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ORIGINAL ARTICLE

Secukinumab after first-line tumor necrosis factor-alpha inhibitor therapy in psoriatic arthritis: A real-world retrospective cohort study

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ABSTRACT

Objectives: This study compared the secukinumab treatment responses and adverse effects in psoriatic arthritis patients who received secukinumab as second-line with those that received secukinumab after two or more tumor necrosis factor-alpha (TNF-α) inhibitors.

Patients and methods: The retrospective study included 68 psoriatic arthritis patients followed up between October 2018 and October 2021. The patients were divided into two groups according to their anti-TNF-α treatment history. Group 1 consisted of 29 patients (11 males, 18 females; mean age: 45.3±13.3 years; range, 21 to 69 years) who had previously received one anti-TNF-α agent, while Group 2 included 39 patients (18 males, 21 females; mean age: 46.4±13.0 years; range, 24 to 70 years) who had been treated with two or more anti-TNF-α agents. Treatment responses of the groups were measured and compared using the Bath Ankylosing Spondylitis Disease Activity Index (BASDAI) and Visual Analog Scale (VAS). A posttreatment BASDAI score ≤4 was used as a criterion for remission.

Results: The mean duration of secukinumab treatment was 16.6±12.7 months for Group 1 and 16.0±11.6 months for Group 2 (p=0.84). Both groups responded significantly to secukinumab in terms of BASDAI and VAS scores (p<0.001 and p<0.001, respectively). Group 1 had a greater decline in BASDAI and VAS scores than Group 2 (p=0.045 and p=0.032, respectively). Furthermore, the remission rate was greater in Group 1 compared to Group 2 (58% *vs.* 34%, p=0.03). The adverse effects of secukinumab treatment were an allergic reaction in Group 1 and one case of ulcerative colitis in Group 2.

Conclusion: Second-line secukinumab treatment resulted in a greater decline in BASDAI and VAS scores. Moreover, secukinumab achieved a significantly higher rate of remission when it was used as second-line therapy after one anti-TNF-α agent.

Keywords: Adverse effects, anti-IL-17, anti-TNFα, psoriatic arthritis, secukinumab.

Psoriatic arthritis (PsA) is a chronic inflammatory musculoskeletal disease that is seen in 10 to 40% of patients with psoriasis.[1] Although the development of psoriasis precedes arthritis in most cases, approximately 15% of the patients develop psoriasis after presenting with arthritis.[2]

The treatment of PsA should focus on reducing arthritis and skin manifestations while preserving joint function and improving the quality of life. Today, the mainstay of PsA treatment is comprised of disease-modifying antirheumatic drugs (DMARDs). Conventional synthetic DMARDs (csDMARDs) are mainly used for peripheral arthritis and skin manifestations. Biological DMARDs (bDMARDs) are used to treat axial disease in addition to peripheral arthritis and skin manifestations. Tumor necrosis factor-alpha (TNF-α) inhibitors are most of the time the first-line bDMARDs. If the patient is refractory to treatment, a different TNF-α inhibitor can be tried before switching to another agent in a different class.[3] Interleukin (IL)-17 inhibitors are used in patients who are resistant or have contraindications to TNF-α inhibitors.[4]

Secukinumab (SEC) is a human anti-IL-17A antibody that is used in ankylosing spondylitis, nonradiographic axial spondyloarthritis, PsA, and plaque psoriasis. Its efficacy against PsA has been shown, and it was found to be effective across key PsA domains.[5,6] There is still a debate regarding the selection of a second-line bDMARD after treatment failure with a TNF-α inhibitor agent, and real-world studies could help clinicians to decide what is best for their patients.

In this cross-sectional cohort study, which provides real-world data regarding SEC treatment in PsA, we aimed to evaluate and compare the SEC treatment responses and side effects of patients who had used one TNF-α inhibitor agent and patients who had used two or more TNF-α inhibitor agents. We used widely utilized patient-reported outcome measures, namely Bath Ankylosing Spondylitis Disease Activity Index (BASDAI) and the Visual Analog Scale (VAS), to evaluate the treatment response.[7-9]

PATIENTS AND METHODS

Sixty-eight PsA patients who were diagnosed and followed up in the rheumatology clinic of Istanbul University-Cerrahpaşa, Cerrahpaşa Medical Faculty between October 2018 and October 2021 were included in this retrospective study. Patients who had active arthritis in at least two joints or BASDAI scores ≥4 and fulfilled the CASPAR (classification criteria for PsA) were diagnosed with PsA. Patients under 18 years old or unable to consent were excluded from the study. PsA patients were divided into two groups, Groups 1 and 2, based on their exposure to TNF-α inhibitors prior to the initiation of SEC treatment. Group 1 consisted of 29 patients (11 males, 18 females; mean age: 45.3±13.3 years; range, 21 to 69 years) who received only one TNF-α inhibitor. Group 2 consisted of 39 patients (18 males, 21 females; mean age: 46.4±13.0 years; range, 24 to 70 years) who previously received two or more different TNF-α inhibitors. The reason for switching to a different TNF-α inhibitor for patients in Group 2 was either inadequate treatment response or the development of side effects. SEC was started for patients in both groups due to side effects or inadequate response to TNF-α inhibitors. SEC treatment initiation was largely based on expert opinion and drug availability since the guidelines do not have strong recommendations on this matter. SEC loading dose was 300 mg per week for five weeks, followed by maintenance doses every month. The patients in both groups were further divided based on their SEC treatment response into three categories: patients still using SEC, primary nonresponders, or secondary nonresponders. Primary nonresponders were the patients who did not respond to the SEC treatment after loading the dose. Secondary nonresponders were patients who developed symptoms again after at least six months of remission. BASDAI and VAS scores after the completion of the loading dose for primary nonresponders, best on-treatment scores for secondary nonresponders, and last visit scores for patients still using SEC were used.

All patients had used csDMARDs and nonsteroidal anti-inflammatory drugs (NSAIDs) before beginning a biologic agent. TNF-α inhibitors that were used by the patients in both groups were adalimumab, infliximab, golimumab, certolizumab pegol, and etanercept. The patients in both groups did not receive any other biologic agents. Some patients who were partially responsive to methotrexate (MTX) or leflunomide continued their treatments while SEC was added to their treatment regimen.

The age and sex of the patients, disease duration, joint involvement characteristics, and side effects of the SEC treatment were evaluated. BASDAI was used to evaluate the disease activity, and scores ≥4 meant active disease. VAS score was also used as a patient-reported disease activity measure along with BASDAI. An expert rheumatologist assessed the BASDAI and VAS scores of the patients on their visits. Pre- and posttreatment BASDAI and VAS scores, and score differences between pre- and posttreatment BASDAI and VAS scores were evaluated. A posttreatment BASDAI score ≤4 was the criterion for remission in this study.

Statistical analysis

All analyses were performed using IBM SPSS version 21.0 software (IBM Corp., Armonk, NY, USA). Descriptive statistics were indicated as numbers and percentages for categorical variables and mean and standard deviation for numerical

variables. Patients' sex and achievement of remission were evaluated using Pearson's chi-square test. Student's t-test was used for the comparison of two independent means. Changes in the pre-and posttreatment BASDAI & VAS scores in both groups were evaluated by the paired t-test method. Pre- and posttreatment BASDAI and VAS score difference in both groups was evaluated by the Mann-Whitney U test. A *p* value <0.05 was regarded as statistically significant.

RESULTS

The baseline characteristics of both groups are given in Table 1. There was no significant difference in sex and the means of age, disease duration, and duration of anti-TNF-α between the groups (p>0.05). While the percentage of females was higher in Group 1, males constituted a slightly greater proportion in Group 2 (p=0.49). The patients' ages were similar between the groups (p=0.74). Disease duration and duration of anti-TNF-α therapy was longer in Group 2 (p=0.23 and p=0.31, respectively). While SEC was used alone in most patients (n=44, 65%), it was also used in combination with MTX (n=17, 25%) or leflunomide (n=7, 10%).

Treatment responses (still using, primary nonresponders, and secondary nonresponders) between Group 1 and Group 2 did not differ significantly (p=0.15). The mean duration of SEC treatment (16.6±12.7 months for Group 1 and 16.0±11.6 months for Group 2) was not significantly different between groups (p=0.84, Table 2).

The mean pretreatment BASDAI score was 6.33±2.04 and the mean posttreatment BASDAI score was 3.69±2.41 for Group 1 (p<0.001). The mean pretreatment BASDAI score was 5.98±1.89

Table 1. Selected baseline characteristics of the patients

	Group 1 Previously received one anti-TNF-α (n=29)			Group 2 Previously received two or more anti-TNF-α (n=39)			
	n	%	Mean±SD	n	%	Mean±SD	*p*
Age (year)			45.3±13.3			46.4±13.0	0.74
Sex							0.49
Female	18	62.1		21	53.8		
Male	11	37.9		18	46.2		
Duration of PsA (month)			117±73			141±87.8	0.23
Duration of anti-TNF-α therapy before SEC (month)			40±36.2			49.6±33.9	0.31

TNF-α: Tumor necrosis factor alpha; SD: Standard deviation; PsA: Psoriatic arthritis; SEC: Secukinumab.

Table 2. Treatment responses of the patients

	Group 1 Previously received one anti-TNF-α (n=29)			Group 2 Previously received two or more anti-TNF-α (n=39)			
	n	%	Mean±SD	n	%	Mean±SD	*p*
Patients still using SEC	19	65.5		17	43.6		
Primary nonresponders	7	24		12	30.8		0.15
Secondary nonresponders	3	10.3		10	25.6		
Duration of SEC treatment (month)			16.62±12.7			16.03±11.6	0.84

TNF-α: Tumor necrosis factor alpha; SD: Standard deviation; SEC: Secukinumab.

and the mean posttreatment BASDAI score was 4.58±2.49 for Group 2 (p<0.001, Table 3). The mean pretreatment VAS score was 7.8±2 and the mean posttreatment VAS score was 4.3±2.7 for Group 1 (p<0.001). The mean pretreatment VAS score was 7.6±1.8 and the mean posttreatment VAS score was 4.3±2.4 for Group 2 (p<0.001). The difference between groups' pre- and posttreatment BASDAI and VAS scores was nonsignificant (p=0.46 for pretreatment BASDAI scores, p=0.146 for posttreatment BASDAI scores, p=0.40 for pretreatment VAS scores, and p=0.45 for posttreatment VAS scores). The difference in pre- and posttreatment BASDAI scores between groups was 3.1 (interquartile range [IQR]: 0.4-5.35) for Group 1 and 0.9 (IQR: –0.2-3.0) for Group 2 (p=0.045). Furthermore, the remission rate was greater in Group 1 (n=17, 58%) compared to Group 2 (n=13, 34%; p=0.03).

While certolizumab pegol and adalimumab were most commonly used in Group 1, adalimumab and etanercept were more common in Group 2. The causes of TNF-α inhibitor treatment cessation included urticarial rash, hepatotoxicity, paradoxical psoriasis, maculopapular rash, erythematous rash, recurrent herpes labialis, allergy, alopecia, and injection site reaction (Tables 4 and 5). Among the adverse effects, paradoxical psoriasis was the most common cause that led to the cessation of anti-TNF-α agents, and it was observed with all of them except for golimumab. In our cohorts, we found that infliximab (n=5) and certolizumab (n=4) were the most frequent culprits of paradoxical psoriasis events. The percentages of primary and secondary nonresponders to anti-TNF-α agents were the same in Group 1, and primary unresponsiveness was the major cause of anti-TNF-α cessation in Group 2. Anti-TNF-α-related adverse effects constituted 32%

Table 3. Comparison of pre- and posttreatment BASDAI scores of the groups

	Pretreatment BASDAI scores	Posttreatment BASDAI scores		Pretreatment VAS scores	Posttreatment VAS scores	
	Mean±SD	Mean±SD	*p*	Mean±SD	Mean±SD	*p*
Group 1 Previously received one anti-TNF-α	6.33±2.04	3.69±2.41	<0.001	7.8±2	4.3±2.7	<0.001
Group 2 Previously received two or more anti-TNF-α	5.98±1.89	4.58±2.49	<0.001	7.6±1.8	4.3±2.4	<0.001

BASDAI: Bath Ankylosing Spondylitis Disease Activity Index; VAS: Visual Analog Scale; SD: Standard deviation; TNF-α: Tumor necrosis factor alpha.

Table 4. Causes of cessation of anti-TNF-α agents in Group 1

	Primary nonresponders		Secondary nonresponders		Adverse effects	
Anti-TNF-α agents	n	%	n	%	n	%
Infliximab*	1		_		1-Paradoxical psoriasis 1-Hepatotoxicity	
Adalimumab†	2		5		1-Paradoxical psoriasis	
Etanercept‡	3		3		1-Urticaria	
Certolizumab pegol§	4		2		1-Maculopapular rash 1-Headache, 2-paradoxical psoriasis	
Golimumab¶	-		-		1-Urticaria	
Total	10	34	10	34	9	32

TNF-α: Tumor necrosis factor alpha; * Infliximab was administered intravenously at a 5 mg/kg loading dose at weeks 0, 2, and 6, followed by a 5 mg/kg maintenance dose every eight weeks; † Adalimumab was administered 40 mg subcutaneously (SC) every 14 days; ‡ Etanercept was administered 50 mg SC weekly; § Certolizumab was administered 400 mg SC initially and at weeks 2 and 4, followed by 200 mg every other week; ¶ Golimumab was administered 50 mg SC once a month. If the patient was over 100 kg, golimumab was administered 100 mg SC once a month.

Table 5. Causes of cessation of anti-TNF-α agents in Group 2

	Primary nonresponders		Secondary nonresponders		Adverse effects	
Anti-TNF-α agents	n	%	n	%	n	%
Infliximab*	2		5		4-Paradoxical psoriasis 1-Allergy+alopecia	
Adalimumab†	11		7		1-Fever, 1-erythematous rash 1-Paradoxical psoriasis 1-Recurrent herpes labialis	
Etanercept‡	5		5		1-Hepatotoxicity 2-Paradoxical psoriasis 2-Injection site reaction	
Certolizumab pegol§	9		1		2-Paradoxical psoriasis	
Golimumab¶	4		1		-	
Total	31	47	19	29	16	24

TNF-α: Tumor necrosis factor alpha; * Infliximab was administered intravenously at a 5 mg/kg loading dose at weeks 0, 2, and 6, followed by a 5 mg/kg maintenance dose every eight weeks; † Adalimumab was administered 40 mg subcutaneously (SC) every 14 days; ‡ Etanercept was administered 50 mg SC weekly; § Certolizumab was administered 400 mg SC initially and at weeks 2 and 4, followed by 200 mg every other week; ¶ Golimumab was administered 50 mg SC once a month. If the patient was over 100 kg, golimumab was administered 100 mg SC once a month.

in Group 1 and 24% in Group 2. One patient in Group 1 had an allergic reaction, and one patient in Group 2 had an exacerbation of ulcerative colitis after SEC treatment initiation. No other adverse effect was observed.

DISCUSSION

In this study, we evaluated the effect of SEC on patients taking SEC as a second-line treatment after an anti-TNF-α agent and patients taking SEC after two or more anti-TNF-α agents were tried. We found that both groups significantly responded to SEC treatment in terms of BASDAI and VAS scores. Pre- and posttreatment BASDAI score decline was significantly higher in Group 1 compared to Group 2. Furthermore, SEC was significantly more successful in achieving remission in Group 1 than in Group 2.

IL-17A is overexpressed in psoriatic skin lesions and synovial fluid of PsA patients. This evidence provided the rationale for developing IL17 inhibitors in the psoriasis treatment landscape.[10-12] SEC, a fully human immunoglobulin G1/K monoclonal antibody targeted against IL17A, became the first agent in this class. Hence, SEC received approval for the treatment of both psoriasis and PsA in numerous countries, including the USA and the European Union.[13,14] The therapeutic efficacy of SEC was evaluated in several randomized, double-blind, placebo-controlled, multicenter, phase III trials: FUTURE, MAXIMISE, and ULTIMATE.[15-21] We evaluated SEC efficacy on arthritis by patient-reported BASDAI and VAS scores, whereas the primary endpoints of these prospective trials were assessed by the American College of Rheumatology (ACR) 20% response criteria (ACR20), the Assessment of Spondyloarthritis International Society (ASAS) 20% response criteria (ASAS20), and the global OMERACT (Outcome Measures in Rheumatology)-EULAR (European Alliance of Associations for Rheumatism) synovitis score (GLOESS), respectively. Similar to our study, FUTURE trials included patients with active arthritis despite previous treatments with NSAIDs, csDMARD, and anti-TNF-α agents. Likewise, patients who had previously received anti-TNF-α were enrolled if they had had an inadequate response or had developed adverse effects or intolerance. Across all trials, the mean ages of patients were also close to that of our study (47-50 *vs.* 46±13.1, respectively). In contrast to our research, FUTURE trials included anti-TNF-α-naïve patients, who constituted the majority of patients (65-76%).[15-29] In FUTURE 2 and FUTURE 3 trials, SEC was

administered as a loading dose at weeks 0, 1, 2, 3, and 4, and then every four weeks for maintenance. We used SEC 300 mg at weeks 0, 1, 2, 3, and 4, and then every four weeks.[13,14] While SEC doses were varied between FUTURE trials, as in our study, 300 mg was used in FUTURE 2 and 3.[16,17] The primary endpoint was the ACR20 at week 16 in FUTURE 4 and 5 and at week 24 in FUTURE 1, 2, and 3.[15-19] Clinical response was achieved with SEC in terms of ACR20 response rates at week 16 or week 24.[15-29] In prespecified (FUTURE 3) or post hoc analyses (FUTURE 1 and 2), ACR response rates at week 24 were significantly higher with SEC regardless of concomitant MTX use.[15-17] In our study, patients who had concomitant MTX use responded to SEC treatment along with those who did not use it. Furthermore, it has been shown that SEC achieves ACR 50% response criteria (ACR50) and 75% and 90% improvement in Psoriasis Area Severity Index (PASI) as secondary endpoints at week 16 or 24.[15-19] The clinical responses achieved at week 16 or 24 were maintained through 52 weeks and 104 weeks of treatment.[15-19,22,23] Although long-term radiographic responses regarding the inhibition of radiographic progression over three years were achieved with SEC treatment, we did not evaluate the radiographic progression in the present study.[25] Patient-reported outcomes of quality of life were shown to be improved significantly by several measurement systems.[15-19,25,26] Post hoc analyses were conducted with Disease Activity Index for Psoriatic Arthritis and Psoriatic Arthritis Disease Activity Score scores to evaluate the capability of SEC to achieve remissions or low disease activity. It was found that SEC provided remissions in both scores at week 16, with responses maintained through two years.[27,28] Thus, our study confirmed the outcomes of FUTURE trials regarding the SEC efficacy in anti-TNF-α-experienced patients in the real-world setting.

As in our study, arthritis was defined using patient-reported scores, namely VAS and BASDAI scores, at the beginning of the MAXIMISE trial.[20] Contrary to our study, patients who had prior use of bDMARDs, including anti-TNF-α agents, were excluded. Additionally, patients were permitted to use MTX at enrolment through to the end of the trial if there was no dose change from baseline to week 12. SEC doses of 150 mg or 300 mg or placebo (1:1:1) were administered for four weeks and then every four weeks. A significant proportion of patients achieved the primary endpoint at week 12 by meeting ACR20 ($p<0.0001$). Furthermore, response rates continued to increase through 52 weeks of treatment.[20] Patients who had signs of joint synovitis on power Doppler ultrasonography and at least one site of clinical enthesitis were included in the ULTIMATE trial.[21] Similar to the MAXIMISE trial, this study was conducted in biologic agent-naïve patients with active PsA, and all patients used csDMARDs before SEC treatment.[20] The patients were randomized to receive SEC doses of 150 mg or 300 mg or placebo (1:1:1) for four weeks and then every four weeks. Responses were evaluated by GLOESS, and significant improvement in synovitis was achieved at week 12 ($p=0.004$). SEC was also associated with significantly higher ACR20 and ACR50 response rates.[21] Although those trials did not assess the SEC response in anti-TNF-α-experienced patients, our study suggested that SEC is efficacious in patients exposed to anti-TNF-α agents regardless of concomitant MTX use.

Despite several real-world studies that confirmed SEC efficacy on PsA, current guidelines still tend to prioritize anti-TNF-α agents in different stages of PsA treatment.[29-33] This is because there is more experience in the treatment of PsA with anti-TNF-α agents. These studies showed that SEC was also associated with high patient and physician satisfaction levels with considerable retention rates.[29,34,35] Our study confirmed that SEC has high retention rates in anti-TNF-α-experienced PsA patients with >16 months mean duration of treatment. According to the 2018 ACR guideline, switching to a different anti-TNF-α agent was recommended over switching to an anti-IL17 agent in patients with active PsA despite treatment with anti-TNF-α biologic monotherapy.[33] Furthermore, biologic monotherapy was recommended over a combination with MTX or another biologic. If the patient has a partial response to the existing regimen or has concomitant uveitis that might respond to MTX therapy or severe psoriasis, combination therapy with biologics and MTX may be used. However, all recommendations for patients with active PsA despite anti-TNF-α treatment were low- to very

low-quality evidence.[33] This situation underlines the importance of conducting real-world studies concerning SEC efficacy in different stages of PsA. The preliminary results of the AQUILA study, which included 641 PsA patients on SEC treatment and compared their adherence rates in biologic-naïve and biologic-pretreated groups, showed that patients who received SEC as first-line therapy had a higher persistence rate than those pretreated with biologics.[35] As in our study groups, the interim analysis of the AQUILA demonstrated that SEC is a reliable treatment in biologic-pretreated patients with PsA in a daily routine setting.[35] Furthermore, our study suggested that using SEC as a second-line therapy after anti-TNF-α agents was significantly more effective than later use (p=0.045), although the treatment duration was not different between groups (p=0.84). Currently, why SEC is more efficacious in earlier stages of PsA treatment is a matter of debate. We consider that antidrug antibodies induced by shared epitopes with anti-TNF-α agents or changes in cytokine pathways caused by TNF-α inhibition may have roles in this phenomenon. Although the combination of infliximab and adalimumab with MTX provides longer treatment persistence by inhibiting the formation of anti-drug antibodies, it is not well known whether combination therapy with SEC and MTX is associated with higher retention rates and responses.[36] Therefore, studies evaluating treatment duration and response should be conducted in patients using SEC alone and in combination with MTX.

The EXCEED is the only study conducted to compare SEC and an anti-TNF-α (adalimumab) head-to-head.[37] In this study, all patients were biologic-naïve, used csDMARDs, and had an inadequate response to NSAIDs. Patients were randomized to receive SEC 300 mg at weeks 0, 1, 2, 3, and 4, and then every four weeks until week 48 (n=426) or adalimumab 40 mg every two weeks until week 50 (n=427). ACR20 response was the primary endpoint at week 52 and was 67% with SEC and 62% with adalimumab. 14% of SEC recipients and 24% of adalimumab recipients discontinued treatment by week 52, and SEC was not more effective than adalimumab for PsA.[37] Due to the lack of strong recommendations regarding the selection of biologics, head-to-head studies comparing the efficacies of SEC versus anti-TNF-α agents in particular treatment stages are still needed to determine our treatment strategies in PsA.

Subcutaneous SEC 300 mg was generally well tolerated in clinical trials.[14] The most common adverse reactions in clinical trials and postmarketing reports were upper respiratory tract infections.[14] Although physicians were warned that candidiasis and tuberculosis might develop with SEC treatment in different studies, we did not observe any infection in our patient groups.[13,14] Instead, we observed two adverse events: an allergic reaction and an exacerbation of ulcerative colitis, and both were not serious. SEC has been reported to cause new-onset inflammatory bowel disease or exacerbate preexisting inflammatory bowel disease.[13,14] Furthermore, hypersensitivity reactions ranging from drug eruptions to anaphylaxis have been reported in patients receiving SEC.[13,14] Thus, the safety profile of SEC in our study was in line with those previously reported.

There are some limitations to this study. Since this study was designed retrospectively, patients' arthritis was evaluated only with the patient-reported disease activity measures, namely BASDAI and VAS scores. Nevertheless, since these scores are based on patients' reports, it is important in terms of indicating treatment response and patients' quality of life. Because the PASI scores of the patients were evaluated in the dermatology clinic, PASI scores could not be obtained from the medical records of the patients. Furthermore, we included a relatively limited number of patients as SEC recently gained approval for PsA in Türkiye, and our data were obtained from single-center registries. However, more real-world studies on SEC use will improve our treatment strategies and guide rheumatologists when selecting biologics in different treatment steps.

In conclusion, SEC is a generally well-tolerated and efficacious biologic agent for PsA in anti-TNF-α-experienced patients. According to our study, after first-line biologic monotherapy with anti-TNF-α agents, second-line use of SEC seemed more effective than in later stages. However, additional well-designed studies directly comparing SEC with anti-TNF-α agents in patients with PsA are still needed.

Ethics Committee Approval: The study protocol was approved by the Cerrahpaşa Medical Faculty Clinical Research Ethics Committee (date: 11.10.2021, no: 203356). The study was conducted in accordance with the principles of the Declaration of Helsinki.

Patient Consent for Publication: A written informed consent was obtained from each patient.

Data Sharing Statement: The data that support the findings of this study are available from the corresponding author upon reasonable request.

Author Contributions: Wrote the manuscript: T.A., A.Y.A.; Reviewed the literature to provide a basis for discussion: T.A.; Collected the patients' data: T.A., L.M., Y.C.; Performed the statististical analysis: G.C.; Interpreted the results: T.A., A.Y.A., G.C., S.U.; Designed the study and acted as supervisor: S.U., T.A., L.M., Y.C., A.Y.A., G.C.; Provided critical review, integrity and clarity to the manuscript: S.U.; All authors discussed the conclusions and approved the final version.

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