

Ixekizumab Associated New-Onset Inflammatory Bowel Disease

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ABSTRACT

Ixekizumab is a monoclonal antibody targeting interleukin-17 approved for the treatment of psoriasis. In a recent post hoc meta-analysis of Phase-I to Phase-III clinical trials of anti-interleukin-17 agents for the treatment of plaque psoriasis, there was a rare association (<1%) with induction or exacerbation of inflammatory bowel disease. We report a case of new-onset ileal Crohn's disease in a 48-year-old woman on ixekizumab for psoriasis.

INTRODUCTION

Interleukin-17 (IL-17) is a proinflammatory cytokine secreted by a variety of immune cells including T-helper 17 cells. Inhibition of IL-17 by secukinumab, brodalumab, and ixekizumab has been shown to be beneficial in the treatment of plaque psoriasis.¹⁻³ Interestingly, IL-17 has also been shown to have higher expression in the intestinal mucosa of patients with inflammatory bowel disease (IBD).⁴ However, clinical trials investigating IL-17 inhibition in IBD have not only failed to demonstrate clinical efficacy but also suggest that it may cause relapse in patients with IBD.^{5,6} Common adverse events associated with ixekizumab are nasopharyngitis, upper respiratory infection, injection site reaction, and headache.

CASE REPORT

A 48-year-old woman presented to the emergency department with a 2-day history of abdominal pain and vomiting. On initial assessment, her blood pressure was 121/72 mm Hg; there were no symptoms or signs of infection present. Her medical history consisted of chronic diffuse plaque psoriasis for which she had been started on ixekizumab therapy approximately 12 weeks before presentation. She was diagnosed with psoriasis approximately 15 years before presentation and had previously been treated with calcipotriol and betamethasone ointments, as well as phototherapy; however, she failed to respond to these previous therapies approximately 5 months before this presentation. She was thereafter on cyclosporine for 2 weeks, stopped because of elevation in her blood pressure and subsequently was on methotrexate for approximately 5 weeks. Owing to failure to respond and developing nausea with methotrexate, she was then switched to ixekizumab which she was on for 12 weeks before presentation.

On review of systems, she reported having experienced intermittent erythema, warmth, and swelling of the small joints of her hands, which was suspected to be psoriatic arthritis. While on ixekizumab, she had experienced significant improvement in her psoriasis and joint pains. On presentation, she did not have any inflamed joints. She had no family medical history of IBD and is a smoker with a 15 pack-year smoking history.

Her white blood cell count was elevated at 13,700/mm³, C-reactive protein (CRP) was 84.1 mg/L, and erythrocyte sedimentation rate was 32 mm/hr. Of note, she had previously presented similarly and was found to have diverticulitis. Accordingly, she underwent an abdominal computed tomography which demonstrated mural thickening in the terminal ileum and proximal cecum. Subsequently, she underwent a colonoscopy which demonstrated mild erythema and punctate ulcerations in the terminal ileum (Figure 1). Biopsies from this area demonstrated active inflammation with the presence of granuloma (Figure 2). Stains for fungus (Grocott

methenamine silver) and mycobacteria (Ziehl-Neelsen) were negative. Random biopsies from the cecum and rest of the colon were normal. Stool cultures, parasite and *Clostridium difficile*, and human immunodeficiency virus serology were negative.

The patient was diagnosed with Crohn's disease. A subsequent literature review revealed a possible association between IL-17 inhibition by ixekizumab and induction of IBD. Ixekizumab was stopped in this patient, and then, she was started on budesonide as a bridge to definitive therapy. Thereafter, she experienced a resolution of her abdominal pain and vomiting with a decline in her CRP to 19.6 mg/L. She was discharged from the hospital with plans to follow up in the IBD clinic. In the interim, she was also seen in the rheumatology clinic and diagnosed with psoriatic arthritis. After a discussion among the gastroenterology, rheumatology, and dermatology services, the patient was started on adalimumab, which resulted in significant improvement in her Crohn's disease, plaque psoriasis, and psoriatic arthritis. She was seen in a follow-up 3 months after discharge and remained symptom-free from all 3 conditions and had a CRP of 1.9 mg/L.

DISCUSSION

In the UNCOVER trials, 14 of the 3,866 patients enrolled in the studies developed IBD. All of these patients were exposed to ixekizumab, suggesting that further evaluation is warranted to better understand the relationship between inhibition of IL-17 and IBD.⁷ During postmarket surveillance to date, there has been 1 reported case of a young man who developed ulcerative colitis after treatment with ixekizumab and 2 case reports and one case series of 3 patients who developed IBD after treatment with secukinumab.⁸⁻¹¹ In a recent post hoc meta-analysis of 7 randomized controlled and uncontrolled Phase-I to Phase-III trials of patients with moderate to severe plaque psoriasis who were on ixekizumab for up to 256 weeks, it was reported that the incidence of new-onset IBD in patients treated with anti-IL-17

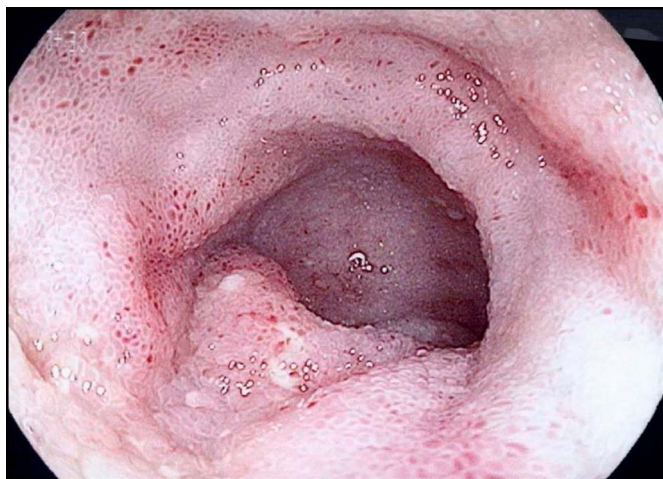


Figure 1. Colonoscopy demonstrated mild erythema and punctate ulcerations in the terminal ileum.

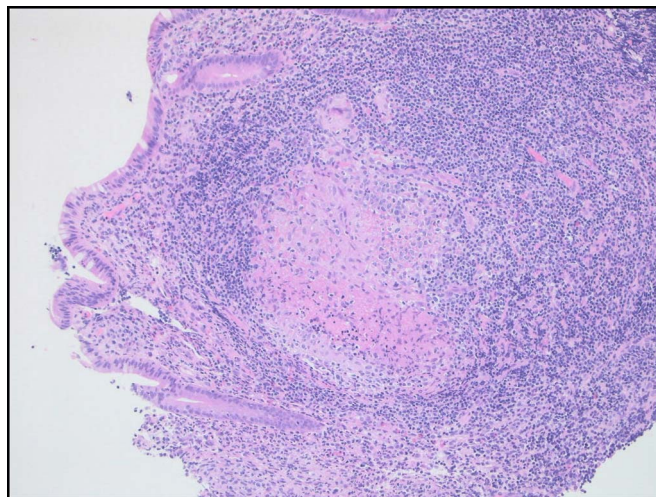


Figure 2. Biopsies from the terminal ileum demonstrated active inflammation with the presence of granuloma.

agents was reported as 2.4 cases per 1,000 patients-years (<1%).¹² This may represent an underestimation because post hoc analyses lack prospective assessment for prespecified symptoms suggestive of new-onset IBD.

Psoriasis and IBD are both thought to be autoimmune conditions with a well-known association. Many biologic agents aiming at inhibition of proinflammatory cytokines (tumor necrosis factor- α , IL-6, IL-12, IL-13, IL-17, IL-18, IL-21, IL-23, and more) have been studied in both IBD and psoriasis. Biopsies from patients with IBD demonstrate higher expression of IL-17.⁴ Although murine studies have demonstrated a protective effect of IL-17 inhibition, human studies have failed to demonstrate this effect in patients with IBD.^{13,14}

Given the complexity of the immune response in psoriasis and IBD, it is possible that inhibition of 1 proinflammatory cytokine may improve 1 condition but worsen the other. Importantly, chronicity of symptoms, endoscopy, and histopathology often confirm the diagnosis of IBD. In this case, perhaps because of the relatively acute presentation, there were no chronic changes seen in the biopsy. Accordingly, other differential diagnoses for terminal ileitis remain possibilities and may be revealed with time.¹⁵

Physicians should be aware of a potential association between anti-IL-17 exposure and the induction of IBD. Future cases of such association should be reported to enrich postmarket surveillance. We suggest that before starting anti-IL-17 agents, physicians be mindful of this rare association and screen their patients with detailed personal and family history which may be suggestive of IBD. This should include at the very least a history of chronic abdominal pain, altered bowel habits, bloody bowel movements, and family history of IBD. Furthermore, we suggest that if this screening is positive, physicians consider non-anti-IL-17 agents because the use of anti-IL-17 agents may potentially cause induction of IBD.

In addition, at the time of initiation of anti-IL-17 agents, all patients should be counseled on this association and be asked to monitor for new or worsening abdominal symptoms, which may suggest induction or relapse of previously undiagnosed IBD. In patients with symptoms suggestive of IBD, in addition to thorough investigations to test for and treat other etiologies which may present similarly to acute IBD, a thorough medication history should always be taken, taking into consideration previous exposure to anti-IL-17 agents as a known but rare cause of induction of IBD. Furthermore, close follow up of these patients should always include continued consideration of other etiologies because clinical and histopathologic chronicity are often features that differentiate IBD from other causes of terminal ileitis.

DISCLOSURES

Author contributions: A. Nazarian and DT Wijeratne wrote and revised the manuscript for intellectual content. A. Grin revised the manuscript. DT Wijeratne is the article guarantor.

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REFERENCES

- Langley RG, Elewski BE, Lebwohl M, et al. Secukinumab in plaque psoriasis—Results of two phase 3 trials. *N Engl J Med*. 2014;371(4):326–38.
- Wu JJ. Phase 3 studies comparing brodalumab with ustekinumab in psoriasis. *J Psoriasis Psoriatic Arthritis*. 2018;1(2):61–.
- Leonardi C, Matheson R, Zachariae C, et al. Anti-interleukin-17 monoclonal antibody ixekizumab in chronic plaque psoriasis. *N Engl J Med*. 2012;366(13):1190–9.
- Fujino S, Andoh A, Bamba S, et al. Increased expression of interleukin 17 in inflammatory bowel disease. *Gut*. 2003;52(1):65–70.
- Hueber W, Sands BE, Lewitzky S, et al. Secukinumab, a human anti-IL-17A monoclonal antibody, for moderate to severe Crohn's disease: Unexpected results of a randomised, double-blind placebo-controlled trial. *Gut*. 2012;61(12):1693–700.
- Targan SR, Feagan B, Vermeire S, et al. A randomized, double-blind, placebo-controlled phase 2 study of brodalumab in patients with moderate-to-severe Crohn's disease. *Am J Gastroenterol*. 2016;111(11):1599–607.
- Gordon KB, Blauvelt A, Papp KA, et al. Phase 3 trials of ixekizumab in moderate-to-severe plaque psoriasis. *N Engl J Med*. 2016;375(4):345–56.
- Philipose J, Ahmed M, Idiculla PS, Mulrooney SM, Gumaste VV. Severe de novo ulcerative colitis following ixekizumab therapy. *Case Rep Gastroenterol*. 2018;12(3):617–21.
- Lozano MJF, Giménez RS, Fernández MC. Emergence of inflammatory bowel disease during treatment with secukinumab. *J Crohns Colitis*. 2018;12(9):1131–3.
- Wang J, Bhatia A, Cleveland NK, et al. Rapid onset of inflammatory bowel disease after receiving secukinumab infusion. *ACG Case Rep J*. 2018;5(1):e56.
- Vernero M, Astegiano M, Ribaldone DG. New onset of inflammatory bowel disease in three patients undergoing IL-17A inhibitor secukinumab: A case series. *Am J Gastroenterol*. 2019;114(1):179–80.
- Yamada A, Wang J, Komaki Y, Komaki F, Micic D, Sakuraba A. Systematic review and meta-analysis: Risk of new onset IBD with the use of anti-interleukin-17 agents. *Aliment Pharmacol Ther*. 2019;50(4):373–85.
- Owaga E, Hsieh RH, Mugendi B, Masuku S, Shih CK, Chang JS. Th17 cells as potential probiotic therapeutic targets in inflammatory bowel diseases. *Int J Mol Sci*. 2015;16(9):20841–58.
- Strzypa A, Szczepanik M. IL-17-expressing cells as a potential therapeutic target for treatment of immunological disorders. *Pharmacol Rep*. 2011;63(1):30–44.
- Dilauro S, Crum-Cianflone NF. Ileitis: When it is not Crohn's disease. *Curr Gastroenterol Rep*. 2010;12(4):249–58.

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