Isotretinoin and Risk for Inflammatory Bowel Disease

A Nested Case-Control Study and Meta-analysis of Published and Unpublished Data

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Objective: To examine the association between isotretinoin and the risk for inflammatory bowel disease (IBD) among women of reproductive age.

Design: Nested case-control study and meta-analysis.

Setting: A US health claims database.

Participants: We formed a cohort of women aged 18 to 46 years who had received at least 1 oral contraceptive prescription from May 1, 2001, through December 31, 2009. The IBD cases were required to have 3 health care contacts with documentation of IBD or a single health care contact followed by use of a drug to treat IBD. Twenty controls were selected for each case using incidence-density sampling, matched on age and date of diagnosis.

Main Outcome Measures: Risk ratios (RRs) were formed for incident cases of IBD associated with the use of isotretinoin. A subgroup analysis examined the risk for IBD among those diagnosed as having Crohn disease (CD) and ulcerative colitis (UC). A meta-analysis of published and unpublished studies assessing isotretinoin and IBD used a random-effects model to estimate a pooled RR.

Results: In the case-control study, we identified 2159 IBD cases (1056 with UC and 1103 with CD) and matched them with 43 180 controls. Only 10 cases (0.46%) and 191 controls (0.44%) were exposed to isotretinoin. The adjusted RR for IBD was 0.99 (95% CI, 0.52-1.90). The RRs for UC and CD were 1.10 (95% CI, 0.44-2.70) and 0.91 (0.37-2.25), respectively. For the meta-analysis, the pooled RR for IBD for the 5 studies was 0.94 (95% CI, 0.65-1.36).

Conclusions: The results of this study do not suggest an increase in the risk for IBD, including UC or CD, with use of isotretinoin. Because inflammatory acne in children and adolescents carries a high psychological burden, clinicians should not be discouraged from prescribing this drug owing to a putative association with IBD.


Isotretinoin is a popular vitamin A derivative approved for the treatment of severe recalcitrant nodulocystic acne. Recent reports of a possible link between isotretinoin and inflammatory bowel disease (IBD)\(^1\)\(^,\)\(^2\) compounded by lawsuits against the manufacturers of isotretinoin may have discouraged some dermatologists from prescribing this highly effective drug to their patients.

The main body of evidence regarding a possible link between isotretinoin and IBD is derived from 2 large epidemiologic studies.\(^1\)\(^,\)\(^2\) The first was a large case-control study from Canada that did not find a harmful association between isotretinoin and IBD.\(^3\) However, another case-control study using a large health claims database in the United States did find a harmful association between the use of isotretinoin and ulcerative colitis (UC).\(^2\)

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tibiotics, which was deemed a possible confounding variable in both studies.3

Isotretinoin remains a highly effective therapy for inflammatory acne. A potential link of the drug to IBD is one of the most important drug safety questions facing children and young adults who might benefit from the use of isotretinoin. Clinical trials are not well suited to address this question, mainly owing to the rarity of the outcome. Thus, the best evidence is likely to come from a well-conducted pharmacoepidemiologic study that can adequately control for potential confounding variables.

METHODS

CASE-CONTROL DESIGN

Data Source

We used the IMS LifeLink health plan claims database,6 which contains paid claims from 102 health care plans in the United States. The database contains fully adjudicated medical and pharmacy claims for more than 68 million patients, including inpatient and outpatient diagnoses and procedures (International Classification of Diseases, 9th Revision, Clinical Modification [ICD-9-CM]) in addition to retail and mail-order prescription records. The data are representative of US residents with private health insurance in terms of geography, age, and sex. The LifeLink database is subject to quality checks to ensure data quality and minimize error rates.6 The study was approved by the University of British Columbia Behavioral Ethics Board.

Sample Size Calculation

Using a 1-sided $\alpha$ of 0.05 and assuming a 0.05% underlying exposure to isotretinoin, we conducted a priori power analysis. We determined that we would need 1939 IBD cases to have 80% power to detect an RR of at least 2.00 for IBD.

Study Design and Cohort Formation

Isotretinoin has known fetal toxic effects, and women taking this drug for the treatment of severe recalcitrant nodular cystic acne are required by the iPledge program to demonstrate 2 forms of contraception.1 For women of childbearing age, the iPledge program requires physicians to report the form of contraception taken by the patient, and the pharmacist must confirm this in addition to verifying a negative pregnancy test result before dispensing isotretinoin.1 Because all women taking isotretinoin must demonstrate the use of 2 forms of contraception and because oral contraceptives are the most commonly used form of contraception in the United States,6 we nested our analysis in a group of women taking combined oral contraceptives (COCs).

The study time frame was May 1, 2001, through December 31, 2009. Women aged 18 to 46 years were eligible for the nested cohort after 1 year of enrollment with no claim for IBD. Women entered the cohort at their first claim for 1 of the following COCs containing no more than 0.035 mg of ethinyl estradiol and progestin: desogestrel, drospirenone, levonorgestrel, norethidrone, norethindrone acetate, norgestimate, or norgestrel. Women remained in the cohort until the development of a study outcome or an end to enrollment eligibility.

Case Definition

Our case definition was developed in IMS data6 and has been used in a previous study of isotretinoin and IBD.2 Cases were required to have 3 health care contacts with documentation of IBD (codes 555 or 556 from the ICD-9-CM) within 30 days: mesalamine, olsalazine sodium, balsalazide disodium, sulfasalazine, mercaptopurine, azathioprine sodium, infliximab, adalimumab, and enteral budesonide. These medications were selected from a prior validation analysis in IMS data, which found that less than 0.08% of patients without IBD took these medications.9 The combination of these medications with an ICD-9-CM code will provide a high specificity. Oral formulations of corticosteroids (prednisone, prednisolone, and methylprednisolone) were more commonly used by patients without IBD (15.3%).6 Including these medications in the algorithm would lead to a lower IBD specificity; thus, they were not incorporated into the algorithm. A patient was determined to have IBD on the date of meeting either of the inclusion criteria (index date). If a patient met criteria for UC and CD at the index date, we examined as many as the previous 9 diagnostic claims and recorded the patient as having the condition with the greater number of claims.

Control Definition

Twenty controls were selected for each case using density-based sampling (cases were matched to controls who were still eligible to become cases at the time of matching). Controls were matched by age ($\pm 5$ years) and index date ($\pm 6$ weeks). This method of control selection has been shown to approximate closely the odds ratio from a case-control study to an RR in a cohort study.10

Exposure Definition

Isotretinoin use was assessed as at least 1 dispensed prescription for isotretinoin regardless of the dosage during the 365 days before the first IBD claim (and in corresponding calendar time for controls). Assessing drug exposure after this claim could induce a protopathic bias whereby patients could change their behavior (drug exposure) after this early sign of IBD.

STATISTICAL ANALYSIS

Descriptive statistics were used to examine the covariate distribution between the cases and controls (Table 1). Conditional logistic regression was used to model the association between isotretinoin and IBD. The model was adjusted by disease states (asthma, chronic obstructive pulmonary disease, diabetes mellitus, hyperlipidemia, hypertension, and obesity); indications for COC use (ie, acne [all forms, including nodulocystic], polycystic ovary syndrome, premenstrual disorder, and menstrual irregularity); a claim for tobacco cessation counseling; the numbers of previous hospitalizations, emergency department visits, and office visits (during the prior year); use of drugs associated with IBD (ie, nonsteroidal anti-inflammatory drugs and antibiotics including tetracycline hydrochloride, minocycline hydrochloride, and doxycycline formulations); the number of colonoscopies in the prior year; a recent appendectomy; and the US geographic region. Covariates were defined during the year before the index date. We added a cumulative exposure term to the model assessing isotretinoin use during the year before the case index date. This term was used to evaluate the change in the RR for isotretinoin exposure and IBD among those with an additional 30 and 90 days of cumulative drug exposure compared with nonusers.
META-ANALYSIS

We conducted a meta-analysis of published and unpublished studies to capture a global effect of isotretinoin and IBD. For the meta-analysis, we searched MEDLINE and EMBASE from 2000 through May 2012 using the following terms: isotretinoin, retinoids, inflammatory bowel disease, ulcerative colitis, and Crohn disease. We also searched reference lists of retrieved articles and major gastrointestinal and dermatology journals for relevant published studies or abstracts. We selected only large epidemiologic studies that presented RRs or odds ratios and excluded case reports or case series because these cannot examine the association between isotretinoin and IBD effectively. We used the rare disease assumption and considered odds ratios to be a close approximation of RRs. We pooled each study’s odds ratio using the random-effects model, which takes into account between-study heterogeneity. Heterogeneity was assessed using the I² statistic, which measures the degree of heterogeneity between the studies ranging from 0% to 100%.

RESULTS

We identified 2159 IBD cases (1056 with UC and 1103 with CD) and matched them to 43,180 controls. Only 10 cases (0.46%) and 191 controls (0.44%) were exposed to isotretinoin. Among IBD cases exposed to isotretinoin, 5 had CD and 5 had UC. Characteristics of the cases and controls are shown in Table 1. The adjusted RR for IBD was 0.99 (95% CI, 0.52-1.90) (Table 2). The adjusted RRs for UC and CD were 1.10 (95% CI, 0.44-2.70) and 0.91 (0.37-2.25), respectively. An additional 30 (RR, 0.96 [95% CI, 0.87-1.05]) and 90 (0.87 [0.66-1.16]) days of isotretinoin therapy were not associated with increased IBD risk when we compared these subgroups with nonusers of isotretinoin. To demonstrate the potential variability in the point estimate for the subanalysis of UC and CD cases, we randomly selected a UC case exposed to isotretinoin and intentionally misclassified it as CD. The RR for UC changed from 1.10 to 0.87 (95% CI, 0.32-2.36), whereas the RR for CD changed from 0.91 to 1.11 (0.49-2.54).

For the meta-analysis, our search resulted in 3 published1,2,11 and 1 unpublished study.12 The pooled RRs did not indicate that isotretinoin confers increased risk of IBD (RR, 0.94 [95% CI, 0.65-1.36]), UC (1.61 [0.88-2.95]), or CD (0.75 [0.46-1.24]) (Table 3).

COMMENT

The results of our study and the totality of evidence from previous studies are consistent with a lack of association between isotretinoin use and IBD. The risk did not change among those with CD or UC. Our study is, to our knowledge, the first to adjust for 2 main confounders that may have led to an overestimation of the risk for CD with isotretinoin use in previous studies;2 mainly, a diagnosis of acne and use of oral tetracycline antibiotics. Because oral contraceptives are a common treatment for acne, diagnosis of acne was controlled for by the nested design with further adjustment for nodulocystic acne in

### Table 1. Characteristics of the Cases and Controls

<table>
<thead>
<tr>
<th>Patient characteristic</th>
<th>Cases (n = 2159)</th>
<th>Controls (n = 43,180)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Age, median (IQR), y</td>
<td>29 (24-34)</td>
<td>29 (24-34)</td>
</tr>
<tr>
<td>Enrollment time, median (IQR), y</td>
<td>1.43 (0.6-2.6)</td>
<td>1.43 (0.6-2.6)</td>
</tr>
</tbody>
</table>

### Table 2. Association Between Isotretinoin and Inflammatory Bowel Disease

<table>
<thead>
<tr>
<th>Disease</th>
<th>RR (95% CI)</th>
<th>Adjusted a</th>
</tr>
</thead>
<tbody>
<tr>
<td>Inflammatory bowel disease</td>
<td>1.05 (0.55-1.98)</td>
<td>0.99 (0.52-1.90)</td>
</tr>
<tr>
<td>Ulcerative colitis</td>
<td>1.07 (0.44-2.60)</td>
<td>1.10 (0.44-2.70)</td>
</tr>
<tr>
<td>Crohn disease</td>
<td>1.03 (0.42-2.50)</td>
<td>0.91 (0.37-2.25)</td>
</tr>
</tbody>
</table>

Abbreviations: COPD, chronic obstructive pulmonary disease; IQR, interquartile range; NSAIDs, nonsteroidal anti-inflammatory drugs.

a Adjusted for disease states; indications for combined oral contraceptive use; a claim for tobacco cessation counseling; the number of prior hospitalizations, emergency department visits, and office visits (during the prior year); use of drugs associated with irritable bowel syndrome; the number of colonoscopies in the prior year; a recent appendectomy; and the US geographic region (detailed in Table 1).
lished study12 have examined the association between the 4 studies was still consistent with no increase in risk in the study by Crockett et al,2 the pooled RR for CD from for IBD, UC, or CD. Despite the increase in risk for UC do not indicate that isotretinoin confers increased risks RR of all the published studies and data from this study isotretinoin and IBD. As indicated in Table 3, the pooled cohort also provides the following 2 additional advan-

gram), a reference-comparator taking COCs could pro-

COC users. Because most women using isotretinoin

treatment by means of a subgroup analysis for isotreti-

tion among the cases and

ting by COC use. Reference comparator taking COCs could provide a more homogeneous reference group. The nested cohort also includes the following 2 additional advantages: (1) acne is an indication for COC and isotreti-

the model. We also controlled for oral antibiotics, such as tetracyclines, that have been associated with IBD previously.5

At present, 3 published studies2-3,11 and 1 unpub-

lished study12 have examined the association between isotretinoin and IBD. As indicated in Table 3, the pooled RR of all the published studies and data from this study do not indicate that isotretinoin confers increased risks for IBD, UC, or CD. Despite the increase in risk for UC in the study by Crockett et al,2 the pooled RR for CD from the 4 studies was still consistent with no increase in risk (Figure).

The study by Crockett et al2 used the same database as our study to examine the risk for IBD with isotreti-

noin treatment by means of a subgroup analysis for UC and CD. The main difference between the 2 studies is that we nested our cohort in a population of COC users. Because most women using isotretinoin will also be taking COCs (based on the iPledge program), a reference comparator taking COCs could provide a more homogeneous reference group. The nested cohort also includes the following 2 additional advantages: (1) acne is an indication for COC and isotreti-

noin treatments and the nested cohort limits confound-

ing by indication and (2) COCs have been associated with IBD development, so this design limits confound-

our study and that by Crockett et al2 also differ in the matching criteria for cases and controls. Specifically, Crockett et al2 matched cases and controls by 3-month increments of enrollment time, which may have provided a less precise match on calendar time. Density sampling, as performed in this study, matches exactly on follow-up time, whereas our matching criteria also included calendar time within 6 weeks and age within 5 years. For example, if a 35-year-old woman entered the nested co-

hort on January 1, 2005, and became a case on January 1, 2007 (having exactly 730 days of follow-up), 20 controls were selected who entered the nested cohort within 6 weeks of January 1, 2005; were 30 to 40 years of age;

and were still eligible to become cases after 730 days of follow-up (the date of matching). Thus, in the study by Crockett et al,2 one cannot exclude the possibility of dif-

ferring prescribing of isotretinoin among the cases and controls. The bias may have been augmented by the lack of control for calendar time. Prescription patterns for isotretinoin in the past 10 years may have changed with the introduction of new generic formulations of the drug and reports of adverse events, including depression,13 sui-

Figure. Forest plot of studies that examined the association between isotretinoin and inflammatory bowel disease (IBD), Crohn disease (CD), and ulcerative colitis (UC). Data points indicate risk ratios (RRs); bars, 95% confidence intervals; and ellipses, not determined. *Risk ratios were pooled using a random-effects model that takes into account between-study heterogeneity.

<table>
<thead>
<tr>
<th>Source Study</th>
<th>IBD RR (95% CI)</th>
<th>CD RR (95% CI)</th>
<th>UC RR (95% CI)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Bernstein et al2 2009</td>
<td>1.16 (0.73-1.77)</td>
<td>1.15 (0.61-2.02)</td>
<td>1.16 (0.56-2.20)</td>
</tr>
<tr>
<td>Crockett et al2 2010</td>
<td>1.68 (0.98-2.66)</td>
<td>0.68 (0.28-1.68)</td>
<td>4.36 (1.97-9.66)</td>
</tr>
<tr>
<td>Present study</td>
<td>0.99 (0.52-1.90)</td>
<td>0.91 (0.37-2.25)</td>
<td>1.10 (0.44-2.70)</td>
</tr>
<tr>
<td>Etminan and Delaney,12 2012</td>
<td>0.62 (0.42-0.88)</td>
<td>NC</td>
<td>NC</td>
</tr>
<tr>
<td>Pooled RR</td>
<td>0.94 (0.65-1.36)</td>
<td>0.75 (0.46-1.24)</td>
<td>1.61 (0.88-2.95)</td>
</tr>
</tbody>
</table>

Table 3. Characteristics of 5 Published Case-Control Studies of Isotretinoin and Inflammatory Bowel Disease

Abbreviations: NC, not conducted; RR, risk ratio.

Risk ratios were pooled using a random-effects model that takes into account between-study heterogeneity.

a 2 = 40%.

b 2 = 67%.

c 2 = 63%.

Source Population Exposure Case/Controls, % Inflammatory Bowel Disease Crohn Disease Ulcerative Colitis
Bernstein et al,3 2009 Residents of Manitoba, Canada 1.3/1.1 1.16 (0.73-1.77) 1.15 (0.61-2.02) 1.16 (0.56-2.20)
Crockett et al,2 2010 US health claims database 0.29/0.012 1.68 (0.98-2.66) 0.68 (0.28-1.68) 4.36 (1.97-9.66)
Present study US women using oral contraceptives 0.46/0.44 0.99 (0.52-1.90) 0.91 (0.37-2.25) 1.10 (0.44-2.70)
Etminan and Delaney,12 2012 US residents with private health plan 0.62 (0.42-0.88) NC NC
Racine et al,11 2012 French national health insurance 0.4/0.5 0.68 (0.41-1.10) 0.40 (0.19-0.85) 1.29 (0.68-2.44)
Pooled risk ratioa 0.94 (0.65-1.36) 0.75 (0.46-1.24) 1.61 (0.88-2.95)
cid1, 13 and IBD. 1 Thus, calendar time may act as a possible confounder because it may be associated with isotretinoin prescription and onset of IBD. Calendar time bias has been implicated as a reason for harmful associations with prescription drugs, including the increase in the risk for CD secondary to antibiotic use. 14

As with all pharmacoepidemiologic studies, our study is subject to limitations. Owing to the nature of the study cohort, the results of our study are only generalizable to young women taking COCs. Given that IBD affects the same number of men and women, we do not believe that the risk for IBD associated with isotretinoin may differ among men or any other population. We could not control for all risk factors, including ethnicity, smoking, diet, or family history of IBD. However, not all these variables are potentially strong confounders because clinicians are unlikely to prescribe isotretinoin differentially to their patients on the basis of ethnicity, smoking, or diet.

The results of this study are consistent with other published studies that do not suggest an increase in the risk for IBD with isotretinoin use. Given the high burden of psychological stress associated with cystic acne in adolescents and young adults, 15,16 clinicians should not be discouraged from prescribing isotretinoin therapy to their patients owing to concerns of an unproven association with IBD.

Accepted for Publication: September 10, 2012.

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Author Contributions: Drs Etminan, Bird, and Bressler had full access to all the data in the study and take responsibility for the integrity of the data and the accuracy of the data analysis. Study concept and design: Etminan, Bird, Delaney, and Bressler. Acquisition of data: Etminan and Brophy. Analysis and interpretation of data: Etminan, Bird, Delaney, and Bressler. Drafting of the manuscript: Etminan and Bird. Critical revision of the manuscript for important intellectual content: Etminan, Bird, Delaney, Bressler, and Brophy. Statistical analysis: Etminan, Bird, and Brophy. Administrative, technical, or material support: Etminan and Brophy. Study supervision: Etminan and Bressler.

Conflict of Interest Disclosures: Dr Bird is employed by the Food and Drug Administration (FDA).

Disclaimer: This study represents the views of the authors and not those of the FDA.

REFERENCES