Alleged isotretinoin-associated inflammatory bowel disease: Disproportionate reporting by attorneys to the Food and Drug Administration Adverse Event Reporting System

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Background: Some studies have purported to link isotretinoin prescribed for acne with the development of inflammatory bowel disease (IBD).

Objective: We sought to identify existence of disproportionate attorney-initiated reporting of isotretinoin-associated IBD in the Food and Drug Administration Adverse Event Reporting System (FAERS).

Methods: A total of 3,338,835 cases (2003-2011) were downloaded from the FAERS. These were queried for IBD cases reported with isotretinoin for a usage indication of acne while recording reporter category. Trends were analyzed over time for reports by attorneys for all medications compared with reports of IBD with isotretinoin. Signal inflation factor was calculated to determine the distortion of pharmacovigilance signals for IBD with isotretinoin.

Results: There were 2214 cases of IBD resulting from isotretinoin. Attorneys reported 1944 (87.8%) cases whereas physicians reported 132 (6.0%) and consumers reported 112 (5.1%) cases (P value $< .01$). For the entire FAERS, only 87,905 of the total 2,451,314 (3.6%) reports for all drug reactions during the same time period were reported by attorneys (P value $< .01$). The signal inflation factor for IBD with isotretinoin for attorney-initiated reports was 5.82, signifying a clear distortion.

Limitations: The accuracy of reports was not ascertained.

Conclusions: Attorney-initiated reports inflate the pharmacovigilance signal of isotretinoin-associated IBD in the FAERS. (J Am Acad Dermatol 2013;69:393-8.)

Key words: acne vulgaris; acne vulgaris/drug therapy; dermatologic agents/adverse effects; inflammatory bowel diseases; inflammatory bowel diseases/chemically induced; isotretinoin; postmarketing; product surveillance.

Isotretinoin (13-*cis*-retinoic acid) is considered to be a safe and effective treatment for acne.[1,2] However, in 2006, Reddy et al[3] suggested a possible relationship between isotretinoin and inflammatory bowel disease (IBD).[3] In their review of the Food and Drug Administration (FDA) Adverse Event Reporting System (FAERS), 4 cases were found

Abbreviations used:

FAERS:	Food and Drug Administration Adverse Event Reporting System
FDA:	Food and Drug Administration
IBD:	inflammatory bowel disease
VAERS:	Vaccine Adverse Event Reporting System

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to be "highly probable" and 58 cases "probable" for drug-induced IBD using the Naranjo Scale.[3] On the other hand, a case-control study in the University of Manitoba IBD epidemiology database failed to show an association between exposure to isotretinoin and the subsequent development of IBD.[4]

FAERS and the vaccine counterpart, Vaccine Adverse Event Reporting System (VAERS), are not immune to potential pitfalls. The issue of increased reporting of clinically significant adverse events in the VAERS has been studied by Goodman and Nordin.[5] They determined that there was an excess of attorney reporting of adverse event terms related to pending litigation. The effect of this reporting was inflation of vaccination-related adverse event reports.[5] The reporting of cases and their associated signals is of the utmost importance for unbiased and accurate identification of drug side effects and for estimating the likelihood of these negative outcomes. However, the inflation of adverse event reports, especially those related to pending litigation, can produce distorted or false signals,[6] such as vaccines being linked to autism.[5]

Similarly, in the FAERS, an excess of attorney-initiated reports for neurologic adverse events including tardive dyskinesia was reported after the issuance of a black box warning for these events with metoclopramide. This was associated with a distortion in the pharmacovigilance signal for these events.[7] We hypothesized that the pharmacovigilance signals and signal strength of drug-induced IBD secondary to isotretinoin exposure may be similarly distorted because of disproportionate reporting by attorneys to the FAERS.

CAPSULE SUMMARY

- Isotretinoin has been linked to inflammatory bowel disease, but the literature is unclear.
- Attorneys have submitted a disproportionate number of isotretinoin-associated inflammatory bowel disease cases to the Food and Drug Administration.
- Avoiding use of isotretinoin for fear of inducing inflammatory bowel disease should be reconsidered.

METHODS

The FAERS database is freely available from the FDA and is used for postmarketing surveillance of all FDA-approved drugs. Reports to the FDA are filed voluntarily by physicians, pharmacists, other health care professionals, consumers, and attorneys.

All reports were downloaded from the FDA for the period between January 2003 until the end of December 2011[8] and imported into software (SPSS 20, IBM Corp, Armonk, NY). A total of 3,338,835 individual safety reports of adverse events were identified and analyzed.

A search was conducted for cases of IBD reported with the drug isotretinoin as primary suspect with the usage indication of acne. The process of selecting cases can be seen in Fig 1. The *Medical Dictionary for Regulatory Activities* was first used to identify the following acne indications within the FAERS database: "acne," "acne aggravated," "acne bromata," "acne comedonal," "acne conglobata," "acne conglobate," "acne cosmetica," "acne cystic," "acne detergicans," "acne excoriee," "acne follicular," "acne follicular papular pustularetc," "acne fulminans," "acne infantile," "acne keloid," "acne keloidalis nuchae," "acne medicamentosa," "acne neonatorum," "acne nos," "acne occupational," "acne papular," "acne pustular," "acne rosacea," "acne scars," "acne steroid," "acne steroid-induced," "acne varioliformis," "acne vulgaris," "acneiform dermatitis," "acneiform eruption," "acnes," "chloracne," "comedone," "cystic acne," "dermatitis acneiform," "exacerbation of acne," "infantile acne," "iodo acne," "mechanical acne," "oil acne," "other acne," "pustular acne," "pyogenic sterile arthritis pyoderma gangrenosum and acne syndrome," "rash acneform," "rash acneiform," "SAPHO syndrome," and "steroid acne." Other unapproved indications were excluded as some indications have been shown to be independently associated with IBD.[9]

This restricted data set was then queried for cases where the drug implicated as primary suspect was isotretinoin or one of its trade names. Finally, the only cases selected were those that had a reaction term reported indicating IBD as defined by the *Medical Dictionary for Regulatory Activities*: "colitis ulcerative," "colitis ulcerative aggravated," "proctitis ulcerative," "Crohn's disease," "Crohn's disease aggravated," "inflammatory bowel disease," and "inflammatory bowel disease nos." In addition, 2 levels of safety checks to avoid duplication were used. Duplicate reports were first eliminated using individual safety report numbers, the unique identification number given to each FAERS report and linking multiple data files. However, multiple reports may be filed with different individual safety report numbers under the same case number. Hence, as a second step, we further eliminated duplicate reports, by eliminating duplicate case numbers. A hierarchy was also decided upon, a priori, ranking the reporter