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## Is the use of secukinumab after anti-TNF therapy greater than expected for the risk of developing inflammatory bowel disease?



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### ABSTRACT

**Objective:** In this study, our objective was to present real-life data on the incidence of inflammatory bowel disease (IBD) among patients receiving secukinumab treatment.

**Methods:** The study consisted of 209 patients who had prior exposure to anti-tumor necrosis factor (TNF) or were biologically naive. Patients with a pre-existing history of IBD were excluded from the study.

**Results:** Of the 209 patients in the study, 176 (84.3%) had ankylosing spondylitis, while 33 (15.7%) had psoriatic arthritis. 112 (53.6%) patients had prior exposure to at least one anti-TNF treatment before initiating secukinumab. IBD developed in 10 (4.8%) of the 209 patients. The incidence of IBD among patients who initiated secukinumab as their first biologic agent was 1%. For patients who had previously received any anti-TNF treatment and subsequently transitioned to secukinumab, the incidence of IBD was 8% ( $p = 0.018$ , odds ratio (OR): 8.38, 95% CI: 1.04–67.45). A mean of 3.67 months ( $\pm 4.3$ ) after anti-TNF use, whereas IBD symptoms developed in the biologically naive patient after 15 months.

**Conclusion:** Our study observed IBD incidence in 4.8% of patients using secukinumab. Patients who initiated secukinumab after previous anti-TNF treatment exhibited a significantly higher rate and risk of developing IBD. The onset of IBD occurred earlier in these patients (mean 3.67 months), whereas a single case of IBD showed a longer duration (15 months). Further studies with larger patient numbers are warranted to provide a more comprehensive understanding of our findings.

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## El uso de secukinumab tras la terapia anti-TNF es mayor de lo esperado por el riesgo de desarrollar enfermedad inflamatoria intestinal?

### RESUMEN

**Objetivo:** En este estudio, nuestro objetivo fue presentar datos de la vida real sobre la incidencia de la enfermedad inflamatoria intestinal (EII) entre los pacientes que reciben tratamiento con secukinumab.

**Métodos:** El estudio consistió en 209 pacientes que habían tenido una exposición previa al factor de necrosis antitumoral (TNF) o eran biológicamente naive. Los pacientes con antecedentes preexistentes de EII fueron excluidos del estudio.

**Resultados:** De los 209 pacientes del estudio, 176 (84,3%) tenían espondilitis anquilosante, mientras que 33 (15,7%) tenían artritis psoriásica. 112 (53,6%) pacientes tenían exposición previa a al menos un tratamiento anti-TNF antes de iniciar secukinumab. La EII se desarrolló en 10 (4,8%) de los 209 pacientes. La incidencia de EII entre los pacientes que iniciaron secukinumab como primer agente biológico fue del 1%. Para los pacientes que habían recibido previamente algún tratamiento anti-TNF y posteriormente hicieron la transición a secukinumab, la incidencia de EII fue del 8% ( $p = 0,018$ , odds ratio (OR): 8,38, IC del 95%: 1,04-67,45). Una media de 3,67 meses ( $\pm 4,3$ ) después del uso de anti-TNF, mientras que los síntomas de la EII se desarrollaron en el paciente biológicamente naive después de 15 meses.

#### Palabras clave:

Secukinumab

Enfermedad inflamatoria intestinal

Espondilitis anquilosante

Artritis psoriásica

Datos del mundo real

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**Conclusión:** Nuestro estudio observó una incidencia de EII en el 4,8% de los pacientes que usaban secukinumab. Los pacientes que iniciaron secukinumab después de un tratamiento anti-TNF previo mostraron una tasa y un riesgo significativamente mayores de desarrollar EII. El inicio de la EII ocurrió antes en estos pacientes (media de 3,67 meses), mientras que un solo caso de EII mostró una duración más prolongada (15 meses). Se justifican más estudios con un mayor número de pacientes para proporcionar una comprensión más completa de nuestros hallazgos.

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## Introduction

Spondyloarthritis (SpA) encompasses a group of immune-mediated diseases that exhibit common clinical features. Their distinct laboratory, genetic, and imaging characteristics distinguish them from other types of inflammatory arthritis. In this group, ankylosing spondylitis (AS) serves as the prototype, encompassing conditions such as psoriatic arthritis (PsA), inflammatory bowel disease (IBD)-associated arthritis, reactive arthritis, juvenile chronic arthritis, and undifferentiated SpA.

The relationship between IBD and SpA has been well-established in recent years. Axial SpA and PsA exhibit a close association with IBD, particularly in genetically susceptible individuals, leading to an increased prevalence of IBD cases in recent times.<sup>1</sup> SpA is observed in approximately 10% of individuals with IBD,<sup>2</sup> while IBD develops in approximately 6–10% of those with AS.<sup>3</sup>

Tumor necrosis factor (TNF)-alpha and interleukin (IL)-23/17 cytokine pathway play prominent roles in the pathogenesis of SpA, Chron's disease (CD), and ulcerative colitis (UC). In the last two decades, anti-TNF agents have proven successful in treating both SpA and IBD. However, there remains an unmet need in this field, leading to the exploration of therapeutic agents targeting different cytokine pathways. It is emerging as a new avenue for treating chronic inflammatory diseases.<sup>4</sup>

IL-23 stimulates T helper (Th17 cells) and causes their differentiation into IL-17-producing cells. IL-17A plays an important role in the pathogenesis of immune-mediated inflammatory diseases such as PsA, SpA, IBD, and psoriasis. Additionally, it plays a critical role in controlling extracellular bacterial and fungal infections.<sup>5</sup>

Secukinumab, a fully recombinant human immunoglobulin G1k monoclonal antibody, is the first treatment agent that acts by blocking IL-17A. It has shown promising clinical outcomes in managing axial and peripheral SpA, psoriasis, and PsA.<sup>6</sup> However, in UC and CD, IL-17 induces the release of proinflammatory cytokines in the intestinal mucosa. Because of this pathophysiological situation, secukinumab has been used as a treatment agent for CD, but it has led to disease exacerbation.<sup>7</sup> Side effects associated with secukinumab use are now well-documented. Notable side effects of IL-17 inhibitors are known to cause CD or UC in the gastrointestinal tract.<sup>8</sup>

This study aims to present real-life data and share our experience regarding the development of IBD following secukinumab treatment in patients with AS or PsA.

## Material and methods

### Participants

Participants for this retrospective study were enrolled from two rheumatology centers in Turkey. The study included patients diagnosed with AS based on the modified New York criteria or PsA according to the 2006 CASPAR criteria and received secukinumab treatment. Secukinumab, an IL17 inhibitor, has been approved for treating AS and PsA since 2018, whereas ixekizumab is only approved for treating psoriasis. Therefore, our focus was on AS or PsA patients who received secukinumab treatment between April

2018 and December 2021, and were reviewed to identify any subsequent development of IBD. Patients with pre-existing IBD diagnoses have not been selected for treatment with IL17 inhibitors.

### Data collection

Approval was obtained from the Ethics Committee of Firat University. Ethics committee approval was received on 26.04.2022 as 8125 registration number. Patient records were reviewed to collect data on age, gender, age at diagnosis, duration of diagnosis, imaging evaluations, C-reactive protein (CRP) values, HLA-B27 results, previous treatments received, history of IBD (including family history), start date of secukinumab, and duration of drug use.

In cases where patients developed gastrointestinal symptoms during secukinumab use, the diagnosis of IBD was confirmed through colonoscopy biopsy findings. It was documented whether these patients continued secukinumab treatment afterward or which treatment they switched to.

### Statistics

Statistical analysis was performed using the IBM-SPSS version 26 software (Armonk, New York, USA). The data were given as percentages and mean standard deviation. When comparing groups with and without IBD, the Chi-square test was utilized for categorical variables, while the Mann-Whitney *U* test was selected for continuous variables. *p* values < 0.05 were accepted as statistically significant.

## Results

A total of 209 patients using secukinumab were included in the study. Among the patients, 88 (42.1%) were female, and 121 (57.9%) were male. Out of the total, 176 (84.3%) patients were diagnosed with AS, while 33 (15.8%) were diagnosed with PsA. Among the patients who underwent HLA-B27 testing, 56 (38%) tested positive. Secukinumab was initiated as the first biological treatment in 99 (47.4%) patients, with a mean treatment duration of  $9.04 \pm 5.73$  months. Before secukinumab treatment, 110 patients received at least one biologic DMARD. Additionally, 45 patients had a history of active smoking. The demographic characteristics of the patients are summarized in [Table 1](#).

A total of 10 patients underwent colonoscopy due to gastrointestinal complaints and were diagnosed with IBD. The biopsy results obtained from the patients were consistent with UC, and the clinical and demographic characteristics of the patients diagnosed with UC are summarized in [Table 2](#). Among the patients diagnosed with UC, nine had AS, and one had a PsA diagnosis. Eight AS patients and one PsA patient had previously received at least one anti-TNF treatment before starting secukinumab. The remaining patient initiated secukinumab as the first-line biologic DMARD.

The duration of secukinumab treatment ranged from 1 month to 34 months. Among the patients who developed UC, the mean duration of stay in secukinumab treatment was  $5.10 \pm 5.25$  months. In patients who received anti-TNF treatment and developed IBD, the

**Table 1**  
Demographic characteristics of patients.

Age (years)	39.1 ± 10.3
Diagnosis time (years)	7.2 ± 4.5
Female/male	88/121
AS, n (%)	176 (84.2)
PsA, n (%)	33 (15.8)
HLA-B27 positive, n (%)	56 (38)
C-reactive protein, mg/dL	19.3 ± 16.2
Secukinumab treatment duration, months	9.04 ± 5.73
Number of prior anti-TNF therapies, n (%)	209 (100)
0	99 (47.4)
1	59 (28.2)
2	28 (13.4)
3	12 (5.7)
>3	11 (5.2)
Smoking, n (%)	45 (21.5)
Family history of IBD, n (%)	0 (0)

mean duration of stay in secukinumab treatment was 3.67 ± 4.3 months, while it was 15 months in one patient who was anti-TNF naive. The mean survival time in secukinumab treatment for patients without IBD was 9.27 ± 5.68 months, and there was a statistically significant difference compared to patients with IBD (*p* = 0.01). Drug survival time was significantly shorter in patients with IBD, as secukinumab treatment was discontinued upon the diagnosis of IBD.

Among the nine patients who developed UC, at least one biologic DMARD was used prior to secukinumab treatment. UC developed in 9 (5.1%) out of 176 patients with AS and 1 (3.0%) out of 33 patients with PsA. However, these two groups had no statistically significant difference (*p* = 0.876).

Two (4.4%) patients who developed UC were smokers, and there was no statistically significant difference between the patients who did not develop IBD and those who did not develop UC in terms of smoking (*p* = 0.369). The clinical and demographic characteristics of patients with and without IBD are summarized in Table 3. In 90% of cases that developed IBD, there was at least one instance of anti-TNF use prior to secukinumab treatment, which showed a statistically significant difference compared to cases that did not develop IBD (*p* = 0.01).

Considering the association between anti-TNF treatment and IBD development, six of the patients who developed IBD had received etanercept treatment, indicating a significant risk for IBD development and was statistically significant (*p* = 0.006, OR: 5.28, 95% CI: 1.42–19.55) another noteworthy observation is that four of the patients who received infliximab prior to secukinumab treatment developed IBD. There was a statistically significant difference in terms of the risk of developing IBD when comparing them to patients without IBD (*p* = 0.006, OR: 3.75, 95% CI: 1.00–14.10).

**Table 2**  
Clinical and demographic characteristics of cases with IBD.

Cases	Age	Gender	Diagnosis	Diagnosis duration (years)	The time between biological therapy and IBD (months)	Biological treatments previously used	Treatment initiated after IBD
Case-1	39	M	AS	11	7	IFX, ETN	ADA
Case-2	37	F	AS	6	14	ADA, ETN	IFX
Case-3	53	F	AS	8	1	ADA, IFX, ETN	IFX
Case-4	46	F	AS	8	1	ADA, IFX, CZP, ETN	GLM
Case-5	35	M	AS	6	2	ETN	ADA
Case-6	32	M	AS	7	1	IFX	ADA
Case-7	27	F	AS	3	15	None	ADA
Case-8	33	M	AS	3	3	GLM	ADA
Case-9	47	M	AS	16	2	GLM	ADA
Case-10	55	F	PsA	9	2	ETN	ADA

ADA: adalimumab; ETN: etanercept; GLM: golimumab; IFX: infliximab; CZP: certolizumab pegol.

Of the 209 patients, secukinumab was the first biologic in 47.4%, the second in 28.2%, the third in 13.4%, the fourth biologic in 5.7%, the fifth biologic in 3.8%, and the sixth biologic in 1.5%. IBD developed in 1% of patients receiving secukinumab on the first biologic, 8.5% in the second biologic, 7.1% in the third biologic, and 8.3% in the fourth biologic. However, this difference did not reach statistical significance (Chi-square test: *p* = 0.242). However, 1% of secukinumab first biologics who had no previous biologic experience developed IBD, while 8% of patients who had previously used any anti-TNF and subsequently switched to secukinumab developed IBD (Chi-square *p* = 0.018, OR: 8.38, 95% CI: 1.04–67.45). Patients using first-line secukinumab appear to remain in the safe range for IBD after anti-TNF compared with those who switched to secukinumab. It is noteworthy that the highest number of cases were seen in the group using secukinumab as the second choice. The OR value for IBD in patients using secukinumab after anti-TNF was 8.71 (2.33–32.63) when compared to those using first-choice secukinumab (Fig. 1).

Sex, smoking status and co-treatment with csDMARD were unrelated to the development of IBD. However, after secukinumab treatment, IBD was detected in 1.1% of HLA-B27 negatives and 7.1% of HLA-B27 positives.

## Discussion

Colonoscopic biopsy studies have revealed mucosal inflammation in around 50% of patients with AS and PsA.<sup>9,10</sup> Additionally, approximately 7% of these patients may develop UC or CD in the future.<sup>10</sup> It is known that the frequency of IBD is three times higher in patients with AS and PsA compared to the general population.<sup>2</sup> Genetic causes, environmental factors, smoking, infection, and especially the use of nonsteroidal anti-inflammatory drugs (NSAIDs) in AS patients compose a risk in the development and exacerbation of IBD.<sup>11,12</sup> Clinicians need to prove whether anti-IL-17 therapy is a potential factor for developing or exacerbating IBD.<sup>8</sup> Our study revealed an incidence rate of 4.8% for IBD among patients with AS and PsA who received secukinumab treatment. A significant majority of the cases that develop IBD consist of patients who started secukinumab after anti-TNF therapy. Our study includes real-life data with the highest incidence of IBD after secukinumab treatment in the literature.

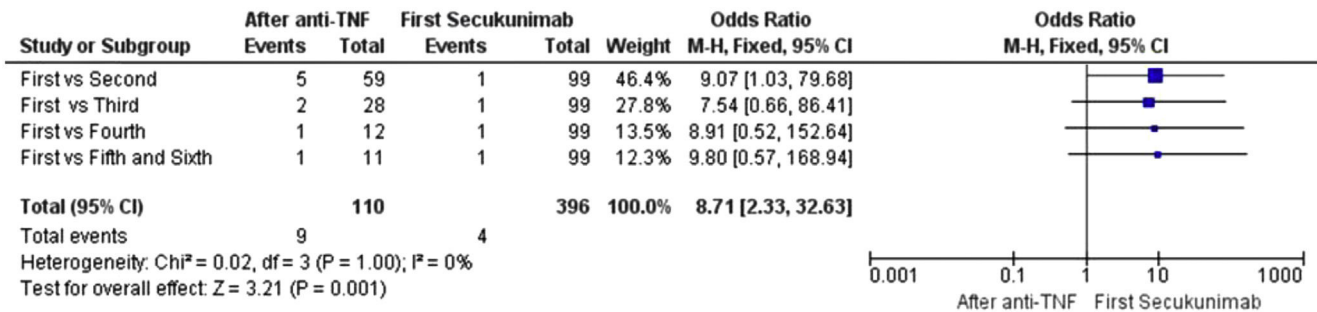
In the FUTURE and MEASURE studies with secukinumab, cases with IBD were excluded, and the incidence of IBD was found to be 0.1%. In the MEASURE 1 study, the incidence of IBD was 0.5%. In addition, CD constitute the majority of cases.<sup>12</sup> In the meta-analysis, in which 21 clinical studies on secukinumab were evaluated together, the incidence of IBD was found to be 0.56%.<sup>10</sup> In the study conducted by Orrell et al., UC was developed in only one out of 142 patients using secukinumab selected from the RADAR (Research on Adverse Drug Events and Reports) program.<sup>13</sup> In a

**Table 3**  
Clinical and demographic characteristics of patients with and without IBD.

	IBD (n=10)	Non-IBD (n=199)	p values
Age (years)	40.4 ± 9.3	39.07 ± 10.3	0.559*
Gender			
Female, n	5	83	0.604*
Male, n	5	116	
Diagnosis			
AS	9	167	0.876*
PsA	1	32	
CRP (mg/dL)	16.9 ± 13.2	19.5 ± 16.3	0.772**
HLA-B27, n (%)	4 (40)	52 (36)	0.07*
Previously used anti-TNF, n (%)	9 (90)	103 (51.8)	0.01**
Secukinumab used period (months)	5.1 (min–max: 1–15)	9.2 (min–max: 1–34)	0.01**
Smoking			
Yes, n	2	43	0.369*
No, n	8	84	

\* Chi-square test was used,  $p < 0.05$  is significant.

\*\* Mann-Whitney test was used,  $p < 0.05$  is significant.



**Fig. 1.** OR value for IBD in patients using secukinumab after anti-TNF was 8.71 (2.33–32.63) when compared to those using first-choice secukinumab.

systematic review and meta-analysis of 38 randomized controlled clinical trials, the risk of developing new-onset IBD using IL-17i in patients with AS, PsA, PsO, and rheumatoid arthritis (RA) was evaluated. In the 60-week follow-up of 16,690 patients, 12 new cases of IBD (5 CD, 7 UC) associated with IL17i were detected.<sup>14</sup> In our study, UC was developed in 10 (4.8%) of 209 patients using secukinumab. The high incidence rate observed in our study may be attributed to the limited number of patients included or that the patients in our study reside in an area with a high genetic predisposition toward developing IBD, which could contribute to these rates.

The initiation of secukinumab therapy and the subsequent development of IBD in patients who have not responded to anti-TNF treatments suggest that the underlying disease may be inadequately controlled. It can be said that it is even more difficult for the disease to enter remission, especially in patients receiving more than one anti-TNF therapy. The relationship between intestinal mucosal inflammation and the pathogenesis of AS and PsA is known, and there is evidence that IL-17 plays a protective role in intestinal mucosal defence. In a placebo-controlled study of IL-17 inhibition in CD, the study was terminated at week six due to worsening in the Crohn's disease arm during secukinumab use.<sup>7</sup> Inhibiting IL-17 interferes with its intestinal protective function and role in tissue homeostasis repair, impairing intestinal wall integrity and exacerbating the disease.<sup>15</sup> As a result, Anti-IL-17 therapy may lead to the development of new IBD or exacerbation of the existing disease.<sup>16</sup> In SpA group diseases, IBD may develop during the treatment process. The frequency of exacerbation or new onset of IBD in AS was evaluated as 2.2/100 patient-years with etanercept and 0.2/100 patient-years with infliximab in placebo-controlled and open-label extension studies.<sup>17</sup> For example, the incidence of IBD after etanercept use is 0.41%.<sup>18</sup> Considering the

cases who developed IBD in our study, etanercept was used before, and 12% of these patients developed IBD, and it was found to be statistically significant ( $p = 0.006$ , OR: 5.28, 95% CI: 1.42–19.55). In addition, 11.8% (4 cases) of patients using infliximab before secukinumab treatment developed IBD ( $p = 0.037$ , OR: 3.75, 95% CI: 1.00–14.10). The high risk of developing IBD after initiating secukinumab treatment in cases where the disease remains uncontrolled despite prior use of etanercept and infliximab suggests a potential association.

In our study, most cases that developed IBD had previously underwent anti-TNF therapy. Among the cases who initiated secukinumab after anti-TNF treatment and developed IBD, the onset of IBD occurred on average after 3.6 months. The duration was longer (15 months) in the single case who received secukinumab and subsequently developed IBD. In studies with secukinumab, the development of IBD generally occurred within the first 3–6 months, and a similar period was found in our study. This period is not as long as the development of IBD associated with an immune checkpoint inhibitor<sup>19</sup> or NSAID use.<sup>20</sup> However, anti-TNF treatments seem to be shorter than their paradoxical effects.<sup>18</sup> Anti-TNF use before secukinumab treatment may mask the development of IBD. In addition, the disease may flare up after this treatment. In this regard, it is advisable to closely monitor patients for gastrointestinal complaints during the initial six months of commencing secukinumab treatment, particularly in cases where anti-TNF therapy has shown limited efficacy. It can be difficult to clearly say that it occurs due to the duration of drug exposure, exacerbation of the underlying IBD, or uncontrolled disease. If the disease remains uncontrolled despite multiple anti-TNF therapies, and if the decision is made to initiate secukinumab, it is advisable to thoroughly inquire about the patient's history of IBD and their family history.

Checking the fecal calprotectin level in feces can guide us in this regard. In our study, the patients had no family history of IBD, and their fecal calprotectin levels could not be measured before the treatment.

Our study has some limitations. Before initiating secukinumab treatment, the patients included in this study did not undergo gastroenterological screening, such as fecal calprotectin, stool occult blood tests, or colonoscopy. Secondly, it is worth noting that a higher number of patients in the study could have resulted in a potentially lower incidence rate of IBD. Thirdly, the cumulative NSAID use of the patients included in the study could not be evaluated regarding the risk of IBD development.

In conclusion, care should be taken regarding IBD development, especially in patients who started secukinumab after anti-TNF. Patients should be followed closely, especially in the first six months. The results of this study should be supported by other studies with more cases.

### Authors' contributions

All the authors contributed equally to the conception and article design, acquisition, analysis, interpretation of the data, work drafting, and critical revision of the intellectual content. Additionally, the authors decided on the final version to be published and are responsible for all aspects of the work.

### Ethics

All studies were conducted the Declaration of Helsinki. Approval was obtained from the Ethics Committee of Firat University. Ethics committee approval was received on 26.04.2022 as 8125 registration number. Study-related documents were reviewed and approved by independent ethics committees and institutional review boards. All patients provided written informed consent before participation in the study.

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### Conflict of interest

The authors declare that they have no conflict of interest.

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