**Case Series: Ulcerative Colitis, Multiple Sclerosis, and Interferon-beta 1a**

*To the Editor:*

The etiology of inflammatory bowel disease (IBD) has not been elucidated, although data indicate that a change of mucosal immunity in the gut of IBD causes an imbalance of inflammatory cytokines and migration of leukocytes into the bowel, thus leading to dysregulated inflammation. Treatment of IBD focuses on suppressing and blocking the inflammatory process. In the past years various therapies were tested, including the use of interferon therapy, which showed no benefit in patients with IBD.1,2

Curiously, there are conflicting data on interferon treatment in IBD. There are indeed a few published cases of development of ulcerative colitis (UC) following interferons (IFN) x and β.3–5 It remains undemonstrated whether an association between UC and multiple sclerosis (MS) exists, or if it is an adverse effect of IFN-β1. We herein report 4 cases of colitis developed after a diagnosis of MS, in which 3 were after the introduction of IFN-β1a and 1 before its administration.

**CASE REPORT 1**

A 29-year-old Caucasian male noticed alterations in left lower limb sensitivity and Lhermitte sign that persisted for 2 weeks and resolved spontaneously. Seven months later the same symptoms recurred. Diagnosis of relapsing-remitting MS was established using standard diagnostic criteria.6 The patient initiated therapy with pulse corticosteroid therapy with methylprednisolone (1 g for 5 days) and 1 year later began treatment with IFN-β1a (Avonex, Biogen, Research Triangle Park, NC) initiated at a dose of 30 μg (6 million IU, i.m. q.w.) obtaining clinical remission (Fig. 1).

Three years after treatment with IFN-β1a, the patient complained of bloody stools, diarrhea, and abdominal cramping. He was referred for a colonoscopy which revealed a segmental colitis from the splenic flexure to the distal transverse colon (Fig. 2a). The patient maintained IFN-β1a and abdominal complaints subsided without treatment. Due to worsening of bloody diarrhea the patient was submitted to a colonoscopy 7 months later, which showed an extension to the proximal transverse colon. He was started on 5-aminosalicylic acid (5-ASA) 1000 mg p.o. t.i.d. and oral steroid treatment (prednisolone 40 mg). The symptoms improved and the patient maintained treatment with IFN-β1a. After 2 years the patient experienced a relapse of the colitis symptoms and was treated with 5-ASA. He is presently asymptomatic and taking mesalamine 3 g/daily and IFN-β1a.

**CASE REPORT 2**

A 23-year-old Caucasian male developed partial epileptic seizures and the subsequent work-up, including a head magnetic resonance imaging (MRI), was consistent with the diagnosis of MS. The patient was initially

![FIGURE 1. Timeline of events in patients 1, 2, 3, and 4.](image-url)
started on methylprednisolone 1 g/daily for 5 days and then began treatment with IFN-β1a (Rebif 22, s.c., t.i.w.; Ares-Serono, Switzerland) 2 months following diagnosis. The disease remained stable for ≈1 year, when he began to experience numbness in his right thigh and an EEG revealed persistent epileptiform activity requiring an increased dose of interferon. Concomitantly, the patient had significant weight loss and complained of bloody stools and diarrhea. He was referred to a gastroenterologist who performed a colonoscopy which showed continuous mucosal inflammation and ulceration of the rectum and distal sigmoid colon (Fig. 2b). Combined oral (mesalamine 3 g/daily) and topical (mesalamine 500 mg/day) aminosalicylates was started and the patient’s symptoms subsided. The patient is currently asymptomatic treated with oral mesalamine 1 g t.i.d. (Fig. 1).

CASE REPORT 3

A 20-year-old Caucasian woman complained of a sensation of electric shocks during movement in the dorsal region. She fulfilled criteria for the diagnosis of MS (McDonald) and was treated with an initial dose of dexamethasone 0.5 mg t.i.d. for 2 weeks. Two months following diagnosis the patient began IFN-β1a (Rebif 22) therapy (Fig. 1). Four and a half years later the patient reported abdominal cramping, weight loss, bloody stools, and diarrhea. She was submitted to a colonoscopy which revealed mucosal inflammation and ulcers from the rectum to the ascending colon consistent with the diagnosis of extensive colitis and began treatment with aminosalicylates (Fig. 2c). Four months later the patient was admitted to our hospital, started on steroid therapy with prednisolone 60 mg, and interferon therapy was suspended. Presently, 5 months following hospital admission the patient is asymptomatic and recently started treatment with natalizumab.

CASE REPORT 4

A 23-year-old Caucasian man previously diagnosed with MS 5 years preceding complaints of abdominal cramps and bloody stools. A sigmoidoscopy was performed that revealed mucosal inflammation, friability, and erosion from the rectum to the proximal sigmoid colon (Fig. 2d). He was started on i.v. steroids and oral 5-ASA, obtaining remission. At the time the patient had only been treated with methylprednisolone during acute exacerbations of MS (1 year prior to diagnosis of UC) (Fig. 1). Four months following the diagnosis of UC the patient began IFN-β1a (Rebif 22) due to frequent neurological symptoms. Currently, due to severe refractory UC the patient is treated with oral 5-ASA, azathioprine, and cyclosporine and IFN-β1a (Avonex) for MS.

These case reports illustrate a strong association between MS and UC. A connection between IBD and MS has been discussed previously in the literature, some previous to the use of IFN-β1a in MS, although prospective studies are required in order to explore the precise pathogenesis. Whether this translates into an increased prevalence of UC in MS or merely demonstrates a side effect associated with IFN treatment remains ambiguous.

In recent years several studies have been published exploring a shared underlying pathogenesis between IBD and other perceived autoimmune diseases. Some studies have revealed a connection between IBD and MS, although some have only demonstrated
a link between MS and UC, curiously failing to find an association with Crohn’s disease (CD),\textsuperscript{10} and others such as Beaugerie et al\textsuperscript{11} found an association between CD and MS (0.5%). Cohen et al\textsuperscript{8} demonstrated that patients with IBD were at higher risk for MS with an odds ratio (OR) of 1.5, presenting an increased risk for UC (OR 1.47; confidence interval [CI] 1.11–1.95) and CD (OR 1.59; CI 1.17–2.16). In a retrospective cross-sectional study conducted by Gupta et al\textsuperscript{9} a small but significant association of IBD with demyelinating diseases, with a relative odds of being diagnosed with a demyelinating disease of 1.54 (CI 1.03–2.32) for CD and 1.75 (CI 1.28–2.39) for UC.

The identification of an association between IBD and MS may contribute to finding common environmental or genetic factors leading to the development of these diseases. Genetic profiling has indicated that the CARD15 gene and the IBD5 locus may contribute to finding common environmental factors leading to the underlying link between UC and MS, or a risk of development of colitis as a side effect following IFN-β1a, clinicians should be alerted to the need of prospective studies in order to clarify these associations.

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REFERENCES