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CASE REPORT

Isotretinoin-induced inflammatory bowel disease

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ABSTRACT

Three case reports on inflammatory bowel disease associated with use of isotretinoin are described. All three patients were male adolescents, in good health when starting isotretinoin (for acne treatment for about six months). Several weeks after discontinuation of isotretinoin the patients developed severe symptoms requiring hospitalisation. The diagnosis of ulcerative colitis was made in two of these patients, while in the third patient Crohn's disease was diagnosed.

Although inflammatory bowel disease is described as an adverse drug reaction in the product information of isotretinoin, few cases have been described so far. The link with prior isotretinoin use may not be recognised by the patient or the physician, since the diagnosis of inflammatory bowel disease is often preceded by several years of vague symptoms. On the other hand, spontaneous onset of inflammatory bowel disease (not related to isotretinoin) cannot be excluded. We appeal to the readers for a reaction to this, to shed more light on the likeliness of this alleged association.

KEYWORDS

Adverse drug reaction, Crohn's disease, IBD, isotretinoin, ulcerative colitis

INTRODUCTION

Isotretinoin (Roaccutane®) was approved for marketing in the Netherlands in 1984. It is used for the treatment of severe forms of acne, resistant to adequate standard therapy with systemic antibiotics and topical treatment. Isotretinoin affects the acned skin by decreasing sebum production and normalising increased skin shedding.[1] In the product information of isotretinoin it is stated that gastrointestinal adverse drug reactions occur with a chance of less than 1/10,000. Furthermore, in the section 'special warnings and precautions for use' inflammatory bowel disease has been associated with isotretinoin therapy in patients without a prior history of intestinal disorders.[1] Although inflammatory bowel disease (IBD) is described as a possible adverse drug reaction in the product information of isotretinoin, this association has been given little attention in the literature. We present three case reports on this association, and invite specialists to comment on this alleged relationship.

MATERIAL AND METHODS

The Netherlands Pharmacovigilance Centre Lareb maintains the spontaneous adverse drug reaction reporting system in the Netherlands on behalf of the Dutch Medicines Evaluation Board. Physicians and pharmacists have been reporting adverse drug reactions (ADRs) to Lareb since 1985. Patients may report ADRs since April 2003. Lareb reports are sent to the European Medicines Agency (EMEA), and are included in the worldwide database of the World Health Organisation (WHO).

RESULTS

In the period between 1985 and August 2005 the Netherlands Pharmacovigilance Centre Lareb received three reports of inflammatory bowel disease associated with the use of isotretinoin.

Case report 1

The first report came from a 19-year-old male patient who gave Lareb permission to contact his gastroenterologist for additional information. The patient had taken isotretinoin for acne vulgaris, 20 mg three times daily, for a period of five and a half months. He was not on any other medications. There were no intestinal disorders in either his own medical history or that of his family. Seven months after starting isotretinoin, thus one and a half month after discontinuation of isotretinoin, he developed bloody diarrhoea, dehydration and severe weight loss. He was hospitalised after losing 10 kg weight within two weeks. An infectious cause of diarrhoea was excluded by faeces cultures and parasitology. Colonoscopy revealed ulcerative (pan)colitis. This was confirmed by histology which showed ulcerative colitis with crypt abscess and cryptitis. Ultrasound examination of the abdomen showed no involvement of the small intestine, making Crohn's disease unlikely. The patient was treated with intravenous prednisone, mesalazine and tube feeding. Within four weeks there was a significant improvement and the patient could be discharged from hospital. The patient is in clinical remission, even after cessation of prednisone.

Case report 2

A second patient report concerns a 17-year-old male who had taken isotretinoin for acne (20 mg three times daily) for a period of six months. He had no medical history of (inflammatory) bowel disease and was in very good health. After discontinuation of isotretinoin he developed an inflammation of the colon and small intestine and abscess. This resulted in hospitalisation six months after isotretinoin cessation. The diagnosis of probable Crohn's disease was made. He was treated with prednisone and mesalazine after which the symptoms improved.

Case report 3

The third case (reported by a general practitioner) concerned a 17-year-old male with no previous medical history, who had taken isotretinoin for a period of six months for the treatment of acne conglobata. Three months after discontinuation of the isotretinoin he developed abdominal pain, bloody diarrhoea and fatigue. After hospitalisation and colonoscopy chronic inflammation of the colon (at the least) was established. In addition he had a cholestatic liver function disorder, most probably primary sclerosing cholangitis (PSC). It should be noted that about 70% of all PSC cases are associated with inflammatory bowel disease, especially ulcerative colitis. The patient was treated with mesalazine and prednisolone. Follow-up on this report, three and a half years later, revealed that the patient was recently found to have inflammatory bowel disease, most likely to be ulcerative colitis.

LITERATURE

Inflammatory bowel disease induced by isotretinoin use has been described in several case reports.[2-4] These case reports relate to teenagers with no previous medical history who developed gastrointestinal symptoms after several weeks to months of isotretinoin treatment, eventually leading to the diagnosis ulcerative colitis[2,3] or proctosigmoiditis.[4]

Over 200 cases of gastrointestinal adverse drug reactions occurring during or after treatment with isotretinoin have been reported to the Federal Drug Administration. These include Crohn's disease and ulcerative colitis. Abnormalities may not appear until months to a year or more after the discontinuation of isotretinoin.[5]

The database of the Uppsala Monitoring Centre of the WHO contains 101 reports on isotretinoin and ulcerative colitis and 35 reports on isotretinoin and Crohn's disease. Both ADRs are statistically significantly more often reported in association with isotretinoin than with other drugs (odds ratio on ulcerative colitis 19.5, 95% CI 15.9 to 24.0; odds ratio on Crohn's disease 18.7, 95% CI 13.1 to 26.5). These findings support the association between isotretinoin and IBD. The views expressed here are purely those of the writer and may not in any circumstances be regarded as a statement on the official position of the WHO.

DISCUSSION

Inflammatory bowel disease (IBD) is defined as an idiopathic and chronic intestinal inflammation. Ulcerative colitis and Crohn's disease are the two major types of IBD. The aetiology and pathogenesis of IBD have not been fully clarified.[6] Both Crohn's disease and ulcerative colitis have a variable course and the peak onset age is between 10 and 30 years. Therefore, it cannot be excluded that the onset of this disease was spontaneous in the adolescents described in this article. On the other hand, all three reporters made the association with the use of isotretinoin, and this association seems to be consolidated by several cases reported worldwide. To our knowledge there is no relationship between acne and IBD.

The mechanism behind isotretinoin-induced inflammatory bowel disease is not fully elucidated. In our view it seems plausible that the inhibition of cell growth, which is effective for the treatment of acne, may be harmful in intestine tissue, where rapid turnover of the intestinal cells is indispensable. Several mechanisms for the effect of synthetic retinoids have been proposed: disturbance of epithelial cell maturation resulting in inflammation, alterations in glycoprotein metabolism compromising the colonic mucosal integrity, and induction of killer T-cell

activity. A fourth hypothesis is that retinoids influence phenotypic expression by colonic epithelial cells, which might serve as a stimulus for an inflammatory response.[4] IBD is considered an immune-modulating disease, with unregulated or excessive T-cell responses to normal stimuli, due to failing counter-regulatory mechanisms.[7,8] In this light, an effect of isotretinoin on IBD could be explained by its proposed effect on T-cell activity in susceptible patients.

With respect to all three patients described in our article, onset of IBD took place after the cessation of isotretinoin use. This finding is in line with the case report described by Reniers and Howard: their patient developed IBD shortly after completion of the treatment with isotretinoin.[3] Also Prokop pointed to the possibility of extended disease latency to diagnosis: he stated that abnormalities may not appear at all until months to a year or more after isotretinoin treatment is terminated.[5] This phenomenon may be due to the fact that the symptoms have their origin in the process of restoration of the original cell growth of the intestinal mucosa. Discontinuation of isotretinoin may induce a disturbed re-growth of the intestinal tissue.

It should be noted that patients with IBD may have a wide range of vague symptoms for several years before the diagnosis is made. Therefore the association with prior isotretinoin use can easily go unnoticed. It may therefore be useful to ask patients who are diagnosed with IBD about possible use of isotretinoin in the past.[5] On the other hand it cannot be excluded that patients diagnosed with IBD during or after use of isotretinoin already had an (unnoticed) pre-existent inflammatory bowel disorder for a longer period of time. In this case, isotretinoin would have been acting merely as the trigger for the eventual manifestation of IBD symptoms.

The reported incidence of this adverse drug reaction is low. With this article we would like to ask for your attention for this alleged association. We would appreciate your reactions, reflecting your personal experience on this subject, either by additional case reports, which strengthen the association between isotretinoin and IBD, or on the other hand by arguments or case reports which speak against this association.

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