Ulcerative Colitis and Familial Mediterranean Fever: Can Anakinra Treat Both?

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ABSTRACT
Anakinra is a biological drug used in rheumatoid arthritis and several autoinflammatory diseases. Its main side effects are injection site reactions and increased infection rate. We present a 28-year-old man with familial Mediterranean fever, whose disease went into remission on anakinra, with concomitant flare of his ulcerative colitis.

INTRODUCTION
Anakinra, a biological drug, is a recombinant human interleukin 1 receptor antagonist (IL1Ra), which was initially approved by the Food and Drug Administration (FDA) for the treatment of rheumatoid arthritis and subsequently approved for the treatment of several autoinflammatory diseases.1 Recently, anakinra has shown evidence of efficacy in intractable familial Mediterranean fever (FMF).2 FMF, an autoinflammatory disease related to pyrin gene mutations, is characterized by episodes of fever, serositis, and elevated acute phase reactants. Uncontrolled, the disease puts patients at risk for developing secondary amyloidosis. About 5%–10% of patients with FMF are resistant to conventional treatment based on colchicine, and for them, anti–IL-1 therapy is most useful. We report the case of a patient with intractable FMF, unresponsive to maximal colchicine treatment, who achieved remission on anakinra, but with a concomitant flare of his ulcerative colitis (UC).

CASE REPORT
A 28-year-old man with poorly controlled FMF, despite treatment with colchicine 2 mg daily, presented with pleuritis, peritonitis, and a fever at least twice per month. He was diagnosed with FMF as an infant with the genetic profile: E148Q and V726A mutations for Mediterranean fever. His relevant medical history also included UC in remission with 6-mercaptopurine. Attempts to treat his FMF with anti–tumor necrosis factor agents failed and these were discontinued.3 Treatment was initiated with anakinra, one subcutaneous injection of 100 mg a day. Within 3 weeks, the FMF improved and the patient subsequently achieved complete remission.

Three months after the initiation of anakinra, he was admitted with bloody diarrhea that had lasted for one month, despite concomitant 6-mercaptopurine treatment, while his FMF was still in remission. The flare up was associated with markedly elevated c-reactive protein 105 mg/dL, hypoalbuminemia, and low total cholesterol, but normal cell blood count and normal thyroid stimulating hormone (TSH). Stool cultures were negative. UC flare up was diagnosed and anakinra was stopped. He received a high dose of methylprednisolone pulse, improved and stabilized clinically within a week, and was then discharged with a prednisone taper.

Anakinra was reintroduced the day after his discharge from the hospital. Four days later, he was readmitted with a severe flare of the UC with evidence of pancolitis on endoscopy and moderate activity score on histology. Intravenous methylprednisolone pulse and parenteral feeding were introduced with a good clinical response of his UC and full recovery after 2 weeks of hospitalization.
DISCUSSION

Mutation of the gene encoding for pyrin has been implicated in FMF pathogenesis. Pyrin is a regulatory component of the inflammasome, an intracellular complex required for conversion of pro-interleukin (IL) 1β to IL1β and consequent inflammation cascade. Thus, a rationale exists for the treatment of patients with FMF with IL-1β blockade.

Our patient rapidly achieved complete remission of FMF on anakinra. However, UC flare-up immediately after re-exposure to anakinra suggested that the UC flare was induced by anakinra. The most commonly reported adverse events with anakinra are injection site reactions and an increased infection rate. So far, there are only 4 other cases in the literature reporting a worsening or new onset of inflammatory bowel disease (IBD) secondary to anakinra.

IBD pathogenesis is complex and poorly understood. Chronic intestinal inflammation may arise from an imbalance between different players within this process. The inflammasome is known to contribute to host protection by inducing immune responses such as secretion of cytokines IL1β/IL18, and apoptosis (programmed cell death), which limits microbial invasion. Increased serum cytokine levels including IL8, IL6, IL1β, and IL18 have been demonstrated in patients with IBD, and secretion of the inflammasome effector cytokines IL1β and IL18 seems to be associated with intestinal inflammation and an increased risk for developing IBD. Induced-colitis animal models have shown increased IL1β and IL1Ra synthesis in the colon. Administration of specific neutralizing antibodies to IL1Rα increased intestinal inflammation and mortality, whereas exogenous administration of recombinant IL1Ra attenuated intestinal inflammation in rabbits. Moreover, the IL1Ra/IL1β ratio is decreased in intestinal mucosal biopsies in patients with IBD.

Two cases of Crohn’s disease have been reported as responsive to anakinra. Another theory suggests that polymorphism of IL1β and IL1Ra gene is associated with genetic susceptibility to IBD and could be a marker of its severity. All the above would seem to support IL-1 blockade as a good option for blocking the inflammation cascade in IBD. Based on these theories, a phase 2 trial of IL-1 blockade in acute severe UC is ongoing.

Although it is premature to advance any conclusion about an underlying pathological mechanism, it is important to be aware of a possible exacerbation of UC in patients with FMF treated with IL-1 blockade. The frequency of IBD in patients with FMF is higher than in the general population. Thus, despite our experience described herein, probably a short acting IL-1 blocking agent may be initially preferred in a patient with FMF and an already known IBD, because its effect could be quickly reversed if this "paradoxical" effect was to be induced.

To our knowledge, we report the fifth published case of IBD exacerbation related to anakinra, in the present case, UC exacerbation in a patient with FMF. Although there is some evidence that UC and FMF may have a shared pathogenesis pattern based on the inflammasome and IL1β, treatment by IL1 blockade might induced UC exacerbation. Anakinra is under evaluation for its efficacy in IBD. A short acting IL1 blockade treatment would be preferred in a patient with FMF and concomitant IBD.

DISCLOSURES

Author contributions: L. Kaly wrote the manuscript. M. Rozenbaum, D. Rimar, G. Slobodin, N. Boulnan, A. Awasit, S. Ginsberg and N. Jiries edited the manuscript. I. Rosner revised the manuscript and is the article guarantor.

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