Exacerbation of inflammatory bowel disease with isotretinoin

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This case study demonstrates the potential exacerbation of inflammatory bowel disease secondary to using isotretinoin (Roaccutane®) for treatment of severe acne.

Case report

A 27-year-old female medical student experienced an episode of intermittent bloody diarrhoea for 6 weeks. She had no prior illnesses, no family history of note and had not undergone any recent travel. Routine blood and stool tests by her GP were normal. A colonoscopy showed patchy moderately active colitis and biopsies revealed patchy mild to moderate chronic active inflammation with cryptitis and no granulomas. The features were in keeping with, but not diagnostic of, ulcerative colitis. Since symptoms had completely abated, the patient decided against starting treatment.

Six months later, she started a 16-week course of isotretinoin 40 mg daily for acne vulgaris. During week 14 of the treatment she developed bloody diarrhoea three to four times a day, which was treated with enteric coated mesalasine by her GP. At the end of the isotretinoin course her symptoms worsened – her stool frequency increased to 15 bloody motions daily with a CRP of 46 mg/L. She was treated with intravenous hydrocortisone and high-dose mesalazine. However, after 3 days the stool frequency and CRP had not fallen. A flexible sigmoidoscopy revealed severely active colitis with multiple superficial ulcers. Intravenous ciclosporin produced no response and a subtotal colectomy and ileostomy was performed. Histology showed severe acute-on-chronic ulcerative colitis with no viral inclusions or granulomas.

Discussion

Inflammatory bowel disease (incorporating Crohn’s disease and ulcerative colitis) is a common condition affecting 1 in 400 people in the UK, and the incidence is continuing to rise.1 It is usually diagnosed in young adults, mostly between the ages of 20 and 40 years, but can present at any age. Acne vulgaris is a common skin condition affecting up to 80% of adolescents, with 13% visiting a GP and 0.3% seeing a dermatologist.2 Initial therapy includes topical treatments such as benzyl peroxide and clindymicin and systemic antibiotics such as tetracyclines for resistant cases. Those not responding to systemic and topical therapy can be offered a 4–6 month course of isotretinoin – a vitamin A derivative. Its use is controversial due to rare side-effects of depression and suicide3,4 and it should be avoided in young women due to its teratogenicity. A transient elevation in liver transaminases is relatively common and all patients should have their liver enzymes monitored. Other gastrointestinal side-effects were thought to be rare, however, this case report highlights the under-appreciated, potentially serious side-effect of intestinal inflammation.

The product literature on isotretinoin includes gastrointestinal side-effects with an incidence of less than 1:10,000 and includes colitis, ileitis and inflammatory bowel disease.5 The medicines and healthcare products Regulatory Agency have received a total of 325 gastrointestinal adverse effects associated with isotretinoin between 1966 and 2009. Twenty-four of these cases were exacerbations of ulcerative colitis, three exacerbations of crohn’s disease and 19 were described as ‘inflammatory bowel disease and non-infective colitis’.5 The statistical nature of the data means that the history of the cases is not known.

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There have been several case reports dating back over two decades of isotretinoin inducing or exacerbating inflammatory bowel disease. Martin et al. reported a 17-year-old boy, with no prior history of bowel disease, had developed acute proctosigmoiditis after receiving isotretinoin for four weeks. His symptoms resolved after withdrawing the drug.6

Another 17-year-old boy was diagnosed with ulcerative colitis post isotretinoin treatment. Five months after symptoms first presented, the patient required a subtotal colectomy and ileostomy.7 Spada et al. described a case of a 22-year-old man diagnosed with pan-enteritis after taking isotretinoin for 15 days.8 The Netherlands Pharmacovigilance Centre reports three cases of inflammatory bowel disease being associated with isotretinoin between 1985 and 2005, none of which had prior histories of intestinal disease. They all developed inflammatory bowel disease after completing isotretinoin treatment, and required aminosalicylates and steroids to control their symptoms.9

Reddy et al. reviewed 85 cases (36 ulcerative colitis, 30 Crohn’s disease and 19 unclassified colitis) associated with isotretinoin reported to the US Food and Drug Administration (FDA) between 1997 and 2002.10 Each case was given a Naranjo probability score of the likelihood of isotretinoin causing an adverse effect. Of the 85 cases, four were thought to be a ‘highly probable’, 58 reported as ‘probable’ and 23 as ‘possible’. None of the reports were considered ‘doubtful’.

The mechanism by which (endogenous and exogenous) retinoids cause or exacerbate intestinal inflammation is not understood. Retinoic acid affects intestinal epithelial growth and is involved in cell repair and apoptosis. Retinoids also impair neutrophil chemotaxis, a mechanism involved in Crohn’s disease.11 The production of induced regulatory T cells (iTreg) and T helper 17 (Th17) cells is also controlled by retinoic acid – these also being involved in gut epithelial homeostasis.12

The potential for isotretinoin to cause or exacerbate existing colitis is overlooked. Any patient with pre-existing inflammatory bowel disease should not be prescribed isotretinoin. Patients should be informed of the risk of developing inflammatory bowel disease and advised to stop the medication if abdominal symptoms occur.

References
1 The National Association for Colitis and Crohn’s Disease. Inflammatory Bowel Disease Basics. St Albans: The Association; 2009. See http://www.nacc.org.uk/content/ibd.asp
2 Purdy S, De Berker D. Clinical review: Acne. BMJ 2006;333:949–53
3 Medicines and Healthcare products Regulatory Agency. UK Public Assessment Report Isotretinoin 40 mg soft capsules PL 04560/0723. See http://www.mhra.gov.uk/home/groups/l-unitl/documents/websites/resources/con2031286.pdf
4 Kontaxakis VP, Skourides D, Ferentinos P, Havaki-Kontaxaki BJ, Papadimitriou GN. Isotretinoin and psychopathology: a review. Ann Gen Psychiatry 2009;8:2
5 Medicines and Healthcare products Regulatory Agency. Drug Analysis Print: Isotretinoin. See http://www.mhra.gov.uk/home/groups/public/documents/sentineldocuments/dap_1242828880005.pdf
6 Martin P, Manley PN, Depew WT, Blakenab JM. Isotretinoin-associated proctosigmoiditis. Gastroenterology 1987;93:606–9
7 Reniers DE, Howard JM. Isotretinoin-induced inflammatory bowel disease in an adolescent. Ann Pharmacother 2001;35:1214–16
8 Spada C, Riccioni ME, Marchese M, Familiarini P, Costamagna G. Isotretinoin-associated pan-enteritis. J Clin Gastroenterol 2008;42:923–5
9 Passier JL, Srivastava N, van Puijenbroek EP. Isotretinoin-induced inflammatory bowel disease. Neth J Med 2006;64:52–4
10 Reddy D, Siegel CA, Sands BE, Kane S. Possible association between isotretinoin and inflammatory bowel disease. Am J Gastroenterol 2006;101:1569–73
11 Marks DJ, Harbord MW, MacAllister R, et al. Defective acute inflammation in Crohn’s disease: a clinical investigation. Lancet 2006;367:668–78
12 Shale M, Kaplan GG, Panaccione R, Ghosh S. Isotretinoin and intestinal inflammation: what gastroenterologists need to know. Gut 2009;58:737–41