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Case and Review

Secukinumab in the Treatment of Plaque Psoriasis in Patients with Malignancy

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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.

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].

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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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References

1 Korman NJ, Zhao Y, Pike J, Roberts J. Relationship between psoriasis severity, clinical symptoms, quality of life and work productivity among patients in the USA. Clin Exp Dermatol. 2016 Jul;41(5):514–21.
2 Kirby B, Richards HL, Mason DL, Fortune DG, Main CJ, Griffiths CE. Alcohol consumption and psychological distress in patients with psoriasis. Br J Dermatol. 2008 Jan;158(1):138–40.
3 Abuabara K, Azfar RS, Shin DB, Neimann AL, Troxel AB, Gelfand JM. Cause-specific mortality in patients with severe psoriasis: a population-based cohort study in the U.K. Br J Dermatol. 2010 Sep;163(3):586–92.
4 Neimann AL, Shin DB, Wang X, Margolis DJ, Troxel AB, Gelfand JM. Prevalence of cardiovascular risk factors in patients with psoriasis. J Am Acad Dermatol. 2006 Nov;55(5):829–35.
5 Najarian DJ, Gottlieb AB. Connections between psoriasis and Crohn's disease. J Am Acad Dermatol. 2003 Jun;48(6):805–21.
6 Menter A, Gottlieb A, Feldman SR, Van Voorhees AS, Leonardi CL, Gordon KB, et al. Guidelines of care for the management of psoriasis and psoriatic arthritis: Section 1. Overview of psoriasis and guidelines of care for the treatment of psoriasis with biologics. J Am Acad Dermatol. 2008 May;58(5):826–50.
7 Menter A, Korman NJ, Elmets CA, Feldman SR, Gelfand JM, Gordon KB, et al.; American Academy of Dermatology Work Group. Guidelines of care for the management of psoriasis and psoriatic arthritis: section 6. Guidelines of care for the treatment of psoriasis and psoriatic arthritis: case-based presentations and evidence-based conclusions. J Am Acad Dermatol. 2011 Jul;65(1):137–74.
8 Margolis D, Bilker W, Hennessy S, Vittorio C, Santanna J, Strom BL. The risk of malignancy associated with psoriasis. Arch Dermatol. 2001 Jun;137(6):778–83.
9 Geller S, Xu H, Lebwohl M, Nardone B, Lacouture ME, Kheterpal M. Malignancy Risk and Recurrence with Psoriasis and its Treatments: A Concise Update. Am J Clin Dermatol. 2018 Jun;19(3):363–75.
10 Lee JH, Kim HJ, Han KD, Kim HN, Park YM, Lee JY, et al. Cancer risk in 892 089 patients with psoriasis in Korea: A nationwide population-based cohort study. J Dermatol. 2019 Feb;46(2):95–102.
11 Paul CF, Ho VC, McGeown C, Christophers E, Schmidtmann B, Guillaume JC, et al. Risk of malignancies in psoriasis patients treated with cyclosporine: a 5 y cohort study. J Invest Dermatol. 2003 Feb;120(2):211–6.
12 Kaushik SB, Lebwohl MG. Psoriasis: Which therapy for which patient: Psoriasis comorbidities and preferred systemic agents. J Am Acad Dermatol. 2019 Jan;80(1):27–40.
13 Di Cesare A, Di Meglio P, Nestle FO. The IL-23/Th17 axis in the immunopathogenesis of psoriasis. J Invest Dermatol. 2009 Jun;129(6):1339–50.
14 Lowes MA, Kikuchi T, Fuentes-Duculan J, Cardinale I, Zaba LC, Haider AS, et al. Psoriasis vulgaris lesions contain discrete populations of Th1 and Th17 T cells. J Invest Dermatol. 2008 May;128(5):1207–11.
15 Kagami S, Rizzo HL, Lee JJ, Koguchi Y, Blauvelt A. Circulating Th17, Th22, and Th1 cells are increased in psoriasis. J Invest Dermatol. 2010 May;130(5):1373–83.
16 Lynde CW, Poulin Y, Vender R, Bourcier M, Khalil S. Interleukin 17A: toward a new understanding of psoriasis pathogenesis. J Am Acad Dermatol. 2014 Jul;71(1):141–50.
17 Res PC, Piskin G, de Boer OJ, van der Loos CM, Teeling P, Bos JD, et al. Overrepresentation of IL-17A and IL-22 producing CD8 T cells in lesional skin suggests their involvement in the pathogenesis of psoriasis. PLoS One. 2010 Nov;5(11):e14108.
18 de Boer OJ, van der Meer JJ, Teeling P, van der Loos CM, Idu MM, van Maldegem F, et al. Differential expression of interleukin-17 family cytokines in intact and complicated human atherosclerotic plaques. J Pathol. 2010 Mar;220(4):499–508.
19 Lin AM, Rubin CJ, Khandpur R, Wang JY, Riblett M, Yalavarthi S, et al. Mast cells and neutrophils release IL-17 through extracellular trap formation in psoriasis. J Immunol. 2011 Jul;187(1):490–500.
20 Gaffen SL. Structure and signalling in the IL-17 receptor family. Nat Rev Immunol. 2009 Aug;9(8):556–67.
21 Kolls JK, Lindén A. Interleukin-17 family members and inflammation. Immunity. 2004 Oct;21(4):467–76.
22 Nograles KE, Zaba LC, Guttman-Yassky E, Fuentes-Duculan J, Suárez-Fariñas M, Cardinale I, et al. Th17 cytokines interleukin (IL)-17 and IL-22 modulate distinct inflammatory and keratinocyte-response pathways. Br J Dermatol. 2008 Nov;159(5):1092–102.
23 Harper EG, Guo C, Rizzo H, Lillis JV, Kurtz SE, Skorcheva I, et al. Th17 cytokines stimulate CCL20 expression in keratinocytes in vitro and in vivo: implications for psoriasis pathogenesis. J Invest Dermatol. 2009 Sep;129(9):2175–83.
24 Chiricozzi A, Guttman-Yassky E, Suárez-Fariñas M, Nograles KE, Tian S, Cardinale I, et al. Integrative responses to IL-17 and TNF-α in human keratinocytes account for key inflammatory pathogenic circuits in psoriasis. J Invest Dermatol. 2011 Mar;131(3):677–87.

25 Arican O, Aral M, Sasmaz S, Ciragil P. Serum levels of TNF-alpha, IFN-gamma, IL-6, IL-8, IL-12, IL-17, and IL-18 in patients with active psoriasis and correlation with disease severity. Mediators Inflamm. 2005 Oct;2005(5):273–9.
26 Yilmaz SB, Cicek N, Coskun M, Yegin O, Alpsoy E. Serum and tissue levels of IL-17 in different clinical subtypes of psoriasis. Arch Dermatol Res. 2012 Aug;304(6):465–9.
27 Krueger JG, Fretzin S, Suarez-Farinas M. IL-17A is essential for cell activation and inflammatory gene circuits in subjects with psoriasis. J Allergy Clin Immunol. 2012 Jul; 130(1):145–54.e9.
28 Zou W, Restifo NP. T(H)17 cells in tumour immunity and immunotherapy. Nat Rev Immunol. 2010 Apr;10(4):248–56.
29 He D, Li H, Yusuf N, Elmets CA, Athar M, Katiyar SK, et al. IL-17 mediated inflammation promotes tumor growth and progression in the skin. PLoS One. 2012;7(2):e32126.
30 Murugaiyan G, Saha B. Protumor vs antitumor functions of IL-17. J Immunol. 2009 Oct;183(7):4169–75.
31 Kryczek I, Wei S, Szeliga W, Vatan L, Zou W. Endogenous IL-17 contributes to reduced tumor growth and metastasis. Blood. 2009 Jul;114(2):357–9.
32 Kryczek I, Banerjee M, Cheng P, Vatan L, Szeliga W, Wei S, et al. Phenotype, distribution, generation, and functional and clinical relevance of Th17 cells in the human tumor environments. Blood. 2009 Aug;114(6):1141–9.
33 Kryczek I, Zhao E, Liu Y, Wang Y, Vatan L, Szeliga W, et al. Human TH17 cells are long-lived effector memory cells. Sci Transl Med. 2011 Oct;3(104):104ra100.
34 Li HC, Zhang YX, Liu Y, Wang QS. Effect of IL-17 monoclonal antibody Secukinumab combined with IL-35 blockade of Notch signaling pathway on the invasive capability of hepatoma cells. Genet Mol Res. 2016 Jul;15(2). https://doi.org/10.4238/gmr.15028174.
35 Prabhala RH, Fulciniti M, Pelluru D, Rashid N, Nigroiu A, Nanjappa P, et al. Targeting IL-17A in multiple myeloma: a potential novel therapeutic approach in myeloma. Leukemia. 2016 Feb;30(2):379–89.
36 Fabre J, Giustiniani J, Garbar C, Antonicelli F, Merrouche Y, Bensussan A, et al. Targeting the Tumor Microenvironment: The Protumor Effects of IL-17 Related to Cancer Type. Int J Mol Sci. 2016 Aug;17(9):E1433.
37 Frieder J, Kivelevitch D, Menter A. Secukinumab: a review of the anti-IL-17A biologic for the treatment of psoriasis. Ther Adv Chronic Dis. 2018 Jan;9(1):5–21.
38 Langley RG, Elewski BE, Lebwohl M, Reich K, Griffiths CE, Papp K, et al.; ERASURE Study Group; FIXTURE Study Group. Secukinumab in plaque psoriasis—results of two phase 3 trials. N Engl J Med. 2014 Jul;371(4):326–38.
39 Paul C, Lacour JP, Tedremets L, Kreutzer K, Jazayeri S, Adams S, et al.; JUNCTURE study group. Efficacy, safety and usability of secukinumab administration by autoinjector/pen in psoriasis: a randomized, controlled trial (JUNCTURE). J Eur Acad Dermatol Venereol. 2015 Jun;29(6):1082–90.
40 Blauvelt A, Reich K, Tsai TF, Tyring S, Vanaclocha F, Kingo K, et al. Secukinumab is superior to ustekinumab in clearing skin of subjects with moderate-to-severe plaque psoriasis up to 1 year: results from the CLEAR study. J Am Acad Dermatol. 2017 Jan;76(1):60–69.e9.
41 van de Kerkhof PC, Griffiths CE, Reich K,, Leonardi CL, Blauvelt A, Tsai TF, Gong Y, Huang J, Papavassilis C, Fox T. Secukinumab long-term safety experience: a pooled analysis of 10 phase II and III clinical studies in patients with moderate to severe plaque psoriasis. J Am Acad Dermatol. 2016 Jul;75(1):83–98.e4.
42 Puig L, Augustin M, Blauvelt A, Gottlieb AB, Vender R, Korman NJ, et al. Effect of secukinumab on quality of life and psoriasis-related symptoms: A comparative analysis versus ustekinumab from the CLEAR 52-week study. J Am Acad Dermatol. 2018 Apr;78(4):741–8.
43 Bissonnette R, Luger T, Thaçi D, Toth D, Lacombe A, Xia S, et al. Secukinumab demonstrates high sustained efficacy and a favourable safety profile in patients with moderate-to-severe psoriasis through 5 years of treatment (SCULPTURE Extension Study). J Eur Acad Dermatol Venereol. 2018 Sep;32(9):1507–14.
44 Galluzzo M, Talamonti M, De Simone C, D'Adamio S, Moretta G, Tambone S, et al. Secukinumab in moderate-to-severe plaque psoriasis: a multi-center, retrospective, real-life study up to 52 weeks observation. Expert Opin Biol Ther. 2018 Jul;18(7):727–35.
45 Esfahani K, Miller WH Jr. Reversal of Autoimmune Toxicity and Loss of Tumor Response by Interleukin-17 Blockade. N Engl J Med. 2017 May;376(20):1989–91.