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# IL-17 inhibitor-associated inflammatory bowel disease: A study based on literature and database analysis

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**Objective:** Few real-world studies have shown clear association between interleukin (IL)-17 inhibitors and inflammatory bowel disease (IBD) onset. This study investigated the reporting prevalence and evaluated the clinical features and management of IL-17 inhibitor-related IBD events.

**Methods:** We used the US FDA Adverse Event Reporting System database and retrieved data, from 2015 to 2022, on IL-17 inhibitors to identify gastrointestinal inflammatory events and conduct disproportionality analyses by estimating the reporting odds ratios (RORs) and corresponding 95% confidence intervals (CIs). Furthermore, case reports and case series, from 2015 to 30 November 2022, on IBD induced by IL-17 inhibitors were collected for retrospective analysis.

**Results:** A total of 388 cases of primary suspected IL-17 inhibitor-associated gastrointestinal events were reported (268 IBD and 120 colitis), including 348 cases involving secukinumab (SEC), 36 cases involving ixekizumab (IXE), and 4 cases involving brodalumab (BRO). Statistically significant reporting rates of total IBD events were observed for SEC and IXE (ROR = 2.13, 95% CI [1.96-2.30] and ROR = 2.79, 95% CI [2.39-3.27], respectively), whereas BRO did not trigger a safety signal. Twenty-nine studies, which included 34 cases, showed evidence of IBD, following SEC (79.4%) and IXE (20.6%) treatment. The median age was 42 years; typical initial symptoms included diarrhea (90.9%), abdominal pain (57.6%), bloody diarrhea (51.5%), and fever (36.4%). The median time to onset of IBD symptoms was 2.9 months. Some cases were accompanied by elevated white blood cell (WBC) count (87.5%), erythrocyte sedimentation rate (ESR; 85.7%), C-reactive protein (CRP; 100%), and fecal calprotectin (FC; 100%). Cessation of IL-17 inhibitors plus treatment with corticosteroids and TNF antagonists, as either monotherapy or in combination, could lead to complete clinical remission. The median time to remission after IL-17 inhibitor discontinuation was 4 weeks.

**Conclusion:** IL-17 inhibitor treatment is associated with exacerbation and new onset of IBD and colitis. Obtaining a detailed patient history before initiation of treatment and monitoring gastrointestinal symptoms and intestinal inflammatory biomarkers during IL-17 inhibitor treatment is important for safe use of these drugs.

## KEYWORDS

IL-17 inhibitors, inflammatory bowel disease, FAERS database, pharmacovigilance, drug safety

## Introduction

Interleukin (IL)-17 is a significant proinflammatory cytokine and a therapeutic target for rheumatological diseases as blocking IL-17 reduces disease activity and improves patient quality of life (Ouyang et al., 2008). The anti-IL-17 agents secukinumab (SEC), ixekizumab (IXE), and brodalumab (BRO), which were launched in January 2015, April 2016, and July 2017, respectively, are monoclonal IgG4 antibodies directed against IL-17A (SEC and IXE), or against the IL-17 receptor (BRO) (Langley et al., 2014; Griffiths et al., 2015; Lebwohl et al., 2015), and have been used to treat various autoimmune disorders, such as psoriasis (Pso), psoriatic arthritis (PsA), ankylosing spondylitis (AS), and axial spondyloarthritis (ax-Spa) (van der Heijde et al., 2017; Menter et al., 2019; Gossec et al., 2020; Wendling et al., 2022; Ramiro et al., 2023). Promising efficacy results in dermatology and rheumatology prompted the evaluation of these drugs in treatment of inflammatory bowel disease (IBD). Unfortunately, they were ineffective and induced paradoxical events (disease exacerbation after treatment with a theoretically curative drug) that prevented approval for treatment of patients with IBD. Increasing cases of induction or exacerbation of IBD have been reported among patients treated with drugs inhibiting IL-17 (Caron et al., 2022; Burisch et al., 2020), which suggests that rheumatologists and dermatologists should increase awareness of the risk and improve safety measures to prevent drug-induced IBD, as well as evaluate patients carefully to identify any contraindications before the initiation of IL-17 inhibitor therapy for psoriasis and/or rheumatological diseases (Felice et al., 2019).

To date, the pathophysiological mechanisms underlying these paradoxical effects are not well-defined, there is limited real-world data demonstrating the association between IL-17 inhibitor therapy and the onset of IBD, and there are no clear guidelines for the management of patients who experience these adverse events. We aimed to assess differences in safety signals using the FDA Adverse Event Reporting System (FAERS) database, and describe characteristics, management, and prognosis of IBD flare or new onset in patients after anti-IL-17 drug therapy in a real-life setting, which provides valuable information about emerging gastrointestinal safety issues related to IL-17 inhibitors.

## Methods

### Pharmacovigilance study

In this study, we conducted a retrospective, disproportionality, pharmacovigilance analysis. Data from 2015 Quarter 1 (Q1) to 2022 Q3 were retrieved from the publicly available FAERS database in FDA website to evaluate the risk of gastrointestinal inflammatory conditions with the use of different IL-17 inhibitor therapies.

We assessed the use of IL-17 inhibitors in a large-scale population. Study drugs were IL-17 inhibitors on the market: SEC, IXE, and BRO. To identify IL-17 inhibitor-related records, both brand names and generic names were used. Furthermore, IBD and colitis case reports in FAERS were coded using the preferred term (PT) according to the Medical Dictionary for Regulatory Activities Terminology (MedDRA). Drugs were assigned a role (primary suspect, secondary suspect, concomitant, and interacting) by the person reporting the adverse drug reaction (ADR). ADRs were categorized into two main groups: 1)

“IBD,” including reported diagnoses of ulcerative colitis (UC), Crohn’s disease (CD), and undifferentiated IBD (uIBD); 2) “colitis,” including reported diagnoses of colitis (microscopic, ischemic, eosinophilic, and undifferentiated), proctitis, and enteritis. The effects of disproportionality analysis were evaluated using the established pharmacovigilance index reporting odds ratio (ROR), which were calculated as  $(a*d)/(b*c)$  (Supplementary Table S1). In our study, an event was defined as significant when the lower limit of the 95% CI of the ROR >1 and there were at least three cases to define a signal (van Puijbroek et al., 2002).

### Descriptive study

A comprehensive search of multiple electronic databases, including PubMed, Embase, Wanfang, China National Knowledge Infrastructure (CNKI), and China Biology Medicine disc (CBMdisc), from January 2015 to September 2022, regarding IL-17 inhibitor-induced IBD was conducted, with no language restrictions. The search terms were “secukinumab or Cosentyx”, “Ixekizumab or Taltz”, “Brodalumab or Siliq”, “Ulcerative colitis”, “Crohn’s disease”, and “Inflammatory bowel disease”. Case reports and case series were included, and reviews, mechanistic studies, animal studies, and articles for which the full text was not available were excluded. Two reviewers searched the literature independently and examined the relevant studies for further assessment of inclusion/exclusion criteria and to identify clinical characteristics; collected data included the region of patient location, age, sex, Indication of IL-17 inhibitors, medical history, time to onset, clinical manifestations, laboratory tests, histopathological examinations, treatment, and prognosis of IL-17 inhibitor-induced IBD. The time to onset of target IBD was defined as the time from the start date of IL-17 inhibitor administration to the onset of the associated IBD.

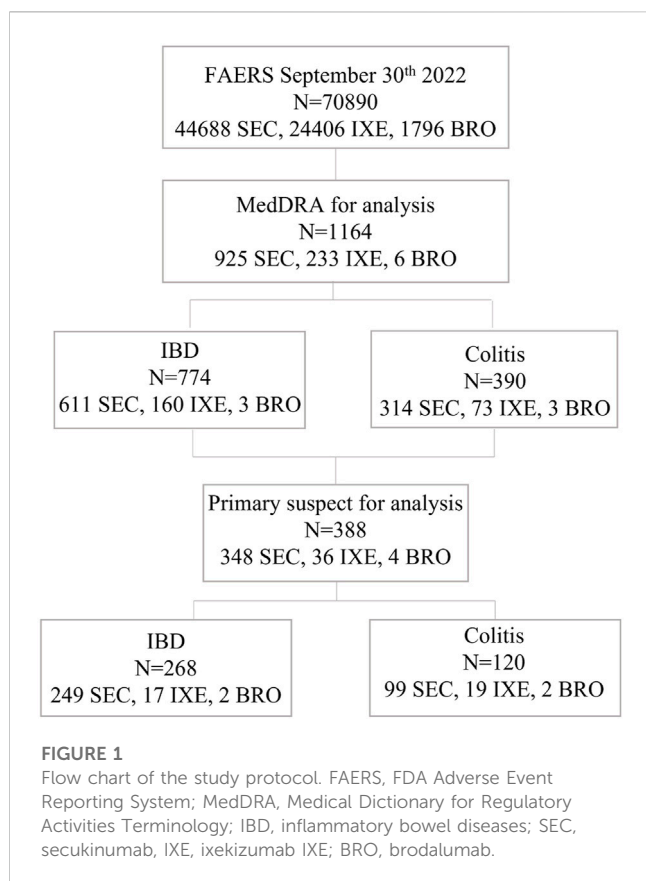
## Results

### IL-17 inhibitor-associated IBD in the FAERS database

Up to 2022 Q3, the numbers of reported adverse event (ADE) cases in the FAERS database related to SEC, IXE, and BRO were 44,688, 24,406, and 1,796, respectively. From screening individual IL-17 inhibitor-related gastrointestinal inflammatory case reports, a total of 388 cases of primary suspect IL-17 inhibitor-associated inflammatory bowel disease and colitis were reported, of which 348 were SEC, 36 were IXE, and 4 were BRO. These cases included 268 IBD diagnoses and 120 colitis diagnoses (Figure 1). The main characteristics of the patients, disease seriousness, delay of onset, and disease outcomes are detailed in Table 1.

### Disproportionality analyses

From the entire database, the disproportionality analyses identified three unique preferred terms (PTs) for IBD and 12 PTs for colitis. Globally, all cases of IBD after SEC and IXE treatment accounted for 1.36% and 0.66% of all reported cases, respectively,



and there was a statistically significant reporting rate of total IBD events observed among patients treated with SEC and IXE (ROR = 2.13, 95% CI [1.96–2.30] and ROR = 2.79, 95% CI [2.39–3.27], respectively), whereas this proportion was lower for BRO (0.17%; ROR = 1.48, 95% CI [0.48–4.6]) (Table 2). All colitis cases after SEC and IXE treatment accounted for 0.70% and 0.30% of all reported cases, respectively, and statistically significant reporting rates were also observed for total colitis events after SEC and IXE treatment (ROR = 1.60, 95% CI [1.43–1.79] and ROR = 1.96, 95% CI [1.56–2.47], respectively) (Table 3).

## Descriptive analysis

A total of 29 studies were identified in the published literature, including 25 case reports (Ehrlich et al., 2018; Grimaux et al., 2018; Paul et al., 2018; Wang et al., 2018; Achufusi et al., 2019; Grossberg, 2019; Haidari et al., 2019; Johnston and Veettil, 2019; Philipose et al., 2019; Rodriguez et al., 2019; Shimizu et al., 2019; Smith et al., 2019; Darch et al., 2020; Fieldhouse et al., 2020; Marin et al., 2020; Merino Gallego et al., 2020; Nazarian et al., 2020; Ali et al., 2021; Mu et al., 2021; Obeidat and Murakami, 2021; Ma et al., 2022; Sykaras et al., 2022; Kukol et al., 2019; Nallapeta et al., 2019; Sethi et al., 2019) and 4 case series (Fobelo et al., 2018; Shukla et al., 2018; Vernerio et al., 2019; Lee et al., 2020); a total of 34 cases raised evidence of IBD occurrence during therapy with SEC (27 cases, 79.4%) and IXE (7 cases, 20.6%). Characteristics of the included cases are presented

in Table 4. The patient sex ratio (male/female) was 1, the median age of included patients was 42 years (range 19–76 years), and 23 patients (67.7%) were between 26 and 50 years old. Data on race showed that 93.9% of patients (32 cases) were white, and two were Asian. Three patients (8.8%) had a prior history of IBD, and five patients (14.7%) had a family history of IBD. History of smoking was reported for eight patients (23.5%). The main indication for anti-IL-17 therapy was Pso (20 cases, 58.8%), followed by AS (7 cases, 20.6%), PsA (4 cases, 11.8%), and Pso with PsA (3 cases, 8.8%). Twenty-four patients had prior exposure to a TNF antagonist with inadequate response, of whom 13 received prior adalimumab and 11 received prior etanercept. The time between IL-17 inhibitor treatment start and symptom onset was assessable in 27 cases, showing a median time to onset of 2.9 months (range, 0.47–48 months); onset of symptoms occurred in 5 cases (18.5%) in less than a month, in 9 cases (33.3%) between 1 and 3 months, and in 10 cases (37.1%) between 3 and 12 months.

## Clinical manifestations and laboratory and radiological features

Among the 34 cases included, IBD classification was reported in 28 cases, with 13 cases (46.4%) identified as UC, 10 cases (35.7%) as CD, and 5 cases (17.9%) as unclassified IBD. Symptoms were reported for 33 patients; the most common initial symptoms were diarrhea (30 cases, 90.9%), followed by abdominal pain (19 cases, 57.6%), bloody diarrhea (17 cases, 51.5%), and fever (12 cases, 36.4%). Other accompanying symptoms included weight loss (5 cases, 15.2%), chills (4 cases, 12.1%), and nausea (4 cases, 12.1%). One patient underwent colonoscopy for colorectal cancer screening, which revealed asymptomatic Crohn's disease (Table 5).

The laboratory results for IL-17 inhibitor-induced IBD cases are summarized in Table 5. Elevated white blood cell count (WBC) was observed in seven patients (87.5%) out of eight reported cases, elevated erythrocyte sedimentation rate (ESR) levels were observed in six patients (85.7%), and increased C-reactive protein was reported in 16 patients (100%). Levels of fecal calprotectin were increased in four patients (100%).

Computed tomography (CT) results were reported for 10 patients. Typical imaging features were bowel wall thickening (5 cases, 50.0%), pancolitis (2 cases, 20.0%), and colon perforation (1 case, 10.0%); two patients showed normal CT results.

## Colonoscopy and histopathological examination

Colonoscopy results were reported for 28 patients, with deep ulcerations found in 13 patients (46.4%) and superficial ulcerations found in 6 patients (21.4%); eight patients (28.5%) showed active inflammation, four patients (14.3%) had friable mucosa, and four patients (14.3%) had loss of the normal vascular pattern. Intestinal mucosal biopsies were performed in 25 patients, and the characteristics of histopathological examination presented mainly as chronic inflammation (11 cases, 39.3%), cryptitis (8 cases, 32.0%),

TABLE 1 Main characteristics of primary suspect cases in FAERS database.

N	388	%
<b>Age (years)</b>		
≤25	10	2.6
26–50	50	12.9
51–75	60	15.5
≥ 76	4	1.0
Unknown	264	68.0
<b>Gender</b>		
Female	171	44.1
Male	124	32.0
Unknown	93	23.9
<b>Reporting country</b>		
United States	222	57.2
Other countries	104	26.8
Unknown	62	16.0
<b>Reporting year</b>		
2015–2016	28	7.2
2017–2018	133	34.3
2019–2020	133	34.3
2021–2022	94	24.2
<b>Anti-IL-17 as primary suspect drugs</b>		
Secukinumab	348	89.7
Ixekizumab	36	9.3
Brodalumab	4	1.0
<b>Outcome of IBD events</b>		
Death	9	2.3
Life-threatening	6	1.5
Hospitalization-initial or prolonged	84	21.7
Disability	3	0.8
Required intervention	3	0.8
Other medical significant condition	224	57.7
Unknown	59	15.2
<b>Reported indication for IL-17 inhibitors</b>		
Ankylosing spondylitis	51	13.1
Psoriasis	100	25.8
Psoriatic arthropathy	53	13.7
Others	10	2.6
Unknown	174	44.8
<b>Bowel disease</b>		
All IBD	268	69.1
UC	87	32.5
CD	96	35.8
uIBD	85	31.7
All colitis	120	30.9
<b>Onset time of symptoms, month</b>		
<1	6	1.5
1–3	20	5.1
3–6	12	3.1
6–12	15	3.9
12–24	8	2.1
>24	9	2.3
Unknown	318	82.0

uIBD, Unclassified Inflammatory bowel disease; UC, ulcerative colitis; CD, Crohn's disease; IL-17, Interleukin (IL)-17.

crypt abscesses (8 cases, 32.0%), and granulomatous lesions (7 cases, 28.0%).

## Treatment and prognosis

A total of 31 patients discontinued IL-17 inhibitor therapy after the onset of IBD. Among the 34 included patients, 19 (61.3%) underwent monotherapy for IBD; corticosteroid therapy was administered in 10 cases (32.3%), TNF antagonist therapy in 6 cases (19.4%), ustekinumab therapy in 2 cases (6.4%), and mesalazine therapy in 1 case (3.2%). A total of 11 patients (35.5%) received combination therapy, and one patient did not receive any treatment. Six patients failed in treatment with corticosteroids alone or in combination with mesalazine; they obtained significant improvement when treatment was changed to infliximab alone or in combination with corticosteroids (Table 5). All patients showed improvement, except for two patients who relapsed after 2 and 3 months of remission, respectively. Symptom improvement occurred between 2 days and 3 months after discontinuation of IL-17 inhibitor therapy, with three patients (20.0%) experiencing improvement within 2 weeks, seven patients (46.7%) between 2 and 4 weeks, and five patients (33.3%) showing improvement after more than 4 weeks. The median time to remission after discontinuation of IL-17 inhibitor treatment was 4 weeks. After discontinuation of IL-17 inhibitors, three patients (17.7%) switched to a TNF antagonist, five patients switched to ustekinumab (35.3%), and four patients (23.5%) selected another type of monoclonal antibody, such as tildrakizumab or guselkumab.

## Discussion

To the best of our knowledge, this is the first real-life comparative safety study using data from the FAERS database that assessed onset or exacerbation of IBD and colitis associated with all three IL-17 inhibitors in current use. Our study has provided supportive disproportionality analysis and data on the clinical characteristics of these rare adverse events. We found, from the perspective of pharmacovigilance, that the IL-17 inhibitors SEC (ROR = 2.13, 95% CI [1.96–2.30]) and IXE (ROR = 2.79, 95% CI [2.39–3.27]) can trigger IBD, while BRO did not trigger safety signals. We have also provided practical information about IBD and colitis types, time to symptom onset, and outcomes of treatment with IL-17 inhibitors, which had not been the focus of previous studies. A total of 388 case reports of primary suspect IL-17 inhibitor-related gastrointestinal inflammatory conditions were identified in the FAERS database, which included 268 IBD diagnoses and 120 colitis diagnoses. We detected four cases associated with BRO treatment, whereas the number of IBD cases that occurred after SEC treatment was 10 times greater than that observed after IXE therapy (89.7% vs. 9.3%). In a post-marketing study *via* Vigibase in 2021, no IBD was detected among patients in the BRO group, and the number of IBD cases associated with SEC treatment was five times that observed in the IXE treatment group (83.3% vs. 16.2%) (Petitpain et al., 2021), which is consistent with our findings. The number of IBD cases among patients treated with SEC, IXE, and BRO could, in part, be traced back to the different launch data (January 2015, April 2016, and July 2017, respectively). It is also worth noting that IL-17 inhibitors are not identical as they differ in pharmacology and target molecules. IXE is a humanized

**TABLE 2 Interleukin -17 inhibitors associated with Inflammatory bowel disease and the reporting odds ratios in FAERS database.**

PT	Secukinumab		Ixekizumab		Brodalumab	
	No. of AEs	ROR(95%CI <sup>a</sup> )	No. of AEs	ROR(95%CI <sup>a</sup> )	No. of AEs	ROR(95%CI <sup>a</sup> )
Crohn's disease	233	1.57 <sup>b</sup> (1.38-1.79)	43	1.45 <sup>b</sup> (1.08-1.96)	1	0.81 (0.11-5.73)
Colitis ulcerative	196	2.08 <sup>b</sup> (1.81-2.40)	67	3.58 <sup>b</sup> (2.81-4.55)	2	2.54 (0.63-10.17)
Inflammatory bowel disease	182	4.0 <sup>b</sup> (3.43-4.61)	50	5.421 <sup>b</sup> (4.10-7.17)	0	NA
Total events of interest	611	2.13 <sup>b</sup> (1.96-2.30)	160	2.79 <sup>b</sup> (2.39-3.27)	3	1.48 (0.48-4.6)

CI, confidence interval; NA, not available; ROR, reporting odds ratio; AEs, adverse events.

<sup>a</sup>Two-sided CI for ROR.

<sup>b</sup>ROR lower-bound CI values >1 and with ≥3 patients.

**TABLE 3 Interleukin-17 inhibitors associated with Colitis and the reporting odds ratios in FAERS database.**

PT	Secukinumab		Ixekizumab		Brodalumab	
	No. of AEs	ROR(95%CI <sup>a</sup> )	No. of AEs	ROR(95%CI <sup>a</sup> )	No. of AEs	ROR(95%CI <sup>a</sup> )
Colitis	223	2.09 <sup>b</sup> (1.83-2.39)	53	2.50 <sup>b</sup> (1.90-3.27)	3	3.37 <sup>b</sup> (1.08-10.47)
Microscopic colitis	28	1.91 <sup>b</sup> (1.32-2.78)	8	2.74 <sup>b</sup> (1.37-5.49)	0	NA
Ischaemic colitis	10	0.41 (0.22-0.76)	2	0.41 (0.10-1.65)	0	NA
Proctitis	10	1.36 (0.73-2.54)	0	NA	0	NA
Proctitis ulcerative	4	1.93 (0.72-5.19)	0	NA	0	NA
Proctitis haemorrhagic	0	NA	1	18.92 (2.59-138.44)	0	NA
Enteritis	22	1.30 (0.85-1.97)	2	0.59 (0.15-2.37)	0	NA
Enterocolitis	10	0.61 (0.33-1.13)	1	0.31 (0.04-2.17)	0	NA
Enterocolitis haemorrhagic	5	0.82 (0.34-1.98)	4	3.34 <sup>b</sup> (1.25-8.92)	0	NA
Eosinophilic colitis	1	0.70 (0.10-4.98)	1	3.54 (0.50-25.28)	0	NA
Colitis erosive	1	2.29 (0.32-16.59)	1	11.64 (1.61-84.21)	0	NA
Total events of interest	314	1.60 <sup>b</sup> (1.43-1.79)	73	1.96 <sup>b</sup> (1.56-2.47)	3	NA

CI, confidence interval; NA, not available; ROR, reporting odds ratio; AEs, adverse events.

<sup>a</sup>Two-sided CI for ROR.

<sup>b</sup>ROR lower-bound CI values >1 and with ≥3 patients.

IgG4 antibody that has strong affinity for IL-17A, while SEC and BRO are fully humanized antibodies. Both SEC and IXE work by inhibiting IL-17A homodimers and IL-17A/F heterodimers, while BRO blocks the IL-17 receptor, thereby blocking all IL-17 isoforms and exerting a broader, less targeted effect (Fauny et al., 2020a). These data provide a potential explanation for the lower number cases of IBD associated with IXE or BRO therapy compared to treatment with SEC.

To date, studies based on pooled data from clinical studies, observational studies, retrospective studies, and meta-analyses have not provided substantial detail regarding the clinical features of IBD induced by IL-17 inhibitors (Onac et al., 2021; Schreiber et al., 2019; Caron et al., 2022). Our study has provided separate analyses of initial symptom onset, laboratory features, colonoscopy results, histopathological examination, treatment, and outcome. By collecting medical records from published

case reports and case series involving IL-17 inhibitor-associated IBD, we revealed that diarrhea, bloody diarrhea, abdominal pain, and fever were the most common symptoms, which were often accompanied by elevated WBC count, ESR, C-reactive protein, and fecal calprotectin level. A systematic review concluded that gut histological and macroscopic mucosal inflammation occurred in up to 100% of patients with rheumatological disease, and 80% of these patients had increased fecal calprotectin levels (Fauny et al., 2020b), revealing that fecal calprotectin may act as a useful and non-invasive marker to predict IBD in patients with SpA or AS. Therefore, fecal calprotectin should be monitored to guide physicians' decisions and enable stratification of patients to ensure optimal treatment. We also summarized colonoscopy and histopathological examination data from the included cases. According to the literature, ileocolonoscopy allows an accurate diagnosis of Crohn's



**TABLE 4 Summary of demographic features of patients with interleukin (IL)-17 inhibitors-induced Inflammatory bowel disease.**

Variable	N	%
Total	34	/
<b>Data resource (n = 29)</b>		
Case reports	25	86.2
Case series	4	13.8
<b>Gender</b>		
Female	17	50.0
Male	17	50.0
<b>Age, years (n = 34)</b>		
≤25	1	2.9
26–50	23	67.7
51–75	9	26.5
≥76	1	2.9
<b>Reporter region (n = 33)</b>		
USA	11	33.3
Europe	13	39.4
Canada	6	18.2
Asian	2	6.1
Other	1	3.0
<b>IL-17 inhibitors (n = 34)</b>		
Secukinumab	27	79.4
Ixekizumab	7	20.6
<b>Pre-existing of IBD (n = 34)</b>		
New onset of IBD (n = 34)	31	91.2
Family history of IBD (n = 34)	5	14.7
<b>Indication for IL-17 inhibitors (n = 34)</b>		
PsO	20	58.8
PsA	4	11.8
Pso and PsA	3	8.8
AS	7	20.6
<b>History of smoking (n = 34)</b>		
Yes	8	23.5
No	4	11.8
Not mention	22	64.7
<b>Prior exposure (with inadequate response) to TNF antagonist (n = 24)</b>		
Adalimumab	13	54.2
Etanercept	11	45.8
<b>Onset time of symptoms, months (n = 27)</b>		
<1	5	18.5
1–3	9	33.3
3–6	7	25.9
6–12	3	11.1
12–24	2	7.4
>24	1	3.7

AS, ankylosing spondylitis; PsA, psoriatic arthritis; PsO, psoriasis; IBD, Inflammatory bowel disease; UC, ulcerative colitis; CD, Crohn's disease.

disease or ulcerative colitis in 90% of cases (Passos et al., 2018); therefore, it is recommended that patients with diarrhea, abdominal pain, bloody stools, or fever should be alerted to the possibility of IBD and undergo colonoscopy during IL-17 inhibitor treatment.

In the descriptive analysis, we observed that 91.2% of the cases were new-onset IBD, and about half of the new-onset cases were detected within 3 months of starting anti-IL-17 therapy. A study by Deodhar et al. (2019) reported that 30 of the 41 retrieved IBD cases (73.2%) were new-onset cases (Deodhar et al., 2019). Another analysis based on VigiBase data indicated that 91.8% of cases were new-onset IBD, and approximately three-quarters of IBD relapse cases were detected within 3 months of starting anti-IL-17 therapy (Petitpain et al., 2021). Given the long half-life of IL-17 inhibitors, the relatively short interval between drug use and IBD onset revealed an early impact of the drug on disease symptoms. However, it remains difficult to demonstrate whether anti-IL-17 drugs are coincidentally present or potential causative inducers of new or latent IBD. Previous research had demonstrated that patients with Pso, PsA, or AS may be at higher risk of developing IBD and that populations of patients with these rheumatologic diseases and populations with IBD have considerable overlap (Fieldhouse et al., 2020). In a genome-wide association study, several IBD loci were identified as overlapping with those of other immune-mediated inflammatory diseases (IMIDs), most notably AS and Pso (Jostins et al., 2012). The prevalence of IBD in Pso is estimated to be 1%–2% compared to 0.4% in the general population (Eppinga et al., 2017). Therefore, some Pso patients might have subclinical IBD triggered by IL-17 inhibitors. Since no recommendations are available regarding the management of patients with a history of IBD before starting an anti-IL-17 drug, it is of great importance to complete comprehensive patient history assessments, including the patient's personal and family history of inflammatory bowel disease and other IMIDs before initiating treatment to help guide selection of the most appropriate management options. In recent years, the number of studies describing the correlation between slow and rapid onset of IBD, following IL-17 inhibitor treatment, has gradually increased. However, the pathogenesis of these paradoxical reactions after IL-17 administration remains unclear. The pathophysiology behind IBD involves upregulation of proinflammatory and immune-regulatory cytokines in the mucosa of the small and large intestines. IL-17 is a cytokine that is thought to contribute to the development of IBD and has strong proinflammatory activity (Magyari et al., 2014), which is significantly elevated in patients with active ulcerative colitis and Crohn's disease (Seiderer et al., 2008). A previous study in mice has shown that blocking IL-17 leads to worsening of colitis by increasing tumor necrosis factor- $\alpha$ , interferon- $\gamma$ , IL-6, and cytokines that promote the inflammatory response (Ogawa et al., 2004). Furthermore, IL-17A or IL-17RA inhibition has been associated with severe weakening of the intestinal epithelial barrier and reduction of intestinal epithelial integrity, which causes leakage of microorganisms and inflammation (Maxwell et al., 2015). However, it is important to note that IL-17 might also have beneficial effects within the intestinal tract. In animal models, gut-protective IL-17A was shown to be independently produced in the colonic lamina propria, where it promoted epithelial barrier function by regulating tight junction proteins after acute intestinal injury (Lee et al., 2015). This suggests a delicate balance between potentially favorable effects and detrimental effects orchestrated by IL-17 in the gut.

At present, there is no clinical guidance for the management of patients with disease flare or new-onset IBD after IL-17 inhibitor therapy.

**TABLE 5 Clinical information of interleukin (IL)-17 inhibitors-induced Inflammatory bowel disease.**

Parameter	Clinical features	Value (%)
IBD classify ( <i>n</i> = 28)	UC	13 (46.4)
	CD	10 (35.7)
	Unclassified IBD	5 (17.9)
Initial symptoms ( <i>n</i> = 33)	Diarrhea	30 (90.9)
	Bloody diarrhea	17 (51.5)
	Abdominal pain	19 (57.6)
	Fever	12 (36.4)
	Chills	4 (12.1)
	Nausea	4 (12.1)
	Weight loss	5 (15.2)
	Asymptomatic	1 (3.0)
	WBC account (*10 <sup>9</sup> /L, <i>n</i> = 8)	Normal
Elevated		7 (87.5)
CRP (mg/L, <i>n</i> = 16)	Elevated	16 (100)
ESR (mm/hr, <i>n</i> = 7)	Normal	1 (14.3)
	Elevated	6 (85.7)
Fecal calprotectin ( <i>n</i> = 4)	Elevated	4 (100)
Computed tomography examination ( <i>n</i> = 10)	Normal	2 (20.0)
	Bowel wall thickening	5 (50.0)
	Pancolitis	2 (20.0)
	Colon perforated	1 (10.0)
Colonoscopy examination ( <i>n</i> = 28)	Edematous	5 (17.9)
	Erythematous mucosa	6 (21.4)
	Hemorrhagic	3 (10.7)
	Friable mucosa	4 (14.3)
	Absent vascular pattern	4 (14.3)
	Superficial ulceration	6 (21.4)
	Deep ulcerations	13 (46.4)
	Active inflammation	8 (28.5)
Histopathology examination ( <i>n</i> = 25)	Cryptitis	8 (32.0)
	Crypt abscesses	8 (32.0)
	Granulomatous lesions	7 (28.0)
	Chronic inflammation	11 (39.3)

(Continued in next column)

**TABLE 5 (Continued) Clinical information of interleukin (IL)-17 inhibitors-induced Inflammatory bowel disease.**

Parameter	Clinical features	Value (%)
Therapy ( <i>n</i> = 31)	None	1 (3.2)
	Corticosteroids	10 (32.3)
	TNF antagonist	6 (19.4)
	Ustekinumab	2 (6.4)
	5-ASA	1 (3.2)
	Corticosteroids plus TNF antagonist	6 (19.4)
	Corticosteroids plus 5-ASA	4 (12.9)
	Corticosteroids plus Ustekinumab	1 (3.2)
Outcome of IBD event ( <i>n</i> = 29)	Recovered/recovering	27(93.1)
	Relapse	2(6.9)
Time to symptom relief ( <i>n</i> = 15)	Within 2 weeks	3 (20.0)
	2-4w	7 (46.7)
	>4w	5 (33.3)

IBD, Inflammatory bowel disease; UC, ulcerative colitis; CD, Crohn's disease; WBC, white blood cell; ESR, erythrocyte sedimentation rate; CRP, C-reactive protein; TNF antagonist, Tumor Necrosis Factor antagonist; 5-ASA, 5-aminosalicylic acid.

Our study suggests that alternative treatments to improve gastrointestinal symptoms and treatment of the underlying pathology have included mainly corticosteroids and TNF antagonists, as either monotherapy or combination therapy; mesalazine and other biological agents (such as ustekinumab) were shown to be effective as well. Corticosteroids were used in 66.7% of cases in our study, and the type, dose, and duration in each case depended on the improvement of symptoms. Discontinuation of IL-17 inhibitors resulted in substantial improvement of symptoms in all patients, except for two who experienced relapse after 2 or 3 months of remission. Generally, the prognosis of IBD related to IL-17 inhibitors was excellent, and we observed that most patients (66.7%) recovered within 4 weeks. However, we still recommend that these patients be followed up for a longer period to monitor for potential recurrence.

## Conclusion

Our retrospective analysis demonstrated that use of IL-17 inhibitors is associated with exacerbation or new-onset of IBD and colitis within 6 months of therapy. Rheumatologists and dermatologists should be on alert for gastrointestinal symptoms,

such as diarrhea, bloody diarrhea, abdominal pain, and fever, along with elevated WBC count, ESR, C-reactive protein, and fecal calprotectin levels during IL-17 inhibitor therapy. It is essential to complete a comprehensive patient history prior to the initiation of treatment, include appropriate workup to monitor intestinal inflammatory markers, such as fecal calprotectin, and perform colonoscopy during treatment to help identify early symptoms and prevent severe complications. Early detection of adverse events *via* prompt evaluation, cessation of IL-17 inhibitors, and initiation of alternative treatment (e.g., corticosteroids and anti-TNF therapy) can generally lead to clinical remission of IBD. Further prospective studies are needed to evaluate and confirm risk factors for development of IBD associated with IL-17 inhibitor therapy.

## Data availability statement

The raw data supporting the conclusions of this article will be made available by the authors, without undue reservation.

## Author contributions

ChW and ZD conceived of the study; ChW and ZD drafted and revised the manuscript; and CuW and SW made data elaboration and performed statistical analyses. All authors contributed to the final manuscript and approved the submitted version.

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## Conflict of interest

The authors declare that the research was conducted in the absence of any commercial or financial relationships that could be construed as a potential conflict of interest.

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## Supplementary material

The Supplementary Material for this article can be found online at: <https://www.frontiersin.org/articles/10.3389/fphar.2023.1124628/full#supplementary-material>



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