

# Vitamin A: History, Current Uses, and Controversies

M. Shane Chapman, MD

Vitamin A is required for the proper functioning of many important metabolic and physiologic activities, including vision, gene transcription, the immune system and skin cell differentiation. Both excessive and deficient levels of vitamin A lead to poor functioning of many human systems. The biologically active form, retinoic acid, binds to nuclear receptors that facilitate transcription that ultimately leads to its physiological effects. Retinoids are derivatives of vitamin A that are medications used to treat acne vulgaris, psoriasis, ichthyosis (and other disorders of keratinization), skin cancer prevention as well as several bone marrow derived neoplasias. Systemic retinoids are teratogenic and have to be prescribed with caution and close oversight. Other potential adverse events are controversial. These include the relationship of retinoid derivatives in sunscreens, their effects on bone mineral density, depression and suicidal ideation and inflammatory bowel disease. These controversies will be discussed in detail.

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Vitamin A is a fat-soluble vitamin that is required for the proper functioning of a diverse array of metabolic and physiologic activities. Vision, hematopoiesis, embryonic development, skin cell differentiation, immune system function, and gene transcription all require vitamin A.

Vitamin A was first discovered around 1906 and first synthesized in 1947. The common structural thread in vitamin A is its  $\beta$ -ionone ring and isoprenoid chain. All vitamin A activity is linked to these 2 structural features. In food, vitamin A is found in 2 main forms, retinols and carotenoids. Both of these entities can be considered as vitamin A.

Retinol is a yellow fat-soluble form of vitamin A that is found most commonly in animal food sources. It is a relatively unstable substance and needs to be stored in the retinyl ester form in tissues. It is found in the highest concentrations in the liver. Retinol is converted to retinal (retinaldehyde) via retinyl esters. It is the form of vitamin A that is essential for vision. It is needed in the retina in the form of light-absorbing

molecules, retinal, for both low-light- and color vision. Retinol is also converted to retinoic acid, which is a hormone-like growth factor important for epithelial cell growth and differentiation. It is required for skin and bone health, but in this form, it has no visual function.

Carotenoids are organic hydrocarbon-based pigments naturally occurring in plants, some bacteria, and algae. These pigments are the primary yellow colors we see in nature, including fruits, vegetables, and the fall foliage of deciduous trees. There are 2 types of carotenoids: xanthophylls (oxygen containing) and carotenes (without oxygen). The carotenes are vitamin A-related substances produced by plants but cannot be synthesized by animals. Carotene is a yellow-orange pigment, which is photosynthetic and found in many fruits and vegetables. Carotene is the primary reason human fat has a yellow-orange color. There are several forms of the carotenes but only 4 forms—alpha, beta, gamma, and  $\beta$ -cryptoxanthin—have vitamin A activity in humans. The alpha and beta forms are the 2 primary forms found in plants.

$\beta$ -carotene is probably the best-known carotenoid. It is the red-orange pigment found in many fruits, vegetables, and green leafy plants. The more orange the color of the fruit or vegetable (carrots, sweet potatoes, pumpkin), the more  $\beta$ -carotene is present. It is primarily absorbed in the duodenal portion of the small intestine. Absorption is dependent on whether the food is cooked or raw, on the intake of fat, and on the presence of oils at the time of absorption. Besides enhancement of vision and other metabolic human functions, carotenes also have antioxidant properties.

Section of Dermatology, Department of Surgery, Dartmouth-Hitchcock Medical Center, Lebanon, NH; Dartmouth Medical School, Hanover, NH.

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Address reprint requests to M. Shane Chapman, MD, Section of Dermatology, Department of Surgery, Dartmouth-Hitchcock Medical Center, Lebanon, NH 03756. E-mail: Michael.Shane.Chapman@hitchcock.org

Retinoids are geometric isomers and chemically related derivatives of vitamin A. They are required for normal metabolic functioning and can be used for a variety of medicinal purposes as well. They are primarily used to help regulate epithelial cell growth and differentiation. In clinical practice, retinoids are primarily used to treat teenage acne and psoriasis, but a growing body of evidence is proving their use in treating many internal malignancies and preventing skin cancer.<sup>1-5</sup>

## Vitamin A Metabolism and Retinoid Function

Retinol is absorbed in the small intestine, incorporated into the liver in the ester form, and stored in the hepatocytes. When needed, it is de-esterified, attaches to retinol-binding protein, and is transported to the appropriate tissue. It is then moved intracellularly via cellular retinoic acid-binding protein. From there, retinol can be transformed into retinyl esters, retinal, and retinoic acid.

$\beta$ -carotene is the most efficient carotenoid to be converted into vitamin A. The retinyl esters of carotenes that are absorbed are converted to retinol, which is then stored in the liver and transported by being bound to retinol-binding protein and transthyretin.

Retinoid acid (all-trans retinoic acid, tretinoin) is the biologically active form of vitamin A that ultimately binds to nuclear receptors and facilitates transcription. Intracellularly, retinoic acid is found in all-trans and in 9-cis configurations. All-trans retinoic acid is the predominant form and is the active ligand that binds to the known retinoid receptors. These receptors are found in 2 similar groups—retinoic acid receptors and retinoid X receptors—and belong to a superfamily of nuclear receptors that act as transcription factors, which promote the physiologic effects on DNA transcription.

These binding properties and transcriptional actions on the nucleus are responsible for the antiproliferative and antiinflammatory effects of the retinoids. There may also be some relationship between the expression of these retinoid receptors and activation of toll-like receptors.<sup>6,7</sup>

## Recommended Daily Intake and Sources of Vitamin A

Infants should receive 400-600  $\mu\text{g}/\text{d}$  up to 12 months, and about 600-800  $\mu\text{g}/\text{d}$  for children up to 8 years old. An adequate intake for adult men is 900  $\mu\text{g}/\text{d}$  and 800  $\mu\text{g}/\text{d}$  for women, with an upper limit of 3000  $\mu\text{g}/\text{d}$ .

Women should be cautious about excessive vitamin A intake when pregnant because of the potential teratogenic effects. An adequate level of intake of vitamin A during pregnancy is approximately 700  $\mu\text{g}/\text{d}$  and should not exceed 3000  $\mu\text{g}/\text{d}$ .

There are many natural sources of vitamin A. Carrots, which are perhaps the best known and most consumed form of vitamin A, contain about 93% of the recommended daily average of  $\beta$ -carotene per 100 g. Liver, from many animal sources (including cod liver), contains the most vitamin A per gram. Broccoli leaf, sweet potato, spinach, pumpkin, col-

lard greens, and cantaloupe are also efficient food sources of vitamin A.

It is difficult to measure how much carotene in the diet is converted into retinol. Roughly, 1  $\mu\text{g}$  of  $\beta$ -carotene is equivalent to a 0.5  $\mu\text{g}$  of retinol. Only one-twelfth of  $\beta$ -carotene in the regular diet is equivalent to retinol.

Vitamin A absorption is also affected by the lipid content of the food. There is a higher absorption rate with high lipid content in the food. Although fruits and vegetables are still a good source of vitamin A, there is more retinol and  $\beta$ -carotene in many available oils and supplements.

## Hypervitaminosis A

Too much vitamin A is not a good thing. Excessive intake can lead to a variety of health issues, including nausea, vomiting, anorexia, headaches, blurry vision, hair loss, muscle weakness, and altered mentation. Long-term results of increased vitamin A levels lead to anemia, weight loss, and bone fractures in addition to all the other symptoms mentioned. These signs and symptoms can also be observed with synthetic retinoids. Pseudotumor cerebri is a unique syndrome of headache, blurred vision, confusion, and increased intracranial pressure and can occur at appropriate doses of isotretinoin and other systemic retinoids.

Over a long period, high levels of vitamin A have been associated with osteoporosis and an increase in hip fractures. Vitamin A may compete with the same receptor as vitamin D, and thus lead to a decrease in bone mineral density.

The toxic effects of vitamin A and its derivatives on a developing fetus are well established and will be discussed in more detail later in the text. Fetal cephalic neural cell activity is particularly susceptible to vitamin A toxicity and can occur with excessive intake of synthetic retinoids, supplements, and foods high in vitamin A, such as liver. Excessive  $\beta$ -carotene does not seem to have similar teratogenic effects, but can cause a yellow-orange dyschromia of the skin, especially to the palms and soles.

## Vitamin A Deficiency

Deficiency of vitamin A is a significant problem in young children in developing nations around the world. An estimated 500,000 children under 5 years of age die each year because of vitamin A deficiency and more than 250,000 children become blind.<sup>8</sup> Asia and Africa have the highest incidence. Primary vitamin A deficiency occurs from poor dietary intake and early weaning from breast milk. Secondary deficiency occurs from malabsorption of lipids and zinc, which is necessary for vitamin A uptake. Excessive alcohol intake can also lead to inhibition of proper vitamin A functioning.

An early manifestation of vitamin A deficiency is reduced vision in low light or “night blindness.” Continued deficiency results in dryness of the conjunctiva and increased keratinization of the ocular mucosa. Keratomalacia, or destruction and scarring of the corneal surface, eventually leads to total blindness. Vitamin A deficiency also leads to poor or im-

paired immunity and an increase in common infections. Improvement in vitamin A and zinc uptake has been shown to reduce malaria<sup>9</sup> and decrease the mortality rate in measles.<sup>10</sup>

## Synthetic Vitamin A Derivatives: The Retinoids

Retinoids, synthetic isomers of vitamin A, are used as medications for a broad array of diseases and regulation of gene function. Each retinoid has a unique pharmacologic and physiologic effect, but they also have some common characteristics. All topical retinoids tend to cause xerosis, irritation, erythema, and desquamation. The desquamation corresponds to the hyperproliferative response and increased cell turnover of the epidermal keratinocytes. For all systemic retinoids, absorption is enhanced when taken with food, especially lipid-rich meals. Cheilitis, mucosal dryness, pseudotumor cerebri, and photosensitivity are part of the systemic retinoid side effect profile. Hypertriglyceridemia is also common to all. There are some uncommon and unique potential side effects of some of the retinoids, such as hypothyroidism, leukopenia, and agranulocytosis. Teratogenicity is by far the most troublesome, but preventable, adverse event that can occur with systemic retinoids.

The **first-generation** retinoids include 2 monoaromatic forms: tretinoin and isotretinoin. Tretinoin is the all-trans retinoic acid form of vitamin A and commonly used for the treatment of acne vulgaris. It has many branded names for its cream and gel forms, including Retin-A, Renova, Refissa, Atralin, and Avita. Topical tretinoin is also used to reduce rhytids and photoaging. An oral form of the drug is available for the treatment of acute promyelocytic leukemia in combination with other chemotherapeutic agents.

Isotretinoin (13-cis-retinoic acid) is a naturally occurring retinoid that results from the metabolism of retinol and is found in small amounts in the body. Isotretinoin was first synthesized in 1955. It was a proposed treatment for psoriasis, but its use was abandoned because of its mediocre effects. It was later rediscovered as an effective treatment for lamellar ichthyosis. Isotretinoin's primary use has been to treat severe cystic scarring acne in teenagers. Isotretinoin has also been beneficially used for the treatment of hidradenitis suppurativa (HS), Darier's disease, granulomatous rosacea, and several of the congenital ichthyoses. It also has been used to treat various bone marrow cancers and neuroblastoma.

Isotretinoin is so effective that it can be life changing for some patients and reduce or prevent adulthood scarring for almost all patients who complete a full course. It was first approved, prescribed, and marketed under the trade name Accutane (Basal, Switzerland) by Hoffman-La Roche for severe cystic, scarring acne vulgaris in 1982. More than 13 million patients with severe acne have been treated worldwide. After its patent expired and generic variations increased, Accutane's market share was significantly reduced, which led to cessation of its production in 2009. Other generic brands of isotretinoin are available and include Claravis, Sotret, Amnesteem, and Decutan to name a few.

**Second-generation** retinoids include alitretinoin, etretinate, and acitretin. Alitretinoin (9-cis-retinoic acid) is a potent topical retinoid approved for use in AIDS-related Kaposi's sarcoma. It also has been used as a hand eczema treatment with moderate success. Acitretin (Soriatane) is an oral retinoid used mostly to treat psoriasis. It is a metabolite of etretinate, which was used as a psoriasis treatment before acitretin was available. Etretinate (Tegison) has a long 120-day half-life (compared with acitretin, 2 days), making dosing difficult. Acitretin can be reverse metabolized by alcohol, into etretinate, thus limiting the use of alcohol in patients on the drug. There is a 3-year recommendation of pregnancy avoidance in women and advice against giving blood for at least 3 years in women and men who take the drug. In addition to psoriasis and ichthyosis, acitretin has also been shown to be effective in reducing skin cancer, especially squamous cell carcinoma, in solid organ transplant patients.<sup>11,12</sup>

The **third-generation** retinoids are polyaromatic (arotinoids): adapalene, tazarotene, and bexarotene. Adapalene is prescribed for mild to moderate acne. It was approved under the trade name Differin in 1996. It is used as a cream and a gel. Its increased value above other topical retinoids is that it enhances the effectiveness of topical clindamycin and retains its efficacy when applied with benzoyl peroxide.<sup>13</sup> Tazarotene is a topical retinoid cream and gel prescribed for acne, psoriasis, and photodamage. Trade names for tazarotene include Tazorac, Avage, and Zorac. Its use on the face is limited by the excessive dryness and irritation it causes. Bexarotene is marketed under the trade name Targretin and is available as both oral capsule and topical gel. Targreti is a retinoid X receptor-selective antimetabolite approved for the treatment of cutaneous T-cell lymphoma. In the oral form, it also has a beneficial effect on Kaposi's sarcoma, lung cancer, and breast cancer.

## Controversies: Sunscreen

Retinoids do not offer any ultraviolet blocking or protection but have been used in sunscreens as antioxidants, with some likely beneficial effect on free radical scavenging, but not without controversy. Retinyl palmitate is an ester of retinol. It is used as a vitamin supplement and sometimes added to low-fat milk. It is also believed to have antioxidant properties and therefore is included in some sunscreens to reduce the risk of skin cancer. It is neither an active sunscreen nor a sunscreen preservative.

In 2010, the Environmental Working Group published a "manuscript" suggesting that retinyl palmitate "could pose a cancer risk." The Environmental Working Group based its statements on its interpretation of data from the National Toxicology Program, a federal research agency. The group's studies showed that mice (laboratory animals) coated in vitamin A-laced cream, when exposed to 9 minutes of maximum intensity sunlight each day, showed accelerated tumor growth compared with controls.<sup>14</sup> Unfortunately, the media and others implicated all sunscreens as potential carcinogens. The situation was further exacerbated when New York Sen-

ator Charles Shumer stated that “your sunscreen may give you cancer.”

The Food and Drug Administration later released a statement suggesting that a solvent used in the cream applied to some of the mice might itself be carcinogenic, but has not released further statement on this issue.

In a critical analysis on the subject, Lim and colleagues<sup>15</sup> published a concise clarification on the issue regarding retinyl palmitate and sunscreen. To date, there have been no human studies on the potential of retinyl palmitate or the other retinoids to cause cancer. In fact, oral retinoids have clearly been successful at reducing cutaneous squamous cell carcinoma and various bone marrow-derived cancers. They concluded that, based on the current available data from *in vitro*, animal, and human studies, there is no convincing evidence to support the notion that retinyl palmitate in sunscreens causes cancer. One may choose to use sunscreens that do not contain retinyl palmitate, but it is untrue that all sunscreens may be harmful. Further study is required.

Most of the dermatology community believes that sunscreens are not only safe but also essential in reducing sunburns and skin cancer risk.

## Controversies: Bone Metabolism

Because vitamin A can compete with vitamin D receptors, there have been concerns regarding its effect on the bone metabolism since its approval. It is well accepted that long-term use of systemic retinoids in young patients with ichthyosis and other chronic conditions, such as psoriasis, may cause premature epiphyseal plate closure. It remains somewhat controversial as to whether bone density is affected by a 20-week course of isotretinoin for acne. Some studies have shown up to a 4.4% decrease in bone density at Ward's triangle.<sup>16</sup> However, there are no follow-up data available to assess if the loss of bone density improves or recovers once the medication is stopped. Others point out that Ward's triangle should not be used to assess osteoporosis, and that spinal and femoral neck bone densities are not reduced with isotretinoin.

More recent studies are more reassuring. Erdogan et al<sup>17</sup> showed that a single 20-week course of isotretinoin does not impair bone turnover and bone mineral density. Even if bone density is affected, the fracture rate may be a more relevant marker for adverse effects of retinoids on bone. A large Danish registry of more than 124,000 patients showed that vitamin A analogs were not associated with the risk of bone fracture.<sup>18,19</sup>

The mounting evidence is that isotretinoin is probably safe and does not affect bone mineral density enough to cause fractures when used over short 20-week courses for acne vulgaris. When retinoids are used at higher doses over longer periods for chronic diseases, such as ichthyosis and skin cancer prevention, it may be advisable to supplement with vitamin D and calcium and to closely monitor bone mineral density with periodic dual-energy x-ray absorptiometry (DEXA) scans.

## Controversies: Teratogenicity

The most troublesome potential adverse event associated with systemic retinoids is teratogenicity. Although isotretinoin has received the most attention regarding this issue, all systemic retinoids are teratogenic. There is no safe minimal dose. Embryos seem to be most susceptible to these teratogenic effects in the first trimester of pregnancy, in particular in the 4th week, when neural crest cells are most vulnerable.

Retinoid embryopathy involves craniofacial, cardiovascular, central nervous systemic, and limb anomalies. Atresia of the ear canal, microtia, anotia, and cleft palate are some of the most common craniofacial abnormalities. Transposition of the great vessels, tetralogy of Fallot, septal defects, and interrupted aortic arch anomalies occur. Many exposed fetuses are not viable.

In 2006, a Food and Drug Administration-mandated distribution program, iPledge, was enacted to reduce the number of pregnancies that occurred in women on isotretinoin. Unfortunately, despite everyone's best efforts, the pregnancy rate in women on isotretinoin has remained steady, around 120 per year.<sup>20</sup>

Isotretinoin has a 20-hour half-life. It and its metabolites may be present for over 2 weeks after discontinuation, so continuing contraception should be considered for 1 month or more post-therapy. Contraception should be advised even longer in patients on acitretin.

## Controversies: Depression and Suicidal Ideation

There have been discussions and publications on the association of isotretinoin and mood, depression, and suicidal ideation for years. Unfortunately, these reports have not been substantiated with prospective population-based data. There is considerable skepticism regarding the data we have. The difficulty extends in large part because the teenage population is particularly susceptible to depression and suicide, and there is uncertainty on the expected number of suicides in the population. Thus, the controversy continues.

The depression and suicide question controversy came to a head in 2000, when the son of a US Representative from Michigan, Bart Stupak, committed suicide after taking isotretinoin in 1999. He believed that the drug contributed to his son's suicide and testified in Congress in 2002 on this issue.<sup>21</sup> However, his lawsuit against the drug maker, Roche, was dismissed, and he was not allowed to sue the company.

Throughout the literature, there are small studies on animals and humans alike that show a relationship between isotretinoin and mood alterations.<sup>22</sup> However, there is an equal, if not greater, number of references showing that the beneficial effects of acne eradication with isotretinoin far outweigh the potential adverse event risk in large populations.<sup>23,24</sup>

In many recent reports, isotretinoin improved anxiety, mood alteration, and depression.<sup>25</sup> In 2001, Wysowski et al<sup>26</sup> showed that the analysis of reported depression and suicide reported between 1982 and 2001 for those taking



isotretinoin was similar to the expected rate in the population.

Despite more recent reassuring data on this issue, concerns about depression and suicidal ideation related to isotretinoin therapy continue increasing the anxiety over the use of the drug, for both parents and patients. Because of the pervasive unregulated media and medicolegal perception on this relationship, good scientific data may not be enough to overcome this perception.

All isotretinoin-prescribing dermatologists should be aware of these issues, review the literature for themselves, and have a scientifically based discussion with patients and their families.

## Controversies: Isotretinoin and Inflammatory Bowel Disease

It is clear to most practicing dermatologists that isotretinoin has the most reproducible and consistent therapeutic effect on cystic and scarring acne, and therefore is worth the complex prescribing and medicolegal issues associated with its use. Despite the lack of a clear causal relationship with inflammatory bowel disease (IBD), the notion that isotretinoin is a proven cause of IBD has continued to be perpetuated by the media and our legal system. Several multimillion dollar lawsuits have been awarded to plaintiffs who have sued isotretinoin makers for causing ulcerative colitis and Crohn's disease over the past 2-3 years.

The issue between isotretinoin and IBD is not new. It was first discussed in 1985,<sup>27</sup> and other case reports followed. More recently, Reddy et al<sup>28</sup> again suggested a causal relationship based on cases reported to Medwatch between 1997 and 2002. Further inspection of the report and its interpretation led to significant skepticism in the medical and dermatology community. In the report, 85 cases of IBD were associated with isotretinoin use. Using the Naranjo adverse drug reaction (ADR) probability scale, 4 cases were listed as highly probable, 58 cases as probable, and 23 as possible. Their conclusion was not definitive, but stated that "isotretinoin might serve as a trigger of IBD." This ultimately led to a surge of lawsuits against the makers of the drug, with many substantial payouts to plaintiffs. Further population-based studies followed. Crockett et al<sup>29</sup> reviewed case reports, case series, and clinical trial data, and using the Hill criteria, found no prospective or retrospective studies on the subject and concluded that "current evidence is insufficient to confirm or refute a causal association between isotretinoin and IBD."

In the same year, a larger population-based study from Manitoba showed that 1.2% of IBD cases used isotretinoin before a diagnosis of IBD was made, which was similar to what would be expected in the general population.<sup>30</sup> This led the authors to conclude that "isotretinoin is not likely to cause chronic IBD."

Another population-based control study from an insurance claims database showed that ulcerative colitis is increased more than would be expected and may be associated with isotretinoin exposure, but not Crohn's disease. The au-

thors added that the absolute risk of developing ulcerative colitis after taking isotretinoin is likely small.<sup>31</sup>

In a more recent commentary, Popescu and Popescu reviewed the available published data and concluded that these studies are inherently flawed with recall bias, publication bias, and lack of follow-up data, which seriously limits interpretation. There is perhaps a very small absolute risk of ulcerative colitis with isotretinoin use, but this low risk has to be weighed against the higher risk of disfiguring lifelong acneiform scarring.<sup>32</sup> Another editorial review by Mostow<sup>33</sup> also concurred that we do not have the answer, further studies are needed, and the concerns we all have are not really different from the many known and unknown risks associated with many more commonly prescribed medications.

Thakrar and Robinson<sup>34</sup> suggested that the studies showing an association may be inadequately controlled, which leads to confounding and a bias in selection of controls. This would explain the bias of the results in favor of an association between isotretinoin and ulcerative colitis; thus, the results of the studies should be interpreted with caution.

## Ideas for a Compromise/In Favor of Isotretinoin

Is there another explanation for this association? There is mounting evidence that the 2 diseases themselves, IBD and severe cystic scarring acne, may be associated or linked. The follicular tetrad of acne conglobata, dissecting cellulitis of the scalp, pilonidal cysts, and HS is well established. The literature is replete with cases of HS occurring in association with IBD and responding to similar treatments, including monoclonal antibodies.<sup>35-37</sup> In a single study looking at the association between HS and IBD, 16% of IBD patients reported signs and symptoms of HS.<sup>38</sup> Because we know that HS and severe cystic scarring acne are associated, it makes some sense that severe acne may also be related to IBD. Indeed, there are data on that subject, which show that acne conglobata is associated with pyoderma gangrenosum, a cutaneous manifestation of IBD.<sup>39</sup> About 30% of patients with HS and severe acne have pyoderma gangrenosum, and about 80% of patients with pyoderma gangrenosum had another inflammatory disease, including severe acne.<sup>40,41</sup> PAPA syndrome is the combination of pyogenic arthritis, pyoderma gangrenosum, and acne. It may be that IBD is associated with severe acne, but not severe acne therapy.

Another question within this argument is, "why are the tetracyclines or other retinoids not being implicated in causing IBD, as almost all severe acne patients have had a trial of one of the tetracyclines, if not several?" Well, the tetracyclines and other retinoids are now being implicated as well,<sup>42,43</sup> again without any supportive scientific data. Once again, this may be more of a medicolegal issue than it is a scientific, medical, or pharmacological one.

What does this all mean? This situation is not only a failure of our health care system and legal system, but also of our medical culture. There have been many false claims, bad

science, and poor statistical interpretation and publication on this issue, but no prospective studies to confirm or dissociate the relationship between isotretinoin and IBD.

There is some solace in the American Academy of Dermatology (AAD) position statement on isotretinoin. It concludes that the current evidence is insufficient to prove either an association or a causal relationship between isotretinoin use in IBD in the general population. The AAD states that the prescription of isotretinoin for severe nodular acne continues to be appropriate as long as prescribing physicians are aware of the issues related to isotretinoin use.<sup>44</sup>

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