Glatiramer Acetate: A Novel Therapeutic Approach in Crohn's Disease?

To the Editor:

In the early 1960s, a research team at the biophysics department of the Weizman Institute of Science, Rehovot, Israel, was determined to develop polypeptides able to elicit an immune response when injected into animals. To this end, they designed an immunogenic polypeptide of approximately 4000 Da (glatiramer acetate, copolymer 1, Copaxone) consisting of only 4 amino acids (alanine, glutamic acid, lysine, and tyrosine) and resembling the protein composition of myelin basic protein (MBP). MBP is the main protein component of the myelin sheath in the spinal cord and of white matter in the brain and represents one of several putative autoantigens in multiple sclerosis (MS). Several mammalian animal models have demonstrated that crude injections of myelin-containing tissue causes experimental allergic encephalitis (EAE), which closely mimics MS. Surprisingly, injection of glatiramer acetate (GA) suppressed rather than induced EAE in mammalians.[1,2] A first prospective, double-blind, placebo-controlled clinical trial in MS patients conducted by Bornstein et al provided the first evidence of therapeutic effects of GA. Daily subcutaneous injections of 20 mg of GA for 2 years significantly reduced disease progression and frequency of relapse in MS patients.[3] Large multicenter trials confirmed the initial observations made by Bornstein et al.[4] In 1996, GA was eventually approved by the Food and Drug Administration (FDA) for the treatment of the relapsing-remitting form of MS. Today, Copaxone constitutes an important therapeutic tool in the treatment of MS and is characterized by a high safety profile and only minimal side effects such as irritation at injections sites and, rarely, transient vasomotor response. Extensive studies on the mechanisms of action of GA demonstrated that GA exerts its therapeutic effect by modulating the immune response at different levels of specificity. GA binds promiscuously and with high affinity to various class II major histocompatibility (MHC) molecules of murine and human origin, displacing antigens from the MHC antigen-binding site. This leads to the inhibition of various pathological effector functions.[5] Furthermore, GA acts as a potent inducer of Th2/3 cells that secrete high amounts of regulatory substances such as interleukin-10 (IL-10) and transforming growth factor-β (TGF-β), but not Th1 inflammatory cytokines, thus deviating the immune response from a Th1- to a Th2-biased cytokine profile.[6] The Th1-mediated immunopathological nature of inflammatory bowel disease (IBD), in particular, Crohn's disease, prompted researchers to examine the effects of GA in IBD. Indeed, previous studies convincingly demonstrated that GA treatment ameliorates the various pathological manifestations of several IBD animal models including trinitrobenzene sulfonic acid–induced colitis and dextran sulfate sodium (DSS)–induced colitis, as well as a spontaneous model of colitis in C3H/HeJBir IL-10-deficient mice.[7,8] In these mouse models amelioration of clinical symptoms such as weight loss, intestinal bleeding and diarrhea was accompanied by reduced expression of proinflammatory cytokines such as tumor necrosis factor–α and interferon-γ and enhanced levels of regulatory anti-inflammatory TGF-β and IL-10. Recently, the finding of a direct association between the therapeutic effects of GA in IBD and its immunomodulatory effect in the injured colon was unveiled.[9] In this study, naive mice were immunized by GA, leading to the generation of a Th2/3-subtype T-cell population that drastically suppressed disease manifestation on their adoptive transfer to mice with DSS-induced colitis. In contrast, adoptive transfer of control lysozyme-specific cells did not result in any beneficial effect on the disease. In addition, GA-specific short-term T-cell lines were in the inner layer of the colon after intraperitoneal injection in colitis-induced mice and secreted the regulatory cytokine TGF-β in situ.[9]

Here, we report a 33-year-old male white patient who was diagnosed with the relapsing-remitting form of MS 7 years ago at age 26. One year later, in April 2001, Crohn's disease with mild to moderate ileocoecal involvement was diagnosed, and treatment with steroids and regular follow-up visits in our IBD outpatient clinic were initiated. In September 2001, daily injections of 20 mg of Copaxone were started for treatment of MS. Retrospectively, bowel symptoms such as abdominal pain, stool frequency, and intestinal bleeding were drastically reduced a few weeks after commencement of Copaxone treatment, and the patient achieved full remission of Crohn's disease without the need of any concomitant IBD treatment. In 2006, the Copaxone treatment was discontinued because of remittent exacerbations of the MS, and methotrexat treatment (10 mg/week) was started. Soon after the termination of Copaxone, bowel symptoms flared up again, and the patient complained of abdominal pain and increasing stool frequency with the addition of blood. Furthermore, ultrasonography revealed markedly enhanced disease activity in the terminal ileum (Fig. 1). After consultation with the neurologist in charge, we decided to reinitiate Copaxone treatment. Soon after, bowel symptoms alleviated, and the patient again achieved full remission of

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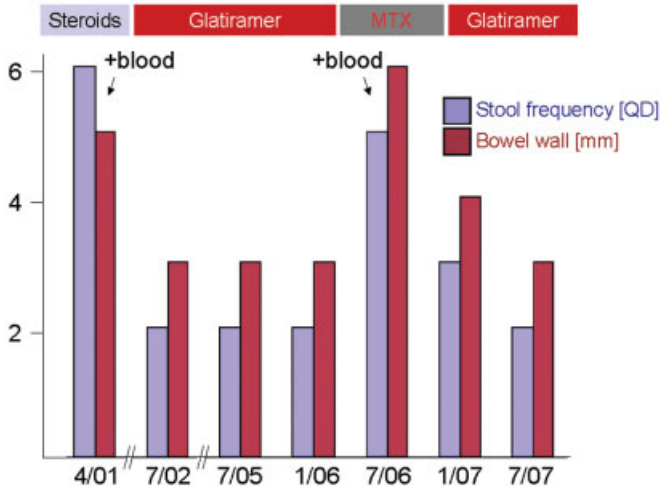

FIGURE 1. Effect of glatiramer acetate on stool frequency and bowel wall thickness in the terminal ileum as indicators of disease activity. Note that stool frequency and bowel wall thickness were markedly increased during the period when glatiramer acetate was withdrawn [blue bar, stool frequency/day; red bar, ultrasonography of the bowel wall (mm) of the terminal ileum]. [Color figure can be viewed in the online issue, which is available at www.interscience.wiley.com.]

the disease (Fig. 1). Thus, the therapeutic effect of glatiramer acetate was indirectly confirmed in this patient.

Although we describe a single observation here, we believe that this might be the advent of a novel treatment approach for Crohn's disease. In view of the experimental data mentioned above, it seems quite realistic that glatiramer acetate has a therapeutic effect in mild/moderate forms of Crohn's disease because of its potential to deviate the immune response from a Th1-dominated to a Th2-biased cytokine profile. In contrast, ulcerative colitis as mainly Th2-mediated inflammation does not appear to be an appropriate candidate for glatiramer acetate. A single case report underlines this hypothesis. Schott et al recently reported a case of ulcerative colitis and MS in which Copaxone failed to demonstrate any additional benefit for the induction of remission.[10]

In summary, glatiramer acetate is an approved drug for the relapsing-remitting form of MS and is characterized by a high safety profile and minimal side effects. Here, we report the first case of successful induction of remission in a patient with active Crohn's disease by glatiramer acetate. Because of the abundant evidence of the therapeutic effect of glatiramer acetate in several IBD animal models and the lack of severe side effects in MS patients, further clinical trials are warranted to evaluate its role in patients with IBD. If proven to be effective, glatiramer acetate might not only represent a novel drug but also constitute an entirely different therapeutic approach to IBD management from an immunosuppressive toward an immunomodulating therapy regimen.

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