

Exacerbation of Organic Anxiety Disorder with Suicidal Ideation Following Infliximab for Ulcerative Colitis: A Case Report and Review of the Literature

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Abstract

A 23-year-old man with prior generalized anxiety disorder experienced acute terrors with suicidal ideation following each of 3 induction infliximab infusions for the treatment of ulcerative colitis. This side effect has been reported only once previously. Review of the literature suggests that psychiatric adverse events can be severe and may be under-recognized; further controlled studies are needed to better measure their incidence.

Key Words: Hematochezia, inflammatory bowel disease, mood disorder, TNF-alpha

Disclosure: Dr. Kisiel, Dr. Fan, and Dr. Kane disclose no relevant conflicts of interest.

Introduction

The authors present the case of a 23-year-old man with prior generalized anxiety disorder who experienced acute terrors with suicidal ideation following each of 3 induction infliximab infusions for the treatment of ulcerative colitis. While this side effect has been reported only once previously, the literature suggests that psychiatric adverse events can be severe and may be under-recognized. The following report explores the patient's history, presentation, and treatment.

Case Report

The patient was diagnosed with ulcerative colitis at the age of 15 following the onset of bloody diarrhea and anemia. He had good symptomatic control for 4 years on a regimen of balsalazide 2.25 g by mouth 3 times daily and mesalamine retention enemas 4 g per rectum nightly but experienced a severe flare with moderate anemia during his first semester at college, where he admitted his medication compliance was suboptimal. Following a course of systemic steroids, he was started on azathioprine therapy, which was discontinued after 3 weeks due to the development of pancreatitis.

After this azathioprine reaction, the patient was diagnosed with a mood disorder with mixed features of depression and anxiety. At that point, he was placed on paroxetine 25 mg, which was increased to 75 mg daily.

His mood symptoms remained stable, but he continued to have recurrent episodes of rectal bleeding while on the previously described mesalamine regimen. He required multiple courses of prednisone, with tapers lasting several months. These occurred roughly 3 times yearly for a 3-year period. His course was further complicated by 2 episodes of *Clostridium difficile* colitis, which were treated with oral metronidazole and an unspecified probiotic tablet.

Because of ongoing hematochezia and symptomatic anemia on mesalamine therapy, the patient was prescribed infliximab as an alternative to colectomy. Eleven days after receiving his first infusion, he noted a decrease in appetite and a sensation of panic. He was placed on a short course of steroids, which improved his appetite. He tolerated his second infusion well but 24 days later developed shaking chills and a severe headache.

He was hospitalized and treated with intravenous steroids and fluids for a presumptive diagnosis of delayed hypersensitivity. After additional findings included fever of 104°F and an elevated leukocyte count (15,000/ μ L), his diagnosis was changed to sepsis; steroids were discontinued and antibiotics were added.

The patient recovered, was discharged, and received his third infliximab infusion. Ten days later, he presented with nausea, vomiting, anorexia, and severe panic symptoms, described by the patient as “terrors.” Quetiapine was prescribed at 100 mg by mouth 2 times daily.

After his induction series of infliximab infusions, the patient reported that his hemochezia, diarrhea, and urgency symptoms had dramatically improved but his psychiatric symptoms were too severe to consider continuing this medication. After discussion with his local gastroenterologist about remaining therapeutic options, he presented to the authors' tertiary referral center clinic for a second opinion.

On presentation, the patient's colitis symptoms consisted of approximately 2 bloody bowel movements daily. He described decreased energy and easy fatigue with marked levels of dysphoria, discouragement, anhedonia, agitation, irritability, loss of interest, absent appetite, indecisiveness, poor concentration, worthlessness, insomnia, and absent sexual interest. He acknowledged suicidal fantasies with his hopelessness but denied potential for carrying these through. A Patient Health Questionnaire-9 score was 24 points out of 27, indicating severe depression.¹

His medication regimen consisted of balsalazide 750 mg, 3 tablets by mouth 3 times daily; alprazolam 1 mg, 4 to 5 tablets by mouth daily; quetiapine 50 mg, 2 tablets by mouth 2 times daily; mesalamine retention enema, 4 grams per rectum nightly; probiotics, not otherwise specified, 2 tablets by mouth daily; and multivitamin, 1 tablet by mouth daily.

On examination, the patient's vital signs, skin, head, eyes, ears-nose-throat, thyroid, lymph nodes, heart, lungs, rectum, neurologic system, and musculoskeletal system were normal. There was mild epigastric tenderness on deep palpation. His mental status exam showed that affect was reserved, dysphoric, and apprehensive; he did not maintain eye contact. He was otherwise pleasant, cooperative, and casually and comfortably dressed. Although speech and language were mildly slowed and soft, abnormalities to his thought form or content were not observed nor were perceptual distortions. His attention, concentration, judgment, and insight were largely intact.

Laboratory study results are listed in Table 1. Colonoscopy showed moderately severe, left-sided chronic colitis. Biopsies were negative for cytomegalovirus. Stool studies were negative for Salmonella, Shigella, Campylobacter, Aeromonas, and *E. coli*

Table 1
Results of Laboratory Tests

Variable	Value	Reference Range
Hematocrit	12.4	38.8%–50%
Hemoglobin	38.8	13.5–17.5 g/dL
Mean corpuscular volume	72.4	81.2–95.1 fL
Leukocyte count	8.1	3.5–10.5 $\times 10^9$ /L
Neutrophils	6.46	1.7–7.0 $\times 10^9$ /L
Monocytes	0.70	0–0.9 $\times 10^9$ /L
Lymphocytes	0.86	0.9–2.9 $\times 10^9$ /L
Basophils	0.04	0–0.3 $\times 10^9$ /L
Eosinophils	0.06	0.05–5.0 $\times 10^9$ /L
Platelet count	388	150–450 $\times 10^9$ /L
Erythrocyte sedimentation rate	5	0–22 mm/h
Ferritin	7	24–336 mcg/L
Sodium	141	135–145 mmol/L
Potassium	4.1	3.3–5.2 mmol/L
Creatinine	1.0	0.8–1.3 mg/dL
Blood urea nitrogen	11	8–24 mg/dL
Alkaline phosphatase	104	45–115 U/L
Aspartate aminotransferase	25	8–48 U/L
Alanine aminotransferase	18	7–55 U/L
Bilirubin, total	0.3	0.1–1.0 mg/dL
Albumin	4.4	3.5–5.0 g/dL
C-reactive protein	6.3	< 8.0 mg/L

O157:H7 but positive for *Clostridium difficile* toxin by rapid polymerase chain reaction assay.

The patient declined psychiatric hospital admission. He was then treated for recurrent *Clostridium difficile* colitis with oral vancomycin 125 mg every 6 hours for 10 days. His energy level and hemochezia improved within 6 days. Over the next 2 months, he noted gradual improvement in his mood symptoms and anorexia with a weight gain of 6.2 kilograms.

Discussion

The authors report a case of organic anxiety disorder worsening with severe features, including suicidal ideation, after administration of infliximab for ulcerative colitis. To the best of the authors' knowledge, this has been reported only once previously.² As in that case, the present report highlights the temporal association in which infliximab infusion preceded the anxiety and panic symptoms. Although this patient had pre-existing mood disorder symptoms, he had never previously had symptoms of this severity, and his symptoms improved significantly after discontinuation of infliximab. Moreover, he had recurrence of the same symptom pattern with rechallenge.

In the only prior detailed case report, Roblin et al² described a young woman who had severe panic attacks after infliximab

administration and a suicide attempt with rechallenge of infliximab for Crohn's disease.

Among more than 5,700 patients with inflammatory bowel disease and inflammatory arthritis who have been treated with infliximab in safety and efficacy studies, manufacturer data, as reported in the package insert, show a 0.1% suicide or suicide attempt rate (Centocor, Malvern, Pennsylvania). A post-market report of 100 Crohn's patients treated with infliximab included a single anxiety event.³

While many post-market safety analyses of anti-tumor necrosis factor-alpha agents have been performed on patients with inflammatory bowel disease, the focus of data collection has been on infection, malignancy, and allergic infusion reactions; many studies have not specifically examined psychiatric effects of infliximab^{4,5-8} or adalimumab.⁹ Other studies have reported events only if serious, if meeting a minimum threshold of > 5% occurrence,¹⁰ or if plausibly related to the study drug.¹¹

However, a recent Danish population-based cohort study of infliximab safety listed depression as the fourth most common severe adverse event (behind abscess, pneumonia, and sepsis) occurring in 8 of 651 patients.¹² Another recent study from Belgium reported a suicide in a cohort of 734 infliximab-treated patients.¹³ There were no such events in a 666 non-infliximab-treated inflammatory bowel disease control group.

The biologic mechanism for this effect is unknown. While previous authors have reported that depressive disorder in inflammatory bowel disease patients may be a marker for poor treatment response to infliximab,¹⁴ others have shown benefit to mood symptoms in infliximab-treated patients with psoriasis.¹⁵ In both human and animal models, elevated levels of tumor necrosis factor-alpha have been associated with mood disorder symptoms and are decreased after therapy directed toward anxiety or depressive disorders.^{16,17} Moreover, mood symptoms have been induced in animal and human subjects who have been infused with endogenous cytokines, specifically interleukin(IL)-1 β , IL-2, and lipopolysaccharide, presumably through modulation of the hypothalamic-pituitary-adrenal axis.^{16,18-20} In human subjects with rheumatoid arthritis, blockade of tumor necrosis factor-alpha by infliximab has been shown to increase levels of IL-2 mRNA expression²¹ as well as increasing levels of IL-4 and interferon- γ in peripheral blood monocytes.²² While these effects may be associated with improved inflammatory symptoms, it may be that modification of cytokine profiles by infliximab can produce mood disturbances outside of a direct tumor necrosis factor alpha-mediated effect.

Conclusion

The occurrence of severe psychiatric illness should be studied further in the post-market setting in comparison to appropriate control patients.

Acknowledgments

Written consent for publication was obtained from the patient. Dr. Fan's contributions to this manuscript were supported by a grant from the Crohn's Colitis Foundation of America.

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