Case and Review

Secukinumab in the Treatment of Plaque Psoriasis in Patients with Malignancy

Alessio Gambardella

Dermatology Unit, University of Campania, Naples, Italy

Keywords

Plaque psoriasis · Secukinumab · Safety · Bladder carcinoma

Abstract

Although available data are conflicting, psoriasis seems to be associated with an increased baseline risk of malignancy. In addition, some antipsoriatic systemic treatments have been associated with risk of malignancy. There is not enough data on the association of interleukin (IL)-17 and IL-23 inhibitors with malignancy rate, but there have been no cases reported so far. Secukinumab is a recombinant human monoclonal immunoglobulin G1/κ antibody that selectively targets IL-17A; it was demonstrated to be effective and safe for the treatment of moderate to severe psoriasis that may be appropriate in frail subjects, as patients previously experienced malignancy, as in the case reported.

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Psoriasis and Risk of Malignancy

Psoriasis was associated with multiple comorbid conditions, such as psoriatic arthritis, cardiovascular disease, stroke, metabolic syndrome, autoimmune conditions, malignancies, and psychiatric disorders [1–7]. In 2001, Margolis et al. [8] published a study comparing 17,000 psoriasis patients with patients with hypertension, showing an increased risk ratio of overall malignancy in patients with severe psoriasis (1.78, 95% confidence interval 1.3 to 2.40). An association between psoriasis and lymphoproliferative diseases has been found, and a large population-based cohort study showed an increased risk for non-melanoma skin cancers in psoriasis patients [9]. Overall, adjusted cancer risk was higher in psoriatic subjects than in subjects without psoriasis in a cohort study (hazard ratio 1.065, 95% confidence interval 1.049–1.081) [10].

Psoriasis Treatment and Risk of Malignancy

Systemic treatments for psoriasis have significantly improved disease burden, but concerns are persisting regarding their association with increased risk of malignancy. Several studies found oral psoralen and ultraviolet A (PUVA) was associated with an increased risk of skin cancer in a dose-dependent fashion [9]. Cyclosporine increased the overall incidence of malignancy two-fold (6-fold increase in squamous cell carcinoma, SCC) in 1,252 psoriasis patients after an average of 1.9 years of treatment [11]. Risk of SCC was associated with cyclosporine and methotrexate treatment and was further increased by PUVA exposure [9]. A warning against the use of anti-tumor necrosis factor (TNF)- α agents in patients with concurrent or past history of malignancy is present in prescribing information, and these drugs should be avoided especially in the presence of multiple cutaneous SCCs [12]. Nevertheless, recent meta-analyses and observational studies found no significantly increased risk of systemic malignancies, including lymphoma for anti-TNF- α in psoriasis. On the contrary, an increased risk of SCC has been confirmed by several recent studies [9, 12]. The development of biologic drugs, through the identification of key cytokines integral to the psoriasis inflammatory process, has recently improved the outcomes of psoriasis treatment. There is not enough data on malignancy potential of interleukin (IL)-17 and IL-23 inhibitors, but there have been no reported associations with malignancy so far [12].

The T-Helper-17/IL-17 Pathway in the Pathogenesis of Psoriasis

There is a considerable amount of data supporting the central role of IL-17 in the pathogenesis of psoriasis, and the importance of IL-17-targeted biologic therapy in the treatment of moderate to severe psoriasis. T-helper-17 (Th17) cells express IL-23R and IL-17A, in response to several cytokines. Th17 are present in psoriatic lesional skin and represent a key contributor to the proinflammatory state of psoriasis [13, 14]. After Th17 cell exposure to IL-23, other chemokines such as IL-17A, IL-17F, IL-22, and TNF- α [15, 16] are released. IL-17A is the primary effector cytokine of the Th17 cells, and it is also expressed by mast cells and neutrophils in psoriasis and in a number of immune-mediated diseases [17–19]. Keratinocytes express IL-17A receptors on their surface and, upon IL-17A binding, the production of several chemokines is increased, which play a role in recruiting inflammatory cells to lesional skin and stimulating the innate immune system [20–23]. This pathway contributes to psoriasis pathogenesis by promoting epidermal hyperproliferation and skin barrier dysfunction. Moreover, IL-17A and TNF- α exert a synergistic effect on keratinocytes, with upregulation of genes involved in the psoriasis gene signature [16, 24]. IL-17A serum level significantly correlates to psoriasis severity [25–27].

The T-Helper-17/IL-17 Pathway in Tumor Immune Physiopathology

The relationship between Th17 cells and tumor immune physiopathology is controversial. In preclinical studies, IL-17 produced anti-tumor effects in immune-competent mice, but pro-tumor effects in immune-deficient mice [28]. Accumulating evidence indicates that IL-17 has tumor-promoting effects, especially in the context of inflammation. In a mouse model, it was found that IL-17 was required for induced carcinogenesis in the skin and that blockade of IL-17 suppressed inflammation-mediated tumor development and progression [29].

It is thought that the pro-tumor versus anti-tumor effect balance of IL-17 depends on the IL-17-induced inflammatory mediators. These factors regulate the plasticity of the T-cell differentiation, so that many of the inflammatory functions of IL-17 can initially benefit the host, but when the microenvironment is altered, IL-17 starts promoting tumor growth [30].

Studies in mice and humans have suggested that Th17 cells and IL-17 enhance tumor surveillance and immunity [31–33]. In vitro, blockade of Notch signaling pathway on the invasive capability of hepatoma cells was found with secukinumab combined with IL-35 [34]. It was demonstrated that IL-17A-producing Th17 cells were significantly elevated in blood and bone marrow in multiple myeloma (MM) and that IL-17A promoted MM cell growth via the expression of IL-17 receptor. In addition, an anti-human IL-17A monoclonal antibody inhibited MM cell growth [35]. Recent advances supported the promoting role of IL-17/IL-17 receptor axis in carcinogenesis, tumor metastasis, and resistance to chemotherapy of diverse solid cancers [36].

Secukinumab: Efficacy and Safety in Plaque Psoriasis

Secukinumab is a recombinant human monoclonal immunoglobulin G1/κ antibody that selectively targets IL-17A and blocks its interaction with the IL-17 receptor. Inhibition of the downstream effects of this proinflammatory cytokine interferes with key psoriasis disease pathways and promotes normalization of immune function and lesion histology [37]. Clinical trials demonstrated clinical efficacy of secukinumab for the treatment of moderate to severe plaque psoriasis, in comparison with placebo and etanercept, in terms of PASI 75 response and rate of clear or almost clear psoriatic disease [38, 39].

In a head-to-head, double-blind study, secukinumab demonstrated a sustained superior efficacy in comparison with ustekinumab in clearing skin through week 52, greater improvement in quality of life, and a favorable and comparable safety profile [40]. Secukinumab is generally well tolerated and has a favorable safety profile. The most common adverse events include upper respiratory tract infections and headache [41]. In addition, a post hoc analysis of this study showed that significantly more patients treated with secukinumab achieved a complete relief of pain at weeks 16 and 52 (all $p < 0.05$). Complete relief of itching and scaling occurred significantly faster with secukinumab (median, 4 weeks faster for itching and 8 weeks faster for scaling [$p < 0.001$]). Response as measured by the Dermatology Life Questionnaire Index (DLQI) was 4 weeks faster with secukinumab ($p < 0.0001$). Cumulative benefits were greater with secukinumab (all $p < 0.05$) [42].

Skin clearance, improved quality of life, and favorable safety, previously observed in a phase 2/3 program with secukinumab 300 mg, were maintained throughout 5 years in patients with moderate-to-severe psoriasis in the SCULPTURE extension study [43]. Data from randomized clinical trials were reinforced by real-life experiences. In a multicenter, retrospective study with an observation period of 52 weeks, in a real-life setting, a cohort of 107 patients with moderate-to-severe plaque psoriasis was observed. PASI 90 and PASI 100 were reported in 67.5 and 55% of patients at week 12, respectively. A rapid improvement of skin lesions was observed particularly in young patients and in patients naïve to biologics, and the drug was well tolerated [44].

Caution in the systemic treatment of psoriasis in an oncologic patient is mandatory, especially in the presence of concomitant anti-tumoral therapy [45]. In the pooled analysis of 10 phase II and III clinical studies with secukinumab, which included 3,430 patients, no increased risk of malignancy risk was reported throughout the 52 weeks of treatment [41].

Case Report

A male patient of 68 years, with plaque psoriasis for 25 years, affected by blood hypertension and type 2 diabetes, who had surgery for a bladder in situ carcinoma 1 year before, presented with psoriasis recurrence (PASI: 28; BSA: 20; DLQI: 14) in 2016. In previous years, psoriasis had been treated with topical agents, UVB phototherapy, and cyclosporin. Phototherapy failed to improve the skin lesions. Traditional immunosuppressant agents and anti TNF- α agents were avoided, due to the history of cancer, and good tolerability was mandatory due to compromised general conditions. Therefore, secukinumab 300 mg was administered at weeks 0, 1, 2, 3, 4, and every 4 weeks. Skin clearance was rapidly obtained (PASI 2, BSA 1, DLQI 1, at week 12). After 24 weeks of treatment, PASI was 0 and no adverse event was observed.

Conclusion

Secukinumab is an efficacious anti-IL-17A biologic agent for the treatment of moderate to severe plaque psoriasis. Specifically, secukinumab is associated with a rapid rate of clinical response and correlates to greater improvements in health-related quality of life measures. In regard to safety, secukinumab is generally well tolerated and no increased risk of malignancy has been reported. Indeed, preclinical studies suggested that the block of IL-17 could have some anti-tumor effects, although inconsistent results were reported [28, 31–35]. Therefore, it will be very important to consider upcoming clinical evidence to decide when and if therapy with secukinumab is a valid solution for the treatment of psoriasis in patients with malignancy, as reported by the case described.

Key Message

IL-17-targeted biologic therapy is an effective and well-tolerated treatment for moderate to severe psoriasis that may be suitable for frail subjects.

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Statement of Ethics

The author declares that the research was conducted in accordance with the World Medical Association Declaration of Helsinki. The patients have given their written informed consent to publish their case, including publication of images.

Disclosure Statement

Author has no conflicts of interest to declare.

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