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REVIEW

Secukinumab in the Treatment of Psoriasis: A Narrative Review on Early Treatment and Real-World Evidence

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ABSTRACT

Psoriasis is a chronic, immune-mediated, inflammatory skin disease, associated with multiple comorbidities and psychological and psychiatric disorders. The quality of life of patients with this disease is severely compromised, especially in moderate-to-severe plaque psoriasis. Secukinumab, a fully humanized monoclonal antibody, was the first anti-interleukin (IL)-17 biologic approved for treating psoriasis. Secukinumab demonstrated long-lasting efficacy and a good safety profile in individuals with plaque psoriasis, and it is associated with an improvement in health-related quality of life. While there is evidence that early treatment with systemic therapy can affect disease progression and improve long-term outcomes in other

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autoimmune diseases, evidence is limited in psoriasis, especially in real-world settings. This review provides an overview of studies describing the effectiveness of secukinumab in the treatment of psoriasis summarizing the literature and focusing on real-world evidence and early intervention.

Keywords: Psoriasis; Secukinumab; Treatment; Early treatment

Key Points
Secukinumab has long-term clinical efficacy and safety in the treatment of psoriasis, but more focus is needed on early intervention.
Early treatment of psoriasis with secukinumab improves the quality of life of people with the disease and supports the prevention of long-term disabilities and comorbidities, such as psoriasis arthritis.
Secukinumab is safe to use and shows benefits also in hard-to-treat populations and difficult-to-treat body areas.
Secukinumab should be considered as a treatment option for psoriasis, not only for individuals at early disease stages but also for those with a long history of the disease.

INTRODUCTION

Psoriasis (PsO) is a common chronic, systemic, immune-mediated inflammatory disease that affects the skin. PsO affects 125 million people worldwide, and its prevalence and incidence vary according to geographic region, gender, and age [1, 2]. PsO is associated with several comorbidities, including psoriatic arthritis (PsA), Crohn's disease (CD), and psychological/psychiatric disorders (e.g., depression, and anxiety). In recent years, also metabolic syndrome, inflammatory bowel disease, diabetes, cardiovascular diseases, malignancies (e.g., lymphoma), and infections have been associated with PsO [3]. In addition, individuals with PsO are at a higher risk of reduced life expectancy [4]. Manifestations of the disease may involve itching, stinging, and burning of the skin, which together with extracutaneous clinical manifestations, significantly affects the health-related quality of life (HRQoL) of these patients [5]. Disease progression is often unpredictable, with different degrees of severity and progression. PsO management can minimize physiological and physical harm by treating patients early in the disease to modify its course, preventing associated comorbidities, reducing risks of negative outcomes, and aiming at remission [6]. The pathogenesis of psoriasis is influenced by the interleukin (IL)-23/IL-17 pathway, which is involved in the inflammatory processes underlying this chronic skin condition. IL-23 is a cytokine that fosters the production of IL-17; in the pathogenesis of PsO, the T helper 17 pathway and cytokine interleukin 17 (IL-17) play a fundamental role. The mechanism of action of several antipsoriatic treatments currently in use and under development is aimed at blocking IL-17 and its mediated downstream immunological cascade. IL-17 effectors include IL-17A, IL-17C, IL-17E, and IL-17F, which are responsible for the pro-inflammatory feed-forward cycle in plaque psoriasis [7]. The interplay between IL-17 and IL-23 maintains the chronic inflammatory state characteristic of psoriasis. Monoclonal antibodies targeting interleukin IL-23, like guselkumab and resankizumab, and IL-17, like secukinumab and ixekinumab, showed efficacy in the treatment of moderate-to-severe psoriasis. IL-17 and IL-23 inhibitors are both effective treatments for psoriasis, although they differ in their mechanisms of action and clinical outcomes (Table 1). IL-17 inhibitors target the IL-17 cytokine, thus leading to rapid relief of the symptoms due to the direct action on inflammation. IL-23 inhibitors target the IL-23 cytokine, which is key for the production of IL-17, thus providing sustained control [8, 9]. Drug survival, defined as the duration of a specific treatment, seems accordingly to be more favorable for IL-23 inhibitors in terms of long-time effectiveness [10–14].

Secukinumab is a fully humanized anti-IL-17A monoclonal antibody that was approved

Table 1 Psoriasis and treatments

Event	Characteristics	Treatment
Psoriasis triggers (environmental)	Stress, infections, and skin gaps can activate dendritic cells in people predisposed to psoriasis	
Dendritic cell activation	Release of IL-23, a cytokine crucial for the differentiation and maintenance of Th17 cells	
IL-23	Promotes the differentiation of Th17 cells and supports their survival	IL-23 inhibitors: ustekinumab, guselkumab, tildrakizumab, and risankizumab
IL-17 production	Th17 cells produce IL-17, which acts on different skin cells (such as keratinocytes, endothelial cells, and fibroblasts)	IL-17 inhibitors: secukinumab, ixekizumab, and brodalumab
Inflammatory cascade	IL-17 stimulates keratinocytes to produce pro-inflammatory cytokines and chemokines. These attract neutrophils and other immune cells, amplifying the inflammatory response, and leading to the formation of psoriatic plaque	Anti-inflammatory treatments: biologics targeting IL-23 and IL-17 and systemic treatments
Chronic inflammation	Creation of a loop, sustaining chronic inflammation and resulting in the hyperproliferation of keratinocytes, which form psoriasis plaques	Long-term disease management with biologics (such as IL-23 and IL-17 inhibitors) and phototherapy

in 2015 by the US Food and Drug Administration and the European Commission as the first biologic for the treatment of moderate-to-severe plaque psoriasis, active psoriatic arthritis (PsA), and axial spondyloarthritis (axSpA) [15]. Secukinumab is indicated and well received for the treatment of moderate-to-severe plaque psoriasis in children > 6 years old, adolescents, and adults who are eligible for systemic therapy. In pediatric plaque psoriasis (adolescents and children from the age of 6 years to 18 years old), the recommended dose of secukinumab is based on body weight, while in adult plaque psoriasis it is 300 mg. Secukinumab is administered by subcutaneous injection with initial dosing at weeks 0, 1, 2, 3, and 4, followed by monthly maintenance dosing [16]. In adults, a maintenance dose of 300 mg every 2 weeks can provide additional benefits after initial assessment of clinical response. A multicenter, randomized clinical trial evaluated two different dosing regimens (i.e., secukinumab 300 mg every 2 weeks vs secukinumab 300 mg every 4 weeks) in patients with bodyweight > 90 kg [17]. After 16 weeks, the 2-week dosing demonstrated higher efficacy compared to the 4-week regimen psoriasis area and severity index (PASI) 90, 73.2% vs 55.5%, $p = 0.0003$. In multiple phase II and III clinical trials, secukinumab was shown to be superior to placebo and to other biologics, such as etanercept and ustekinumab, in the treatment of moderate-to-severe plaque psoriasis, and its clinical efficacy correlated with large improvements in patients' quality of life [18]. Secukinumab also showed a long-term safety profile in multiple phase II and III clinical trials for the treatment of moderate-to-severe plaque PsO. A pooled safety analysis of ten Phase II and III studies showed

that secukinumab has a favorable safety profile that is similar between the 300 and the 150 mg doses [19]. The safety profile of secukinumab was comparable to that of etanercept over 52 weeks in patients with moderate-to-severe plaque psoriasis. Secukinumab also showed a safety profile comparable to ustekinumab in long-term follow-up studies [20]. A pooled analysis including 21 randomized controlled clinical trials examined the long-term (5 years) safety and tolerability profile of secukinumab for the treatment of moderate-to-severe psoriasis, psoriatic arthritis, and ankylosing spondylitis (AS) [21]. The study results suggest that secukinumab has a favorable safety profile over a long treatment period in patients with these chronic conditions. In alignment with previous research, the study supports the long-term use of secukinumab in the treatment of PsO, PsA, and AS, as these disorders share IL-17A overexpression [15, 22]. However, as reported for other biologics, patients with autoimmune diseases taking IL-17 inhibitors are at increased risk of infections, and the most commonly described adverse events associated with secukinumab are upper respiratory tract infections, neutropenia, candidiasis, and rare cases of new or worsening inflammatory bowel disease [19, 23–25]. Of note, secukinumab might have a beneficial effect on the cardiometabolic risks associated with psoriasis as a reduction in systemic inflammation could also contribute to indirectly mitigating the risk of adverse cardiovascular conditions [26, 27].

There is evidence that in immune-mediated inflammatory diseases, such as rheumatoid arthritis, early intervention, defined as a time window for the onset of therapy (systemic or biologic) of 6–12–24 months after disease manifestation, with targeted systemic therapy can improve long-term patient outcomes [28]. Similarly, it has been hypothesized that early intervention with systemic agents in plaque psoriasis may alter the course of the disease, improve cutaneous symptoms, and reduce long-term adverse outcomes [28, 29]. Given the high prevalence of this condition in the population and its detrimental impact on patients' quality of life, evaluating the long-term effectiveness, safety, and comorbidity control of secukinumab in the treatment of psoriasis in a real-world setting is of paramount importance. This review aims to provide a comprehensive overview of the effectiveness of secukinumab in the treatment of psoriasis, also summarizing findings on early interventions (considered as occurring within two years of disease onset) through an analysis of the latest evidence available in the field (Table 2).

METHODS

In July 2022, all the authors met to discuss the available evidence on the use of secukinumab in the early treatment of psoriasis, aiming at having a broader view of its use in clinical practice and at supporting the unmet medical needs of individuals affected or at higher risk of the disease. The authors reviewed the literature available, focusing in particular on real-world evidence.

A systematic search of the literature using the Embase database was conducted between inception and June 2022. Without applying restrictions, the terms searched used were the following: "real life setting," "real world," "RW," "real world evidence," "RWE," "real life," "evidence," "case report," "case series," "observational studies," "observational study," "prospective observational studies," "retrospective observational studies," "retrospective study," "prospective study," "secukinumab," "Cosentyx," "SEC," "Italy," "italian," "psoriasis," "PSO," "early treatment," "naïve," "Nail," "Scalp," "Palmoplantar Psoriasis," "problematic area," "psoriatic arthritis," "arthritis," "PSA," "early PSA," "naïve," "quality of life," "QoL," "adherence," "adherence to treatment," "treatment adherence," "compliance to therapy," "therapy compliance," "adherence to therapy," "compliance to treatment," "treatment compliance," "therapy adherence," "discontinued," "discontinue," "rates of adherence," "non-adherence," "Survey," "questionnaire," "suspension," "retention rate," "Long term use," "long term," "naïve," "biologic-naivety," "Biologic Disease-Modifying Antirheumatic Drugs," "bDMARDs," "DMARDs," "de novo," "systemic treatment naïve," "treatment failure," "anti-TNFα failure,"

Table 2 Summary of recent literature assessing the effectiveness and safety of secukinumab in patients with PsO, PsA, and axSpA in a real-world setting

Duration of the study	Disease model	Outcome measures	Notes	References
72 weeks	PsO	PASI	–	Russo et al. 2023 [13]
240 weeks	PsO	PASI	–	Dastoli et al. 2023 [14]
136 weeks	PsO	PASI, Quantiferon-TB test, serology for HBV, HCV, HIV	–	Galluzzo et al. 2020 [40]
104 weeks	PsO, PP	PASI, PGA, ppPGA, sPGA, DLQI	–	Rompoti et al. 2019 [41]
8 years	PsO	PASI, PGA, BSA, DLQI,	Bio-naive patients	Melgosa Ramos et al. 2023 [43]
2 years	PP	PASI, ppPASI	–	Galluzzo et al. 2022 [51]
48 weeks	Pustular psoriasis, erythrodermic psoriasis	PASI	–	Avallone et al. 2022 [54]
84 weeks	PsO	PASI, BSA, DLQI	–	Megna et al. 2019 [80]
52 weeks	PsO	PASI, DLQI	Secukinumab in combination therapy	Damiani et al. 2022 [81]
2 years	PsO	PASI, BSA	Olderpatients	Megna et al. 2020 [83]
3 years	GPP	JDA	Pediatric patients	Miao et al. 2023 [85]
48 weeks	GPP	GPPASI, GPPPGA	Pediatric patients	Ruan et al. 2023 [55]
52 weeks	PsO	PASI	Bio-naive patients vs prior exposure to biologics patients	Galluzzo et al. 2018 [87]
24 weeks	PsO	PASI, DLQI, VAS	Oncologic patients	Pellegrini et al. 2022 [88]
52 weeks	PsO	PASI, BSA, DLQI	–	Chiricozzi et al. 2020 [89]
24 months	PsA	PASI, BASDAI, ASDAS, DAPSA	Naive or TNF-inhibitors failure	Lorenzin et al. 2020 [67]
3 years	PsA, axSpA	DAPSA, ASDAS	Retention rate measurement	Favalli et al. 2020 [69]
36 months	PsO	PASI	–	Goodehram et al. 2023 [44]
4 years	PsO	PASI	Included difficult-to-treat areas	Kyrmanidou et al. 2024 [52]

Table 2 continued

Duration of the study	Disease model	Outcome measures	Notes	References
16 weeks	PsA	PASI, QoL	Naive or TNF-inhibitors failure	Kivitz et al. 2024 [70]
52 weeks	PsA	ASDAS, DAS-28	–	Colella et al. 2023 [71]

Summary of the real-world studies assessing the effectiveness and safety of secukinumab in patients with moderate-to-severe plaque psoriasis (PsO), psoriatic arthritis (PsA), and axial spondyloarthritis (axSpA)

Palmoplantar psoriasis (PP), Psoriasis Area Severity Index (PASI), Body Surface Area (BSA), Dermatology Life Quality Index (DLQI), Physician Global Assessment (PGA), palmoplantar PGA (ppPGA), scalp PGA (sPGA), Japanese Dermatological Association (JDA), Generalized Pustular Psoriasis (GPP), Generalized Pustular Psoriasis Area and Severity Index (GPPASI), Generalized Pustular Psoriasis Physician Global Assessment (GPPPGA), visual analog scale (VAS), Ankylosing Spondylitis Disease Activity Score (ASDAS), Disease Activity in Psoriatic Arthritis (DAPSA)

and "tnf-inhibitor failure." The literature search was updated in June 2024 to select additional articles relevant to the topic.

This article is based on previously conducted studies and does not contain any new studies with human participants or animals performed by any of the authors.

Early Treatment with Secukinumab in PsO

Psoriasis is often not diagnosed or treated in atimely manner, leading to worse clinical outcomes for the patients. Early systemic treatment of immune-mediated inflammatory diseases, such as rheumatoid arthritis and Crohn's disease, has been shown to improve long-term patient outcomes [28]. However, to date, there is no universally accepted definition of what constitutes an "early" intervention in PsO treatment as clinicians still need to agree on the criteria to screen patients [28, 29]. Girolomoni and colleagues [28] defined an early intervention as the "time window for the onset of therapy between 6 and 24 months after disease manifestation," based on observations from other chronic diseases. However, the authors highlighted how immediate treatment at disease onset might favorably impact the long-term course of the disease and halt mental health issues [28].

There are different clinical trials in the literature exploring the effects of secukinumab early treatment in patients with PsO. A randomized, double-blind, placebo-controlled phase II trial showed that early suppression of the IL-23/IL17 axis in individuals with psoriasis by secukinumab treatment improved plaque histopathology and promoted plaque resolution at week 12 [30]. In this study, clinical efficacy was associated with histopathological features, immunohistochemistry (IHC) cell counts, and mRNA transcription profile of lesional plaques and non-lesional skin biopsy specimens collected at baseline, weeks 1, 4, 12, and 52. In these patients, the levels of the upstream genes IL-23 and the related IL-17F were reduced, suggesting that secukinumab disrupts the IL-17A-dependent feedback mechanisms that drive plaque chronicity [30]. A phase II regimen-finding study reported that early and monthly induction therapy with secukinumab 150 mg resulted in significantly higher response rates of Psoriasis Area Severity Index (PASI) 75 than placebo therapy (54.5% and 42.0% vs. 1.5%; $p<0.001$ for both regimens) at week 12; similarly, PASI 90 response rates were significantly higher with early and monthly treatment than with placebo (31.8% and 17.4% vs. 1.5%, respectively; $p<0.001$ for both regimens) [31]. In a sub-analysis of this study, an improvement in health-related quality of life was observed in patients treated with different secukinumab doses compared to placebo [32]. The early secukinumab regimen was also associated with improvement in difficult-to-treat areas [33]. Interestingly, secukinumab showed early response rates in patients who

switched from cyclosporine A (CyA) therapy after inadequate response to treatment. A total of 37 patients were treated subcutaneously with 300 mg secukinumab and 41.2% of patients reached PASI 50 by week 2; 82.4% of patients met the primary endpoint PASI 75 at week 16. PASI 90/100 and IGA 0/1 were met by 64.7%, 29.4%, and 70.6%, respectively. Of note, higher response rates were observed in biologic-naive patients than in patients with prior biologic exposure [34].

The STEPin study was the first trial designed to determine whether early intervention with either standard narrowband UVB (nb-UVB) or secukinumab treatment in patients with new-onset (< 12 months) plaque psoriasis could alter the natural history of the disease [35]. Results at 52 weeks showed that 91.1% (70/77) of patients in the secukinumab arm achieved a PASI 90 response compared to 42.3% (32/76) in the nb-UVB arm ($p < 0.0001$). This supports the notion that early treatment with secukinumab is more effective than standard treatment with nb-UVB in patients with new-onset moderate-to-severe plaque psoriasis [36]. Of note, recent and ongoing clinical trials on guselkumab and rizamkizumab are exploring PsO early interventions for newly diagnosed patients [37, 38], and additional real-world studies would be key to gaining supportive evidence.

Early administration of secukinumab in biologic-naive patients was shown to improve clinical outcomes compared with biologic-experienced patients also in real-life studies, suggesting that it may be considered as a first-line treatment for psoriatic patients [39–43]. A retrospective analysis of real-world data from 151 patients with moderate-to-severe plaque psoriasis, including patients with palmoplantar psoriasis (PP), found a significant association between positive response to secukinumab and no prior use of biologic therapies [40]. Similarly, a recent real-world study found that biologic-naive patients who did not have concurrent PsA derived the greatest benefit from treatment with secukinumab [41]. The study involved 83 patients diagnosed with psoriasis, 25.3% with palmoplantar psoriasis, and the effectiveness of secukinumab and its good retention time were described [41]. Differences in clinical outcomes were also observed in PsA patients who did not receive biologics versus multi-failure patients when treated with secukinumab [42]. Patients receiving secukinumab as first-line therapy with a biologic showed improvements in multiple outcomes, such as ASDAS, PASI, and MDA, compared to patients with multiple therapeutic failures.

Data from the PURE registry, a prospective cohort study in 2362 adult patients with moderate-to-severe plaque psoriasis treated with secukinumab or standard therapy, confirmed the early and sustained resolution of erythema and scaling of the skin [44], also for non-responders [45].

In conclusion, early treatment with secukinumab can be considered a valuable option not only for the treatment of the early stages of the disease but also in patients with a long history of disease as the early introduction of secukinumab as a primary treatment approach led to better clinical outcomes.

Early Treatment of Difficult-to-Treat Body Areas Can Result in Enhanced Secukinumab Efficacy and Effectiveness

Psoriasis affecting hands, feet, nails, scalp, face, and genitals can be underdiagnosed and difficult to treat. The most common difficult-to-treat areas are the scalp, face, nails, soles, genitals, and palms [46]. Although the areas commonly affected by PsO in these sites may be limited, the impact on patients' quality of life is significant, mainly because of the psychosocial consequences. The Palmoplantar Psoriasis Area and Severity index (ppPASI), Nail Psoriasis and Severity Index (NAPSI), and Scalp-modified PASI (S-mPASI) are rating scales specifically designed to measure the impact of the disease in these areas. For patients suffering from PsO in hard-to-treat areas of the body, traditional therapeutic options have limitations, and topical agents may not be effective or well tolerated [47]. However, to date, several therapeutic options are available for this subclass of patients, depending on the severity and extent of the disease. Recent evidence supported the effectiveness of anti-IL-17 and anti-IL-23 agents for the treatment of

difficult-to-treat areas in patients with PsO [48, 49], with anti IL-17 agents achieving a better control of scalp psoriasis. In this regard, biologics such as secukinumab are playing an important role [50]. The randomized controlled trial GESTURE investigated the efficacy and safety of secukinumab 300 mg and 150 mg versus placebo in 205 individuals with PP. At week 16, the percentage of patients achieving clear or nearly clear palms and soles with secukinumab 300 mg and 150 mg was higher compared with placebo (33.3%, 22.1%, and 1.5%, respectively, $p<0.001$). The ppPASI score was significantly reduced with secukinumab 300 mg (54.5%) and 150 mg (35.3%) compared with placebo (4.0%, $p<0.001$) [34]. Interestingly, a sub-analysis of a randomized double-blind, placebo-controlled treatment finding study showed that secukinumab improves PsO on the hands, feet, and nails when administered as early therapy [33].

A prospective clinical study was conducted specifically in patients with moderate-to-severe psoriasis of the scalp [35]. This study was a 24-week, double-blind, phase IIIb trial in which patients with extensive moderate-to-severe scalp psoriasis were randomized in a 1:1 ratio to secukinumab 300 mg or placebo. Results showed that secukinumab was effective and well tolerated in these patients, with the safety profile of secukinumab being consistent with previous studies. At week 12, the Psoriasis Scalp Severity Index (PSSI) 90 was significantly higher with secukinumab 300 mg than with placebo (secukinumab 300 mg 52.9% versus placebo 2.0%, $p<0.001$). In addition, significantly more patients achieved complete remission of scalp psoriasis at week 12 on secukinumab 300 mg than on placebo.

There are few real-world long-term data on the effectiveness and safety of secukinumab in patients with psoriasis in difficult-to-treat areas. A retrospective analysis conducted in 151 patients with chronic plaque psoriasis showed improvement in plaques after 136 weeks of treatment with secukinumab 300 mg. After 8 weeks of treatment with secukinumab, plaques on the scalp, head, nails, suprapubic area, and penis had almost disappeared [40]. Similarly, a 2-year multicenter, observational study investigated the effectiveness of secukinumab in palmoplantar psoriasis [34] and showed that secukinumab was effective in the treatment of palmoplantar psoriasis also in the real-world setting, with a significant improvement in the mean PASI, reduced to 78.2% at week 16. The mean palmoplantar PASI (ppPASI) score also improved significantly, but more gradually, with a decrease of 55.0% and 79.3% after 16 and 104 weeks, respectively. About half of the patients completely healed after 40 weeks. Secukinumab was well tolerated, and no relevant treatment-related adverse events were reported [51]. A single-center, 104-week study evaluated the efficacy of secukinumab in moderate-to-severe chronic plaque psoriasis, including scalp and palmoplantar involvement [41]. The Physician Global Assessment (PGA), PASI75/90/100, and scalp and palmoplantar PGA were assessed. At week 16, the PASI75/PASI90/PASI100 was observed in 83.8/70.0/46.3% of patients, respectively. Scalp and palmoplantar PGA improved rapidly, with 98.7% and 95.5% achieving clear/almost clear skin at week 16, respectively. In this real-world study, secukinumab was shown to be effective in difficult-to-treat areas with a similar safety profile to clinical trials [41]. These results were confirmed in a study on 99 patients with psoriasis where receiving 300 mg of secukinumab was found to be save and efficacious, also in patients with difficult to treat manifestations, such as the scalp, over 4 years [52]. Secukinumab was shown to be safe and effective in real-world clinical practice in patients with PP and palmoplantar pustular psoriasis (PPPP) who did not respond to previous systemic or biologic treatments over a 24-month follow-up period [53]. Interestingly, statistically significant differences in ppIGA scores were observed at 12 months between therapy-naive patients and patients who had previously received biologics therapy. Secukinumab was found to be more effective in therapy-naive patients than in patients who had previously received biologic therapy [53]. In addition, the first real-world monocentric study comparing secukinumab and ixekizumab in the treatment of PP and erythrodermic psoriasis (EP) showed that patients treated with ixekizumab reached PASI 90, PASI < 3, and PASI 100 faster than those treated with secukinumab, with no statistically significant difference at 12-week

follow-up. At 48 weeks, a statistically significant difference was observed between the two groups (100%, 100%, and 75% of patients treated with ixekizumab achieved PASI 90, PASI < 3, and PASI 100, respectively, versus 31%, 46%, and 23% of patients treated with secukinumab, $p = 0.01$). Secukinumab proved effective in the EP group at week-48 follow-up, as PASI 90 and PASI 100 were achieved in 82% and 54% of patients, respectively [54]. Moreover, a 48-week real-world retrospective study performed on 18 pediatric patients with generalized pustular psoriasis (GPP) receiving secukinumab as first-line treatment showed a significant decrease in the GPP-PASI score as well as improvements in Children's Dermatology Life Quality Index score [55].

Preventing the Development of Psoriasis Arthritis by Early Treatment of Psoriasis

Psoriatic arthritis (PsA), a chronic inflammatory disease, develops in around 14.0–22.7% of the individuals affected by PsO. Patients with psoriasis are at higher risk of developing PsA than healthy individuals or individuals with other diseases [56]. The progression from PsO to PsA occurs in a series of phases [57], with clinically evident disease emerging only at late stages. The transitional phase preceding PsA onset, known as prodromal PsA, is characterized by the spread of the disease from the skin to the joints. The prodromal phase of PsA is difficult to diagnose as characterized by non-specific symptoms, such as inflammatory joint lesions, joint pain, or fatigue [58]. As a result, PsA is often not diagnosed in a timely manner, resulting in treatment delays and missed prevention opportunities [59]. The transition phase from PsO to PsA offers the opportunity to identify individuals at increased risk of developing PsA and to implement early treatment and prevention strategies. The current literature suggests that the development of PsA might have its roots in the complex interplay between environmental factors, an individual's phenotype, and genotype. For example, severe psoriasis affecting the nails, scalp, and genitals is associated with the development of PsA in people with systemic conditions [60]. Patients with PsA have a higher incidence and prevalence of cardiovascular risk factors, such as hypertension, diabetes, hyperlipidemia, and obesity [61]. These known risk factors could be considered in current clinical practice to implement prevention strategies [45]; however, research on clinical indicators to identify individuals with psoriasis at higher risk of developing PsA remains limited. A systematic review and meta-analysis [45] attempted to profile PsO patients at higher risk of developing PsA and identified some potential predictors of PsA development. Skin and nail phenotypes of PsA development included PsO severity and nail pitting. Furthermore, other predictors were having arthralgia and higher categories of body mass index (BMI). This research, while limited by the heterogeneity of the included studies, suggests that these risk factors could support the identification of individuals at higher risk of developing PsA who could receive timely treatment, preventing the disease or worse disease outcome [62]. Of note, treatment of PsA with biologics before the onset of structural damage prevents impairment of physical function and permanent disability [63, 64]. Supporting this evidence, preliminary results on a limited number of individuals suggested that early treatment with biologics in patients with PsO carrying a short-term risk of developing PsA may revert the preclinical manifestations of PsA, such as arthralgia or musculoskeletal pain [65]. Notably, in recent years the number of studies investigating the real-world effectiveness of secukinumab in PsA has significantly increased. For example, one study reported that secukinumab was effective in reducing disease activity and was safe in both biologic-naive and non-naive PsA patients [66]. A prospective, multicenter study assessing real-life long-term secukinumab effectiveness and safety showed that after 24 months, biologic-naive patients had a lower PASI ($p = 0.04$), erythrocyte sedimentation rate and C-reactive protein ($p = 0.03$; $p = 0.05$), and joint count ($p = 0.03$) compared to biologic-multi-failure patients [42]. When comparing the effectiveness and safety of secukinumab in biologic-naive patients with those in which TNF inhibitors had failed, DAPSA and ASDAS showed that secukinumab

was effective in PsA patients over a 24-month follow-up period [67]. Another study conducted in patients with axial spondyloarthritis showed that biologic-naive patients had better physical functioning and lower disease activity compared to the TNF inhibitor failure group [BASDAI 2.2 (1.0–3.8) vs 3.9 (2.7–5.0), ASDAS 1.3(1.0–2.2) vs 2.1(1.6–2.9)] at 24 months, with high retention rate [68]. An analysis of the Italian Lombardy Rheumatology Network (LOHREN) registry found a high 3-year retention rate with secukinumab for both PsA and axSpA [69]. A recent study in the US on patients with PsA described rapid improvements in disease management and quality of life upon secukinumab treatment [70]. Secukinumab also confirmed effectiveness and safety in PsA patients in a recent real-life Italian study conducted over 52 weeks [71]. This evidence was confirmed in other studies conducted in Italian settings [42, 72, 73].

The real-world evidence presented in these studies highlights the effectiveness and safety of secukinumab in the management of PsA and axSpA, with a good patient retention rate. The reduction in disease severity scores and good retention rate observed upon treatment with secukinumab emphasize its potential to provide substantial relief to these patients. These findings encourage a shift towards proactive and early intervention strategies, addressed not only to improving the quality of life of the patients but also aiming at preventing long-term disabilities and comorbidities, and potentially disease onset.

Benefits of Early Treatment with Secukinumab on the QoL of Individuals with PSO

The impact of psoriasis on patients' health-related quality of life is considerable, as the disease negatively affects physical, emotional, psychological, and economic aspects of life. A survey of psoriasis patients conducted in the US found that the larger the body surface area, the greater the impact on quality of life [74]. Psoriasis patients report that PsO interferes with daily life activities, such as sleeping, washing, or dressing, and with work-related activities [75–78]. Patients frequently experience a pronounced sense of diminished self-esteem regarding their physical appearance, and they frequently contend with societal stigmatization [79]. This psychological condition triggers coping strategies, such as covering up their lesions or avoiding contact with others, which worsen patients' quality of life [74]. Finally, patients with psoriasis have a higher financial burden of direct and indirect costs, including the cost of treatments and loss of work productivity [5].

In a multicenter, retrospective real-world study of Italian psoriasis patients that lasted 84 weeks, secukinumab appeared to rapidly improve patients' quality of life as assessed by the Dermatology Life Quality Index score (DLQI). Specifically, a significant improvement in DLQI was observed after 4 weeks of treatment with secukinumab ($p < 0.001$ compared to baseline), which improved significantly at each follow-up visit. Interestingly, the data were comparable between patients who had never been treated with biologics and those who had been previously treated with biologics [80]. As further evidence, in a multicenter real-world study, secukinumab showed remarkable effects on patients' quality of life, even when used in combination therapy after the failure of secukinumab monotherapy [81].

Interestingly, a randomized, double-blind, placebo-controlled phase 2 study has shown that patients with moderate-to-severe plaque psoriasis treated early with secukinumab have a better quality of life compared with patients receiving placebo [82]. DLQI response was significantly higher with all secukinumab regimens compared with placebo at both 4 and 12 weeks, but the greatest changes were observed with the monthly and early regimens [82].

Benefits of Early Treatment with Secukinumab in Hard-to-Treat Patient Populations

Secukinumab is safe and effective in the real-life setting, also for patients in whom previous systemic treatments have failed or who have multiple comorbidities, such as older people.

A study following patients > 65 years old with moderate-to-severe PsO treated with secukinumab over a 2-year period reported a mean PASI reduction of 85.1% at week 96, with a significant reduction from week 24 (from 11.4 ± 6.3 at baseline to 2.1 ± 1.7 at week 24, $p < 0.001$) [83]. In addition to older patients, biologics are proving to be a favorable therapeutic choice for pediatric patients as they have an excellent efficacy and safety profile compared to conventional systemic medications [84]. As previously mentioned [55], in a 48-week real-world retrospective study involving 18 pediatric patients diagnosed with GPP who received secukinumab as their initial treatment, a substantial reduction in the GPPPASI score and a concurrent enhancement in the Children's Dermatology Life Quality Index score were evidenced. Notably, at the end of the 48-week period, 88.9% of the patients attained a GPPASI score of 100, while every patient achieved a Children's Dermatology Life Quality Index score of 0 or 1 [55]. Moreover, real-world evidence has shown that secukinumab has more favorable outcomes in pediatric patients with GPP compared to acitretin [85]. These data highlight the effectiveness of secukinumab in all life stages of patients with PsO.

Findings from secukinumab clinical trials were confirmed in a more complicated patient population (e.g., polypharmacy, comorbidities, failure of conventional systemic treatment) in a 2-year, real-world, multicenter retrospective study. Results showed that PASI, BSA, and DLQI scores improved significantly from baseline to each follow-up visit and that no significant differences were observed between naive and biologic-naive or non-naive patients. Treatment was discontinued in 31 of 324 patients (9.5%), 1.8% of these because of adverse events [86]. A heterogeneous patient population with varying disease severity and comorbidities was enrolled in another real-world, multicenter, retrospective study that lasted 52 weeks. Secukinumab was effective and safe but also showed rapid clinical improvement, particularly in young patients, and in certain subgroups of patients, such as those with obesity and multidrug-resistant patients [87]. A multicenter, real-world observational study involving 15 Italian referral centers assessed the efficacy and safety of secukinumab in patients with PsO and a history of cancer, usually excluded from clinical trials of biologic treatments. After 48 weeks, 64.7% of patients scored PASI 90 and 38.2% scored PASI 100. Significant improvement was also observed in DLQI, itch, and pain visual analog scale (VAS) scores. Furthermore, the study suggests that secukinumab is safe in psoriatic patients with a history of cancer [88]. A European, multicenter, retrospective real-world study contributed to the characterization of secukinumab best responders. The study confirmed that secukinumab treatment was more effective in biologic-naive patients than in patients previously treated with biologics. The better response in biologic-naive patients was observed at weeks 24 and 52 [89].

CONCLUSIONS

Biologics therapy is a valuable option for the treatment of moderate-to-severe plaque psoriasis. Secukinumab has long-term clinical efficacy and safety in the treatment of patients with PsO, PsA, and axSpA. While the efficacy of early intervention has been explored and demonstrated in other chronic inflammatory diseases, studies on clinical outcomes of early treatment with secukinumab in individuals with psoriasis are limited. Real-world studies are a valuable resource of information to evaluate the effectiveness of this clinical approach in different groups of patients, with several degrees of disease severity and comorbidities. Real-world data have the advantage of including a broad patient population, often excluded from clinical trials and representative of real-world clinical practice. The analysis of real-world data showed the effectiveness of secukinumab, particularly in biologic-naive patients with a history of diseases. In these patients, early intervention with secukinumab proved to be a valuable treatment option. In addition, secukinumab has a good safety profile, which has been consistently observed in diverse patient cohorts characterized by

different comorbidities, such as cancer, liver, and cardiovascular disease, as well as in pediatric and older patients. The cost-benefit ratio of secukinumab could also be better than that of other biologics, considering the sustained clinical response. In addition, secukinumab showed low immunogenicity (< 1%) in psoriasis patients for up to 5 years and patients with PsA exposed for up to 52 weeks [90]. A systematic review conducted to explore the immunogenicity of several biological agents across inflammatory diseases confirmed an overall rate for secukinumab of 0–1%, lower than the one reported for other biologics, such as infliximab and adalimumab, an IL-17 and tumor necrosis factor inhibitor, respectively [91]. Although limited, the data in the literature support effectiveness, safety, and utility as a treatment option for psoriasis of secukinumab also in biologic-naive patients, with improvements in clinical outcomes comparable to those reported for biologic-experience patients [22, 31]. Furthermore, secukinumab could also be an effective alternative when IL-23 inhibitors do not achieve the desired therapeutic outcomes (92).

Early intervention with secukinumab in the treatment of PsO can potentially improve the overall prognosis by reducing disease severity or altering the natural history of the disease towards more severe and complicated stages, leading to remission and improving the quality of life of these patients. The early intervention may also lead to a reduction of costs in treating this disease. For all these reasons, additional real-world studies exploring intervention and early intervention with secukinumab in PsO is of utmost importance.

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Declarations

Conflict of Interest. Paolo Amerio declares the following conflicts of interest: Novartis, Sanofi, Jannsen, Eli Lilly, Galderma. Laura Atzori has been consultant, PI, speaker for Abbvie, Novartis, Janssen, UCB Pharma, Sanofi Genzyme, Lilly, Pfizer, Almirall, BMS. Anna Balato has served on Scientific Boards and/or has received fees for Scientific Consultations from: Abbvie, Amgen, Boehringer Ingelheim, Janssen, Eli-Lilly, Novartis, UCB. Luca Bianchi has been consultant, PI, speaker for Abbvie, Novartis, Janssen, UCB Pharma, Sanofi Genzyme, Lilly, Pfizer, Almirall, Sun Pharma, BMS. Andrea Chiricozzi has served as advisory board member and consultant and has received fees and speaker's honoraria or has participated in clinical trials for AbbVie, Almirall, Bristol Myers Squibb, Leo Pharma, Lilly, Janssen, Novartis, Pfizer and Sanofi Genzyme. Antonio Costanzo has been principal investigator in clinical trials sponsored by and/or and has received personal fees for participation in advisory board from Abbvie, Almirall, Amgen, Boehringer, BMS, Leo Pharma, Lilly, Novartis, Pfizer, UCB

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