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Secukinumab experience in patients with axial spondyloarthritis: A 3-year real life data of a single centre

Aksiyel spondiloartrtit hastalarında secukinumab deneyimi: Tek merkez 3 yıllık gerçek yaşam verileri

Emine Uslu Yurteri, Didem Şahin Eroğlu, Emine Gözde Aydemir Gülöksüz, Ahmet İlbay, Tahsin Murat Turgay, Gülay Kınıklı, Aşkın Ateş

Ankara University Faculty of Medicine, Department of Internal Medicine, Division of Rheumatology, Ankara, Turkey

Abstract

Objective: Secukinumab is a fully human immunoglobulin G1 kappa monoclonal antibody which binds to interleukin-17A. We aimed to assess the demographic, clinical and laboratory features of axial spondyloarthritis (axSpA) patients using secukinumab and to evaluate drug adherence and adverse effects.

Methods: The study is a retrospective analysis of secukinumab-treated axSpA patients who presented to our center between May 2018 and March 2022.

Results: Of 52 patients, 20 (38.5%) were male, and the mean age at diagnosis of axSpA was 36.5±12.1. The median follow-up period was 89.3 (Q1-Q3: 65.0-160.9) months. Sixteen patients (30.8%) were on tumor necrosis factor-α (TNF-α) inhibitor (TNFi) naive. The overall cumulative secukinumab drug survival rates observed at 12 and 24 months were 96% and 93%, respectively. The duration of drug survival was not significantly different between the TNFi-naive and TNFi- nonresponder (TNF-IR) groups (p=0.18). After starting secukinumab, only 1 patient experienced uveitis for the first time. No exacerbation of inflammatory bowel disease was observed.

Conclusion: Our study presents the real-life experience of secukinumab from Turkey. The treatment response does not change in TNFi-naive and TNF-IR patients which indicates that secukinumab is almost equally efficacious both in TNFi-naive and TNF-IR patients. To conclude, secukinumab is a safe and effective treatment option for patients with axSpA.

Keywords: Secukinumab, axial spondyloarthritis, IL-17A antibody

Öz

Amaç: Secukinumab, interlökin-17A'ya bağlanan insan immünoglobülin G1 kappa monoklonal antikorudur. Secukinumab kullanan aksiyal spondiloartrit (aksSpA) hastalarının demografik, klinik ve laboratuvar özelliklerini ve ilaç uyumunu ve ilaç yan etkilerini değerlendirmeyi amaçladık.

Yöntem: Mayıs 2018-Mart 2022 tarihleri arasında merkezimize başvuran secukinumab ile tedavi edilen aksSpa'lı hastaların retrospektif analizi yapılmıştır.

Bulgular: Elli iki hastanın, 20'si (%38,5) erkek idi. Ortalama aksiyel spondiloartrit tanı yaşı 36,5±12,1 idi. Ortalama takip süresi 89,3 (Q1-Q3: 65,0-160,9) ay idi. Hastaların 16'sı (%30,8) tümör nekroz faktörü-α (TNF-α) ihibitörü (TNFi) kullanmamıştı. On ikinci ve 24. ayda gözlemlenen secukinumab ilacı sağkalım oranları sırasıyla %96 ve %93 idi. İlaç kalma süresi, TNFi-naif ve TNFi yanıtsız (TNF-IR) grupları arasında anlamlı bir fark göstermedi (p=0,18). Secukinumab tedavisine başlandıktan sonra sadece 1 hasta ilk kez üveit atağı geçirdi. enflamatuvar barsak hastalığı alevlenmesi görülmedi.

Sonuç: Çalışmamız Türkiye'den secukinumabın gerçek yaşam deneyimini sunmaktadır. TNFi-naif ve TNF-IR hastalarda tedavi yanıtının değişmemesi, secukinumabın hem TNFi-naif hem de TNF-IR hastalarında neredeyse eşit derecede etkili olduğunu göstermektedir. Sonuç olarak secukinumab, aksSpA'lı hastalar için güvenli ve etkili bir tedavi seçeneği olacaktır.

Anahtar Kelimeler: Sekukinumab, aksiyel spondiloartrit, IL-17A antikoru

Introduction

Axial spondyloarthritis (axSpA) is a chronic inflammatory condition which mainly affects the spine and sacroiliac joints. AxSpA is divided into 2 different types according to the X-ray imaging of sacroiliac joints, radiographic axSpA (r-axSpA) and non-radiographic axSpA (nr-axSpA).[1] Patients with axSpA may also experience dactylitis, enthesitis, and peripheral arthritis. Furthermore, extra-articular findings

Correspondence / İletişim:
Emine Uslu Yurteri MD, Ankara University Faculty of Medicine, Department of Internal Medicine, Division of Rheumatology, Ankara, Turkey
Phone: +90 507 993 97 13 **E-mail:** drusluemine@gmail.com **ORCID ID:** orcid.org/0000-0002-4717-3000
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such as psoriasis, inflammatory bowel disease (IBD), and uveitis may be observed.[1-3]

The exact etiopathogenesis of axSpA is not completely understood. Numerous immune system components and cytokines including interleukin (IL)-17, IL-23, and tumor necrosis factor-α (TNF-α) play a part in the pathophysiology of the disease.[4,5] Non-steroidal anti-inflammatory drugs are the first line therapeutic agents in the treatment of axSpA. In resistant cases, further treatment options, such as TNF-α inhibitors (TNFi), IL-17 inhibitors and JAK/STAT pathway inhibitors, are required.[6]

Secukinumab, a fully human IgG1 kappa monoclonal antibody which binds to IL-17A, has been approved for axSpA treatment. Secukinumab was shown to be rapidly effective in axSpA patients in a phase 3 study.[7] Likewise, in the MEASURE studies, secukinumab treatment was shown to be effective and demonstrated low rates of radiographic progression rate in patients with r-axSpA.[8-10] In the MEASURE 2 study, the patients who received secukinumab showed substantial improvements in Bath Ankylosing Spondylitis Disease Activity Index (BASDAI) scores and Assessment of spondyloarthritis international society.[11] 40 response criteria in both the TNFi-naive and TNFi-nonresponder (TNF-IR) groups.[12] In the PREVENT study, the use of secukinumab improved the symptoms in patients with nr-axSpA.[13] In a real-life study called as CORRONA study, it was shown that patients receiving secukinumab had a decrease in disease activity at a similar rate compared to patients receiving other biologic drugs.[14] However, there are some concerns about its use in patients with IBD and uveitis.[15-18]

In this retrospective observational study, we aimed to assess the demographic, clinical and laboratory features of r-axSpA patients using secukinumab and to evaluate drug adherence and adverse effects.

Materials and Methods

The records of 86 spondyloarthritis (SpA) patients who were seen at the biologic treatment outpatient clinic of the Ankara University Faculty of Medicine between May 2018 and March 2022 and used secukinumab were retrospectively evaluated. Fourteen patients who did not fulfill the ASAS classification criteria and 6 patients who did not have axial involvement were excluded.[19] Among 66 patients with axSpA, 52 who had a follow-up period of 16 weeks, or more were included in the final analyses. Patients' demographic data, extra-articular findings, therapies, BASDAI scores at the beginning of secukinumab treatment, erythrocyte sedimentation rate (ESR), and C-reactive protein (CRP) values were recorded.[19-21] The patients were also screened for the presence of accompanying fibromyalgia syndrome (FMS) according to 2010 ACR fibromyalgia diagnostic criteria.[22]

Patients who did not receive TNFi prior to secukinumab were considered TNFi-naive, patients who received one or more TNFi, and developed ineffectiveness before secukinumab initiation were considered as TNFi non-responder (TNF-IR). Patients who did not respond or were intolerant to secukinumab at the 12th week of treatment were called primary non-responders, and patients who did not respond to treatment beyond the 6th month were called secondary non-responders.

Drug adherence was defined as the condition in which patients continued to take their medication without discontinuing for any reason, including inefficacy, difficulty in using medication, side effects and loss to follow-up.

This study was conducted in accordance with the Declaration of Helsinki on Ethical Principles and was approved by the Ethics Committee of Ankara University Faculty of Medicine (approval number: İ11-697-22, date: 10.01.2023).

Statistical Analysis

Data are shown as total numbers and percentages for categorical variables. Chi-square and Fisher exact test (in case of an expected count <5) was used to investigate the relationship between two categorical variables. Continuous variables were compared by either Student's t test or Mann-Whitney test according to normality distribution and given as mean ± standard deviation (SD) or as the median and 25th and 75th percentiles (Q1-Q3). To demonstrate the differences between in the initial and the last and acute phase reactant levels, Wilcoxon rank test was performed. Paired sample t-test was done to compare baseline and the last BASDAI scores. Statistical significance was defined as a two-sided p-value <0.05. All statistical analyses were conducted with SPSS software version 26.

Results

Of the 52 patients, 20 (38.5%) were male, and the mean age at diagnosis of axSpA and onset of secukinumab were 36.5±12.1 and 44.9±10.6, respectively (Table 1). Of 52 patients, 16 patients (30.8%) were TNFi naive (Table 1). There was no significant difference in the baseline BASDAI scores between TNFi-naive and TNF-IR groups (p=0.16). The characteristic features of TNFi naive patients and TNF-IR patients are given in Table 2. There was no significant difference in last BASDAI scores between

Table 1. Demographic characterisctics of patients

	All patients n=52	Secukinumab discontinied n=5 (9.6%)	Drug continuing n=47 (90.4%)	p
Age of diagnosis, year (SD)	36.5 (12.1)	39.7 (16.6)	36.2 (11.7)	0.54
Age at drug onset, year (SD)	44.9 (10.6)	44.1 (14.4)	44.9 (10.3)	0.86
Gender, male, n (%)	20 (38.5)	1 (20.0)	19 (40.4)	0.64
Radiographic SpA, n (%)	39 (75.0)	4 (80.0)	35 (74.5)	>0.99
Smoker, n (%)	20 (47.6)	4 (80.0)	16 (43.2)	0.17
Family history, n (%)	16 (34.8)	0 (0.0)	16 (39.0)	0.15
Inflammatory back pain, n (%)	51 (98.1)	5 (100.0)	46 (47.9)	>0.99
Peripheral arthritis, n (%)	21 (40.4)	0 (0.0)	21 (44.7)	0.073
HLA-B27 positivity	16 (44.4)	1 (33.3)	15 (45.5)	>0.99
Psoriasis, n (%)	7 (13.5)	0 (0.0)	7 (14.9)	>0.99
Inflammatory bowel disease, n (%)	2 (3.8)	1 (20.0)	1 (2.1)	0.19
Uveitis, n (%)	7 (13.5)	1 (20.0)	6 (12.8)	0.53
Enthesitis, n (%)	17 (32.7)	1 (20.0)	16 (34.0)	>0.99
Secukinumab concomitant therapies				
NSAID, n (%)	29 (55.8)	2 (40.0)	27 (57.4)	0.64
Glucocorticoids, n (%)	5 (9.6)	0 (0.0)	5 (10.6)	>0.99
Methothrexate, n (%)	4 (7.7)	0 (0.0)	4 (8.5)	>0.99
Leflunomide, n (%)	0 (0.0)	0 (0.0)	0 (0.0)	-
Sulfasalasine, n (%)	14 (26.9)	0 (0.0)	14 (29.8)	0.31
Biological agent before sec				
Certolizumab, n (%)	8 (15.4)	2 (40.0)	6 (12.8)	0.16
Golimumab, n (%)	7 (13.5)	1 (20.0)	6 (12.8)	0.53
Infliximab, n (%)	11 (21.2)	2 (40.0)	9 (19.1)	0.28
Adalimumab, n (%)	22 (42.3)	2 (40.0)	20 (42.6)	>0.99
Etanercept, n (%)	19 (36.5)	2 (40.0)	17 (36.2)	>0.99
TNFi naive, n (%)	16 (30.8)	0 (0.0)	16 (34.0)	0.31
Taking 1 TNFi, n (%)	13 (25.0)	2 (40.0)	11 (23.4)	
2 TNFi, n (%)	18 (34.6)	2 (40.0)	16 (34.0)	
3 TNFi, n (%)	2 (3.8)	1 (20.0)	1 (2.1)	
4 TNFi, n (%)	3 (5.8)	0 (0.0)	3 (6.4)	
5 TNFi, n (%)	0 (0.0)	0 (0.0)	0 (0.0)	
Ustekinumab, n (%)	1 (1.9)	0 (0.0)	1 (2.1)	>0.99
First CRP-before secukinumab, (mg/dL)	10.3 (4.9-30.4)	6.5 (4.7)	12.1 (8.8)	0.17
First ESH-before secukinumab, (mm/hours)	19 (11-46)	13 (11-28)	19.5 (10.5-48)	0.52
First BASDAI	5.6 (1.8)	4.9 (1.8)	5.7 (1.8)	0.37
The last CRP, (mg/dL), median	6.4 (2.1-13.8)	6.1 (2.2-17.7)	6.5 (2.1-14.3)	>0.99
The Last ESH, (mm/hours)	16.5 (5.3-21.8)	15 (12-22.5)	17 (5-22)	0.77
The Last BASDAI	2.9 (1.9)	3.2 (2.8)	2.8 (1.9)	0.65

BASDAI: Bath Ankylosing Spondylitis Disease Activity Index, CRP: C-reactive protein, ESR: Erythrocyte sedimentation rate, IBD: Inflammatory bowel disease, NSAIDs: Non-steroidal anti-inflammatory drugs, SD: Standard deviation, TNFi: Tumour necrosis factor alpha inhibitors

Table 2. BASDAI scores of TNFi naive and TNF

	TNFi naive n=16 (31.0%)	TNFi-IR n=36 (69.0%)	p-value
First BASDAI score, mean (SD)	5.2 (2.1)	5.8 (1.6)	0.29
Final BASDAI score, mean (SD)	3.2 (2.1)	2.7 (1.9)	0.47

BASDAI: Bath Ankylosing Spondylitis Disease Activity Index, SD: Standard deviation, TNFi: Tumour necrosis factor alpha inhibitors, TNFi-IR: TNFi non-responder

TNFi naive and TNF-IR (p=0.44). There was a significant difference between baseline and final follow-up BASDAI of 16 TNFi-naive patients (p=0.011), the mean difference was -2.0 [95% confidence interval (CI) -0.5-(-3.5)]. There was a significant difference between baseline and final follow-up BASDAIs in 36 TNFi-IR patients (p<0.001), the mean difference was -3.1 [95% CI -2.3-(-3.8)] (Table 2). While the median initial CRP value of our patients was 10.3 (Q1-Q3: 4.9-30.4) mg/L, the final median CRP value was 6.4 (Q1-Q3: 2.1-13.8) (p<0.001). The median initial ESR was 19 (Q1-Q3: 11-46) mm/h, while the final post-treatment ESR was 16.5 (Q1-Q3: 5.3-21.8) mm/h (p<0.001).

Of the 52 patients, 11 (21.2%) had FMS. When we excluded patients with FMS for possible bias, the median duration of secukinumab use in 41 patients was 24.9 (Q1-Q3: 11.5-38.3) months. One-year drug retention was 94% and, both 2 and 3-year drug retention rates were 91%. When baseline and final follow-up BASDAI scores of 41 patients were compared, there was a shift of -2.9 [95% CI -3.6-(-2.3)] (p<0.001).

The median follow-up period of 52 patients from axSpA diagnosis to the last follow-up was 89.3 (Q1-Q3: 65.0-160.9) months). Secukinumab was discontinued in 5 (9.6%) individuals during a median follow-up time of 27.4 (Q1-Q3: 11.9-37.7) months. Secukinumab treatment was terminated due to secondary non-response in 2 patients, pregnancy planning in 1 patient, hypertensive attack in 1 patient, and long-term SpA remission in 1 patient. The overall cumulative secukinumab drug survival rates observed at 12 and 24 months were 96% and 93%, respectively. The duration of drug survival was not significantly different between the TNFi-naive and TNF-IR groups [33.2 months (Q1-Q3: 19.5-39.7) and 24.3 months (Q1-Q3: 10.9-37.1), respectively; p=0.18].

After starting secukinumab medication, no uveitis attack was seen while receiving secukinumab medication, even though 7 patients had a history of uveitis before the initiation of secukinumab. Only 1 patient experienced uveitis episode for the first time, and any attacks did not occur again in this patient over the 39-month follow-up period. In addition, during the follow-up of 2 (3.9%) individuals who had been previously diagnosed with IBD, no exacerbation was detected. Overall, no malignancy was detected, and no patient died during the follow-up period of these 52 patients.

Discussion

Our study is a real-life experience of a single centre that demonstrates the efficacy of secukinumab treatment and the duration of drug survival in axSpA patients.

In terms of treatment response, a previous study showed a change in BASDAI score as -2.6 in the TNFi-naive group and -1.6 in the TNF-IR groups from baseline to week 16.[12] Even though the evaluation period is not identical, in our study, it was found to be -2.0 in the TNFi-naive group and -3.1 in the TNF-IR group, which was not statistically different (Table 3). Similar to the studies such as MEASURE and BIOBADASER, patients who received secukinumab in our study showed a decrease in CRP values, regardless of prior TNFi use.[12,23]

In many studies in the literature, including the ASTURias and EuroSpA studies, the duration of drug retention rate in the TNFi-naive group was higher than that of TNF-IR group.[24-27] Contrary to these studies, in a real-life study of Bektaş et al.,[28] previous use of TNFi did not affect the drug retention rate. In our study the duration of drug survival was not significantly different between the TNFi-naive and TNF-IR groups as in Beştaş et al.'s[28] study (p=0.18). The small sample size of our patients may have resulted in differing conclusions in this regard.

In literature, the rate of drug retention during the first year ranged from 55 to 86%.[24-29] In our study, the 1-year drug retention rate for patients receiving secukinumab was 96%, which is greater than what has been reported in the literature. In this instance, the selection of the appropriate patient may have had a role, and the low number of our patients may have contributed to this outcome.

Secukinumab does not increase the risk of uveitis, according to published Phase 3 studies.[15] In the study by Bektaş et al.,[28] patients receiving secukinumab did not develop a new case of uveitis. However, uveitis attacks have been reported in some case reports following secukinumab treatment.[17] In our study, uveitis attack under treatment was observed only in one patient. The attack did not recur in the following period. Seven patients with a history of uveitis did not experience a new attack during the secukinumab use. This could also suggest that secukinumab does not increase the risk of uveitis. However, long-term, and largely populated studies are required.

Furthermore, there are some studies and case reports demonstrating that secukinumab treatment exacerbates IBD.[30,31] On the contrary, there are studies showing that it does not increase the risk of IBD.[32,33] In our study, neither a new occurrence of IBD in the entire cohort nor an exacerbation of the disease in the 2 individuals who had previously been diagnosed with IBD was seen. However, our case number and duration of follow-up might be insufficient to make firm conclusions.

Table 3. TNFi naive and TNFi-IR patients characteristics

	TNFi-naive	TNFi-nonresponder
Age at daiagnosis, year (SD)	38.7 (13.9)	35.6 (11.3)
Age at drug onset, year (SD)	44.7 (10.6)	44.9 (10.8)
Gender, male, n (%)	5 (31.3)	15 (41.7)
Radyographic SpA, n (%)	13 (81.3)	26 (72.2)
Smoker, n (%)	3 (30.0)	17 (53.1)
Family history, n (%)	3 (25.0)	13 (38.2)
Inflammatory back pain, n (%)	16 (100)	35 (97.2)
Peripheral arthritis, n (%)	5 (31.3)	16 (44.4)
HLA b27 positivity, n (%)	4 (33.3)	12 (50.0)
Psoriasis, n (%)	1 (6.3)	6 (16.7)
Inflammatory bowel diseae, n (%)	0 (34)	2 (5.6)
Uveitis, n (%)	1 (6.3)	6 (16.7)
Enthesitis, n (%)	3 (18.8)	14 (38.9)
Secukinumab concominant therapies		
NSAIDs, n (%)	8 (50.0)	21 (58.3)
Glucocorticoids, n (%)	2 (12.5)	3 (8.3)
Methotrexate, n (%)	0 (34)	4 (11.1)
Leflunomide, n (%)	0 (34)	0 (34)
Sulfasalasine, n (%)	8 (50.0)	6 (16.7)
CRP at secukinumab initiation, mg/dL, median (Q1-Q3)	11.1 (5.1-27.8)	10.2 (4.7-31.8)
ESR at secukinumab initiation, mm/hours, median (Q1-Q3)	19 (11-46)	19 (9-46)
The last CRP, mg/dL, median (Q1-Q3)	4.1 (2.0-9.4)	6.6 (2.3-16.2)
The last ESR, mm/hours, median (Q1-Q3)	16.5 (9.3-21)	16 (5.22.8)

CRP: C-reactive protein, ESR: Erythrocyte sedimentation rate, NSAIDs: Non-steroidal anti-inflammatory drugs, SD: Standard deviation

Secukinumab is safe and efficacious in TNFi-naive and TNF-IR axSPA patients.[24] In the MEASURE 2 study, secukinumab treatment was demonstrated to be safe and effective for both TNFi-naive and TNF-IR patients. [12] During a median follow-up period of 27,4 months, no serious infections, malignancies, or mortality were observed in our study. This is in line with the current literature. However, the follow-up period may not be long enough to detect the development of malignancy. There is a need for larger cohort studies with longer follow-up periods.

Study Limitations

The major limitation of our study is the small number of our study cohort. In addition, the duration of follow-up was short to evaluate drug safety. As for strengths of the study, it presents the real-life experience of secukinumab by also including axSpA patients with extra-articular involvement.

Conclusion

Our results suggest that secukinumab is to be safe and effective treatment option for patients with axSpA regardless of previous TNFi exposure. Likewise, the fact that the treatment response does not change in TNFi-naive and TNF-IR patients indicates that secukinumab is almost equally efficacious both in TNFi-naive and TNF-IR patients. The absence of newly formed IBD implies that secukinumab is a viable treatment option for patients who do not respond to TNFi.

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Ethics

Ethics Committee Approval: This study was conducted in accordance with the Declaration of Helsinki on Ethical Principles and was approved by the Ethics Committee of Ankara University Faculty of Medicine (approval number: İ11-697-22, date: 10.01.2023).

Informed Consent: Retrospective study.

Peer-review: Externally peer-reviewed.

Authorship Contributions

Surgical and Medical Practices: E.U.Y., D.Ş.E., E.G.A.G., A.İ., T.M.T., G.K., A.A., Concept: E.U.Y., D.Ş.E., Design: E.U.Y., D.Ş.E., A.İ., T.M.T., G.K., A.A., Data Collection or Processing: D.Ş.E., E.G.A.G., Analysis

or Interpretation: D.Ş.E., Literature Search: E.U.Y., D.Ş.E., A.İ., Writing: E.U.Y.

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