Treatment of Psoriasis with Secukinumab in Challenging Patient Scenarios: A Review of the Available Evidence

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ABSTRACT

Psoriasis (PsO) is a common, systemic, chronic, inflammatory disease characterized by key clinical symptoms, including itching, pain, and scaling. PsO is associated with a high prevalence of comorbidities, including other autoimmune diseases and malignancies. Furthermore, special populations, such as pregnant, pediatric, and elderly patients, and those with erythrodermic PsO, are challenging to treat and require tightly monitored disease and treatment management. Because certain populations have demographic or clinical characteristics that can affect the presentation of PsO and complicate treatment responses, these patient populations are largely excluded from clinical trials; therefore, most clinical evidence for the treatment of these patients is derived from case reports and series. Secukinumab, a fully human monoclonal interleukin-17A antibody, has been shown in several clinical trials to be effective and safe for the treatment of PsO; however, these studies offer only limited data on the use of secukinumab in patients with chronic illnesses or in special populations. This review explores the use of secukinumab for PsO in special populations, including pregnant women, children, elderly people, patients with erythrodermic PsO, and those with chronic illnesses, including latent tuberculosis, hepatitis B and C, HIV, multiple sclerosis, and malignancies.

Keywords: Hepatitis; HIV; IL-17A inhibitor; Malignancies; Pediatric; Pregnancy; Psoriasis; Secukinumab; Tuberculosis
Psoriasis (PsO) is a chronic, inflammatory, autoimmune disease affecting the skin, with an estimated prevalence of 2–4% (7.4 million people) in the USA [1, 2]. PsO can be difficult to treat as it is frequently accompanied by comorbidities that confound diagnosis and complicate management [3].

Secukinumab selectively targets interleukin (IL)-17A, a cytokine that is considered a key player in the pathogenesis of PsO [3], and was the first and only fully human IL-17A inhibitor approved for PsO in both the USA and Europe [4–6]. The efficacy and safety profile of secukinumab has been studied for up to 5 years in PsO clinical trials [7, 8]. However, clinical trials typically provide evidence from patients without certain comorbidities or active infections that may render them immunocompromised. In the real-world setting, clinicians may be confronted with challenging scenarios, such as prior malignancies and recurrent, chronic infections, for which there are few data to rely upon for guidance [9, 10].

Here, we review the use of secukinumab in patients with PsO who are often excluded from clinical trials because of pregnancy, age (those 17 years or younger, and those 65 years or older), manifestation of erythrodermic PsO, or chronic illnesses, including latent tuberculosis infection (LTBI), infection with hepatitis B and C virus (HBV and HCV, respectively) or HIV, multiple sclerosis (MS), and malignancies.

We conducted a literature search on secukinumab treatment in PsO populations of interest. Individual searches were performed for specific populations (search terms: “pregnan*,” “pediatric OR paediatric,” “special pop*,” “elderly,” “erythroderma”) or patients with comorbid chronic conditions (“cancer OR malign*,” “comorbid*,” “hepatic,” “hepatitis,” “[human immunodeficiency virus] OR HIV,” “multiple sclerosis,” “tuberculosis OR TB”), together with “secukinumab” and “psoriasis.” The search was further refined by only selecting articles published in English, and results with more than 45 citations were further restricted for “treatment” or “quality of life.” Articles of
potential interest were reviewed after manual curation (i.e., consolidation of duplicates, removal of articles not directly relevant); additional references found in these manuscripts were also used. This article is based on previously conducted studies and does not contain any studies with human participants or animals performed by any of the authors.

SPECIAL POPULATIONS

Pregnancy

There is a need for long-term treatment of PsO in patients of childbearing age, but data regarding efficacy and safety of biologics for PsO during pregnancy are limited to small retrospective studies and case studies [11]. Because T helper 17 (Th17) cells are downregulated during pregnancy, and because PsO is a Th17 cell immune-mediated disease, amelioration of PsO-related symptoms may occur during pregnancy [11]. Twice as many patients with PsO reported improvement in symptoms during pregnancy than reported worsening [12]. Traditional treatments, including methotrexate and acitretin, are contraindicated in pregnancy, and cyclosporine should be limited to the lowest dose for the shortest duration possible [13, 14]. Animal studies indicated that secukinumab is not harmful to embryonic or fetal development, parturition, or postnatal development, including immune response (Novartis data on file) [15, 16].

The manufacturer’s global safety database, which records maternal or paternal exposure to secukinumab during pregnancy in all indications, reported 291 pregnancies between December 26, 2017, and December 25, 2018, in which pregnancy outcomes were analyzed [17]. Rates of spontaneous abortion (31 of 291; 10.7%) [17] were similar to that of an earlier analysis (30 of 292; 10.3%) [15] and to rates in the general population (15–20% for women with a mean maternal age of 30.6 years) [18]. Among patients with known outcomes, the rate of congenital abnormalities was similar to that in the general population [17]. Because antibodies were expected to cross the placenta in the third trimester, most patients discontinued secukinumab during the first trimester [17].

One case study reported a 45-year-old woman who developed amenorrhea after 3 months of secukinumab therapy. She had tubal sterilization at age 43 and was treated with other tumor necrosis factor inhibitors (TNFis) from age 40 to 44 prior to receiving secukinumab. Clinicians determined that she had a miscarriage at 6 weeks of gestation. However, she previously had one spontaneous abortion, was multiparous, and was 45 years old—each a major risk factor unrelated to PsO; therefore, it was inconclusive whether secukinumab was related to the spontaneous abortion [19].

Although risks to pregnancy are likely low, there are insufficient data with secukinumab use in pregnant women to advise continuation of secukinumab treatment during pregnancy [16]. At least one group, the Australian Psoriasis Collaboration, has recommended discontinuation of treatment 19 weeks prior to intended conception, enough time to achieve secukinumab washout, to avoid potential risk of teratogenicity, embryo toxicity, or any negative effects on male fertility [20]. Of note, in a study of patients who achieved 75% reduction in their Psoriasis Area Severity Index (PASI75) score after 1 year of treatment with secukinumab and then relapsed after treatment discontinuation, 94% of patients regained a PASI75 score by 16 weeks, suggesting that secukinumab may be the optimal treatment for patients who discontinue secukinumab during pregnancy [21]. Secukinumab is not recommended for use during pregnancy unless the potential benefits of treatment outweigh the potential risks [17].

Pediatric Population

The prevalence of PsO is low (0.55%) in children aged less than 10 years. In patients aged more than 20 years, PsO prevalence increases with age more rapidly in women than in men; differences between the sexes equilibrate after age 20 [22]. Options for treatment of children with PsO are relatively limited. While etanercept is approved by both the US Food and Drug Administration (FDA) and European Medicines
Agency (EMA) for children with PsO, adalimumab is approved by the EMA for children, and ustekinumab is approved by the FDA for adolescents, most systemic treatments are used off-label [23]. Although secukinumab is in ongoing development for the treatment of children aged more than 6 years with PsO, available evidence of the safety and efficacy of secukinumab in children is currently limited to case studies.

Secukinumab was deemed safe and effective for the treatment of a rare, life-threatening autoimmune condition characterized by deficiency of the IL-36 receptor antagonist (DITRA) in a 4-year-old boy refractory to methotrexate, TNFis, and IL-1 inhibitors [24]. The patient presented with generalized pustular rash, fever, and elevated markers of inflammation and was initially diagnosed with generalized pustular PsO. He received topical and systemic corticosteroids, methotrexate, and etanercept, leading to moderate improvement; however, by the time DITRA was diagnosed within the next 4 months, the patient had experienced three disease flares with fever and new pustular skin eruptions. Despite treatment with anakinra at doses as high as 6 mg/kg per day, he continued to experience fever with new skin eruptions; he then started secukinumab 75 mg/week, which led to rapid improvement of skin disease and blood parameters. At last follow-up 2 months later, while receiving secukinumab and prednisolone 2.5 mg/day, the patient presented with completely cleared skin, normalized blood parameters, and normal ultrasound findings on the liver. The authors presented this case as an example of the important benefit of an IL-17 antagonist in a child with DITRA, with rapid and complete improvement of skin and systemic inflammation [24].

Additionally, secukinumab treatment was associated with remission in a 13-year-old boy with recalcitrant chronic erythrodermic PsO [25]. The patient presented with PsO at age 6, which progressed to erythroderma at age 9. He was initially treated with methotrexate and multiple cycles of cyclosporine, acitretin, and phototherapy for 4 years, with minimal improvement and recurrent flares. He started on secukinumab after it became available in his country; following his first injection of secukinumab 300 mg, his PASI score improved from 50 to 11.4, his Dermatology Life Quality Index score improved from 27 to 8, and he experienced relief from his erythroderma. He achieved complete remission by 8 weeks with no adverse effects and went on to complete 1 year of monthly treatment with secukinumab [25].

Currently, two phase 3 clinical trials evaluating the efficacy and safety of secukinumab for the treatment of PsO in a pediatric population (age 6–17 years) are ongoing (NCT03668613 and NCT02471144), with preliminary results anticipated shortly. Given that children do not endure injections well and that secukinumab has more injections than other biologics, such as IL-23 and IL-12/23 inhibitors, this may be considered a disadvantage for secukinumab in pediatric populations. However, while adalimumab, etanercept, and ixekizumab are associated with the highest incidences of injection-site reactions (ISRs) [26], in the FIXTURE study, only 0.7% of patients receiving secukinumab experienced ISRs compared with 11% of patients receiving etanercept, suggesting that secukinumab would be safe and advantageous for the treatment of pediatric patients [7, 8]. While insufficient safety data exist to make specific treatment recommendations in pediatric populations, these trials will provide dermatologists with additional information in this population.

**Elderly Population**

Elderly patients (aged 65 years or more) with PsO are challenging to treat as this population has a higher prevalence of comorbidities, which may lead to inadequate treatment responses and higher risk of adverse events [27]. Although elderly patients with moderate to severe PsO in clinical trials had a higher baseline frequency of cardiovascular and metabolic disorders, the efficacy of secukinumab was comparable to that in a younger population at 52 weeks (percentage of patients experiencing PASI75, 81.8% vs 79.4%, respectively), with a safety profile consistent with that described in other studies of biologics in elderly populations [28].
**CHRONIC ILLNESSES**

**LTBI**

Approximately 25% of the population worldwide has LTBI, the symptomless, noninfectious, and predominantly dominant form of tuberculosis (TB) \[29, 30\]. LTBI screening and treatment are recommended prior to starting biologic therapy for PsO \[31, 32\]. The risk of reactivation is higher with TNFis compared with other classes of biologics because TNFα is associated with the risk of TB reactivation \[33–35\].

IL-17A does not appear to have a major role in host resistance against *Mycobacterium tuberculosis* \[36\]. In a three-dimensional microgranuloma model, latent *M. tuberculosis* was reactivated when infected cells were treated with adalimumab but was not reactivated with secukinumab \[36\]. European S3-Guidelines state that active TB is only a relative contraindication with secukinumab in the treatment of PsO and that TB screening is recommended but not necessary prior to initiating secukinumab \[37\].

Patients with treated LTBI were not excluded from four phase 2, six phase 3, and two phase 4 secukinumab clinical trials \[38\], and no cases of TB activation were reported. In a multicenter study of 324 patients with moderate to severe psoriasis treated with secukinumab including ten patients with LTBI treated, secukinumab was effective and safe, with only one case of LTBI reported \[39\]. In 2014 patients with moderate to severe PsO treated with secukinumab, no cases of TB were observed after 1 year of treatment. In addition, secukinumab treatment was well tolerated in conjunction with chemoprophylaxis administered to patients with LTBI, with no serious adverse liver events \[36\]. Furthermore, in 12 patients with LTBI without previous chemoprophylaxis due to clinical contraindication or patient refusal, no TB reactivation was reported \[40\]. These trials and cases suggest that secukinumab-treated patients do not have an increased risk of developing TB or reactivating LTBI \[38, 41\].

**HBV and HCV**

Approximately 240 million people worldwide are chronically infected with HBV, and 71 million are infected with HCV. HCV is reportedly associated with PsO, with an estimated prevalence of 1.0% based on a multivariate analysis \[42\]. Patients with PsO who receive biologic therapies have a very low risk of reactivation of latent HBV and HCV; screening for HBV and HCV is recommended prior to administering immunomodulating therapies \[43\]. If HBV or HCV infection is diagnosed with concomitant PsO, the National Psoriasis Foundation (NPF) recommends consultation between a dermatologist and hepatologist before and throughout immunosuppressive treatment to define the stage of disease and extent of liver damage \[43–45\]. Active HBV infection must be treated prior to administration of immunosuppressive therapies, and patients should be monitored every 3 months for HBV DNA load and transaminase levels in case of reactivation \[43, 46\].

The data available for patients with PsO with concomitant HBV or HCV infection treated with systemic therapies are limited to case studies and small groups \[43, 47, 48\]. A systematic review found minimal risk of reactivation in low-risk patients seropositive for HBV or HCV treated with biologics, including secukinumab, and highlighted the considerable risk of reactivation in patients with chronic HBV \[49\]. This risk can be mitigated by antiviral treatment prior to initiation of biologics \[37\]. HBV and HCV infection are relative contraindications to secukinumab \[37\].

In a prospective, multicenter study of 63 patients with PsO and HBV or HCV infection treated with secukinumab between June 2015 and January 2018, reactivation of HBV occurred in 7 out of 46 secukinumab-treated patients who did not receive antiviral prophylaxis \[50\]. HBV surface antigen (HBsAg)-positive patients had significantly increased risk compared with HBsAg-negative and HBV core antigen (HBCAb)-positive patients (24.0% vs 4.17%; *P* = 0.047) \[50\]. Reactivation of HCV occurred in 1 out of 14 patients who did not receive antiviral prophylaxis \[50\]. Two patients with PsO and HBV...
infection who had not responded to prior systemic or biologic treatments achieved optimal responses to secukinumab treatment without HBV reactivation [50]. Furthermore, in a multicenter study of 324 patients with moderate to severe PsO treated with secukinumab including six patients with HBV and four patients with HCV, secukinumab was effective and safe, with no reports of HBV or HCV reactivation [39].

In a case study of a 42-year-old man with HBV–HCV coinfection, secukinumab demonstrated therapeutic efficacy without any adverse events or changes in HBV or HCV viral loads up to 14 months of follow-up [51]. The patient had HBcAb-positive, HBsAg-negative, and HCV Ab-positive serum values for at least 30 years with ultrasound signs for hepatic stenosis. Previous treatment with systemic (narrowband UVB, cyclosporine, methotrexate, and acitretin) and biologics (infliximab, etanercept, adalimumab, and ustekinumab) was not effective; therefore, secukinumab 300 mg treatment was initiated and administered at weeks 0, 1, 2, 3, 4, and every 4 weeks thereafter. After 1 week of secukinumab treatment, he achieved PASI50, and by 4 weeks he had achieved PASI90, which was maintained through 24 weeks. Furthermore, in another case study of a 66-year-old man with HBV, he was successfully treated with a combination therapy of secukinumab and entecavir, with no reactivation of HBV over 9 months of follow-up. The patient had PsO vulgaris for 10 years, and treatment with cyclosporine was discontinued because of side effects. He received secukinumab 300 mg at 0, 1, 2, 3, 4, 8, 12, 16, and 20 weeks. His PASI score improved and returned to almost 0 after treatment [52].

Although reactivation of HBV has been observed in some case reports and post-marketing studies, these reports have not warranted an update to the risk assessment of secukinumab [17]. No cases of HBV reactivation have been reported in randomized controlled trials of secukinumab, and real-world data remain relatively scarce. Given this paucity of data, the effect of secukinumab on patients with HBV or HCV is not completely known.

HIV

PsO management in HIV-positive populations is challenging because of poor response to standard treatment [53]. It is perceived that increased infection risk is associated with TNFi use in PsO, but opportunistic infections are less common with IL-17A inhibitors [54]. NPF guidelines recommend biologics as third-line treatment for HIV-associated PsO [55]; however, the literature evaluating the treatment of patients who are HIV-positive and have concurrent PsO is limited to case reports and series [56, 57].

One report describes a 48-year-old HIV-positive woman who was successfully treated with secukinumab for worsening symptoms of PsO [58]. She had a 20-year history of PsO and a 2-year history of psoriatic arthritis (PsA) that was no longer effectively treated with topical corticosteroids and phototherapy. At the time systemic PsO treatment was considered, pretreatment screening revealed the patient was seropositive for HIV, leading to initiation of highly active retroviral therapy in order to reduce HIV levels below the limit of detection. She received apremilast 30 mg twice daily but stopped treatment after 3 months because of lack of efficacy; she then initiated secukinumab 300 mg at weeks 0, 1, 2, 3, 4, and every 4 weeks thereafter [58]. After the 5-week induction period, the patient achieved complete skin clearance (PASI = 0) and clinical remission of PsA (Clinical Disease Activity Index = 0). The patient remained free of psoriatic lesions at her last follow-up visit 12 months after the initiation of secukinumab [58].

MS and Other Demyelinating Conditions

An estimated 5% of patients with MS have concurrent PsO [59, 60]. TNFis are not suitable for use in patients with MS or those with family history of MS [61].

A 40-year-old patient with pustular PsO developed neuromyelitis optica spectrum disorder after long-term use of TNFis, further indicating that patients with demyelinating lesions should not use TNFis [62]. In one patient...
with PsO and concurrent MS, ustekinumab improved skin symptoms, but joint pain worsened. Following a switch to secukinumab, improvement in skin symptoms was maintained along with a reduction in joint pain and C-reactive protein levels; their MS was stable for 2 years [63].

In patients with relapsing–remitting MS, secukinumab reduced the number of combined unique brain lesions detected during weeks 4–24 by 49% and significantly reduced the number of gadolinium-enhancing T1 lesions by 67% (P = 0.003), suggesting that blocking IL-17A may have reduced MS lesion activity assessed by magnetic resonance imaging [64]. By inhibiting IL-17, a key player in immune-mediated demyelination and neurodegeneration, treatments can target downstream signaling that promotes the production of cytokines and chemokines in neurons and oligodendrocytes to prevent further neurological deficits in patients with MS [65]. Although these reports are promising, additional studies are necessary to evaluate the effect of secukinumab on PsO and MS disease activity in patients with both conditions before conclusive treatment recommendations can be made.

Malignancies

Risk of malignancies is increased in patients with PsO, particularly those with a background of smoking, alcohol consumption, and obesity [66]. Overall risk of cancer, excluding non-melanoma skin cancers, is increased in PsO [66]. Patients with immune-mediated disease, including PsO, showed no increased risk of cancer recurrence among groups treated with TNFis, immune-modulator therapy, or combination therapy, or receiving no immunosuppression [67]. However, when cutaneous squamous cell carcinoma was included, several studies showed an increased risk in patients treated with TNFis [68].

Secukinumab studies did not include patients with active carcinoma but did not exclude patients with any known malignancy or history of malignancy within 5 years prior to enrollment [38]. According to European S3-Guidelines, malignancy is a relative contraindication for secukinumab treatment in PsO [37]. However, secukinumab at any dose may not increase risk of malignancy [38]. Following 52 weeks of treatment, the exposure-adjusted incidence rate of unspecified tumors or malignancies was comparable between groups treated with secukinumab 300 mg and etanercept (0.77 vs 0.68, respectively) [38].

Relationships between the IL-17 axis and malignancy are widely debated, and the effects of IL-17 inhibition with secukinumab on the development and progression of malignancy are unclear. Preclinical studies have demonstrated increased numbers of IL-17-producing Th17 cells in patients with multiple myeloma, with a potential role for secukinumab in inhibiting multiple myeloma growth and survival [69, 70]. Additionally, IL-17 has been implicated in carcinogenesis, metastasis, and resistance to chemotherapy of various solid tumors (i.e., prostate, gastric, and breast cancers) [71–77]. However, IL-17 may modulate malignancies in a type-specific manner. A meta-analysis of 2902 patients from 28 studies found correlations between high IL-17 levels and poorer outcomes for certain tumors, although overall survival and progression-free survival were positively associated with high IL-17 levels in patients with esophageal squamous carcinoma and ovarian cancer, respectively [78]. As there is a lack of clinical data regarding the use of secukinumab in patients with PsO with comorbid malignancies, clinicians must be cautious and consider treatment on a case-by-case basis following discussion with an oncologist [37].

Rare Forms of PsO

Erythrodermic PsO is a rare, severe, and potentially life-threatening form of PsO that most often affects patients with unstable plaque PsO; these patients are difficult to treat and tend to have inadequate responses to many treatments [79].

In real-world and case studies, approximately 60% of patients with erythrodermic PsO receiving secukinumab achieved PASI75 by week 4, suggesting that secukinumab may be a
viable, rapid treatment option for this challenging population [80, 81]. However, in patients who experienced failure of multiple prior therapies, the effectiveness of secukinumab was suboptimal [82]. Further research is needed to evaluate the optimal dosage and treatment frequency.

**CONCLUSIONS**

The management of PsO is frequently complicated among special populations of patients, including those with comorbid chronic illnesses, elderly patients, and pregnant women, fully recognizing that comorbid conditions are common in patients with moderate-to-severe PsO. Treatment of these patients, as well as those with the rare and potentially fatal erythrodermic form of PsO, requires careful consideration and frequent monitoring to achieve optimal management (Table 1). Secukinumab has a known safety profile that has been consistent across its approved indications for more than 5 years and should be considered a viable option among patients with chronic illness and in special populations on the basis of the available data (Table 2). Because PsO is a chronic disease that requires continual lifelong treatment, further studies are warranted to evaluate the safety and efficacy of secukinumab in the treatment of patients with comorbidities, and whether secukinumab can not only adequately control the PsO but also potentially improve comorbid conditions, especially cardiovascular disease.
| Population                  | Number of publications | Number of patients | Sex (male/female) | Age                              | Key safety outcome                              |
|-----------------------------|------------------------|--------------------|-------------------|----------------------------------|------------------------------------------------|
| **Special populations**     |                        |                    |                   |                                  |                                                 |
| Pregnant                    | 3                      | 584                | Female; 13.5%     | 31.1 years (mean) [15]; 45 years [19] | No evidence for increased rates of AEs          |
| [15, 17, 19]                |                        |                    | paternal exposure |                                  |                                                 |
| Pediatric                   | 2                      | 2                  | 2/0               | 2 patients: 4 years (deficiency of the IL-36 receptor antagonist) [24]; 13 years (recalcitrant chronic erythrodermic PsO) [25] | Improved skin and no AEs                        |
| [24, 25]                    |                        |                    |                   |                                  |                                                 |
| Elderly [28]                | 1                      | 67                 | 41/26             | 69.3 years (mean)                | Safety profile consistent with general population |
| Erythrodermic PsO [80–82]   | 3                      | 16                 | 14/2              | 36–59 years (range across studies) [80, 81]; 42.6 (11) years (mean [SD]) [82] | Secukinumab is effective and safe                |
| Chronic illnesses           |                        |                    |                   |                                  |                                                 |
| LTBI [36, 39, 40]           | 3                      | 154                | 9/3 [40]          | 29–77 years (range) [40]         | Only 1 patient reported LTBI                    |
| HBV/HCV [39, 50–52]         | 4                      | 75                 | 53/12             | 42–66 years (range across studies) [50–52] | No virus reactivation in patients receiving antiviral prophylaxis |
| HIV [58]                    | 1                      | 1                  | 0/1               | 48 years                         | Complete skin clearance and HIV viral load remained undetectable |
| MS [63, 64]                 | 2                      | 39                 | 18/21             | 42 years [63]; 36.1 (9.8) years (mean [SD]) [64] | Reduced MRI lesions with secukinumab            |
| Malignancies                |                         |                    |                   |                                  | No available clinical data on secukinumab use in patients with PsO and comorbid malignancies |

Not all studies included demographic information for secukinumab-treated patients in special populations or with chronic illnesses.

*HBV* hepatitis B virus, *HCV* hepatitis C virus, *HIV* human immunodeficiency virus, *LTBI* latent tuberculosis infection, *MRI* magnetic resonance imaging, *MS* multiple sclerosis, *PsO* psoriasis.
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