Indexed by : DOAJ Google Crossref Dimension sinta GARUDA

J.Biomed.Transl.Res
ISSN: 2503-2178

JOURNAL OF BIOMEDICINE AND TRANSLATIONAL RESEARCH

Available online at JBTR website: https://jbtr.fk.undip.ac.id

Case Report

Recalcitrant Incomplete Secukinumab Administration in a Psoriasis Patient

Joice Sonya Gani Panjaitan[1], Suhartomi[2*]

[1] *Faculty of Medicine, Universitas HKBP Nommensen, Indonesia*
[2] *Faculty of Medicine, Dentistry, and Health Sciences, Universitas Prima Indonesia, Indonesia*

Article Info
History
Received: 29 Jun 2023
Accepted: 07 Dec 2023
Available: 31 Dec 2023

Abstract

Background: Psoriasis is an immunologic-mediated disease affected by genetic factors that may affect the skin, joints, and cardiovascular system. Some biological agents have been developed and approved by FDA (Food and Drug Administration) to treat psoriasis. One of these biological agents is Secukinumab, a fully human IgG1κ anti-interleukin-17A(IL-17A) monoclonal antibody.

Case Presentation: A seventeen-year-old female teenager came to Dermatovenerology Clinic with scaly patches in the forehead and hairline around ten months ago with a history of repeat Corticosteroid, DMARDs (Disease-Modifying Antirheumatic Drugs), and biologic agent treatment, that was Secukinumab injection. Dermatology examination showed erythema, plaque, and scale in head and extremities with PASI (Psoriasis Area and Severity Index) score of 1.2. The patient was treated with initial and maintenance doses of Secukinumab Injection. After these initial and two maintenance doses, the patient showed a significant clinical improvement by fading off the erythema, plaque, and scale.

Conclusion: It can be concluded that the recalcitrant administration of Secukinumab in Psoriasis patients may decrease the treatment response.

Keywords: *Psoriasis; Secukinumab; Recalcitrant; PASI; IL17A*
Permalink/ DOI: https://doi.org/10.14710/jbtr.v9i3.19100

INTRODUCTION

Psoriasis was known more than 2000 years ago by Hippocrates as psoriasis, which was come from *psora* and *lepra*. Later, psoriasis was described by Ferdinand von Hebra in 1841 as a specialized skin disease. However, recently psoriasis has been defined as an immunologic-mediated disease that is affected by some genetic factors that may affect the skin, joints, and cardiovascular system. Skin clinical presentation of psoriasis is characterized by skin inflammation and epidermal hyperplasia.[1,2]

The prevalence of this disease is different over the world. However, this disease has a lower prevalence rate in Asians. Parisi et al. (2013) reported that the psoriasis prevalence varies in different populations, ranging from 0.91% in the United States to 8.5% in Norway. On the other hand, Bu et al. (2022) also reported that the prevalence of psoriasis ranged from 0.33-0.6% in different races and affected around 125 million people worldwide. However, psoriasis affects males and females equally.[2,3,4]

The epidemiology data for psoriasis in Indonesia is limited. However, a study has been performed in ten different hospitals in Indonesia to investigate the prevalence of psoriasis. This study was performed from 1996-1998 and reported that the prevalence rate of psoriasis in 1996, 1997, and 1998 were 0.62%, 0.59%, and 0.92%, respectively. On the other hand, psoriasis also increases annually with a remission rate of 17-55% in various duration.[1]

Psoriasis has been classified as a multifactorial disease with various clinical presentations caused by uncontrolled keratinocyte proliferation and excessive inflammatory mediator production.

*Corresponding author:
E-mail: *suhartomi@unprimdn.ac.id*
(Suhartomi)

Table 1. PASI (Psoriasis Area and Severity Index) Score System

Skin Rash Scoring							
Score	**0**	**1**	**2**	**3**	**4**	**5**	**6**
Erythema Induration Desquamation	None	Mild	Moderate	Severe	Very Severe	-	-
True Area (%)	0	1-9	10-29	30-49	50-69	70-89	90-100
Percentage Area Score							
Affected Body				**Area Score**			
Head (H)				0.1			
Upper Limbs (UL)				0.2			
Trunk (T)				0.3			
Lower Limbs (LL)				0.4			

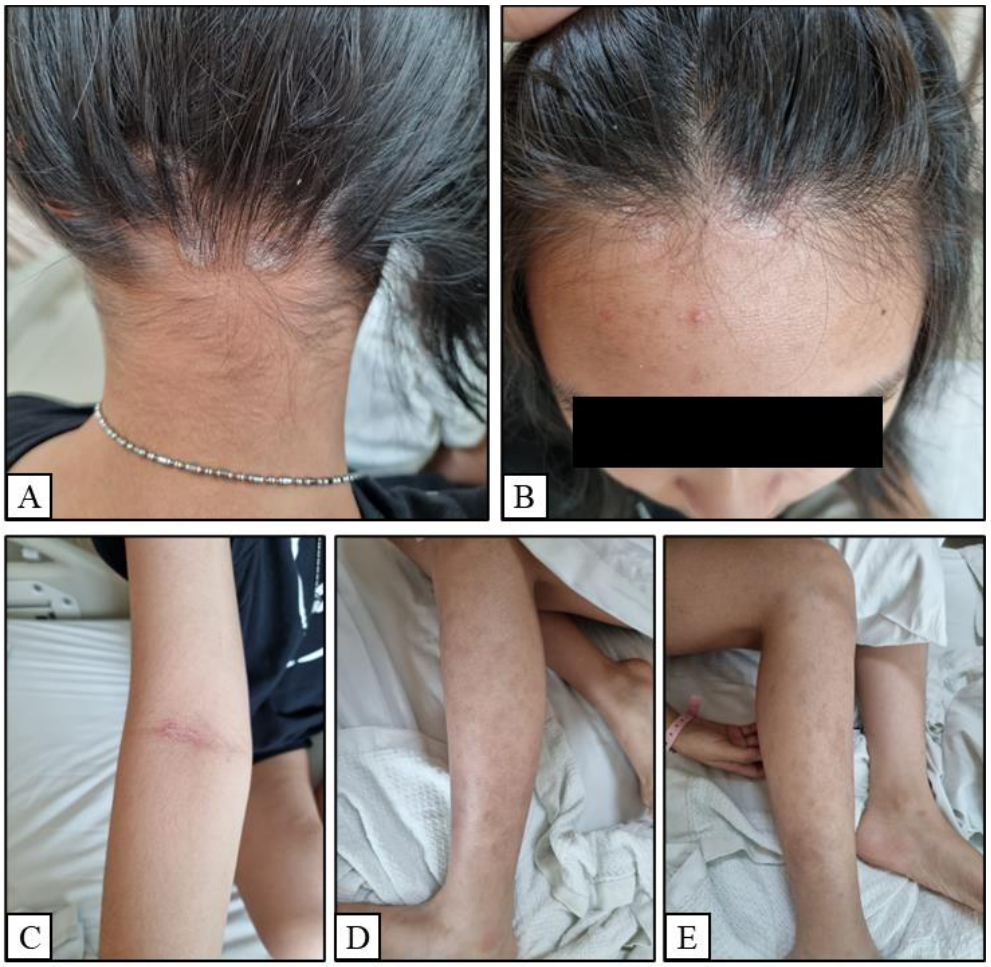

Figure 1. Initial Skin Lesions (Before Initial Dosage of Secukinumab Injection) in (A) Posterior Hairline, (B) Anterior Hairline, (C) Cubital Facies, (D) and (E) Left and Right Cruris

However, the recent postulate believes that the crucial role of psoriasis immunopathogenesis is either CD4+ or CD8+ T Cells. According to psoriasis immuno-pathogenesis, many drugs have been developed to improve the clinical presentation and quality of life in psoriasis patients.[2,5]

PERDOSKI (*Perhimpunan Dokter Spesialis Kulit dan Kelamin Indonesia*) recently recommended some drugs of choice for psoriasis, including topical, phototherapy, systemic medications, and biological agent. The topical therapy includes emollient, corticosteroid, keratolytic, retinoid, Vitamin D analogue, and tar. Phototherapy uses some types of ultraviolet, including Ultraviolet B broadband (BB-UVB), UVB narrowband (NB-UVB), and Ultraviolet A (UVA). Meanwhile, the systemic therapy consisted of methotrexate (MTX), cyclosporine, retinoid, some derivates of mofetil mycophenolate, and sulfasalazine. The last is biologic agents, which can be found in Indonesia as Etarnecept, Ustekinumab, Adalimumab, Infliximab, and Secukinumab.[6]

Some biological agents have targeted some inflammatory mediators, which terminates the inflammation cascade. One of these biological agents is Secukinumab, a fully human IgG1κ anti-interleukin-17A monoclonal antibody. FDA has approved this drug since 2015. However, adherence and persistence to biological agents for psoriasis diseases are still challenging.

Piragine et al. (2022) reported that the adherence and persistence to biological drugs for psoriasis were 61% (95% CI: 48%-73%) and 63% (95% CI: 57%-68%), respectively. Specifically, Piragine et al. also reported that adherence and persistence to Secukinumab were 52% (95% CI: 35%-68%) and 72% (95% CI: 58%-84%), respectively. Another study performed by Huang et al. (2022) also reported that Secukinumab persistence rates in Taiwan were high in the first years of the treatment period and reduced significantly in the second year, which was in contrast to other biologic agents like Ustekinumab, Etanercept, and Adalimumab. Huang et al. (2022) reported that the persistence rate of Secukinumab for psoriasis treatment with a 90-days and 45-days treatment gap was 96.2% (95% CI: 90.7%-100%) and 94.2% (95% CI: 87.7%-100%), respectively. However, the number of patients included in the second year for Secukinumab was very low. Thus the analysis could not be performed.[5,7] Based on these data, it becomes important to report the effect of non-adherence or recalcitrant biologic agent administration, especially Secukinumab. This case report was presented herein to reveal the impact of recalcitrant Secukinumab administration on psoriasis treatment.

CASE REPORTS

A Seventeen female teenager came to a Dermatovenerology Clinic of a Private Hospital in Medan, North Sumatera, Indonesia, complaining of scaly patches in the forehead and hairline around ten months ago with a history of repeat Corticosteroid, DMARDs, and biologic agent treatment, that was Secukinumab Injection. There is no family history of similar diseases.

The patient had been diagnosed with psoriasis for seven years and treated with either topical or oral corticosteroid for around two years since the patient was diagnosed, then she did not show any improvement until a few months later. Due to this reason, the patient's treatment was switched to a DMARDs drug that was MTX for two years, and every two months patient underwent routine blood count. The patient showed good clinical improvement against the MTX treatment. Unfortunately, the patients also had the MTX side effects, including appetite loss, hair fall, and severe weight loss after two years of MTX treatment. After that, the patient was suggested to receive a biological agent, Secukinumab. This patient showed a significant clinical improvement after two doses of the initial Secukinumab injection (Fraizeron^{TM}). However, she lost follow-up after she finished the initial dosage (Five doses). Hence, she did not receive any maintenance doses.

Dermatology examination showed erythema on the hairline, unilateral cubital facies, and both cruris, plaque on the hairline and unilateral cubital facies, and the last desquamation on the hairline and unilateral cubital facies. This efflorescent of the patient skin can be seen in Figure 1, and the PASI score of this patient was 1.2. Meanwhile, the PASI score system was described in Table 1.

The patient was planned to treat again with the Secukinumab injection. Before the patient received the Secukinumab injection, she underwent some

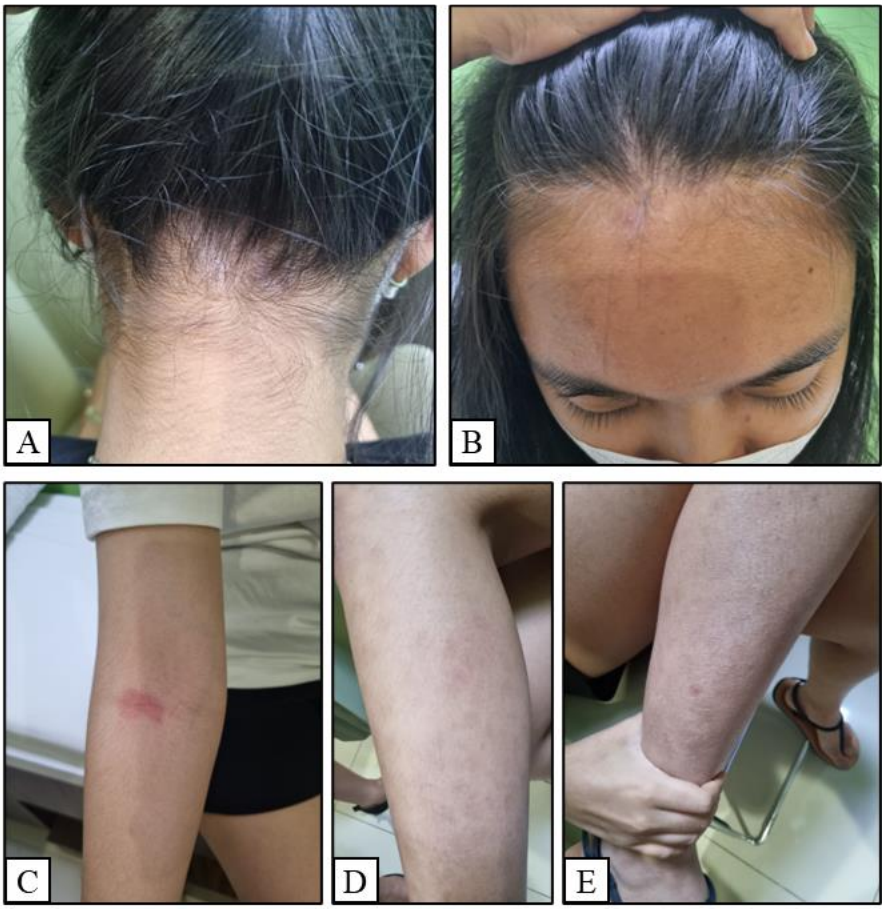

Figure 2. Skin Lesions Before First Maintenance Dose of Secukinumab Injection in (A) Posterior Hairline, (B) Anterior Hairline, (C) Cubital Facies, (D) and (E) Left and Right Cruris

investigation, including full blood count, liver function test, renal function test, randomized blood glucose level, SARS COVID-19 Isothermal Molecular PCR test, IFN-Gamma Release Assay, Electrolytes, and Anti-HCV test. These tests did not show any abnormalities. According to this investigation, the patient was safe to treat again with Secukinumab (Fraizeron^{TM}) injection.

This patient received some doses of Secukinumab (Fraizeron^{TM}) injection based on the manufacturer's instruction, including initial and maintenance doses. The patient received an initial dose of Secukinumab 300 mg via subcutaneous injection for five doses, including the first visit and every week for a month (first to fourth weeks). Afterwards, the patient received the Secukinumab 300 mg injection via subcutaneous injection as the maintenance dosage in the eighth week and then once every four weeks. After first maintenance dosage, the patient was lost to follow-up for the second maintenance dosage. At the last maintenance injection, the patient showed a significant clinical improvement, that was decribed in Figure 2. This clinical improvement rate decreased compared to the last year of Secukinumab injection. The patient showed a significant clinical improvement after the second dose of the initial dose at the last secukinumab injection period.

DISCUSSION

The essential role in the immunopathogenesis of psoriasis is T Cells. The best characterized T Cells in psoriatic lesions are CD4+ and CD8+ with the phenotype memory phenotype ($CD45RO^{+}$). These cells express cutaneous lymphocyte antigen, a ligand for E Selectin (selectively expressed in skin capillaries). Psoriatic lesion seems to enrich interferon- γ (IFN- γ) produced by T Helper (Th1). Then, IFN- γ amplifies the dendritic cells to produce Interleukin (IL)-23, which maintains and expands a subset of CD4+ cells (Th17 and Th22). The production of IL-17 and IL-22 characterizes Th17 and Th22. On the other hand, the activated T Cells and Dendritic cells also produce TNF-α. Then, the IL-17, TNF-α, IFN- γ, and IL-22 synergistically promote the activation of innate keratinocyte defence to produce various antimicrobial substances, other cytokines, and chemokines that amplify the last immune responses.[1,2]

Notably, the majority of biological agents with high therapeutic efficacy in psoriasis only target some axes like IL-12-Th1 and IL-23-Th17 axes.[2] PERDOSKI (2017) reported that some biological agents could be found in Indonesia, including Etanercept, Ustekinumab, Adalimumab, Infliximab, and Secukinumab. Etanercept, Adalimumab, and Infliximab are a group of Monoclonal Antibodies that act as Anti-TNF-α monoclonal antibodies. Etanercept is a dimeric fusion protein composed of human IgG1 with the constant region that may fuse to either TNF-α or TNF-β receptors. Meanwhile, the adalimumab is a complete IgG1 that blocks TNF-α with the TNF receptor on the cell surface, but the adalimumab does not bind to TNF-β. On the other hand, Infliximab is a human-mouse chimeric IgG 1 monoclonal antibody possessing human constant (Fc) regions and murine variable regions with the same anti-TNF-α activity as adalimumab and etanercept. However, Etarnacepts' hal-life is shorter than these agents due to its physical form (fusion protein). Other biologic agents that can be found in Indonesia are Ustekinumab and Secukinumab. Both agents act as anti-Interleukin Monoclonal Antibodies. The ustekinumab is a human IgG1 monoclonal antibody that binds to the p40 subunit of IL-12 and IL-23 cytokines. Furthermore, these blockages inhibit receptor-mediated signalling in lymphocytes.[8] Secukinumab is a fully human IgG1κ anti-interleukin-17A monoclonal antibody that FDA approved in 2015. The current case report used Secukinumab as the biological agent to block the IL-17 activity, preventing T Cells Subset's expansion (Th17). It prevents innate keratinocyte defence from producing various antimicrobial substances, other cytokines, and chemokines.[2,8]

The administration of Secukinumab in the current case report was based on the indication recommended by the local Dermato-Venerology Association (PERDOSKI). PERDOSKI (2017), recommended some indications of biological agent administration for psoriasis treatment. One of these indications is a special consideration in mild psoriasis patients with extensive area on the face that is not responsible for topical treatment, visible location, and any regions that are not unresponsible for topical treatment. In this case report, psoriasis involved the face area that did not respond to topical therapy; thus, the patient was indicated to receive the biologic agent (Secukinumab).[6]

This case report reported that this patient reduced response against the Secukinumab injection. Some hypotheses have been postulated to explain the mechanism of Secukinumab resistance. Berman et al. (2021) believed that the structure of Secukinumab has a lower affinity than another IL-17 monoclonal antibody; hence Secukinumab has a lower equilibrium dissociation constant (Kd) than other IL-17 monoclonal antibodies, allowing a higher potential for IL-17A blockade. Another possible hypothesis is the presence of neutralizing anti-drug antibodies to Secukinumab. Deodhar et al. (2020) reported that Secukinumab has a low incidence of immunogenicity (<1%) within a 52-days weeks course in Psoriatic arthritis and ankylosing spondylitis. Moreover, Deodhar et al. (2020) explained that anti-drug antibodies to Secukinumab may be due to the B cell activation and regulation. However, it remains a theoretical possibility that requires future studies. Although Secukinumab is a fully human antibody, it is still possible that the presence of potential epitopes. It formed within the highly diverse amino acid composition of the complementarity-determining regions (CDRs) of immunoglobulin G (IgG) molecules, the loss of tolerance to self-sequences, and product-specific attributes, such as dosing frequency, dose amount, administration route, and formulation factors such as impurities, host cell proteins, and the tendency to aggregate. A recent study by Reich et al. (2022) reported a similar result as Deodhar (2019). Reich et al. (2022) reported that Secukinumab consistently had low immunogenicity for up to 5 years in moderate-severe psoriasis. However, Reich et al. (2022) concluded that the administration of Secukinumab with low immunogenicity in moderate-severe psoriasis did not affect the efficacy, safety, or pharmacokinetics of this drug.[9,10,11]

Many studies showed various possible hypotheses about the efficacy of Secukinumab. Amschler et al.

(2020) do not agree with the presence of anti-drug antibodies against Secukinumab, which appear not to be relevant as a possible explanation for treatment failure to Secukinumab. Amschler et al. also reported an in-line result to Berman et al. that the affinity of IL-17A also affects the secukinumab resistance, which has 50-100 times lower *in vitro* affinity than the ixekizumab. Moreover, Amschler et al. also explained that their study has limited data on this hypothesis.[9,12]

The patients with mild psoriasis have received an uncompleted dose of Secukinumab. This case report showed the potential mechanism of anti-drug antibody formation. It potentially induces the acquired immune system to eliminate Secukinumab as the low immunogenicity foreign protein. Moreover, this protein with potential epitopes can activate or regulate the B Cells as part of the acquired immune system to produce anti-drug antibodies. However, this case report has limited data to explain this hypothesis, so further study is required to support this hypothesis.

CONCLUSION

This case report can be concluded that the recalcitrant administration of Secukinumab in Psoriasis patients may decrease the treatment response. This patient revealed a reduced treatment response against the Secukinumab in every course, and in the last course, the patient also showed a significant decrease in treatment response against the Secukinumab. This condition may occur due to either a lower equilibrium dissociation constant of Secukinumab or the formation of anti-drug antibodies against the Secukinumab. This case report showed the importance of adherence and persistence of a biologic agent administration in a clinical setting, especially in psoriasis.

REFERENCES

1. Jacoeb TNA. Psoriasis. In: Menaldi SLS, Bramono K, Indriatmi W, eds. *Ilmu Penyakit Kulit Dan Kelamin*. Ketujuh. Badan Penerbit Fakultas Kedokteran Universitas Indonesia; 2015:213-222.
2. Gudjonsson JE, Elder JT. Psoriasis. In: Kang S, Amagai M, Bruckner AL, et al., eds. *Fitzpatrick's Dermatology*. 9th ed. McGraw Hill; 2019:457-497.
3. Parisi R, Symmons DPM, Griffiths CEM, Ashcroft DM. Global epidemiology of psoriasis: A systematic review of incidence and prevalence. *J Invest Dermatol*. 2013;133(2):377-385. doi:10.1038/jid.2012.339
4. Bu J, Ding R, Zhou L, Chen X, Shen E. Epidemiology of Psoriasis and Comorbid Diseases: A Narrative Review. *Front Immunol*. 2022;13(June):1-19. doi:10.3389/fimmu.2022.880201
5. Piragine E, Petri D, Martelli A, et al. Adherence and Persistence to Biological Drugs for Psoriasis: Systematic Review with Meta-Analysis. *J Clin Med*. 2022;11(6). doi:10.3390/jcm11061506
6. Perhimpunan Dokter Spesialis Kulit dan Kelamin Indonesia (PERDOSKI). *Panduan Praktik Klinis Bagi Dokter Spesialis Kulit Dan Kelamin Di Indonesia*. (Widaty S, Soebono H, Nilasari H, et al., eds.). Perhimpunan Dokter Spesialis Kulit dan Kelamin Indonesia (PERDOSKI); 2017.
7. Huang Y-H, Tang C-H, Goh CH, et al. Persistence and Adherence to Biologics in Patients with Psoriasis in Taiwan: A New Biologics User Cohort Study. *Front Pharmacol*. 2022;13(May):1-9. doi:10.3389/fphar.2022.880985
8. Lake DF, Briggs AD, Akporiaye ET. Immunopharmacology. In: Katzung BG, Masters SB, Trevor AJ, eds. *Basic & Clinical Pharmacology*. 12th ed. Mc Graw Hill Lange; 2012:977-1000.
9. Berman J, Furer V, Berman M, et al. Treatment with ixekizumab following secukinumab failure in patients with psoriatic arthritis: Real-life experience from a resistant population. *Biol Targets Ther*. 2021;15:463-470. doi:10.2147/BTT.S326792
10. Deodhar A, Gladman DD, McInnes IB, et al. Secukinumab Immunogenicity over 52 Weeks in Patients with Psoriatic Arthritis and Ankylosing Spondylitis. *J Rheumatol*. 2020;47(4):539-547. doi:10.3899/jrheum.190116
11. Reich K, Blauvelt A, Armstrong A, et al. Secukinumab, a Fully Human Anti-Interleukin-17A Monoclonal Antibody, Exhibits Low Immunogenicity in Psoriasis Patients Treated Up to 5 Years. *J Eur Acad Dermatology Venereol*. 2019;33(9):1733-1741. doi:10.1111/jdv.15637
12. Amschler K, Phillip S, Mohr J, et al. Long-term follow-up of 22 psoriatic patients treated with ixekizumab after failure of secukinumab. *Dermatol Online J*. 2020;26(1):1-5. doi:10.5070/d3262047415