Secukinumab Therapy in Psoriasis Management

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ABSTRACT
Background: In recent years, use of biological therapy in psoriasis has increased as a result of advances in understanding the pathophysiology of psoriasis disease. Biological agents currently approved for the treatment of moderate to severe plaque psoriasis including inhibitor TNF-α (adalimumab, etanercept, infliximab), inhibitor IL-17 (ixekizumab, brodalumab, secukinumab), inhibitor IL-12/IL-23 (ustekinumab), and inhibitor IL-23 (guselkumab, tildrakizumab). Secukinumab is a human monoclonal antibody that selectively neutralizes IL-17A, a cytokine involved in the development of psoriasis. Review: Psoriasis is a chronic skin inflammation with the characteristic form of erythematous plaque firmly, thick scale, layered, and silvery-white. The trigger factors cause damage to the skin and produce cytokines IFN-γ, TNF-α, IL-17, and IL-22. This proinflammatory cytokine induces the proliferation of keratinocytes and subsequently causes skin inflammation, leading to plaque psoriasis formation. Biologic agents are utilized to block those cytokines. There are three main classes of biological agents in the treatment of psoriasis: inhibitor TNFα, inhibitor IL-17, and inhibitor IL-23. Secukinumab is a fully human antibody that selectively binds and neutralizes IL-17A. Conclusion: Biological agents targeting IL-17 receptors are more effective and safer than biological agents that target TNF-α and IL-23 receptors for moderate to severe plaque psoriasis treatment. Secukinumab has been approved for plaque psoriasis therapy in adults, psoriasis arthritis (PsA), and ankylosing spondylitis.

Keywords: Psoriasis, biologic agents, inhibitor IL-17, secukinumab, human & disease.

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BACKGROUND
Psoriasis is a chronic inflammatory skin disease whose main pathological manifestations are inflammation, epidermis hyperproliferation, altered epidermis maturation, and changes in blood vessels. The prevalence of this disease ranges from 0.51% to 11.43% in various countries. Pathogenesis of psoriasis is a combination of irregularities of the immunological system, a vulnerability associated with autoantigen psoriasis, and several environmental factors.1

In recent years, the use of biological therapy in psoriasis has increased as a result of advances in understanding the pathophysiology of psoriasis disease. Biological agents currently approved for the treatment of moderate to severe plaque psoriasis include inhibitor TNF-α (adalimumab, etanercept, infliximab), inhibitor IL-17 (ixekizumab, brodalumab, secukinumab), inhibitor IL-12/IL-23 (ustekinumab), and inhibitor IL-23 (guselkumab, tildrakizumab). Each drug has its unique effectiveness and safety profile.2

Inhibitor interleukin represents a new group of biologic agents with greater specificity to treat psoriasis. In theory, these agents should be more effective and safer than conventional therapies and inhibitor TNF-α, as they selectively target inflammatory pathways that are considered to be the most specific and important in the pathogenesis of psoriasis.3

Secukinumab is a human monoclonal antibody that selectively neutralizes IL-17A, a cytokine involved in the development of psoriasis. Secukinumab has demonstrated long-lasting effectiveness and safety in the manifestations of psoriasis, including on the nails, scalp, palms, and soles, as well as psoriasis arthritis.1

REVIEW
Psoriasis is a chronic inflammation of the skin with the characteristic form of erythematous plaque firmly, thick scale, layered, and silvery-white.4 A systematic study worldwide found the prevalence of psoriasis ranged from 0.5% to 11.4% in adults and 0% to 1.4% in children.5

Disorders in the innate and adaptive skin immune response are responsible for the development of inflammation in psoriasis. Pathogenesis of psoriasis can be conceptualized into an initiation phase that may
be triggered by trauma (koebner phenomenon), infection, or medication, as well as a phase of treatment characterized by chronic clinical development.\textsuperscript{6}

Trigger factors cause damage to the skin and the production of the antimicrobial peptide by keratinocytes. This peptide forms complex DNA or RNA molecules and activates dendritic cells to produce dendritic myeloid cells and T cells. Furthermore, myeloid dendritic cells produce cytokines, including IL-12 and IL-23. Both cytokines enable and induce T Helper cells to produce Th1 and Th17. The active Th1 cells produce IFN-\(\gamma\) and TNF-\(\alpha\), whereas Th17 cells produce IL-17 and IL-22. This proinflammatory cytokine induces proliferation of keratinocytes and subsequently causes inflammation of the skin leading to the formation of plaque psoriasis.\textsuperscript{7}

![Figure 1. Cytokine relationship in psoriasis.\textsuperscript{4}](image)

Five types of psoriasis have been reported, including plaque psoriasis or psoriasis vulgaris, guttate psoriasis or eruption that is characterized by its teardrop-shaped scales, inverse psoriasis is also called intertriginous or flexible psoriasis usually found on the folds of the skin, pustular psoriasis that can take the form of palmoplantar exanthematous (pustular psoriasis in the palm and soles of the feet), or the generalized pustular psoriasis (rare and severe forms of psoriasis), and erythrodermic psoriasis which is rare but severe psoriasis.\textsuperscript{9}

Psoriatic arthritis (PsA) is chronic seronegative arthritis that occurs in about 25% to 30% of individuals with psoriasis, which is characterized by synovitis, enthesitis, dactylitis, or spondylitis. Most patients with psoriatic arthritis also have psoriasis in the skin that is usually preceded by manifestations of joint disease.\textsuperscript{9} Assessment of the disease activity in psoriatic arthritis is an instrument for the following therapeutic response points when removed, traumatizing the dilated capillaries below (Auspitz sign). The most common locations are the scalp, chest, buttocks, and limbs. The surface of the extensor, like the elbow and knee, is often involved. Approximately 80% of patients suffer from mild to moderate degrees that involves less than 10% of the body’s surface area, while the others suffer moderate to severe degrees.\textsuperscript{9}
in clinical practice and clinical trials. Many assessments used in psoriasis arthritis include The Classification Criteria for Psoriatic Arthritis (CASPAR), The Disease Activity Index for Psoriatic Arthritis (DAPSA), and Psoriatic Arthritis Disease Activity Score (PASDAS).10

Figure 2. The clinical picture of plaque psoriasis.4

Diagnosis of psoriasis is generally based on the clinical picture. If the clinical examination and the anamnesis are not enough to establish diagnosis, then a biopsy can be done.4 Psoriasis is characterized by epidermal acanthosis, hyperkeratosis, and parakeratosis. The extends of epidermal rete ridges. In the dermis, the blood vessels are dilated, and winding reaches the end of the dermis papilla. Methods used to assess the severity of psoriasis, especially psoriasis vulgaris are Psoriasis Area and Severity Index (PASI), Body Surface Area (BSA), and Psoriasis Global Assessment (PGA).10

Psoriasis Area and Severity Index (PASI) is a score to measure the severity of diseases such as erythema, induration, or scale thickness, as well as extensive lesions in patients with widespread disease. PASI score is determined as: < 5 (mild), 5–10 (moderate), > 10 (severe).11 Body surface area is also considered in determining the degree of psoriasis, and it is often used beside PASI. BSA calculations are based on the rule of nine. This method commonly uses handprints. Menter et al. mentioned that severity of psoriasis is determined with the following < 3% is mild, if between 3–10% is mild, and severe if it is more than 10%.12,13 PGA is a global assessment on 0–5 scale, with 0 representing clear skin, 1 means almost clear skin, 2 means mild, 3 means moderate, 4 means severe, and 5 means very severe.14

Management of psoriasis can be classified as topical, systemic, or phototherapy. Management of psoriasis, especially psoriasis vulgaris is administered based on the area that affects the body. For surface area less than 10% (mild), the treatment option is topical medication and can be combined with phototherapy. When the area involves 10–30% (moderate), a combined treatment between topical, phototherapy, and daily treatment can be given. Meanwhile, for a surface area of more than 30%, management required is systemic treatment combined with daily care, phototherapy, and topical.4

Topical treatment consists of emollient, glucocorticoids, analog vitamin D, salicylic acid, dithranol, tazarotene, and tar. Phototherapy consists of NB-UVB, BB-UVB, psoralen combined with ultraviolet (PUVA), excimer laser, and climatography. Systemic therapy consists of methotrexate, acitretin, biologic agents (adalimumab, etanercept, infliximab, ixekizumab, secukinumab, and ustekinumab), cyclosporin A, hydroxyurea, 6-thioguanine, cellcept, and sulfasalazine.4 Some parameters should be considered in the selection of treatment, including the characteristics of the disease such as the severity and location of skin lesions, the patient's risk factor including age, history of failed treatment, and the characteristics of care such as effectiveness and safety issues. Some parameters can serve as the basis for consideration of biological agent selection.11

British Association of Dermatologists in 2017 suggest offering biologic therapy to people with psoriasis requiring systemic therapy if methotrexate and ciclosporin treatment is not an option (have failed, cannot be tolerated, or contraindicated), psoriasis has a significant impact on physical, psychological, or social functioning, and one or more of the disease severity criteria apply (psoriasis is extensive with (BSA) >10% or Psoriasis Area and (PASI) ≥ 10, the psoriasis is
severe at localized sites and associated with significant functional impairment and/or high levels of distress (e.g., nail disease or involvement of high impact and difficult to treat sites such as the face, scalp, palms, soles, flexures, and genitals). Consider biologic therapy earlier in the treatment pathway if methotrexate has failed, is not tolerated, or is contraindicated for psoriasis patients who have met the disease severity criteria and who also have active psoriatic arthritis or who have persistent psoriasis, that relapses rapidly or defined as >50% baseline disease severity within 3 months of completion of any treatment of a therapy that cannot be continued in the long-term such as narrow-band ultraviolet B.15

There are three main classes of biological agents in the treatment of psoriasis. They are inhibitor TNFα, inhibitor IL-17, and inhibitor IL-23. There are five inhibitors of TNFα that are approved for clinical use, like adalimumab, certolizumab pegol, etanercept, golimumab, and infliximab. Inhibitor IL-23 is approved for clinical use, including tildrakizumab, risankizumab, and guselkumab, antibodies specifically targeting IL-23, and ustekinumab that targets both IL-12 and IL-23. The use of inhibitor IL-17 is clinical, including ixekizumab, secukinumab, and brodalumab. Ixekizumab is a fully human antibody and secukinumab is a fully human antibody that targets IL-17A while brodalumab is a fully human antibody that has a target IL-17RA.16

Secukinumab is a fully human, fully derived from human antibodies anti-IL-17A IgG1 monoclonal antibody (antibodies made by identical immune cells that are all clones of unique stem cells) that selectively bind and neutralize IL-17A. Interleukin-17A has an important role in the proinflammatory cytokine in the pathogenesis of psoriasis. It can activate keratinocytes, by causing hyperproliferation and excess production of antimicrobial peptides, cytokines, and chemokines, which activates other immune cells, leading to the inflammation of psoriasis.18

Interleukin-17 is is a proinflammatory cytokine released by T-helper-17 (Th17) cells. Under the action of interleukin-6 and transforming growth factor-β, CD4 T cells differentiate into Th17 cells and induce expression of interleukin-23 receptors (IL-23R) and IL-17. Apart from T-cells, mast cells and neutrophils also secrete IL-17. Interleukin-17 and its receptors are also expressed in the synovial tissue, and IL-17 pathway is proposed to contribute to the pathogenesis of psoriatic arthritis. Interleukin-17 may radiate various effector biological functions that can produce inflammation of joints and enthesis, damage, and remodelling of tissues. The binding of IL-17A by secukinumab inhibits interactions with IL-17 receptor, which will inhibit the release of other proinflammatory cytokines, chemokines, and mediators of tissue damage and reduce IL-17A contributions to this inflammatory disease.20

Secukinumab has been approved as a plaque psoriasis therapy in adults, psoriasis arthritis, and ankylosing spondylitis. Secukinumab is also effective in psoriasis in the area of head, neck, nails, palmoplantar, erythrodermic psoriasis, and generalized pustular psoriasis.21 Contraindications from secukinumab are divided into absolute and relative contraindication. Absolute contraindication includes severe acute infections such as active TB, hypersensitivity to secukinumab or excipient, pregnancy or lactation, the conditions needed for concurrent administration with live vaccines. While relative contraindication includes previous acute and chronic infections (latent or active TB, Hepatitis B or C, HIV), malignancy, or lymphoproliferative disorders. Secukinumab should be avoided in patients with pre-existing inflammatory bowel disease such as crohn's disease and inflammatory drugs bowel disease (IBD) as it may increase the risk of infection and exacerbation. Special attention is given to patients with comorbidities such as tuberculosis infections, hepatitis or other liver dysfunction, HIV, malignancy, neurology diseases, ischemic heart disease and congestive heart failure, diabetes mellitus, kidney dysfunction, pregnancy, fertility, psoriasis arthritis, vaccination, and surgery.21

In patients without comorbidity, secukinumab therapy is given after the patients fill a form (if available), objective assessment of diseases (such as PASI/BSA/PGA), Health Related Quality of Life (HRQoL), medical history, and physical examinations including previous exposure to malignancy, Tuberculosis (TB) infections, crohn's disease and medications such as warfarin. Supporting examination before therapy, such as histopathology, ASTO titer, albumin, fat profile, uric acid, complete blood count, complete urine, liver function (AST/ALT), renal function (BUN/Creatinine ratio), electrolyte serum. Patients are also encouraged to conduct hypersensitivity screening, skin cancers, active and chronic infections, contraception and lactation, vaccine needs, tuberculosis, and laboratory control, including pregnancy tests. During therapy, laboratory examination is necessary, such as complete blood screening (Hb, HCT, leukocytes, platelet), CRP, liver enzymes, creatinine serum, pregnancy test, complete urine, hepatitis B and C, HIV and TB test. While after therapy, contraceptive use is recommended 20 weeks after termination of the use of secukinumab.21
Secukinumab is available in single-use of 1 mL in autoinjector pen, and 1 mL prefilled syringes with 27 gauge fixed 1/2 inch needle, each containing 150mg dose of the drug. Secukinumab is also available in lyophilized powder dissolved with sterile water for injection (STWI) by health professionals, with each vial containing 150 mg. The recommended dosage of secukinumab varies depending on psoriasis, as compared to psoriasis arthritis and ankylosing spondylitis. The recommended dose for plaque psoriasis is 300 mg administered subcutaneously in weeks 0, 1, 2, 3, and 4 (loading dose), and every 4 weeks afterward (maintenance). Patients with psoriasis arthritis or ankylosing spondylitis may use a dose with or without a loading dose. With loading dose, 150 mg secukinumab administered at weeks 0, 1, 2, 3, and 4 (loading dose), and every 4 weeks afterward (maintenance). Without loading dose, 150 mg secukinumab can be administered every 4 weeks. Suppose the patient continues to actively suffer from psoriasis arthritis. In that case, the dose may be increased to 300 mg. Patients with psoriasis arthritis and psoriasis moderate to severe is advised to use a dosage recommendation of plaque psoriasis. Each injection should be administered to a different anatomical location such as the upper arm, thigh, every quadrant of the abdomen than the previous injection. The drug should not be injected into tender, bruised, erythematous, indurated, or area affected by psoriasis lesions, scars or stretch marks.

According to the association of Indonesian dermatovenereologist, concerning the procedure of the management of psoriasis vulgaris, monitoring of secukinumab treatment in week 12 with the assessment based on the PASI score with the target of PASI 75, complete peripheral blood screening, liver enzymes, and renal function. When the PASI 75 is achieved, and the monitoring result is good, the provision of the secukinumab can be resumed every 4 weeks accompanied by the PASI score assessment. Furthermore, monitoring is conducted at week 24 and every 24 weeks following the assessment based on the PASI score, complete peripheral blood screening, liver enzymes, and kidney function, and thorax x-ray or interferon-gamma release assay (IGRA) to see the presence of TB infections. Side effects on secukinumab are divided into very frequent, frequent, and occasional.

### Table 1. Side effects of secukinumab

<table>
<thead>
<tr>
<th>Very frequent</th>
<th>Upper respiratory infections (nasopharyngitis, rhinitis)</th>
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</thead>
<tbody>
<tr>
<td>Frequent</td>
<td>Oral herpes, rhinorrhea, diarrhoea, urticaria</td>
</tr>
<tr>
<td>Occasional</td>
<td>Oral candidiasis, neutropenia, tinea pedis, otitis externa, conjunctivitis</td>
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The estimated cost of secukinumab ranges from $75,671 to $105,131 (US $). Secukinumab is known to be more effective than placebo in loading dose therapy based on 75/90 PASI. Four RCT journals evaluate at least 12 weeks of analysis. Secukinumab dose 300 mg superior to 150 mg during the induction treatment with the effectiveness of PASI 75, PASI 90, and PASI 100. Secukinumab 300 mg administered at weeks to 0, 1, 2, 4 (loading dose) is more effective compared with 300 mg administered without a loading dose in induction therapy based on PASI 75/90. Secukinumab dose 300 mg and 150 mg are superior than etanercept which is one of inhibitor TNF-α. Secukinumab is superior to ustekinumab in the induction phase based on PASI 75 and PASI 90, which ustekinumab is inhibitor IL-23. Secukinumab demonstrated high efficacy and a favorable safety profile up to 52 weeks of treatment in the Chinese population with a high disease burden. Similar to the overall population, PASI 75 responses in Asian subjects were significantly higher in secukinumab 300 mg (74.4%) and 150 mg (67.5%) treatment arms compared with placebo (6.8%; P < 0.0001, both doses) or etanercept treatment (27.4%; P < 0.0001, both doses) at week 12. In Asian subjects with moderate to severe psoriasis, secukinumab demonstrated an efficacy and safety profile consistent and comparable.

In phase II and III trials, secukinumab was found to be well tolerated. Currently, clinical trials have been published which demonstrate a safety profile up to 5 years of treatment. No cases of latent tuberculosis reactivation were reported with secukinumab treatment in clinical trials. The safety profile of secukinumab is comparable with other IL-17 biological agents and can be well tolerated up to 5 years of treatment. However, inhibitor TNF-α and ustekinumab have more safety data that includes long term treatment and can be an optimal treatment option for patients requiring long term safety in biological therapies or patients with complex medical conditions.

### DISCUSSION

Psoriasis can be targeted by innovative biological therapies. Treatment using biological agent needs to consider the skin symptoms and the comorbid disease of the patient. Biologic therapies have substantially impacted the management of psoriasis. The interleukin inhibitors, in particular, represent a major therapeutic
advance, as they appear to be highly selective in terms of mitigating the perturbed inflammatory pathways responsible for psoriasis. The unprecedented efficacy of these agents supports that the pathogenesis of psoriasis is largely driven by the Th17 axis.

Biological agents targeting IL-17 receptors are more effective and safer than biological agents that target TNF-α and IL-23 receptors for moderate to severe plaque psoriasis treatment. Secukinumab is a fully human immunoglobulin G1 monoclonal antibody that selectively binds and neutralizes the IL-17A proinflammatory cytokine. Secukinumab has been approved for plaque psoriasis therapy in adults, psoriasis arthritis (PsA), and ankylosing spondylitis. Multiple randomized control trial study evaluating secukinumab versus placebo have established the efficacy of this drug in patients with moderate-to-severe psoriasis.

Secukinumab is a highly-efficacious, fast-acting biologic therapy with a relatively favorable safety profile that can be considered in patients requiring rapid clearance of their psoriasis and patients with psoriasis in difficult-to-treat areas, such as the scalp, palms and soles, or nails. Additionally, secukinumab is a preferred treatment for patients with comorbid psoriatic arthritis or arthralgia symptoms, due to its ability to inhibit progression of arthritic disease. Careful consideration of clinical efficacy, safety, cost, convenience, onset of action, and management of comorbid disease is necessary when selecting treatment for individual patients.

REFERENCES