains possible. A limitation of our study is that it could not account for any individual idiosyncratic reaction that might lead to a true triggering of IBD by isotretinoin; however, if this occurs, it is likely to be highly uncommon. The advantage of our study is that it is population based, and hence minimizes selection bias. The negative outcome of our study underscores the need for caution when generalizing from isolated case reports. There is evidence in the literature that some cases of colitis can be triggered by isotretinoin, remitted with drug withdrawal, and re-induced with drug reintroduction. However, this is likely to be an acute self-limited colitis and not likely to be a part of the spectrum of true IBDs. Our population-based matched case-control study presents the largest study to date to examine for an association between isotretinoin use and IBD. We have shown quite clearly that it is rare for young IBD patients (less than 40 years of age) to use isotretinoin before their IBD diagnosis (1.2%), and that IBD patients were no more likely to use isotretinoin than was the general population. To conclude, it is unlikely that isotretinoin use is associated with the development of bona fide IBD.

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## CONFLICTS OF INTEREST

**Guarantor of the article:** Charles N. Bernstein, MD.

**Specific author contributions:** Charles N. Bernstein drafted the paper and Zoann Nugent assembled the case-control data set. All authors contributed to study design, analysis, and final approval of the paper.

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**Potential competing interests:** In the past year, Charles N. Bernstein has served as a consultant or on the advisory boards of Axcan Pharma, Abbott Canada, and Shire Canada, and has received research funding from UCB Canada. The other authors have no conflict of interest to declare.

## Study Highlights

### WHAT IS CURRENT KNOWLEDGE

- ✓ Isotretinoin is commonly used to treat acne, and acne commonly affects young people who are at an age when inflammatory bowel disease (IBD) can typically present itself.
- ✓ There are case reports of patients developing colitis after being treated with isotretinoin. Some of these cases resolve after discontinuing the drug with reemergence of colitis after reinitiation of the drug. These cases are convincing for a drug effect causing colitis.
- ✓ It has been suggested that isotretinoin can be a cause of IBD; however, it is unclear whether using isotretinoin can in fact lead to chronic colitis and IBD.

### WHAT IS NEW HERE

- ✓ We conducted a case-control study using our population-based database of IBD with matched controls drawn from the same population source to determine whether patients with IBD were more likely to have used isotretinoin before diagnosis than were controls.
- ✓ We found no increased likelihood in patients with IBD using isotretinoin as compared with controls. In fact, there was also a similar prevalence of isotretinoin use after diagnosis of IBD as before diagnosis (1.2%).
- ✓ We conclude that isotretinoin is not likely to be associated with development of IBD.

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