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REVIEW

# Inflammatory bowel disease in patients with psoriasis treated with interleukin-17 inhibitors

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## Abstract

**Background:** Interleukin 17 (IL-17) inhibitors provide an excellent treatment option for patients with psoriasis and psoriatic arthritis, resulting in high levels of efficacy for skin clearance and joint improvement. Safety has also been established in clinical trials for this group of biologic agents; however, rare case reports of exacerbation or induction of inflammatory bowel disease (IBD) have been reported in the literature. No causal relationship has been established. When IL-17 inhibitors were investigated for the management of IBD, no benefit was found and worsening of disease was noted for some patients. IBD is more common in patients with psoriasis and, therefore, it remains unknown if these drugs cause de novo IBD or if the reported cases of IBD in patients on IL-17 therapy is due to the background risk in this predisposed population who may have already had an underlying or subclinical disease.

**Methods/Results:** A literature search was conducted for the terms 'IL-17 inhibitor,' 'ixekizumab,' 'secukinumab,' 'brodalumab' and 'inflammatory bowel disease,' 'ulcerative colitis,' and 'Crohn's disease' in PubMed and Google Scholar. Cases of new-onset or exacerbation of IBD were identified in the literature along with postmarketing pharmacovigilance data. These cases will be reviewed in this paper.

**Conclusions:** IL-17 inhibitors have proven efficacy for the treatment of psoriasis and psoriatic arthritis with a strong safety profile. However, rare cases of IBD onset and exacerbation in patients on IL-17 inhibitors have been reported in the literature, highlighting the need to select patients and therapeutic choices appropriately when treating this population.

**Keywords:** brodalumab, Crohn's disease, IL-17 inhibitor, inflammatory bowel disease, ixekizumab, secukinumab, ulcerative colitis

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## Introduction

Plaque psoriasis is a chronic, hyperproliferative, immune-mediated inflammatory condition characterized by skin manifestations of well-demarcated erythematous plaques with silvery scale.[1] There is a significant impact on the health, well-being, and quality of life of those affected. Although there is no cure for psoriasis and related immune-mediated conditions such as psoriatic arthritis (PsA) and ankylosing spondylitis (AS), various biological agents have been helpful for the management of these conditions.[2,3] A better understanding of the pathogenesis underlying psoriasis has led to significant advancements and highly effective treatments. As the interleukin (IL)-23/T helper (Th)17 pathway plays a pivotal role in the pathogenesis of various autoimmune diseases, there has been interest in targeting this pathway for their treatment.[2,4] Ixekizumab (IXE), secukinumab (SEC), and brodalumab are IL-17 inhibitors that have been approved for the treatment of psoriasis (Table 1).[2] Both IXE and SEC work by inhibiting IL-17A, while brodalumab blocks the IL-17 receptor, thereby blocking all IL-17 isoforms.[2] Bimekizumab is an additional anti-IL-17 agent in clinical trials, which blocks IL-17A and F, and netakimab is an IL-17 inhibitor studied and available only in Russia (Table 1).[5,6]

Psoriasis can be accompanied by multiple comorbidities, including cardiovascular disease, malignancy, PsA, and

**Table 1. Current IL-17 inhibitors available or in development.**

| Drug | Name | Target | Approvals | First approval |
|---|---|---|---|---|
| Bimekizumab | In phase 3 | IL-17 A, F | Not yet approved | N/A |
| Brodalumab | Siliq™/Kyntheum® | IL-17 RA | Psoriasis | 2018 |
| Ixekizumab | Taltz® | IL-17 A | Psoriasis, PsA, AS | 2017 |
| Secukinumab | Cosentyx® | IL-17 A | Psoriasis, PsA, AS | 2015 |
| Netakimab* | Efleira® | IL-17 A | Psoriasis | 2019 |

*Approved in the Russian federation only.
AS, ankylosing spondylitis; IL, interleukin; PsA, psoriatic arthritis.

inflammatory bowel disease (IBD).[7,8] IBD, although a less common comorbidity, can occur and manifest itself in two forms: ulcerative colitis (UC) and Crohn's disease (CD).[9] The estimated prevalence of IBD in psoriasis patients is 1–2% compared to 0.4% of the general population.[10] Although an association between IBD and psoriasis has been reported, the pathophysiologic link between these comorbidities is not well defined.[9] The immune pathways of psoriasis and IBD share in common IL-23/Th17 axis.[9,4] The two main cytokines involved in the IL-23/Th17 pathway are IL-23 and IL-17.[11]

IL-17 is a pro-inflammatory cytokine and key effector molecule,[5,12] and the IL-17 family is composed of a total of six proteins ranging from IL-17A to IL-17F. The two proteins that exhibit the greatest amount of homology are IL-17A and IL-17F, with IL-17A being more potent than its counterpart. IL-17E exhibits the least amount of homology and helps to regulate the activities of IL-17. Proteins IL-17B–D are known as pro-inflammatory cytokines, but their biological role is not entirely made clear within the body.[13] The multiple IL-17 isoforms are derived from a number of cell types, including Th17 and innate immune cells.[5,11] When stimulated by IL-23, naïve T cells differentiate into a Th17 phenotype and also then produce IL-17, which induces inflammatory responses within the gut and skin.[4,5,11] The Th17 cells are a heterogeneous group capable of secreting a diverse variety of cytokines, including IL-6, tumor necrosis factor (TNF), IL-17A, IL-17F, IL-21, and IL-22. There is functional redundancy and reciprocal regulation between IL-17A, IL-17F, and IL-22, and the IL-17 cytokines may consequently drive mucosal inflammation while aiding restitution and repair of the intestinal mucosa following the resolution of inflammation.[14,15] Ultimately, IL-17 is reported to affect epithelial cells, keratinocytes, endothelial cells, fibroblasts, and synovial cells.[5] Due to the role of IL-17 as an effector cytokine regulating the immune responses within the body,[16] targeting this molecule has been successful in the management of psoriasis and PsA. Responses in the treatment of psoriasis are rapid and have exceeded those of previous therapies including TNF antagonists and IL-12/23 inhibitors, with up to 80% of patients achieving clear or almost clear skin.[17–22] Similarly, responses in PsA have matched that of the current gold standard treatment with TNF-antagonists.[23]

Psoriasis and IBD can be treated concurrently because they share common inflammatory pathways.[9] Targeting of TNF-alpha and IL-12/23 has been successful in treating both psoriasis and IBD.[24–26] Unfortunately, studies targeting IL-17 have not shown consistent results in the treatment of both conditions.[9] Clinical trials for IL-17 blockade to treat IBD were either unsuccessful or stopped early due to exacerbation of disease.[27,28] Since complex pathways are being targeted, some patients may develop diarrhea, abdominal pain, and rectal bleeding associated with IBD, while in others the response provides a protective role.[29] Thorough review of the incidence of IBD in clinical trials for IL-17 antagonists has not shown an increased rate of IBD above the background population;[8] however, longer-term studies may be required to identify the true risk. The question remains as to whether IBD develops in predisposed patients despite treatment with an IL-17 antagonist or if targeting IL-17 causes the development of de novo IBD in those individuals with psoriasis, PsA, and AS. This paper reviews all incident cases and exacerbations of IBD reported in the literature during wide-scale use of IL-17 inhibitors beyond the clinical trials.

## Methods

A literature search was completed for the terms 'IL-17 inhibitor,' 'ixekizumab,' 'secukinumab,' 'brodalumab' and 'inflammatory bowel disease,' 'ulcerative colitis,' and 'Crohn's disease' in PubMed and Google Scholar. Cases of new-onset or exacerbation of IBD were identified in the literature along with postmarketing pharmacovigilance data. These cases are reviewed here.

## Cases of IBD related to IL-17 therapy in the literature

Over a 2-year period (2018–2019), multiple case reports were published regarding the onset of IBD after initiating SEC or IXE for the treatment of psoriasis, PsA, and AS (Table 2). The authors identified 21 references in the literature; however, one case was identified as a duplicate as it was published twice in the literature and therefore 20 unique publications reporting on 27 patients were identified.[3,16,29–42]

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**Table 2. Case reports of IBD with IL-17 inhibition reported in the literature.**

| Reference | Drug | Treating | Age of onset | Diagnosis | Duration of therapy | Med History | Treatment | Notes |
|---|---|---|---|---|---|---|---|---|
| Grimaux et al. 2018[30] | SEC | AS | 36F | Ileo-pancolitis | NR | N | UST/steroids | Aphthous ulcers |
| Fobelo Lozano et al. 2018[31] | SEC | Psoriasis (1)<br>AS (1) | 19F | Ileocolic CD<br>UC | 2 mos<br>3 wks | N<br>N | UST/steroids<br>IFX | 2 cases |
| Philipose et al. 2018[3] | IXE | Psoriasis | 31M | Severe UC with C. diff + CMV | 3 mos | N | Abx/steroids/IFX | Duplicate case in the literature |
| Shukla et al. 2018[29] | SEC | Psoriasis (3) | 49F<br>54M<br>28M | Severe colitis | NR | N | 1. Steroids/IFX<br>2. ADA/MTX<br>3. UST | 3 separate cases |
| Wang et al. 2018[16] | SEC | Psoriasis | 41F | Fulminant colitis | 1 wk | N | Steroids/CsA<br>IFX/MTX | Family history mother, daughter |
| Ehrlich et al. 2018[32] | SEC | AS | 42M | UC | 6 wks | NR | Steroids/IFX | |
| Uchida et al. 2018[33] | SEC | Psoriasis | 41F | UC | 5 mos | N | Adalimumab | |
| Grossberg 2019[34] | IXE | Psoriasis | 66F | CD | Several mos | Y | UST/GUS/MTX | Deep remission |
| Fries et al. 2019[35] | SEC | AS, PsA, Psoriasis | 51F<br>55M<br>43F<br>44M | UC | 12 mos<br>2 mos<br>53 mos<br>48 mos | N | Steroids, ADA, Tofacitinib | 4 cases |
| Johnston et al. 2019[36] | SEC | AS | 27M | UC | 4 mos | N | Steroids/IFX | |
| Smith et al. 2019[37] | IXE | Psoriasis | 42M | Crohn's-like colitis | 12 wks | N | Steroids/UST/anti-TNF therapy | |

(*Continued*)

**Table 2.** (*Continued*)

| Reference | Drug | Treating | Age of onset | Diagnosis | Duration of therapy | Med History | Treatment | Notes |
|---|---|---|---|---|---|---|---|---|
| Marin et al. 2019[38] | IXE | Psoriasis | 76F | UC | 60 wks | N | GUS | |
| Moncada et al. 2019[39] | SEC | PsA | 42M | UC | 3 wks | N | Golimumab | Mother has UC |
| Kukol et al. 2019[40] | SEC | Psoriasis | 36M | CD | 2 yrs | N | Prednisone and GUS | Erythema nodosum |
| Achufusi et al. 2019[41] | SEC | Psoriasis | 39M | UC | 6 mos | N | Abx, IFX | Apremilast for psoriasis |
| Vernero et al. 2019[42] | SEC | Psoriasis (2)<br>AS | 27F<br>46F<br>33M | UC<br>IBD | 12 mos<br>5 mos<br>3 mos | N | | 3/5 cases histologically confirmed |
| Haidari et al. 2019[44] | SEC | Psoriasis & PsA | 69M | Asymptomatic CD | 18 mos | N | UST, GUS | Incidental finding |
| Sethi et al. 2019[45] | SEC | PsA | 52F | UC | NR | N | Tofacitinib | Failed TNF in the past |
| Paul et al. 2019[43] | SEC | Psoriasis | 41F | CD | 6 wks | Y | Infliximab | |
| Nallapeta et al. 2019[46] | SEC | AS | 68M | CD | 14 mos | N | Methylprednisone, Mesalamine | |

Abx, antibiotics; AS, ankylosing spondylitis; C. diff, *Clostridium difficile*; CD, Crohn's Disease; CMV, cytomegalovirus; CsA, cyclosporin A; F, female; GUS, guselkumab; IBD, inflammatory bowel disease; IFX, infliximab; IL, interleukin; IXE, ixekizumab; M, male; MTX, methotrexate; mos, months; N, no; NR, not reported; PsA, psoriatic arthritis; SEC, secukinumab; TNF, tumor necrosis factor; UC, ulcerative colitis; UST, ustekinumab; wks, weeks; Y, yes; yrs, years.

Fobelo Lozano et al.[31] presented two cases and Vernero et al.[42] presented three cases where patients developed IBD after treatment with SEC for either psoriasis or AS.[31,42] Another two cases of UC and ileo-pancolitis were reported after using SEC for the treatment of AS.[30,36] The second patient also developed oral ulcers and had previous experience with similar symptoms occurring years earlier with a different treatment that targeted IL-6.[30] In a different case reported by Ehrlich et al.,[32] a patient with no prior diagnosis of IBD also developed UC after using SEC for AS treatment.[32]

Three IBD cases were reported by Shukla et al.,[29] and one case each by Kukol et al.,[40] Achufusi et al.,[41] and Paul et al.[43] where patients were treated for psoriasis with SEC.[29,40,41,43] All three patients reported by Shukla et al.[29] developed symptoms of diarrhea following the treatment, and subsequent colonoscopies indicated severe colitis in all three. Another case reported by Haidari et al.[44] using secukinumab for psoriasis was incidentally found to have CD on a screening colonoscopy and had been asymptomatic.[44] A larger case series reported from Italy presented four different cases with IBD onset (CD and UC) after using SEC for the treatment of psoriasis, PsA, or AS.[35] Out of 434 patients treated with SEC in the region, four cases (1%) presented with the onset of IBD.[35]

Wang et al. and Moncada et al. both described cases of new-onset IBD in patients with a family history of IBD – information that was not reported in the previous cases.[16,39] In the first case, abdominal pain developed 1 week after receiving SEC for psoriasis with the ultimate diagnosis of fulminant colitis. Although the patient had a family history of CD and UC in her mother and her daughter, this was the patient's first presentation of gastroenterological symptoms.[16] In the second case with a family history, a 42-year-old male whose mother has UC also developed UC after receiving secukinumab treatment for PsA.[39] One patient reported by Paul et al.[43] had a prior history of quiescent indeterminate colitis, which resulted in a diagnosis of Crohn's colitis after starting secukinumab for psoriasis.[43]

Philipose et al.,[3] Grossberg,[34] Smith et al.,[37] and Marin et al.[38] also reported IBD after administering IXE to patients with psoriasis. One IXE case was a young patient who experienced abdominal pain along with bloody diarrhea after being treated with IXE, which ultimately led to a diagnosis of a new onset of UC.[3] The second IXE case reported a patient with a previous history of CD that was exacerbated after treatment initiation.[34] The third case reported a 42-year-old male who was treated with IXE for his plaque psoriasis and was diagnosed with Crohn's-like colitis.[37] Lastly, an onset of abdominal pain, fever, and weight loss was seen in a mature patient during treatment with IXE with an ultimate diagnosis of UC.[38] All reports concluded that there was a risk of possible IBD induction and worsening, and recommended the monitoring of patients using IXE.[3,34,37,38]

The authors report on 20 unique publications of IBD, including a total of 27 cases (Table 2).[3,16,29–46] All patients with psoriasis, PsA, or AS who presented with IBD symptoms arising after the administration of the IL-17 inhibitors, SEC, and IXE were reported. In all cases, the IL-17 inhibitor was stopped and the subsequent treatments required to control the bowel disease, summarized in Table 2, consisted of a combination of antibiotics, methotrexate, steroids, tofacitinib, TNF inhibitors, IL-12/23 inhibitor (ustekinumab), or IL-23 inhibitor (guselkumab); all reported successful treatment with clinical remission (see Table 2 for details).[3,16,29–46]

## Pharmacovigilance and epidemiologic evidence

Three large studies of pharmacovigilance or epidemiologic evidence were found in the literature (Table 3). Orrell et al.[47] used large databases including the Research on Adverse Drug Events and Reports and Northwestern Medicine Enterprise Data Warehouse to retrospectively study over 5 million cases of UC or CD patients after the use of SEC or IXE (Table 3).[47] Patients using SEC from January 2015 to August 2017 and IXE from January 2016 to August 2017 were reviewed.[47] The Food and Drug Administration Adverse Event Reporting System determined there was a safety signal for SEC from these cases.[47] They also concluded that there remains the possibility for a class effect for patients exposed to the drugs of IXE or SEC and the new development of UC or CD.[47] Mohy-ud-din et al.[48] used the Explorys (IBM, New York) database of 62 million de-identified electronic medical records to identify patients. They found 2780 patients who received secukinumab. The rates of de novo IBD in secukinumab patients were higher in this group than that of the general population (3.2 *versus* 0.74%; relative risk [RR] – 4.2; 95% confidence interval [CI]: 3.45–5.18). Of these patients, those who developed IBD were younger (age <65: 78 *versus* 65%; odds ratio [OR]: 1.92 [1.17–3.15]), more obese (body mass index [BMI]: 0.30, 22 *versus* 7%; OR: 3.91 [2.38–6.43]) and more likely to use immunomodulators (67 *versus* 10%; OR: 17.81 ([11.49, 27.61]).[48]

A recent study by Egeberg et al.[9] reviewed a cohort of 235,038 adults over the span of 20 years, matching each psoriasis group with a non-psoriasis reference group (Table 3).[9] The study found that there was a baseline association between IBD and psoriasis and that patients with psoriasis were at an increased risk for developing either CD or UC.[9] However, patients who were receiving any biologic for treatment of their psoriasis were not at any higher risk for IBD compared to the reference population, but the biologic classes were not differentiated and included those biologics that also treat IBD.[9]

## Discussion

A better understanding of the IL-23/Th17 axis has allowed for more targeted therapies as well as better control of psoriasis and additional immune disorders alike.[3] Treatment outcomes can be unpredictable, and this highlights the importance of monitoring real-world reports to understand medication

**Table 3. Large-scale pharmacovigilance and epidemiologic studies in the literature.**

| Reference | Study group | Data | Results | Notes |
|---|---|---|---|---|
| Orrell et al. 2018[47] | >5 million UC or CD patients | • Patients' data from RADAR and NMEDW repositories<br>• FAERS was examined for SEC-related UC or CD events<br>• Patients exposed to SEC (Jan 2015–Aug 2017) or IXE (Jan 2016–Aug 2017) | IBD cases determined from reviewed databases | • Safety signal for SEC found in FAERS and AE databases with a PRR of 4.65 (CI: 3.66–5.89)<br>• There remains a potential class effect for new-onset CD or UC with IL-17 inhibition |
| Mohy-ud-din et al. 2019[48] | 62 million electronic health records | • Patient data from Explorys (IBM, New York) from electronic medical records | 2870 received SEC; IBD cases identified | Rates of de-novo IBD after SEC higher than the prevalence of IBD in general population (3.2 *versus* 0.74%; RR – 4.2; 95% CI: 3.45–5.18) |
| Egeberg et al. 2019[9] | 235,038 each of Danish adult cohorts 1:1 with *versus* without psoriasis | • 20-year nationwide cohort study<br>• IBD cases were determined during the follow-up period | Psoriasis patients had increased risk of developing IBD | Less than 1% of psoriasis patients developed CD or UC – no new-onset on all biologics |

AE, adverse event; CD, Crohn's Disease; CI, confidence interval; FAERS, Food and Drug Administration Adverse Event Reporting System; IBD, irritable bowel disease; IXE, ixekizumab; NMEDW, Northwestern Medicine Enterprise Data Warehouse; PRR, proportional reporting ratio, RADAR, Research on Adverse Drug Events and Reports; SEC, secukinumab; UC, ulcerative colitis.

effects in patient populations, who may not have been included in randomized controlled trials.[32] IL-17 inhibitor therapy has been highly effective in the treatment of psoriasis, PsA, and AS, but prescribers should be aware of cases of new-onset or exacerbation of IBD so that patients can be screened and monitored appropriately for the optimal outcomes.

Psoriasis epidermal hyperplasia is substantially improved when IL-17 inhibitors are used with complete skin clearance rates up to 60% of those treated.[12] In comparison, IBD involves damage to the epithelial layers of the gastrointestinal tract.[11] It is not completely understood why IBD can arise after IL-17 inhibition in some patients. It is widely recognized that there is a higher baseline risk of developing IBD in patients with psoriasis,[9] and it is possible that many patients with psoriasis have subclinical IBD,[49] which may be unmasked with the use of IL-17 inhibitors or the disease may develop in its natural course.

It has been postulated that IL-17 may have a protective role in IBD.[50] In this case, a blockade of the ligand or the IL-17 receptor could cause an imbalance and explain the development of symptoms associated with IBD.[16] All the cases reviewed report either SEC or IXE that are widely available and used in the treatment of psoriasis, PsA, and AS. The majority of cases reported to date are with SEC use, but this is likely due to earlier introduction and higher penetration into the market and not related to the agent itself. An additional IL-17 inhibitor, brodalumab, which is newer to the market, has only a psoriasis indication and has not had the same real-world exposure, which may be why there are no cases reported to date.

Bimekizumab is still in clinical trials, and netakimab is newly available only in Russia.[5] Although there are reported cases of new-onset or exacerbation of IBD in patients treated with IL-17 inhibitors, they are rare and need to be considered in context. Before initiation of treatment, it is critical for the physician to perform a thorough history and examination and take into consideration family history and previous gastrointestinal symptomatology before initiating the use of IL-17 inhibitors. It is also important to monitor the patients for symptoms throughout therapy as cases developed anywhere from 1 week to more than 4 years after initiation of therapy.[16,32]

Although retrospective analyses of real-world experience are necessary to report remarkable findings in medicine, these studies have biases and limitations. They lack many components that yield strong empirical evidence, such as controls, randomization, and large datasets. This review summarizes rare cases of IBD following IL-17 inhibition for psoriasis, PsA, and AS to increase awareness of the possibility of this adverse event to help select appropriate patients and to monitor throughout therapy. Larger prospective studies would help increase our understanding of the connection between IBD and IL-17 inhibition and the frequency of occurrence of this rare adverse event.

## Conclusion

Although IL-17 inhibitors are safe and highly effective in the treatment of psoriasis, PsA, and AS, adverse effects

have been reported in rare cases, including the possible new-onset or exacerbation of IBD, although causality has not been established. Clinicians should be aware of the possibility of these concerns when considering this therapy. It is recommended that clinicians take a careful history of their patients prior to the initiation of treatment as well as monitor any adverse side effects that may arise following the initiation of therapy.

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