Long-term Therapy with Sargramostim in a Patient with Crohn’s Disease

To the Editor:

Crohn’s disease (CD) is an inflammatory disorder of the bowel and current treatment emphasizes the use of antiinflammatory and immunosuppressive agents. It has been hypothesized that CD may result from impaired intestinal innate immunity and that enhancement of this system may be beneficial.1 Granulocyte-macrophage colony-stimulating factor (GM-CSF) regulates the proliferation, mobilization, and function of myeloid immune cell lines.2,3 GM-CSF receptors are expressed in intestinal tissue, and it has been shown that GM-CSF protects against experimentally induced colitis as well as promotes intestinal repair.4,6 It is hypothesized that GM-CSF enhances intestinal innate defense and decreases exposure of the lamina propria to luminal microbes and microbial products, thereby diminishing the chronic inflammatory process mediated by T-cells. Sargramostim, a yeast-derived recombinant human GM-CSF, has been studied as a treatment for CD; however, the results are inconsistent.7–9

While further studies are necessary to determine if GM-CSF is safe and efficacious in the treatment of CD, we report a case of a patient with CD who received sargramostim for ≈5 years. To the best of our knowledge, this represents the longest reported use of GM-CSF in the treatment of CD.

The patient is a 50-year-old woman with a 27-year history of inflammatory bowel disease. She was initially diagnosed with ulcerative colitis at age 23 and underwent total colectomy with ileoanal pouch anastomosis (IPA) due to refractory disease. Postoperatively she underwent a pouchoscopy for persistent symptoms, which revealed endoscopic inflammation in her ileum upstream of the IPA. Biopsies confirmed chronic inflammation consistent with CD. She was subsequently treated with mesalamine, budesonide, azathioprine, and infliximab without significant benefit. The only drug that provided her symptomatic relief was prednisone.

The patient was then enrolled in a clinical trial evaluating the effects of sargramostim in CD and she initially received placebo.8 Following her completion of the blinded trial, the patient received open-label active therapy. She received sargramostim at a dose of 6 μg/kg subcutaneously once daily for 5 continuous years. At the time of starting sargramostim, her disease activity and quality of life, as indicated by the Harvey–Bradshaw index (HBI) and short inflammatory bowel disease questionnaire (SIBDQ), were 12 and 52, respectively (Fig. 1).

She responded to sargramostim, as seen by a change in her HBI and SIBDQ scores, which improved to 9 and 59, respectively. Although her disease never remitted, she maintained a level of improvement while taking sargramostim that she had not achieved on other medications. In addition, she neither required systemic steroids nor any rescue medications while on sargramostim. Her clinical course fluctuated and included a single flare of symptoms (Fig. 1).

During the final 15 months of sargramostim therapy she experienced increasing symptoms which ultimately led to discontinuation of sargramostim and initiation of treatment with certolizumab pegol. Of note, the patient experienced a severe flare of her CD 17 days after stopping sargramostim.

Over the 5 years of therapy the patient experienced no significant adverse effects related to sargramostim. She did experience injection site reactions typical of sargramostim; however, they were not severe enough to limit use of sargramostim and improved

FIGURE 1. HBI and SIBDQ score over 5 years of treatment with sargramostim. [Color figure can be viewed in the online issue, which is available at wileyonlinelibrary.com.]
over time. Her blood leukocyte count was consistently elevated while receiving sargramostim and ranged from 14–21 thousand/µL, but rapidly normalized to 5 thousand/µL following discontinuation of treatment. Since discontinuing sargramostim she has had no identifiable adverse events attributable to sargramostim.

GM-CSF’s complex physiologic role is not fully understood and the long-term adverse effects of sustained excess GM-CSF are unknown. GM-CSF is most commonly used for short periods of time in patients with leukopenia secondary to chemotherapy. GM-CSF has been implicated in the pathogenesis of various inflammatory disorders involving the skin, joints, kidneys, and vasculature. In addition, the risk of hematologic malignancy associated with colony-stimulating factors remains controversial.

In this patient with CD, long-term maintenance treatment with sargramostim was safe, well tolerated, and provided symptomatic benefit for several years. The worsening of this patient’s CD while on sargramostim may reflect the natural course of her disease, a waning effect of sargramostim, or a combination of both. Neutralizing antibodies generated against GM-CSF were not tested for in this patient but may have developed, resulting in the waning clinical response. Sargramostim remains a potential treatment option for CD and additional clinical studies are necessary to define if it is safe and effective at maintaining a reduction in symptoms from CD.

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REFERENCES