# Real-world risk of new-onset inflammatory bowel disease among patients with psoriasis exposed to interleukin 17 inhibitors

Shari Wright, BS, Allireza Alloo, MD, Andrew Strunk, MA, and Amit Garg, MD
*New Hyde Park, New York*

***Background:*** Information on the real-world risk of inflammatory bowel disease (IBD) among patients with psoriasis exposed to interleukin-17 inhibitor (IL-17i) is limited.

***Objective:*** To compare IBD risk in patients with psoriasis with and without IL-17i exposure.

***Methods:*** Retrospective cohort analysis of patients with psoriasis with and without IL-17i exposure identified by using electronic health records data. Primary outcomes were 6-month and 1-year IBD incidence.

***Results:*** Crude 6-month IBD incidence was 0.16% (3/1821) among patients with psoriasis exposed to any IL-17i, 0.24% (3/1246) among those exposed to secukinumab alone, and 0.11% (239/213,060) among those unexposed. Crude 1-year IBD incidence was 0.27% (5/1821) among IL-17i–exposed patients with psoriasis, 0.32% (4/1246) among those exposed to secukinumab alone, and 0.19% (412/213,060) among those unexposed. In adjusted analysis, there was no significant difference in odds of developing IBD at 6 months (odds ratio, 1.42; 95% confidence interval, 0.45-4.43) and 1 year (odds ratio, 1.37; 95% confidence interval, 0.57-3.33) between exposed and unexposed patients with psoriasis. Similarly, there was no significant difference in odds of developing IBD at 6 months and 1 year between secukinumab-exposed and -unexposed patients with psoriasis.

***Limitations:*** Analysis may have been limited by the low number of outcome events.

***Conclusion:*** The incidence of IBD among patients with psoriasis exposed to IL-17i is low, and the risk appears similar to that for unexposed patients with psoriasis. (J Am Acad Dermatol 2020;83:382-7.)

***Key words:*** brodalumab; Crohn's disease; Explorys; inflammatory bowel disease; IL-17 inhibitor; interleukin 17 inhibitor; ixekizumab; psoriasis; secukinumab; ulcerative colitis.

The T helper (Th) 17 pathway has a fundamental role in the pathogenesis of psoriasis. Interleukin (IL) 23, the new master cytokine in psoriasis, produced by activated dendritic cells in the dermis, stimulates differentiation, activation, and survival of Th17 cells, the primary producers of IL-17. IL-17 stimulates the keratinocyte to produce proinflammatory cytokines, chemokines, antimicrobial

From the Department of Dermatology, Donald and Barbara Zucker School of Medicine at Hofstra/Northwell, New Hyde Park, New York.

Funding sources: None.

Disclosure: Dr Garg serves as an advisor for AbbVie, Amgen, Boehringer Ingelheim, Janssen, Novartis, Pfizer, Incyte, UCB, and Viela Bio and has received honoraria. Author Wright, Dr Alloo, and Author Strunk have no conflicts of interest to declare.

IRB approval status: Reviewed and approved by the human subjects committee at the Feinstein Institutes for Medical Research at the Northwell Health.

Accepted for publication April 2, 2020.
Reprints not available from the authors.

Correspondence to: Amit Garg, MD, Donald and Barbara Zucker School of Medicine at Hofstra/Northwell, 1991 Marcus Ave, Ste 300, New Hyde Park, NY, 11042. E-mail: amgarg@northwell.edu.

Published online April 11, 2020.
0190-9622/$36.00



https://doi.org/10.1016/j.jaad.2020.04.010

peptides, and other psoriasis-related proteins in the skin, which results in the phenotype.[1-6] Indeed, the currently approved IL-17 inhibitors (IL-17i), namely, secukinumab, ixekizumab, and brodalumab, have shown some of the highest efficacies observed among biologic therapies for moderate to severe psoriasis.[7-9]

However, IL-17 inhibitors have also been implicated in worsening or triggering new-onset inflammatory bowel disease (IBD), based primarily on trial observations.[7-11] Information on risk of new-onset IBD among patients with psoriasis exposed to IL-17i outside of the trial setting is limited. The purpose of this study was to compare the risk of IBD, comprising ulcerative colitis (UC) and Crohn's disease (CD), in patients with psoriasis with and without IL-17i exposure in a real-world population.

**CAPSULE SUMMARY**

- The real-world incidence of inflammatory bowel disease among patients with psoriasis exposed to interleukin 17 inhibitors is largely unknown.
- The incidence of inflammatory bowel disease among patients with psoriasis exposed to interleukin 17 inhibitors is low, and the risk appears similar to that in unexposed patients.

## METHODS

This was a retrospective cohort study using a multi—health system data analytics and research platform (Explorys) developed by IBM Corporation (Armonk, NY), Watson Health.[12] Clinical information from electronic medical records, laboratories, practice management systems, and claims systems was matched by using the single set of Unified Medical Language System ontologies to create longitudinal records for unique patients. Data are standardized and curated according to common controlled vocabularies and classifications systems, including the International Classification of Diseases (ICD), Systemized Nomenclature of Medicine—Clinical Terms,[13] Logical Observation Identifiers Names and Codes,[14] and RxNorm.[15] At present, the database encompasses 27 participating integrated health care organizations. More than 56 million unique lives, representing approximately 17% of the population across all 4 census regions of the United States, are captured. Patients with all types of insurance and those who are self-pay are represented.

The study population was limited to patients 18 years or older with active status in the database between January 1, 1999, and October 21, 2019. We excluded patients with a diagnosis of IBD at any time before the index date. We also excluded patients with missing data on age, sex, or race/ethnicity or with missing diagnosis dates for psoriasis or IBD. Patients with psoriasis were identified using 2 or more ICD, ninth revision (ICD-9) diagnosis codes for 696.0, 696.1, and 696.8. Previous validation studies observed positive predictive values ranging from 81% to 100% with this case definition.[16,17] Patients with psoriasis who received at least 1 prescription for the IL-17 inhibitors secukinumab, ixekizumab, or brodalumab occurring within 30 days of a psoriasis diagnosis comprised the IL-17i—exposed cohort. The index date for the IL-17i—exposed cohort was defined as the date of first IL-17i prescription. The control group was composed of patients with psoriasis who were never exposed to an IL-17 inhibitor. The index date for control patients was defined as the date of first psoriasis diagnosis. The primary outcome was incidence of IBD, defined as 2 or more diagnoses of the Systemized Nomenclature of Medicine—Clinical Terms *Crohn's disease*, corresponding to ICD-9 code 555.x, or *ulcerative colitis*, corresponding to ICD-9 code 556.x. This method has been validated previously, with positive predictive values ranging from 84% to 88%.[18,19] IBD incidence was assessed within 6 months of the index date and within 1 year of the index date. A separate subanalysis was performed to evaluate 6-month and 1-year incidences of IBD among patients exposed only to the IL-17i secukinumab, because this biologic represented the majority of IL-17i exposures.

Incidences of IBD at 6 months and 1 year were compared between patients with any IL-17i exposure and control patients by using an adjusted odds ratio from a logistic regression model, controlling for age, sex, and race. A similar comparison was conducted for patients exposed to secukinumab alone versus control patients.

## RESULTS

Demographic characteristics of 1821 patients with psoriasis with IL-17i exposure and 213,060 patients with psoriasis without IL-17i exposure are shown in Table I. Patients with any IL-17i exposure were predominantly female (56.7%), aged 45 to 64 years (55.1%), and white (89.3%). The distribution of sex and race was similar in patients with no IL-17i exposure, although there was a higher proportion of patients aged 65 years or older in this group. Among patients with any IL-17i exposure, 1246 (68.4%) were exposed to secukinumab alone. The

*Abbreviations used:*

CD: Crohn's disease
CI: confidence interval
IBD: inflammatory bowel disease
ICD: International Classification of Diseases
IL: interleukin
IL-17i: interleukin 17 inhibitor
IR: incidence rate
OR: odds ratio
Th: T helper
UC: ulcerative colitis
PY: person-years

distribution of demographic characteristics of the secukinumab-exposed group was similar to that of the overall IL-17i–exposed group (Table I).

The crude 6-month incidence of IBD was 0.16% (3/1821) among patients with psoriasis exposed to any IL-17i, 0.24% (3/1246) among those exposed to secukinumab alone, and 0.11% (239/213,060) among patients with psoriasis not exposed to IL-17i (Table II). Controlling for age, sex, and race, the odds of developing IBD within 6 months were greater in patients with psoriasis exposed to IL-17i compared with patients with psoriasis not exposed (odds ratio [OR], 1.42; 95% confidence interval [CI], 0.45-4.43; $P = .55$]. However, the increased odds did not reach statistical significance. Similarly, the odds of developing IBD within 6 months were greater among patients with psoriasis exposed to secukinumab alone compared with those unexposed (OR, 2.04; 95% CI, 0.65-6.40; $P = .22$), although this result was not statistically significant (Table II). These ORs correspond to approximately 4 more IBD cases per 10,000 patients exposed to any IL-17i relative to control patients over 6 months (95% CI, 9 fewer cases to 17 additional cases), and 8 more IBD cases per 10,000 patients exposed to secukinumab alone (95% CI, 5 fewer cases to 21 additional cases).

The crude 1-year incidence of IBD was 0.27% (5/1821) among IL-17i–exposed patients with psoriasis, 0.32% (4/1246) among those exposed to secukinumab alone, and 0.19% (412/213,060) among patients with psoriasis not exposed to IL-17i (Table II). In adjusted analysis, the odds of developing IBD within 1 year were greater in patients with psoriasis exposed to IL-17i compared to patients with psoriasis not exposed (OR, 1.37; 95% CI, 0.57-3.33; $P = .48$), although this result did not achieve statistical significance. Similarly, the odds of developing IBD within 1 year were greater among patients with psoriasis exposed to secukinumab alone compared to those unexposed (OR, 1.59; 95% CI, 0.59-4.28; $P = .35$), although this result was not statistically significant. This corresponds to an absolute risk difference of 6 more IBD cases per 10,000 patients exposed to any IL-17i (95% CI, 11 fewer to 23 additional cases) and 9 additional IBD cases per 10,000 patients exposed to secukinumab alone (95% CI, 10 fewer to 28 additional cases) over 1 year of follow-up (Table II).

**Table I.** Patient demographics

| Characteristics, n (%) | Any IL-17 exposure (n = 1821) | Secukinumab exposure* (n = 1246) | No IL-17 exposure (n = 213,060) |
|---|---|---|---|
| Age, years | | | |
| 18-44 | 481 (26.4) | 308 (24.7) | 48,204 (22.6) |
| 45-64 | 1003 (55.1) | 692 (55.5) | 83,635 (39.3) |
| 65+ | 337 (18.5) | 246 (19.7) | 81,221 (38.1) |
| Sex | | | |
| Female | 1033 (56.7) | 744 (59.7) | 115,250 (54.1) |
| Race | | | |
| White | 1627 (89.3) | 1118 (89.7) | 188,489 (88.5) |
| African American | 63 (3.5) | 35 (2.8) | 9,503 (4.5) |
| Other | 131 (7.2) | 93 (7.5) | 15,068 (7.1) |

*IL*, Interleukin.
*Secukinumab exposure group is a subset of the any IL-17 exposure group.

Individual-level characteristics of patients exposed to IL-17i with a diagnosis of new-onset IBD are shown in Table III. Patients with IL-17i exposure and a subsequent diagnosis of either UC or CD were exclusively female and white. Eighty percent (4/5) of patients were exposed to secukinumab, and 60% (3/5) of patients had a diagnosis of incident CD.

## DISCUSSION

In this population analysis, we observed that 6-month and 1-year incidences of IBD among patients with psoriasis exposed to any IL-17i were very low. Although IBD incidence was slightly higher in any IL-17i–exposed and secukinumab-exposed patients compared to control patients, the differences in absolute risk were small and were not statistically significant. For example, for every 1250 patients with psoriasis treated with secukinumab, 1 more case of IBD would be observed within 6 months than would have been observed with no IL-17i exposure. Of a total of 5 incident IBD cases occurring within 1 year of IL-17i exposure, 3 cases occurred in the first 6 months of exposure. The observed cases of IBD among IL-17i–exposed patients occurred exclusively in women, suggesting that risk may differ according to sex.

The association between psoriasis and IBD, regardless of IL-17i exposure, is well established. A recent meta-analysis found that patients with

**Table II.** Incidence of inflammatory bowel disease at 6-months and 1-year according to IL-17 exposure

| Outcome | Any IL-17 exposure (n = 1821) | Secukinumab exposure* (n = 1246) | No IL-17 exposure (n = 213,060) |
|---|---|---|---|
| IBD incidence, 6 months | | | |
| Incidence proportion, % (n cases) | 0.16 (3) | 0.24 (3) | 0.11 (239) |
| Adjusted† OR (95% CI) | 1.42 (0.45-4.43) | 2.04 (0.65-6.40) | Referent |
| *P* value, adjusted OR | 0.55 | 0.22 | NA |
| Adjusted risk difference, % (95% CI)†,‡ | 0.04 (−0.09 to 0.17) | 0.08 (−0.05 to 0.21) | Referent |
| Number needed to harm | 2500 | 1250 | Referent |
| IBD incidence, 1 year | | | |
| Incidence proportion, % (n cases) | 0.27 (5) | 0.32 (4) | 0.19 (412) |
| Adjusted† OR (95% CI) | 1.37 (0.57-3.33) | 1.59 (0.59-4.28) | Referent |
| *P* value, adjusted OR | 0.48 | 0.35 | NA |
| Adjusted risk difference (95% CI)†,‡ | 0.06 (−0.11 to 0.23) | 0.09 (−0.10 to 0.28) | Referent |
| Number needed to harm | 1667 | 1111 | Referent |

*CI*, Confidence interval; *IBD*, inflammatory bowel disease; *IL*, interleukin; *NA*, not applicable; *OR*, odds ratio.
*The secukinumab exposure group is a subset of the any IL-17 exposure group.
†Adjusted for age, sex, and race.
‡Risk in the selected study group minus risk in the no IL-17 exposure group.

**Table III.** Individual-level characteristics

| Age, years | Race | Sex | IL-17 inhibitor | Inflammatory bowel disease | Inflammatory comorbidities* | Systemic anti-inflammatory drugs† | Smoking (ever) |
|---|---|---|---|---|---|---|---|
| 45-49 | White | F | Secukinumab | Crohn's disease | Hidradenitis suppurativa, rheumatoid arthritis, psoriatic arthritis | Azathioprine, etanercept | Yes |
| 55-59 | White | F | Secukinumab | Ulcerative colitis | Psoriatic arthritis | Ustekinumab | No |
| 60-64 | White | F | Ixekizumab | Ulcerative colitis | Psoriatic arthritis | None | No |
| 65-69 | White | F | Secukinumab | Crohn's disease | Psoriatic arthritis | NSAID | Yes |
| 65-69 | White | F | Secukinumab | Crohn's disease | Psoriatic arthritis | NSAID | Yes |

*IL*, Interleukin; *NSAID*, nonsteroidal anti-inflammatory drug.
*Systemic inflammatory comorbidities ever (psoriatic arthritis, systemic lupus erythematosus, rheumatoid arthritis, pemphigus vulgaris, hidradenitis suppurativa).
†Immune-modulating or anti-inflammatory drugs 6 months before initiation of IL-17 inhibitor.

psoriasis had 1.7 to 2.5 times the risk of having CD and approximately 1.7 times the risk of having UC compared with control individuals.[20] It is speculated that the pathogenesis of psoriasis and IBD may be linked to aberrant activation of the IL-23/IL-17 axis, because IL-17 expression is increased in lesional skin and in the gut mucosa and serum of patients with IBD.[5,6,21] Exposure to IL-17 outside of the context of psoriasis has also been linked to worsening of baseline disease across 2 phase 2 trials in CD.[10,11] In 1 trial, 10% (4/39) of participants treated with secukinumab reported worsening CD, compared with 5% (1/20) of placebo participants.[10] In the other trial, 25% (24/96) of participants receiving brodalumab reported worsening of CD, compared with 6.3% (2/32) of placebo participants.[11]

Among patients with psoriasis, evidence supporting the link between IL-17i exposure and incident IBD is also based largely on clinical trial data. Phase 3 psoriasis trials have described slightly increased incidence rates (IR) of CD and UC among patients exposed to IL-17i compared with control individuals.[7-9] However, estimates of IR across these trials are based on a limited number of cases. In the Full Year Investigative Examination of Secukinumab vs. Etanercept Using Two Dosing Regimens to Determine Efficacy in Psoriasis (FIXTURE) trial, there was 1 incident case of UC and 1 of CD among participants receiving secukinumab, resulting in an IR of 0.2 per 100 person-years (PY) for each condition.[7] In the Efficacy of Response and Safety of Two Fixed Secukinumab Regimens in Psoriasis (ERASURE) trial, there were 2 incident cases of UC

and no cases of CD among participants receiving secukinumab. The IR for UC was 0.3 per 100 PY.[7] In the UNCOVER trials, there were 7 incident cases of UC and 4 incident cases of CD among participants receiving ixekizumab. The pooled IRs for UC and CD were 0.2 per 100 PY and 0.1 per 100 PY, respectively.[8] In the AMAGINE-2 trial, there was 1 incident case of CD and no incident cases of UC. The IR for CD was 0.1 per 100 PY among participants receiving brodalumab.[9] There were no incident cases of UC or CD in AMAGINE-3.[9] An analysis of adjudicated data of 4209 ixekizumab-exposed patients with psoriasis from 7 randomized controlled and uncontrolled trials (UNCOVER-1, UNCOVER-2, UNCOVER-3, UNCOVER-A, UNCOVER-J, a phase 1 study, and a phase 2 study) indicated the IRs for UC, CD, and IBD to be 1.1 per 1000 PY (0.11/100 PY), 1.9 per 1000 PY (0.19/100 PY), and 2.9 per 1000 PY (0.29/100 PY), respectively.[22] Given these observations and the absence of incident IBD among placebo patients across phase 3 psoriasis trials, IL-17i has been implicated in the development of IBD. These trial data have formed the bases for incorporating risk of IBD into the prescribing information for all IL-17i indicated in psoriasis.[23-25] The incidence of IBD observed among IL-17–exposed patients in the present analysis (0.27/100 PY) is similar to that observed in the trials.

To our knowledge, only 2 studies have evaluated the real-world risk of new-onset IBD in IL-17i–exposed patients, although both have important limitations. A single-center case series analysis evaluated the incidences of CD and UC among patients exposed to secukinumab and ixekizumab within a US database.[26] The study found no cases of incident CD with secukinumab exposure, whereas the incidence of UC was 0.7% (1/142). There were no incident cases of CD or UC with ixekizumab exposure.[26] Interpretation of these data is limited by a lack of a control group, inclusion of patients with conditions other than psoriasis, and a small sample of patients. Additionally, cases were evaluated at any time after IL-17i initiation, making it more difficult to link events with exposure and to directly compare event rates with our analysis. Another claims-based analysis evaluated the incidence of IBD after any IL-17i exposure among patients with various chronic inflammatory diseases, including psoriasis, psoriatic arthritis, rheumatoid arthritis, and ankylosing spondylitis.[27] The authors reported a 1-year IBD incidence rate of 1.41% (5/355) among IL-17i–exposed patients, compared with 0.47% (1996/424,767) among those with no exposure. The adjusted odds of incident UC were nearly 4 times greater among IL-17i–exposed patients compared to those without IL-17i exposure, whereas the incidence of CD did not differ significantly between the groups. This study also included patients exposed to IL-17i regardless of the treatment indication, and thus, it is unclear whether the results are generalizable to patients with psoriasis.

There are limitations to the present study that warrant consideration when interpreting the results. We could not capture patients who did not seek care in health systems included in the database. There is potential for misclassification of psoriasis or IBD status due to erroneous documentation or misdiagnosis. To mitigate the influence of possible misclassification bias, we used validated case definitions to identify patients with psoriasis and IBD. The analysis may have been limited by the low number of outcome events, although this also reflects the rarity of the event. Although the point estimates of the odds ratios for IBD suggest a slight increase in risk associated with IL-17i exposure, our results were compatible with a wide range of true effect sizes, and the null hypothesis of no difference could not be ruled out. Despite these limitations, this population-based analysis reports important data on the risk of IBD among patients with psoriasis exposed to IL-17 inhibitors. Given the size and demographic heterogeneity of our cohort, we believe these results may be generalized to the US health care–seeking psoriasis population.

In conclusion, the real-world incidence of IBD among patients with psoriasis exposed to IL-17i is very low and is similar to that observed in phase 3 trials. In a population, there does not appear to be a significant difference in the likelihood of developing IBD between patients with psoriasis with and without IL-17i exposure. When present, the risk of developing IBD appears to be higher within the first 6 months after IL-17i exposure and may differ according to sex. Assessment of the risks and benefits of IL-17i use in individual patients should continue to be informed by individual characteristics and risk factors for IBD. Individual patient characteristics and risk factors should be taken into consideration before prescribing IL-17i for the treatment of psoriasis. These observations may support shared decision making on the treatment of psoriasis with IL-17 inhibitors and counseling on the risk of development of IBD.

## REFERENCES

1. Blauvelt A, Chiricozzi A. The immunologic role of IL-17 in psoriasis and psoriatic arthritis pathogenesis. *Clin Rev Allergy Immunol*. 2018;55(3):379-390.

2. Malakouti M, Brown GE, Wang E, Kool J, Levin EC. The role of IL-17 in psoriasis. *J Dermatolog Treat*. 2015;26(1):41-44.
3. Ogawa E, Sato Y, Minagawa A, Okuyama R. Pathogenesis of psoriasis and development of treatment. *J Dermatol*. 2018; 45(3):264-272.
4. Girolomoni G, Strohal R, Puig L, et al. The role of IL-23 and the IL-23/TH17 immune axis the pathogenesis and treatment of psoriasis. *J Eur Acad Dermatol Venerol*. 2017;31(10):1616-1626.
5. Harper EG, Guo C, Rizzo H, et al. Th17 cytokines stimulate CCL20 expression in keratinocytes in vitro and in vivo: implications for psoriasis pathogenesis. *J Invest Dermatol*. 2009;129:2175-2183.
6. Johansen C, Usher PA, Kjellerup RB, Lundsgaard D, Iversen L, Kragballe K. Characterization of the interleukin-17 isoforms and receptors in lesional psoriatic skin. *Br J Dermatol*. 2009; 160:319-324.
7. 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):326-338.
8. Gordon KB, Blauvet A, Papp KA, et al. Phase 3 trials of ixekizumab in moderate-to-severe plaque psoriasis. *N Engl J Med*. 2016;375(21):2102.
9. Lebwohl M, Strober B, Menter A, et al. Phase 3 studies comparing brodalumab with ustekinumab in psoriasis. *N Engl J Med*. 2015;373(14):1318-1328.
10. Hueber W, Sands BE, Lewitzky S, et al. Secukinumab, a human anti-IL017A monoclonal antibody, for moderate to severe Crohn's disease: unexpected results of a randomized, double-blind placebo-controlled trial. *Gut*. 2012;61(12):1693-1700.
11. 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):1599-1607.
12. The IBM Explorys Platform: liberate your healthcare data. Solution brief. Available at: ibm.com/downloads/cas/4P0QB9JN. Accessed May 8, 2020.
13. US National Library of Medicine. Overview of SNOMED CT. Available at: https://www.nlm.nih.gov/healthit/snomedct/snomed_overview.html. Accessed May 8 2020.
14. McDonald CJ, Huff SM, Suico JG, et al. LOINC, a universal standard for identifying laboratory observations: a 5-year update. *Clin Chem*. 2003;49(4):624-633.
15. Nelson SJ, Zeng K, Kilbourne J, Powell T, Moore R. Normalized names for clinical drugs: RxNorm at 6 years. *J Am Med Inform Assoc*. 2011;18(4):441-448.
16. Asgari MM, Wu JJ, Gelfand JM, et al. Validity of diagnostic codes and prevalence of psoriasis and psoriatic arthritis in a managed care population, 1996-2009. *Pharmacoepidemiol Drug Saf*. 2013;22(8):842-849.
17. Löfvendahl S, Theander E, Svensson Å, Carlsson KS, Englund M, Petersson IF. Validity of diagnostic codes and prevalence of physician-diagnosed psoriasis and psoriatic arthritis in southern Sweden—a population-based register study. *PLoS One*. 2014;9(5):e98024.
18. Hou JK, Tan M, Stidham RW, et al. Accuracy of diagnostic codes for identifying patients with ulcerative colitis and Crohn's disease in the Veterans Affair Health Care System. *Dig Dis Sci*. 2014;59(10):2406-2410.
19. Thirumurthi S, Chowdhury R, Richardson P, Abraham NS. Validation of ICD-9-CM diagnostic codes for inflammatory bowel disease among veterans. *Dig Dis Sci*. 2010;55(9):2592-2598.
20. Fu Y, Lee C, Chi C. Association of psoriasis with inflammatory bowel disease. A systematic review and meta-analysis. *JAMA Dermatol*. 2018;154(12):1417-1423.
21. Fujino S, Andoh A, Bamba S, et al. Increased expression of interleukin 17 in inflammatory bowel disease. *Gut*. 2003;52(1): 65-70.
22. Reich K, Leonardi C, Langley RG, et al. Inflammatory bowel disease among patients with psoriasis treated with ixekizumab: a presentation of adjudicated data from an integrated database of 7 randomized controlled and uncontrolled trials. *J Am Acad Dermatol*. 2017;76(3):441-448.
23. US Food and Drug Administration. Consentyx (secukinumab) [package insert]. Available at: https://www.accessdata.fda.gov/drugsatfda_docs/label/2016/125504s001s002lbl.pdf; 2016. Accessed December 27, 2019.
24. US Food and Drug Administration. Taltz (ixekizumab) [package insert]. Available at: https://www.accessdata.fda.gov/drugsatfda_docs/label/2019/125521s016lbl.pdf; 2019. Accessed December 27, 2019.
25. US Food and Drug Administration. Siliq (brodalumab) [package insert]. Available at: https://www.accessdata.fda.gov/drugsatfda_docs/label/2017/761032lbl.pdf; 2017. Accessed December 27, 2019.
26. Orrell KA, Murphrey M, Kelm RC, et al. Inflammatory bowel disease events after exposure to interleukin 17 inhibitors secukinumab and ixekizumab: postmarketing analysis from the RADAR ("Research on Adverse Drug Events and Reports") program. *J Am Acad Dermatol*. 2018;79(4):777-778.
27. Edmond B, Ellis LA, Chakravarty SD, Ladouceur M, Lefebvre. Real-world incidence of inflammatory bowel disease among patients with other chronic inflammatory disease treated with interleuin-17a or phosphodiesterase 4 inhibitors. *Curr Med Res Opin*. 2019;35(10):1751-1759.