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Published in:
Dermatologic Therapy

DOI:
10.1111/dth.15151

Publication date:
2021

Document version:
Accepted manuscript

Citation for published version (APA):

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Download date: 28. May. 2024
New Onset Inflammatory Bowel Disease in Patient Treated with Secukinumab: Case Report and Review of Literature

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Author Contribution: AA contributed to the care of involved patient in the inpatient setting and contributed to the concept and design. AA, AT, CP contributed to literature search and manuscript preparation. AA, AT, CP, RB, SF contributed to critical revision of the article and final approval of version to be published.

Funding sources: None

Conflicts of Interest: Steven Feldman has received research, speaking and/or consulting support from a variety of companies including Galderma, GSK/Stiefel, Almirall, Leo Pharma, Boehringer Ingelheim, Mylan, Celgene, Pfizer, Valeant, Abbvie, Samsung, Janssen, Lilly, Menlo, Merck, Novartis, Regeneron, Sanofi, Novan, Quirient, National Biological Corporation, Caremark, Advance Medical, Sun Pharma, Suncare Research, Informa, UpToDate and National Psoriasis Foundation. He is founder and majority owner of www.DrScore.com and founder and part owner of Causa Research, a company dedicated to enhancing patients’ adherence to treatment. Ailia Ali, Arman Torosian, and Caroline Porter have no conflicts to disclose.

Informed consent: All investigators ensure that the planning conduct and reporting of human research are in accordance with the Helsinki Declaration as revised in 2013.

Manuscript word count: 1736
References: 22
Figures: 1
Tables: 0
Keywords: Crohn’s disease, gastrointestinal bleed, interleukin-17, IL-17, IL-17 inhibitor, inflammatory bowel disease, psoriasis, secukinumab, ulcerative colitis

This is the author manuscript accepted for publication and has undergone full peer review but has not been through the copyediting, typesetting, pagination and proofreading process, which may lead to differences between this version and the Version of Record. Please cite this article as doi: 10.1111/dth.15151

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Abstract:
BACKGROUND: Psoriasis is a chronic autoimmune skin disorder that can vary in severity and extent of disease. While localized disease can be managed with topical medications, widespread disease often requires systemic therapy including biologics. This medication class targets different components of the immune system and thus modulates disease activity. The biologic secukinumab is a human monoclonal antibody against interleukin-17A used for the treatment of psoriasis and psoriatic arthritis; cases of inflammatory bowel disease (IBD) have been observed in clinical trials to be associated with this medication.

OBJECTIVE: This review aims to provide evidence for the relationships between secukinumab treatment and the development of inflammatory bowel disease.

METHODS: We have examined review articles and original research papers, published between 2010 and 2020, using the following keywords: psoriasis, psoriatic arthritis, secukinumab, inflammatory bowel disease, Crohn’s disease, ulcerative colitis, interleukin-17, IL-17, IL-17 inhibitor.

RESULTS: Case reports have noted an association between secukinumab use and IBD and have called for IBD pre-screening in patients who will be prescribed this medication. Clinical trials concluded that secukinumab was associated with IBD, while retrospective studies have had mixed results, with most studies showing no statistical significance between secukinumab and IBD but having seen patients with history of IBD or family histories experience new-onset IBD or flare-ups.

CONCLUSION: Given the utilization of secukinumab as a therapy for psoriasis and psoriatic arthritis, appropriate screening and risk stratification could help limit morbidity and mortality that can be associated with secukinumab-induced IBD.

Case Report:
A 70-year-old female with plaque psoriasis on secukinumab therapy presented with hematochezia and hemorrhagic shock, had an acute two-gram drop in hemoglobin, and consequently required intensive care unit (ICU) admission. After hemodynamic stabilization, patient underwent a sigmoidoscopy, which revealed deeply ulcerated and edematous mucosa, with friable tissue covering 50% of circumference throughout the rectosigmoid colon. (Figure 1). Biopsies were taken, and pathology showed chronic active colitis, with large, ulcerated mucosa associated with inflammatory debris and prominent acutely and chronically inflamed granulation tissue with extensive plasma cell infiltrate. A diagnosis of inflammatory bowel disease (IBD)-indeterminate colitis resulting from secukinumab therapy was made. Secukinumab therapy was discontinued, and the patient was initiated on intravenous methylprednisolone. Two weeks after steroid therapy initiation, repeat sigmoidoscopy demonstrated reparative changes of the colonic epithelium (Figure 1). The patient was transitioned to a two-month oral prednisone taper. After one month, the patient unfortunately developed recurrent bleeding requiring embolization of a sigmoid branch of the inferior mesenteric artery, at which time the prednisone taper was further extended. At dermatology follow-up, the patient was started on ustekinumab, an IL-12/23 inhibitor, for psoriasis treatment, with no recurrent episodes of gastrointestinal bleeding.

Ten years prior to this episode, patient had baseline screening colonoscopy which showed diverticulosis in the descending and sigmoid colon but no evidence of inflammatory changes. Based on the benign colonoscopy, a ten-year routine follow-up screening was recommended. The patient started secukinumab four years prior to this presentation and used it intermittently due to
issues with insurance authorization. One year before presentation, the patient restarted secukinumab, and one month following that re-initiation, presented with hematochezia at an outside facility. Colonoscopy and biopsy obtained at that time showed concern for ulcerative colitis. Patient stopped secukinumab for a few months after that event, and the hematochezia resolved. She restarted secukinumab six months prior to this case’s presentation, and at an interval dermatology visit, she did report recurrent hematochezia but unfortunately did not have follow-up until hospital admission.

Discussion:
Secukinumab is a monoclonal antibody directed against IL-17A used for treatment of psoriasis, psoriatic arthritis, and ankylosing spondylitis.\textsuperscript{1,3,11} While IL-17A is a proinflammatory cytokine, it may have a paradoxically protective role in IBD.\textsuperscript{9-10,12,14-15} In clinical trials, secukinumab increased risk of developing IBD.\textsuperscript{2,17,18} Despite this finding, multiple retrospective studies have failed to establish an association between secukinumab and IBD development.\textsuperscript{1-3,6,9-10} One retrospective study of 10 phase 2/3 clinical trials found the exposure-adjusted incidence rate per 100 subject years for secukinumab was 0.33, which authors considered low and comparable to etanercept’s 0.34.\textsuperscript{1} Additionally, the same study reported no clinically meaningful difference between incidence of IBD during treatment with secukinumab over 12 weeks and 52 weeks, indicating longer term use did not increase risk of IBD.\textsuperscript{1} The study also only reported three cases of Crohn’s disease flares, two with pre-existing diagnoses and one possible new-onset in a patient who had previously experienced gastrointestinal (GI) issues.\textsuperscript{1}

Further large retrospective studies have not found a significant statistical association with the use and secukinumab and IBD development.\textsuperscript{2,3} One retrospective analysis of 16,690 patients who either received anti-IL-17 treatment or placebo found 12 new cases of IBD, all of which occurred in those receiving anti-IL-17 treatment; eight of those cases occurred in patients receiving secukinumab in particular. However, this proportion of IBD development in secukinumab versus other anti-IL-17 drugs and placebo was not statistically significant.\textsuperscript{10}

It is important, however, to recognize limitations of such retrospective studies. Many patients with active IBD were excluded from these trials, which may limit our understanding of secukinumab’s contribution to IBD exacerbations.\textsuperscript{6,9} Furthermore, many of these studies lack a control group against which to compare their results.\textsuperscript{3} Lastly, given secukinumab’s association with worsening IBD in a phase 2 clinical trial, physicians may have been hesitant to prescribe secukinumab to patients with GI problems, thereby precluding them from the treatment pool and consequently introducing bias in these studies.\textsuperscript{2}

Despite retrospective studies failing to show an association between secukinumab and IBD development, in a randomized phase 2 clinical trial, patients treated with secukinumab for Crohn’s disease were more likely to experience exacerbations and serious adverse effects compared to placebo.\textsuperscript{18} The clinical trial was terminated prematurely as a result, and subsequent genetic analysis of patients revealed that a polymorphism in the TLA1 gene was associated with persistent inflammation following treatment with secukinumab, hinting at the role genetics may play in the development of IBD in patients treated with secukinumab.\textsuperscript{18} In a phase 2 randomized clinical trial of another anti-IL-17 agent, brodalumab, CD worsening was also detected at a higher rate in the anti-IL-17 treatment group compared with the placebo group (25.0\% vs 6.3\%), leading to the early
termination of the study. In addition to the clinical trial on secukinumab multiple case reports have emerged reporting patients who developed IBD while on secukinumab. Many of them had family histories or previous symptoms of IBD further supporting the role of genetic polymorphism.

In addition, it has been noted in literature that withdrawal of secukinumab along with steroid therapy can lead to improvement of patients’ condition. In 2019 Ribaldone et al. published a case series of three patients who developed new-onset IBD while undergoing secukinumab treatment. The second patient receiving treatment for ankylosing spondylitis achieved remission three months after stopping secukinumab treatment and starting oral steroids, while the third patient achieved remission only after switching to ustekinumab.

Given existing literature, it becomes important to understand if and how IL-17A plays a protective role in the development of IBD. In a mouse model study, inhibition of IL-17A led to increased severity of dextran sulfate sodium (DSS)-induced colitis. Inhibition of IL-17A or the IL-17 receptor A (IL-17RA) led to exacerbation of colitis in mice. Additionally, inhibition of IL-17RA led to decreased neutrophil aggregation, intestinal epithelial barrier breakdown, and decreased gut antimicrobial peptide expression, all of which favored bacterial invasion and increased gut permeability, ultimately leading to inflammation. With the association between IL-17A and epithelial barrier function in mind, a retrospective study of patients in Sicily undergoing secukinumab treatment for dermatologic or rheumatologic indications found 1% of all patients developed IBD, a percentage higher than in previous retrospective studies. This finding further complicates conclusions that could be drawn from retrospective studies and is consistent with clinical trials which reported that IL-17A blockade is associated with increased IBD risk. Following two more case reports of IBD in patients undergoing treatment, clinicians have begun to warn against use of secukinumab in patients with IBD and suggested close monitoring for digestive manifestations. As more literature has become available on the topic, many have called for screening patients for IBD risk before beginning secukinumab therapy. Genetic polymorphisms may stratify risk and be worth considering before prescribing secukinumab. Fecal calprotectin may be another viable screening tool. Practical considerations have even stated that in patients with a fecal calprotectin level above 250µg/g, a gastroenterological evaluation is indicated to rule out active IBD, in which case secukinumab may be best avoided. Additionally, screening for serum perinuclear anti-neutrophil cytoplasmic antibodies (p-ANCA), associated with ulcerative colitis, and anti-saccharomyces cerevisiae antibodies, associated with Crohn’s disease, may be useful in patients experiencing GI symptoms before initiating secukinumab therapy. As more literature is added for secukinumab-induced IBD or flares, it may be prudent to develop a scoring system to determine which patients could be at high or low risk for developing IBD, with points given for previous family history of IBD, previous GI symptoms, previous autoimmune attacks, elevated fecal calprotectin, genetic polymorphisms, and elevated serum markers. Scoring tests already in use for assessing level of clinical disease activity in IBD patients, such as the Crohn's Disease Activity Index (CDAI), may be another viable tool which may help identify those at greater risk of exacerbations. By identifying these at-risk patients, it may be possible to avoid secukinumab-induced IBD exacerbations and flares. With the use of non-invasive tests and scoring systems to identify potential at-risk patients, it may become possible to reduce the risk of secukinumab-induced IBD flares or new-onset IBD.
Conclusion:
The unusual facets of our case include patient’s older age, which is unusual for a new diagnosis of IBD, lack of family history of IBD, and prior negative colonoscopy at age 60 which suggests new-onset IBD after starting secukinumab therapy. While it may be possible that the patient developed IBD after her last colonoscopy, it is rare for patients in her age group to develop this condition, as reports noted only 10% of patients with IBD will have their first flare at age >60 years.\textsuperscript{22} This patient unfortunately was not tested for any genetic polymorphisms that may have contributed to her condition. Additionally, this case, in which the patient developed hematochezia and hemorrhagic shock due to her IBD, highlights that significant morbidity can occur with presumed secukinumab-induced IBD. Implementation of IBD risk screening prior to prescribing secukinumab would likely reduce, but not eliminate, risk of secukinumab-induced IBD and associated adverse events as it would allow early identification of patients that could suffer such adverse events.
References:


Figure 1.
Colonoscopy photos from baseline colonoscopy with diverticulosis in descending and sigmoid colon, otherwise normal. Sigmoidoscopy photos after patient treated with secukinumab (post-secukinumab) showing ulcerated and edematous mucosa in sigmoid colon. The colonoscopy after steroid therapy (post-steroid treatment) shows healing ulceration and scarring consistent with prior inflammation in the sigmoid colon.