



King Saud University
**Journal of the Saudi Society of Dermatology &
Dermatologic Surgery**

www.ksu.edu.sa
www.jssdds.org
www.sciencedirect.com



CASE REPORT

Inflammatory bowel disease and isotretinoin: An overlooked potential side effect?

Sarah Al-Breiki *, Iqbal Bukhari, Heba Bosbait

King Fahad Hospital of the University, Al-Khobar, KSA, Saudi Arabia

Received 27 November 2011; revised 15 May 2012; accepted 15 May 2012

Available online 19 June 2012

KEYWORDS

Inflammatory bowel disease (IBD);
Isotretinoin;
Gastrointestinal tract (GIT);
Adverse drug reaction (ADR)

Abstract Here, we describe two cases of inflammatory bowel disease in two young female patients, after treatment with oral isotretinoin for severe acne vulgaris and hidradenitis suppurativa, respectively. IBD may potentially be a serious side effect to oral isotretinoin in dermatology practice.

© 2012 King Saud University. Production and hosting by Elsevier B.V. All rights reserved.

1. Introduction

Isotretinoin is a vitamin A derivative, and has been used in dermatology since 1982 for treating severe nodulocystic acne, but it also has some well known off-label uses (Reddy et al., 2006). Baseline investigations in the form of liver function tests and lipid profiles are very important and patients need regular follow ups. Female patients in the reproductive age require two forms of contraception prior to using isotretinoin as it is a well known teratogen, and baseline as well as monthly pregnancy tests are required (Roaccutane package insert, 2011; Wolverton, 2007). Isotretinoin is known to cause xerosis of the skin and mucous membranes as one of its most common side effects, but GIT side effects in the form of nausea, diarrhea and abdominal pain are also considered common side effects, although less

commonly observed than xerosis (Roaccutane package insert, 2011; Wolverton, 2007). The GIT side effects can be potentially serious as there are reported cases in the literature documenting serious GIT manifestations namely, IBD flares as well as new onset IBD. The isotretinoin package insert also mentions GIT side effects occurring in isotretinoin users in a chance of less than 1 in 10,000 in which IBD flare and new onset IBD are included (Roaccutane package insert, 2011; Wolverton, 2007).

Case 1: Is a 24 year old single female medical student who was managed with isotretinoin for severe acne vulgaris in a dose of 30 mg/day for 7 months, she started developing GIT symptoms in the form of abdominal pain and diarrhea 2 months after initiating isotretinoin therapy, and in the last 2 months, the diarrhea was described as bloody and with mucus. The patient had lost about 10 kg in that period, developed iron deficiency anemia, and had fatigue. She had no significant past medical history, and no family history of IBD. There was no history of recent travel. A colonoscopy and biopsy revealed a pancolitis, and she was given a diagnosis of ulcerative colitis in October 2009, for which she was started on 5 aminosalicylic acid, systemic steroids and an iron supplement. Her dermatologist discontinued isotretinoin treatment, the patient's condition improved and systemic steroids were

* Corresponding author. Address: P.O. Box 40011, Al-Khobar 31952, Saudi Arabia.

E-mail address: salbreiki@yahoo.com (S. Al-Breiki).

Peer review under responsibility of King Saud University.



Production and hosting by Elsevier

discontinued, but she is still maintained on 5 aminosalicylic acid. Currently she is in clinical remission.

Case 2: Is a 21 year old single female, not known to have any previous medical problems and no family history of IBD, was started on isotretinoin for hidradenitis suppurativa in a dose of 40 mg/day. Four weeks after the initiation of therapy with isotretinoin, she started having abdominal pain and a bloody diarrhea. Her condition progressed in the following months as she developed severe iron deficiency anemia (hemoglobin dropping to 5.5 gm/dl), and had a significant weight loss of about 60 kg in 4 months. The patient discontinued isotretinoin. Encapsulated endoscopy, colonoscopy and a biopsy revealed a diagnosis of Crohn's disease. She was started on systemic steroids, mesalamine, and her severe anemia was managed. Currently, she is maintained on adalimumab 40 mg subcutaneously every 2 weeks and is in clinical remission. Table 1 shows a comparison between the two cases.

2. Discussion

The most common side effect encountered with isotretinoin use is xerosis of the skin and mucous membranes mainly leading to cheilitis. Some patients may have musculoskeletal aches and pains, but there are a number of less commonly reported side effects, and one such potentially serious side effect that may be overlooked is aggravating or triggering IBD in susceptible individuals (Roaccutane package insert, 2011; Wolverton, 2007).

How isotretinoin induces IBD is not clear, some proposed mechanisms include "induction of ulceration and inflammation in the gut mucosa by inhibiting epithelial cell growth, disruption of the mucosal wall integrity by inhibiting glycoprotein synthesis, and epithelial cell injury caused by stimulation of killer T cells with a resultant inflammation" (Passier and Srivastava, 2006; Reniers and Howard, 2001).

Upon reviewing the literature we have found several case reports suggesting the association of isotretinoin use and GIT manifestations including the development of IBD especially ulcerative colitis. Martin et al. was the first to report a case of proctosigmoiditis after isotretinoin exposure in 1987, his case showed relapsing and remitting of the GIT symptoms with reintroduction and withdrawal of isotretinoin, respectively (Martin et al., 1987). Bharmal et al. documented a case of worsening UC after isotretinoin treatment and his case ended up having a subtotal colectomy and an ileostomy reflecting the seriousness of such an adverse event (Bharmal and Anderson, 2010). Papageorgiou et al. reported a case of UC that developed after exposure to isotretinoin and remitted after

the drug was discontinued (Papageorgiou et al., 2009). Spada et al. reported a case of pancolitis after starting treatment with isotretinoin and complete resolution after discontinuation of the medication (Spada et al., 2008). Passier et al. documented 3 cases of IBD that developed in previously healthy individuals a few weeks after the discontinuation of isotretinoin, two of which were ulcerative colitis and the third was a Crohn's disease (Passier and Srivastava, 2006). Crockett et al. suggested that UC not CD may be associated with isotretinoin exposure and that higher doses increase the risk (Crockett et al., 2010). Reniers et al. also reported a case of UC after discontinuation of isotretinoin (Reniers and Howard, 2001), and Reddy et al. reviewed 85 cases of IBD reported with the FDA in 4 years from 1997 to 2000, and analyzed this association using the Naranjo ADR probability scale, and found that "5% scored 'highly probable', 68% scored 'probable', 27% scored 'possible', and there were no 'doubtful' cases" (Reddy et al., 2006; Bernstein et al., 2009; Naranjo et al., 1981).

Some of the reviewed reported cases of IBD showed improvement or complete resolution of the symptoms after withdrawal of isotretinoin, and flare up upon rechallenge (Reddy et al., 2006), others reported onset of GIT symptoms after the completion of their isotretinoin course (Passier and Srivastava, 2006; Reniers and Howard, 2001). Some of the documented cases of IBD especially UC ended up with surgical intervention in the form of a subtotal colectomy and ileostomy (Bharmal and Anderson, 2010; Reniers and Howard, 2001).

Inflammatory bowel diseases (ulcerative colitis and Crohn's disease) are both immune mediated diseases of unknown etiology but genetic predisposition and immune dysregulation along with unknown environmental factors may play a role in the pathogenesis (Reddy et al., 2006), the diseases tend to be more diagnosed in young adults and late teenage years. This age group is also more susceptible to acne vulgaris, which is a very common skin problem affecting about 80% of adolescents (Bharmal and Anderson, 2010). Bernstein et al. in his argument against this association suggested that because of the comparability of the age of onset of both entities, the development of IBD in such patients could be coincidental (Bernstein et al., 2009; Crockett et al., 2009). Also, some patients may actually have pre-existing subclinical IBD in which isotretinoin may have acted as a trigger in unmasking the symptoms in those predisposed individuals (Reddy et al., 2006). The possibility of severe acne or inverse acne being an extra-intestinal manifestation developing in these patients prior to the onset of GIT symptoms is also plausible, as are the well known extra-intestinal manifestations of erythema nodosum and pyoderma gangrenosum (Tharkar, 2011; Rolanda and Macedo, 2007).

Table 1 Comparison between the two cases.

| | Case 1 | Case 2 |
|--|---------------|--------------------------|
| Age | 24 years | 21 years |
| Sex | Female | Female |
| Diagnosis | Acne vulgaris | Hidradenitis suppurativa |
| Isotretinoin dose | 30 mg | 40 mg |
| Isotretinoin duration of use | 7 months | 4 months |
| Onset of GIT symptoms after isotretinoin use | 2 months | 4 weeks |

Godfrey reported his results in managing 4 patients with IBD treated for severe acne with isotretinoin, from these 4 cases only one had a flare of his IBD and the rest had successful courses (Godfrey and James, 1990).

Margolis reported a case of Crohn's disease in a patient who has been exposed to doxycycline for treating acne (Margolis et al., 2010 Dec). Our two cases had no previous history of exposure to tetracycline class of antibiotics.

3. Conclusion

The association between IBD and isotretinoin use is still a controversial issue, just as it is with mood disorders, both have not been adequately measured in any studies although there are numerous case reports. So in prescribing isotretinoin a detailed history including symptoms suggestive of IBD should be obtained, and in previously healthy patients who develop GIT symptoms while on isotretinoin, a referral to the gastroenterologist is advisable.

References

- Bernstein, C.N., Nugent, Z., Longobardi, T., et al., 2009. Isotretinoin is not associated with inflammatory bowel disease: a population-based case control study. *American Journal of Gastroenterology* 104, 2774–2778.
- Bharmal, R., Anderson, S.H.C., 2010. Exacerbation of inflammatory bowel disease with isotretinoin. *Journal of the Royal Society of Medicine Short Reports* 1, 58. <http://dx.doi.org/10.1258/shorts.2010.010099>.
- Crockett, S., Gulati, A., Sandler, R.S., et al., 2009. A causal association between isotretinoin and inflammatory bowel disease has yet to be established. *American Journal of Gastroenterology* 104, 2387–2393.
- Crockett, S., Porter, C., Martin, C., et al., 2010. Isotretinoin use and the risk of inflammatory bowel disease: a case-control study. *American Journal of Gastroenterology* 105, 1986–1993.
- Godfrey, K.M., James, M.P., 1990. Treatment of severe acne vulgaris with isotretinoin in patients with inflammatory bowel disease. *British Journal of Dermatology* 123, 653–655.
- Margolis, D.J., Fanelli, M., Hofstad, O., Lewis, J.D., 2010 Dec. Potential association between the oral tetracycline class of antimicrobials used to treat acne and inflammatory bowel disease. *American Journal of Gastroenterology* 105 (12), 2610–2616.
- Martin, P., Manley, P.N., Depew, W.T., Blakenab, J.M., 1987. Isotretinoin-associated proctosigmoiditis. *Gastroenterology* 93, 606–609.
- Naranjo, C.A., Busto, U., Sellers, E.M., et al., 1981. A method for estimating the probability of adverse drug reactions. *Clinical Pharmacology and Therapeutics* 30, 239–245.
- Papageorgiou, N.P., Altman, A., Shoenfeld, Y., 2009. Inflammatory bowel disease: adverse effect of isotretinoin. *IMAJ* 11, 505–506.
- Passier, J.L., Srivastava, N., 2006. Van puijenbroek EP. Isotretinoin-induced inflammatory bowel disease. *Netherlands Journal of Medicine* 64, 52–54.
- Reddy, D., Siegel, C.A., Sands, B.E., et al., 2006. Possible association between isotretinoin and inflammatory bowel disease. *American Journal of Gastroenterology* 101, 1569–1573.
- Reniers, D.E., Howard, J.M., 2001. Isotretinoin-induced inflammatory bowel in an adolescent. *Annals of Pharmacotherapy* 35, 1214–1216.
- Roaccutane package insert, 2011.
- Rolanda, C., Macedo, G., 2007. Isotretinoin and inflammatory bowel disease. *American Journal of Gastroenterology* 102, 1330.
- Spada, C., Riccioni, M.E., Marchese, M., Familiari, P., Costamagna, G., 2008. Isotretinoin-associated pan-enteritis. *Journal of Clinical Gastroenterology* 42 (8), 923–925.
- Tharkar, B.T., 2011. Isotretinoin use and the risk of inflammatory bowel disease. *American Journal of Gastroenterology* 106, 1001–1002.
- Wolverton, Stephen, (2007). *Systemic Retinoids*. In: Karen Bowler *Comprehensive Dermatologic Drug Therapy*, second ed. Elsevier, Philadelphia, pp. 275–300.