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Pseudomonas Meningitis During Vedolizumab Therapy for Crohn's disease

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To the Editor

Vedolizumab, an $\alpha 4\beta 7$ integrin antagonist, has recently been approved for induction and maintenance of Crohn's disease (CD).(1) The gut-selective immune suppression of vedolizumab provides a more favorable safety profile as compared to conventional tumor necrosis factor (TNF) antagonists; however, gut or systemic infections entering through the gut remain a potential concern. We present a patient who developed meningitis from an opportunistic pathogen potentially entering from the nasopharynx after initiating vedolizumab.

A 19 year-old woman had Crohn's disease with ulceration of the terminal ileum and colon at colonoscopy and associated symptoms of abdominal pain and diarrhea, despite therapy with certolizumab pegol, azathioprine (AZA) 2.1 milligram (mg)/kilogram (kg) and budesonide 9 mg daily. Certolizumab was discontinued. Vedolizumab 300 mg IV was administered, AZA and budesonide were continued. The patient presented to the emergency department ten days after her first vedolizumab infusion with fever, body aches, photophobia, and headache. The patient had a fever (39.5°C), tachycardia, nuchal rigidity, and right lower quadrant abdominal tenderness. White blood cell (WBC) count was 8.9×10^9 cells/microliter with 16% bands. Empiric treatment for meningitis was initiated with cefepime, ampicillin, vancomycin, and acyclovir, as well as methylprednisone. Lumbar puncture (on antibiotics) revealed an opening pressure of 21 cm water, WBC of 3 cells, glucose of 49 mg/deciliter (dL), total protein of 10 mg/dL, and negative herpes simplex virus PCR. The culture grew *pseudomonas stutzeri*. AZA was held and the patient was treated with cefepime for 2 weeks. The patient recovered from the meningitis but continued to have diarrhea, and eventually vedolizumab treatment was resumed (without AZA) along with a tapering course of prednisone.

Patients with CD are at an increased risk for serious infections, due to both disease related infections and immunosuppressive therapies.(2) By selectively inhibiting $\alpha 4\beta 7$ integrin interaction with mucosal addressin cell adhesion molecule (MAdCAM1), vedolizumab blocks T-lymphocyte trafficking to the gut and nasopharynx where MAdCAM1 is expressed on the vascular endothelium. The phase 3 randomized controlled trial for CD revealed a slightly higher numeric but not statistically significant risk for serious infections with VDZ as compared to placebo (relative risk 1.48, 95% CI: 0.67, 3.24).(1) During the phase 3 trials for UC and CD, 2 cases of viral meningitis and 1 case of *Listeria* meningitis were reported

in vedolizumab-treated patients.(3) The case of *Listeria* meningitis occurred in the setting of concomitant AZA therapy and systemic steroids. While an estimated 10% of the population is colonized with *Listeria monocytogenes*, listeriosis is typically only seen in immunosuppressed individuals.(4) The occurrence of *Listeria* meningitis may potentially have been secondary to gut translocation in an immunosuppressed individual.

Pseudomonas stutzeri, an aerobic gram-negative bacillus, is typically an asymptomatic colonizer of the respiratory tract and rarely pathogenic. Although bacteremia and pneumonia have been reported, meningitis is extremely rare with less than 5 cases reported to date, all in the setting of systemic immune suppression.(5–8) Our patient was receiving AZA and budesonide and had only recently discontinued certolizumab. The timing of infection with initiation of vedolizumab, however, raises the possibility of a drug related adverse event. Although vedolizumab has a gut selective mechanism, there is a slight increase in risk of infections which is largely attributed to an increased incidence of upper respiratory tract infections (23% vs. 19%) and inhibition of $\alpha 4\beta 7$ /MAdCAM1 interaction in the nasopharynx.(1) Therefore, inhibition of leukocyte trafficking and immune surveillance by vedolizumab in the nasopharynx may have led to bacterial translocation, resulting in meningitis. Although a clear causal association cannot be made given the patient's concomitant AZA use, this potential association warrants additional future scrutiny in patient populations where respiratory and nasopharyngeal colonization with resistant organisms is common.

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