Editorial

Inflammatory Information

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On February 16, Roche Holding AG was ordered by a New Jersey jury to pay $25.16 million in damages to a former user of isotretinoin (Accutane®) who blamed the acne medicine for inflammatory bowel disease (IBD) (*McCarrell v Hoffmann LaRoche, Inc,* L-1951-03 [NJ Super Ct 2010]).[1] The plaintiff won the verdict at a retrial in Atlantic City, which was ordered after an appeals court overturned a $2.62 million award in May 2007. The verdict was the largest of 6 for isotretinoin users who won awards totaling $56 million. In each case, plaintiffs claimed Roche Holding AG failed to adequately warn patients of the risks.[1]

After all of the obstacles we have overcome in our struggle to hold onto this valuable drug, this ruling is certainly an unwelcome development, especially in light of the fact that studies have failed to consistently demonstrate a causal association between isotretinoin and IBD. Crockett at al[2] critically evaluated the literature to assess if there is a causal relationship. They systematically searched for case reports, case series, and clinical trials evaluating this association, and then applied the Hill criteria to determine causality. Twelve case reports and 1 case series discussed an association between isotretinoin use and subsequent development of IBD. Cases occurred in 7 countries over 23 years and varied with respect to the following parameters: isotretinoin dose, duration of treatment before development of disease, development of disease while on or off medication, and clinical presentation of disease. Per their analysis, an estimated 59 coincident cases of IBD would be expected in isotretinoin users each year, assuming there was no increased risk. The authors concluded that current evidence is insufficient to confirm or refute a causal association between isotretinoin and IBD.[2]

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Bernstein et al[3] also sought to determine if there is an association between isotretinoin use and development of IBD. 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 that was established in 1995. The number of users and duration of isotretinoin use were assessed in both IBD cases and controls. The authors found that 1.2% of IBD cases involved isotretinoin use before IBD diagnosis, which was statistically similar to controls (1.1% users). This rate also was similar to patients with IBD who used isotretinoin after a diagnosis of IBD (1.1%). There was no difference between medication use before Crohn disease (CD) compared to its use before ulcerative colitis (UC). The authors concluded that patients with IBD were no more likely to have used isotretinoin before diagnosis than were sex-, age-, and geography-matched controls.[3]

Crockett et al[4] performed a case-control study using a large insurance claims database. Cases of IBD were identified and matched to 3 controls on the basis of age, gender, geographical region, health plan, and length of enrollment. Isotretinoin exposure was assessed over 12 months before case ascertainment. The study population consisted of 8189 cases and 21,832 controls. A total of 60 participants (24 cases and 36 controls) were exposed to isotretinoin. The researchers found that UC was strongly associated with prior isotretinoin exposure (odds ratio [OR], 4.36; 95% confidence interval [CI], 1.97-9.66). However, they found no association between isotretinoin and CD (OR, 0.68; 95% CI, 0.28-1.68). The study also noted the impact of dose and duration of therapy. Increasing the dose of isotretinoin was associated with elevated risk for UC (OR per 20 mg increase in dose, 1.50; 95% CI, 1.08-2.09). Compared with participants not taking isotretinoin, the risk for UC was highest in those taking medication for more than 2 months (OR, 5.63; 95% CI, 2.10-15.03). They concluded that UC but not CD is associated with prior isotretinoin exposure, with a higher dose of isotretinoin

augmenting this risk. Although the absolute risk for developing UC after taking isotretinoin is probably very small, clinicians prescribing isotretinoin as well as prospective patients should be aware of this potential association.[4]

The data, although conflicting, do present us with issues to consider. While no definitive association between isotretinoin and IBD has been established, we still must allow for the potential association and counsel our patients accordingly. We also will have to see if the data and legal issues will necessitate changes to the package insert or the informed consent process. In any case, this issue certainly should be discussed proactively with prospective isotretinoin candidates.

REFERENCES

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