

Comparative Analysis of Secukinumab and Guselkumab in the Treatment of Plaque Psoriasis

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Abstract. Plaque psoriasis is an inflammatory, chronic skin condition characterized by red, scaly plaques. Further research in immunology led to the development of biologic treatments such as Secukinumab and Guselkumab. The treatments target, specifically, components of the immune system implicated in the pathophysiology of psoriasis. This study treats plaque psoriasis and compares Secukinumab vs. Guselkumab in the treatment of the disease, outlining their similarities and differences.

Keywords: Plaque Psoriasis, Secukinumab, Interleukin-17 (IL-17), Guselkumab, Interleukin-23 (IL-23), Psoriasis Treatment, Clinical Efficacy, Pharmacokinetics

1. Introduction

Psoriasis is a chronic immune-mediated inflammatory skin disorder that manifests in several forms, including pustular, erythrodermic, guttate, flexural, and plaque psoriasis [1]. The most common type is plaque psoriasis, characterized by raised erythematous skin plaques covered with silvery-white scales (Fig. 1). The tendency of the patches is to appear symmetrically on the body, and most commonly, they can be seen on the scalp, trunk, and limbs, especially at the elbow and knee joints [2].

Psoriasis has a worldwide incidence, and it affects men and women of all countries, races, and ages. Nationally published prevalence rates for psoriasis range between 0.09% and 11.4%, [3] and there are at least 100 million people with psoriasis worldwide. In China, it is estimated that 0.47% of the population has psoriasis [4], lower than in Western countries, where it ranges from 2-3% [3]. However, this result is associated with the difference in genetic background, environmental factors, healthcare systems, and, especially, the variation in definitions of cases with psoriasis. Psoriasis markedly affects the quality of life of patients worldwide, with difficulty in disease management being associated by reason of economic and health disparities.



Figure 1. Chronic Plaque Psoriasis Symptom. Characterized by widespread, symmetrical, and clearly defined red, scaly patches. Typically appears on elbows and knees [1]

2. Overview of Plaque Psoriasis

2.1. Pathogenesis of Plaque Psoriasis

The pathogenesis of plaque psoriasis involves an abnormal immune response that is driven by genetic and environmental factors. While the immune system mistakenly targets skin cells at a higher-than-usual rate, an increased turnover of skin cells occurs.

First, environmental stimuli or skin intolerance can induce the production of tumor necrosis factor, which in turn induces the dermal dendritic cells (DCs) [5]. The latter produces interleukin-23 (IL-23), which activates interleukin-17-producing cells T17, including Th17. In turn, keeping an increased number of T17 cells, large amounts of interleukin-17 (IL-17) are produced from IL-23, which then drives the up-regulation of psoriasis-associated genes in epidermal keratinocytes (Fig. 2.A).

As the disease progresses to the early stages, IL-17 induces augmented levels of chemokines and transcriptional regulators [5], which themselves potentiate a feed-forward inflammation response in keratinocytes, attracting a diversified range of immune cells to the site of lesions (Fig. 2.B).

Subsequently, during the chronic phase of plaque psoriasis, mature feed-forward keratinocyte responses at psoriatic lesions create psoriatic plaques—self-reinforcing processes that maintain pathologic immune infiltration. IL-17-induced feed-forward responses promote the production of AMPs acting as psoriatic autoantigens that further drive the disease process [5]. Th17 and Th22, directly stimulated by DC-produced IL-23, will induce the production of IL-22, IL-36, and IL-19 in the lesion area, giving way to epidermal proliferation (Fig. 2C).

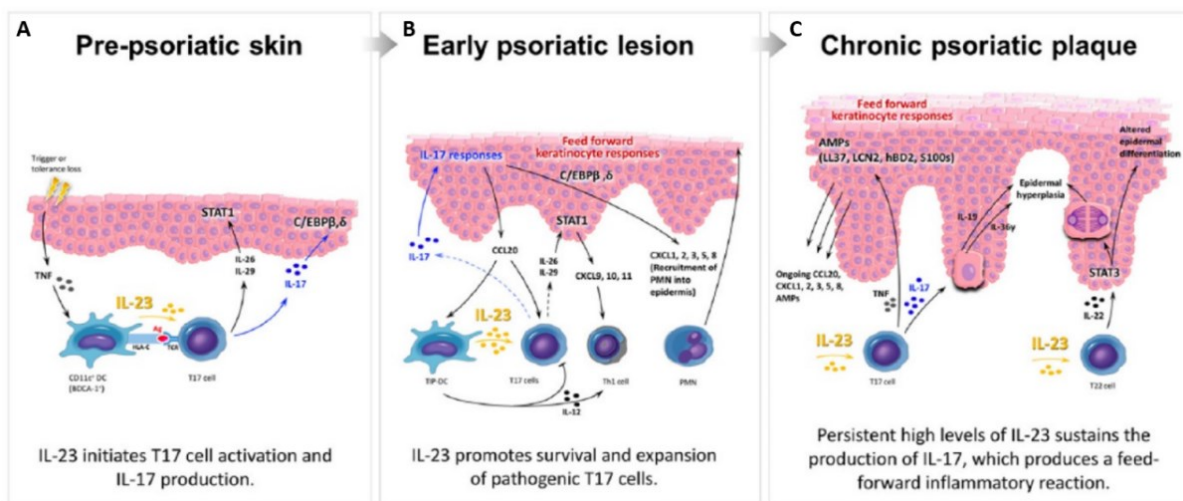


Figure 2. Pathogenic Model of Psoriasis in (A). Pre-psoriatic skin; (B). Early psoriatic lesion; (C). Chronic psoriatic plaque [5].

2.2. Drugs and Treatment of Plaque Psoriasis

Treatments of plaque psoriasis include topical, phototherapy, systemic, and biologic methods. With further research in this area, the IL-23/IL-17 axis has been established as the central pathogenic mechanism of plaque psoriasis (Fig. 3). Hence, biologics such as Secukinumab and Guselkumab have emerged as effective options for moderate-to-severe cases, aiming IL-17 and IL-23 as the target, respectively.

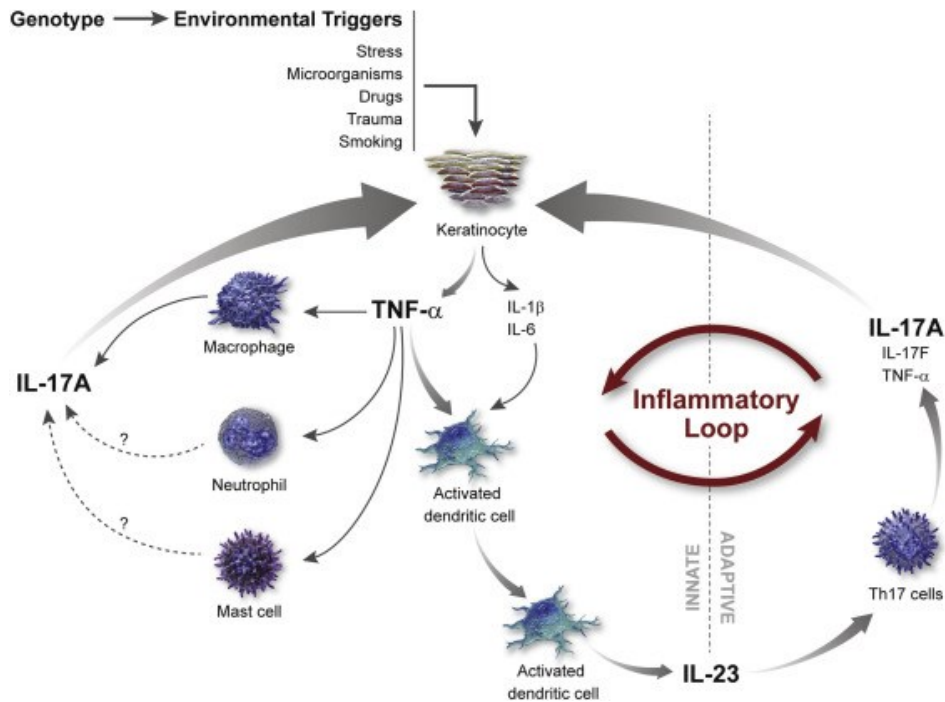


Figure 3. Current model of psoriasis pathogenesis. The IL-23/IL-17 axis is recognized as the key pathogenic pathway [6]

3. Secukinumab

Secukinumab (brand name: Cosentyx) [7] is a fully human monoclonal IgG1/κ antibody that targets interleukin-17A (IL-17A), a pro-inflammatory cytokine involved in several chronic immune-mediated inflammatory disorders, including plaque psoriasis [7]. Secukinumab contributes to the obstruction of the pro-inflammatory pathways giving rise to these diseases by inhibiting the activities of IL-17A. This drug is indicated for the treatment of several chronic inflammatory diseases, including hidradenitis suppurativa, psoriatic arthritis, ankylosing spondylitis, and plaque psoriasis.

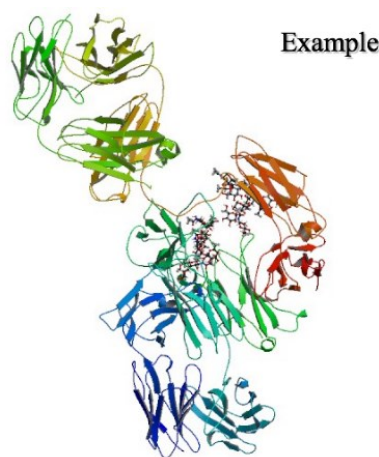


Figure 4. Protein Structure of Secukinumab. The image shows the three-dimensional structure of Secukinumab, highlighting its complex folding and protein domains [7].

3.1. Drug Target & Mechanism of Action of Secukinumab

Upon stimulation by IL-23 and other cytokines, Th17 cells produce IL-17. Besides Th17 cells, IL-17A can also be produced by innate lymphoid cells (ILCs), mast cells, neutrophils, and γδ T cells, particularly

in the setting of plaque psoriasis [8]. Neutrophils and mast cells release IL-17A during a special immune-mediated cell death process that involves forming extracellular traps. However, there is conflicting evidence about the role of neutrophils as a primary source of IL-17A in plaque psoriasis, with some studies showing expression and others not [8].

With increased expression of IL-17A, overexpression of IL-17 receptors triggers the release of a cocktail of proinflammatory chemokines, cytokines, and antimicrobial peptides from cells. Acting as transcriptional activators of keratinocyte genes, these immunocytokines further stimulate T-cell responses (Fig. 5). A vicious circle of inflammation has been established, maintaining the activation of T cells and inflammation in plaque psoriasis. The actions of IL-17A attract T cells bearing CCR6, such as IL-17-producing T cells and mature myeloid dendritic cells (DCs) [8], by inducing keratinocytes to produce chemokine ligand 20 and other factors. It is a chemoattractant for inflammatory cells and sustains an immune response. Alternatively, IL-17A induces the keratinocyte production of IL-19, resulting in keratinocyte proliferation. This is further demonstrated by the levels of autoantigens like catelicidin, LL37, and ADAMTSL5, whose inhibition is described to lead to reduced autoantigen producing cells in psoriatic diseases [8].

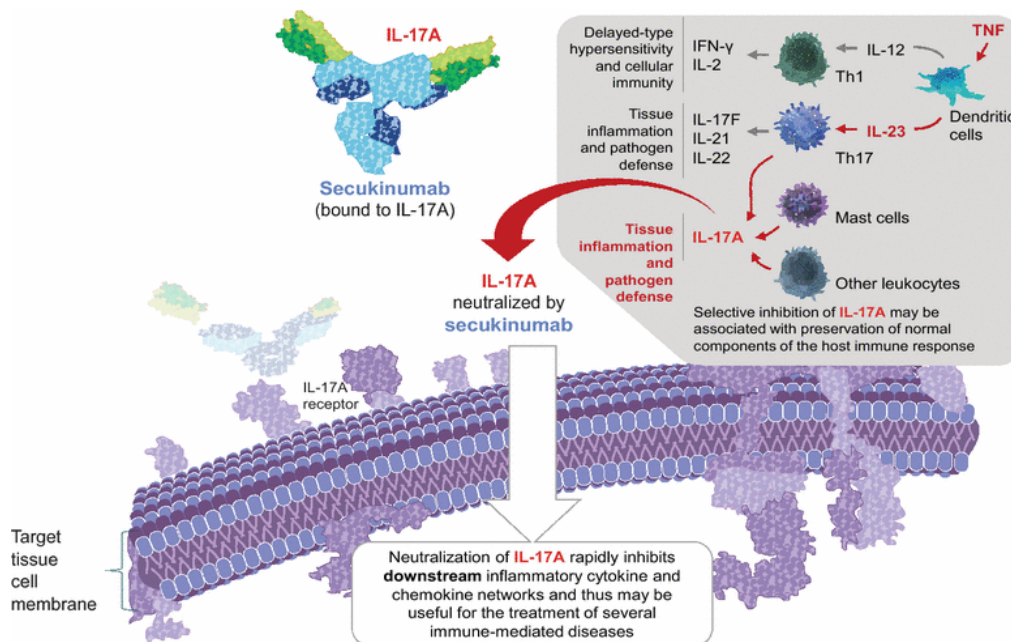


Figure 5. Role of IL-17 and Secukinumab [9]

In therapeutic contexts, biologics aim to intervene early in the disease process with high specificity to minimize side effects. Secukinumab functions by targeting IL-17A to reduce its level in plaque psoriasis, and then blocking the interaction between IL-17A with its receptor IL-17R (Fig. 6). It selectively binds to and neutralizes IL-17A, specifically binding to it and blocking its interaction with IL-17 receptors present on several cell types, including keratinocytes, endothelial cells, chondrocytes, fibroblast-like synoviocytes, and osteoblasts. This reduces IL-17A involvement in autoimmune and inflammatory disorders by preventing the release of tissue-damaging mediators, chemokines, and pro-inflammatory cytokines. When Secukinumab achieves clinically meaningful concentrations in the skin, regional inflammatory markers are reduced. Consequently, treatment with Secukinumab alleviates symptoms such as redness, thickening, and scaling in plaque psoriasis lesions [10].

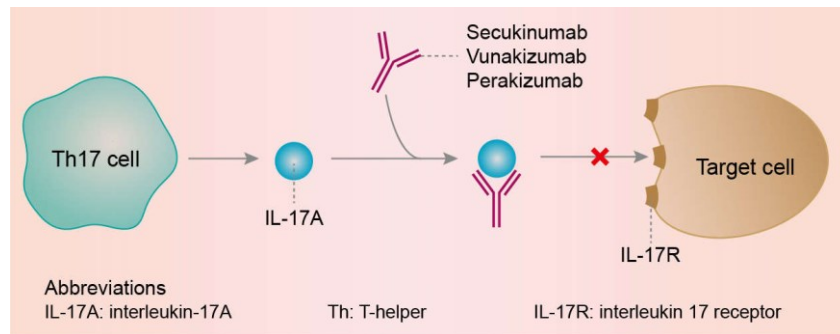


Figure 6. Mechanism of action of Secukinumab. Secukinumab is a biologic agent that blocks the activity of IL-17A by inhibiting its interaction with its receptor on target cells [10].

3.2. Pharmacokinetics and Administration of Secukinumab

A single subcutaneous dose of 150 mg or 300 mg of Secukinumab was found to possess a bioavailability of 55 to 77%. Additionally, the clearance and the volume of distribution of Secukinumab increase with body weight. The observed mean range of Secukinumab serum concentration following a single 300 mg subcutaneous injection was found to range between 27% to 40% after 1 to 2 weeks. However, one is not privy to the information that Secukinumab follows metabolism. The half-life on average was between 22 and 31 days [6].

Adults with plaque psoriasis in treatment with a 300 mg SC injection during the first 5 weeks (including week 0) followed by 300 mg SC injections every 4 weeks. There is a need for more clinical studies to be carried out for some subpopulations of patients [6].

3.3. Clinical Efficacy of Secukinumab

Many phase III clinical trials have shown that Secukinumab has been properly tested and is a very effective therapeutic agent in treating moderate-to-severe plaque psoriasis. Important trials which show the strong therapeutic effectiveness of Secukinumab include ERASURE, FIXTURE, and CLEAR [11,12].

In the ERASURE trial, after 12 weeks of treatment, 81.6% of patients showed at least a 75% improvement in the Psoriasis Area and Severity Index (PASI 75) [11]; compared to a placebo, Secukinumab was being studied. In addition, about 59.2% of patients achieved PASI 90, while 28.6% achieved complete clearance, which is PASI 100, thus proving that Secukinumab is a very potent drug in clearing psoriatic lesions.

The FIXTURE trial, which compared Secukinumab with both placebo and etanercept, reinforced these findings. In this study, Secukinumab demonstrated superior efficacy, with 77.1% of patients achieving PASI 75 at week 12, compared to 44% for those receiving etanercept [11]. This trial highlighted the superior performance of Secukinumab relative to another commonly used biologic therapy.

The CLEAR study provided additional confirmation by directly comparing Secukinumab to the IL-12/23 inhibitor Ustekinumab. In this study, 79% of patients on Secukinumab therapy achieved a PASI 90 at week 16, whereas only 57.6% of patients on Ustekinumab therapy achieved this [12]. These results clearly demonstrate that, compared to other biologics, Secukinumab induces faster alleviation and higher levels of skin clearing.

What is most prominent in this regard is that Secukinumab has a fast onset of action, such that in some patients, improvements were significant as early as week 2. Fast response benefits those patients who are suffering severely and need quick relief.

Overall, the clinical efficacy of Secukinumab is one of the fastest and largest improvements in the severity of psoriasis, with a huge number of patients achieving near complete or complete clearance of lesions. It has been effective in several types of patients, such as the treatment-naïve and those with prior biologic therapy experience, which makes it versatile for the management of psoriasis.

4. Guselkumab

Guselkumab (brand name: Tremfya) is a monoclonal antibody highly specific to human IgG1 λ [13]. Its target is the p19 portion of the extracellular protein human IL-23, inhibiting intracellular signaling and breakdown. Two heavy chains and two light chains that are the same. Covalent disulfide bonds and noncovalent protein-protein interactions bind these four chains together. Thirty-two cysteine residues in Guselkumab create interchain disulfide bonds [14].

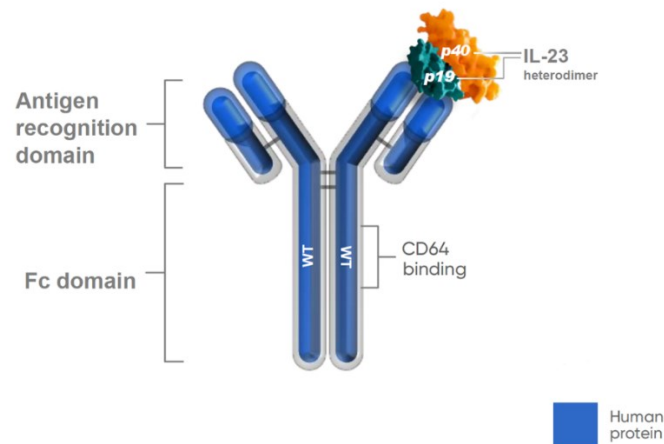


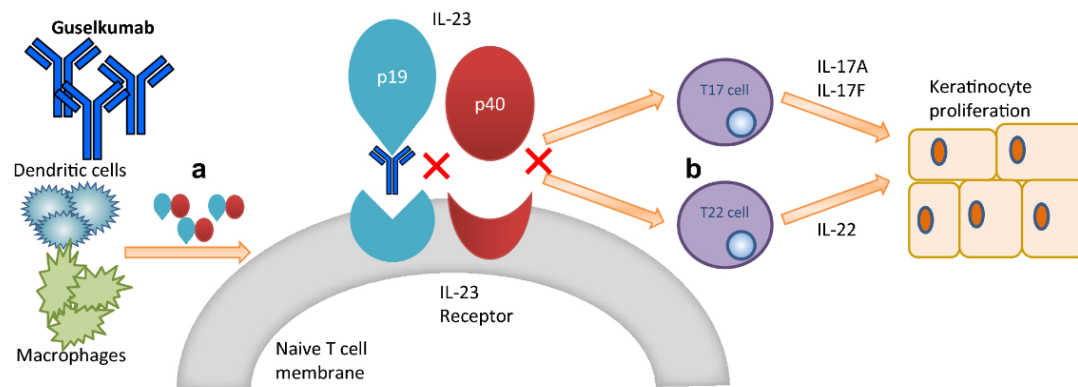
Figure 7. Structure of Guselkumab. CD64=FcyRI; Fc=fragment, crystallizable; WT=Wild-type. The Y-shaped structure of Guselkumab, a monoclonal antibody used in immune therapy [13]

4.1. Drug Target & Mechanism of Action of Guselkumab

IL-23 is a heterodimeric cytokine composed of a unique p19 subunit associated with IL-39 and the same p40 subunit as IL-12. Considerable expression of both IL-23 p40 and p19 subunits has been demonstrated in the plaques of psoriasis lesions. Genetic variation in either p19 or its receptor genes is associated with a high risk of developing symptomatic psoriasis [8].

IL-23 expression has been demonstrated in many cell types, although it is mainly expressed by DCs, more precisely by the dermal myeloid dendritic cells, macrophages, and the epidermal Langerhans cells. It increases the levels of TNF- α and IFN- γ and many transcription factors and influences Toll-like signaling. The receptor for IL-23 is expressed on NK cells, neutrophils, mast cells, ILCs, memory T cells, and macrophages. The complex formed upon the interaction of IL-23 with its receptor, the IL-23/IL-23R complex, polarizes CD4 $^{+}$, CD8 $^{+}$, and $\gamma\delta$ T cells and induces them to produce other pro-inflammatory cytokines in addition to IL-17 [8]. Moreover, IL-23 has been proven to induce TNF- α production in macrophages, which independently of IL-17A was capable of initiating keratinocyte proliferation and induced additional expressions of IL-23R, hence forming a self-amplifying loop [8].

Guselkumab is a high-affinity, selective binder of IL-23. In particular, it attaches itself to the p19 subunit of the cytokine IL-23, blocking its interaction with the cell surface receptor. In this manner, IL-23 would not be able to activate its signaling pathway, and in turn, would not be able to release pro-inflammatory cytokines [15].



When guselkumab binds to the p19 subunit of IL-23, and blocks its interaction with its receptor, the IL-23- mediated signalling pathway and release of pro-inflammatory cytokines are consequently blocked.

Figure 8. Mechanism of action of Guselkumab. Guselkumab interacts with the p19 component of IL-23, potentially hindering the signal cascade that is IL-23-driven, and its effective interaction with its receptor results in further release of pro-inflammatory cytokines [15].

4.2. Pharmacokinetics and Administration of Guselkumab

Bioavailability after a single 100 mg SC injection is about 49%. The typical clearance varies within the range of 3.62–6.03 mL/day/kg; the volume of distribution ranges between 99.38 and 123.22 mL/kg. No precise metabolic pathway for Guselkumab has been reported. The mean half-life for Guselkumab ranges from 12 to 19 days [16].

4.3. Clinical Efficacy of Guselkumab

Guselkumab went through such randomized controlled trials with placebos called VOYAGE 1, VOYAGE 2, and NAVIGATE [17,18]. In these research data, the treatment regimen appears to be very effective for achieving high levels of skin clearance in patients with moderate-to-severe plaque psoriasis.

Guselkumab was involved in the VOYAGE 1 trial against a placebo and a TNF inhibitor called adalimumab. Results indicated that 85.1% of the patients on Guselkumab had attained PASI 75 by week 16 while 73.3% of them had achieved PASI 90; over 49% had attained PASI 100 [17]. This high level of complete clearances is a great example that Guselkumab is efficient in reducing the symptoms of psoriasis. The efficacy of Guselkumab remained higher compared to adalimumab at this period, which had a PASI 90 of 49.7%.

The VOYAGE 2 trial confirmed these results, whereby Guselkumab demonstrated equal rates of PASI response—achieved PASI 75 in 84.2%, PASI 90 in 70%, and PASI 100 in 44% at week 16 [17]. This replicability across studies speaks to the reliability and robustness of efficacy for Guselkumab.

The first study with regard to assessing the efficacy of Guselkumab in patients who did not respond well to treatment by Ustekinumab was known as NAVIGATE. Clearly, significantly higher rates of PASI 90 and PASI 100 responses in patients who switched to Guselkumab were noted compared with those continuing Ustekinumab [18]. This trial showed the ability of Guselkumab to gain better results in patients partially responding to other biologics and marked it as very interesting second-line therapy.

One of the distinguishing features of Guselkumab is its long-term efficacy. The dosing schedule of every 8 weeks after initial loading doses is a contribution to the sustained improvement, with clinical trial extensions showing that many patients keep high levels of skin clearance up to 100 weeks and beyond.¹⁹ Such sustained efficacy may reduce the flaring frequency and improve the quality of life for patients who have chronic plaque psoriasis.

In summary, high, maintained levels of skin clearance achieved and maintained over a long-time course are typical features of the clinical efficacy of Guselkumab. Its better performance in head-to-head trials with other biologics and its efficacy in patients with prior treatment failures make it a strong case for long-term management in psoriasis.

5. Discussion (Comparison of Secukinumab and Guselkumab)

5.1. Difference of Drug Target & Mechanism of Action

Secukinumab and Guselkumab are two biologics targeting certain cytokines involved in the pathogenesis of plaque psoriasis, but they act at different points in the immune response. Secukinumab acts via the inhibition of IL-17A. IL-17A represents a pro-inflammatory cytokine produced mainly by Th17 cells and exerts a main role in the development and persistence of psoriasis through keratinocyte proliferation and other inflammatory mediator production. Inhibiting IL-17A directly, Secukinumab shuts off this pathway. On its own, this leads to a rapid reduction in inflammation and improvement of psoriatic plaques [19].

On the other hand, Guselkumab is directed against IL-23, which is more upstream in the immunological cascade. IL-23 is crucial for the maintenance and expansion of Th17 cells, themselves the major producers of IL-17A. Through inhibition of IL-23, Guselkumab indirectly decreases the production of IL-17A and other Th17 cytokines. This upstream approach may provide broader, more sustained modulation of the immune response and thereby lead to longer periods of remission and reduced risk of disease flare.¹⁸ Again, these differences in targeting reflect a basic divergence in therapeutic approach: Secukinumab provides rapid relief by targeting a direct effector molecule, while Guselkumab modulates the immune system more broadly by targeting a key regulatory cytokine.

5.2. Difference in Clinical Efficacy

The therapeutic efficacy of Secukinumab and Guselkumab has been recorded in several key trials, where the treatments showed extremely high considerable efficacy in patients with moderate-to-severe plaque psoriasis. The greatest strength of Secukinumab is its very rapid onset of action. Many of the responders showed a substantial improvement of symptoms in the first few weeks of treatment, which makes it especially suitable for patients who have more severe symptoms and are looking for quick relief. Clinical trials have awarded high rates for Secukinumab of PASI 75, 90, and even 100 responses within 12 weeks [11].

On the other hand, Guselkumab has been outstanding in achieving and maintaining very high levels of skin clearance during long-term treatment. Guselkumab demonstrated higher efficacy than adalimumab in the randomized controlled clinical trials VOYAGE 1 and VOYAGE 2. Its efficacy in a significant percentage of patients at the PASI 90 and PASI 100 responses has been demonstrated to last up to 48 weeks or longer.¹⁷ This sustained efficacy is very much welcome in the long-term management of the disease; it might lessen the frequency of changes in treatment and decrease the likelihood of relapses.

These efficacy profile differences suggest that the choice between Secukinumab and Guselkumab must be based on individual patient preference and clinical needs. Therefore, patients who value fast relief of symptoms may choose Secukinumab, and those who desire long-term sustained control may opt for Guselkumab.

5.3. Cost and Availability

Critical issues in the application of biologic therapies are their cost and availability. Secukinumab and Guselkumab are very expensive, since these molecules are difficult to produce, and clinical development is very expensive. Healthcare system policies, insurance coverage, and patient assistance programs make a variable difference in this choice between treatments by region and healthcare setting [20].

Secukinumab has a more frequent dosing schedule, typically as an injection every four weeks after initial loading doses, which can add to overall treatment costs compared with Guselkumab, given every eight weeks after the initial dosing period [21]. The longer dosing interval of Guselkumab may provide a cost advantage through a reduced frequency of healthcare visits and a decreased use of health care resources; this might improve patient adherence and decrease overall costs of care.

All these factors should be balanced by healthcare providers in picking the right treatment while considering both clinical efficacy and safety, as well as issues with economics for the patient and the

health system. Advanced therapies with optimal access need to be ensured in countries where cost is a barrier, and this should be done to be more supportive of the poorest patients.

5.4. Long-Term Safety and Considerations

Safety profiles are an extremely key issue in the choice of biologic treatment. Generally, both Secukinumab and Guselkumab were well-tolerated in clinical trials, with similar rates of adverse events such as upper respiratory infections, headache, and injection site reactions reported for both treatments.¹² Mechanistic differences may predict variances in specific side effects or risks.

Longer-term evidence may suggest that due to the upstream action, which has the potential to affect a more comprehensive range of immune responses, and less direct suppression of IL-17A, which is involved in the protection against some infections, Guselkumab has a marginally improved safety profile [21]. Both drugs require ongoing close monitoring for any signs of infections and continuation of therapy for background conditions.

These are considerations that should be made at the level of the individual patient, considering comorbid conditions, previous treatment history, and personal preferences about the frequency of administration. Such decisions through shared decision-making at the level of clinician-patient may facilitate the appropriate tailoring of treatment choices according to individual needs and circumstances in order to produce optimal clinical outcomes with maximal patient satisfaction.

6. Conclusion

In summary, Secukinumab and Guselkumab are two novel biologicals that show specific advantages and considerations for the treatment of moderate-to-severe plaque psoriasis. Secukinumab provides early relief and is more indicated in patients in whom an immediate improvement in their condition is desirable. Guselkumab shows more long-term sustained control and is thus indicated in those patients who have goals of minimizing flares and maximizing clearance over time. Such therapies should be selected based on the integrated assessment of their clinical efficacy, safety, cost, and individual patient factors for optimal therapeutic outcomes.

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