The successful treatment with ixekizumab in a multi-failure psoriasis patient

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Abstract

We report a patient with severe psoriasis who failed to respond to phototherapy, conventional systemic treatment and four biologic agents (etanercept, ustekinumab, adalimumab and secukinumab). Combination of a higher-dose secukinumab regimen with phototherapy had no success. Remarkably, ixekizumab, an IL-17A inhibitor, provided almost complete psoriasis clearance after 24 weeks of treatment. The reason for the success of ixekizumab after the failure to respond to a biologic with same mechanism of action is still unknown. Interestingly, failure of secukinumab does not preclude future therapeutic success with a second IL-17A-inhibitor.

Keywords: psoriasis, ixekizumab, anti-IL17A, biologics

Case Synopsis

We report a 61-year-old woman with a 30-year history of severe psoriasis and several admissions to the hospital because of erythrodermic flares. Her past medical history included obesity, insulin-dependent diabetes mellitus, and liver cirrhosis related to alcoholic and non-alcoholic fatty liver diseases (Child–Pugh class A). Through the years, multiple therapies were attempted including cyclosporine (stopped due to nephrotoxicity), narrowband UVB (NB-UVB) phototherapy (non-responder), etanercept (primary non-responder), ustekinumab (secondary non-responder), and adalimumab (primary non-responder). Given the lack of response to previous treatments, the patient started treatment with secukinumab 300mg as per label. After 8 weeks, a PASI50-75 response was achieved. However, after week 12, the patient started to lose response with reappearance of plaque-type psoriasis (absolute PASI=18). Secukinumab was increased to 300mg every other week and NB-UVB phototherapy was added. No improvement was seen after 12 weeks of this combination treatment. Considering the failure of this combination rescue treatment, the patient initiated ixekizumab with the recommended induction and maintenance dose as per label. Notably, at week 4, the patient was almost completely cleared (absolute PASI<2; PASI 90 response). Currently, after 24 weeks of treatment, the patient maintains an absolute PASI<2; PASI 90 response, without any safety issues.

Case Discussion

We report a challenging case of a patient who did not respond to four different biologic agents (anti-TNF, anti-IL12/23, and anti-IL-17A). Switching to ixekizumab after failure to respond to secukinumab (including every other week maintenance dose) led to a remarkable clinical improvement, even though both agents are IL-17A inhibitors. This is in agreement with a recent report that showed that 88.2 % of 17 secukinumab non-responder patients achieved PASI75 response at week 12 after switching to ixekizumab, regardless of the reason or timing of secukinumab discontinuation [1]. The reason for this is still unknown.

Although ixekizumab and secukinumab share the same mechanism of action, it does not mean that they are equal or have the same clinical results. Small differences in the properties of an antibody, such as affinity, specificity, and solubility, may have a large impact in terms of efficacy. Hypothetical explanations for this distinct clinical outcome include a very high binding affinity of ixekizumab to human IL-17A (KD<3pM), compared to secukinumab (KD between 60–370 pM, average approximately 200pM) [2, 3]. Additionally, the difference in the binding affinity to human IL-17A/F heterodimer may also have clinical impact, as ixekizumab binds to human IL-17A/F heterodimer with high affinity (KD<3pM) whereas secukinumab affinity is considerably lower (KD ~2000pM), [2, 3]. This seems important since IL-17A/F heterodimer and IL-17A homodimers signal through the same IL -17 receptor A/receptor C complex (IL-17RA/RC), [4]. Moreover, IL-17A/F heterodimer is a two-faced cytokine closely mimicking IL- 17A as well as IL-17F [2–4]. Additionally, emerging evidence suggests that IL-17F contributes to chronic tissue inflammation beyond IL-17A alone [5]. Dual neutralization of IL-17A and IL-17F with a new monoclonal antibody bimekizumab showed greater suppression of in vitro cytokine responses and neutrophil chemotaxis than inhibition of IL-17A alone, also showing clinical efficacy in moderate to severe psoriasis and psoriatic arthritis [5, 6]. Albeit secukinumab and ixekizumab do not show significant interaction with human IL-17F homodimer; there is a significant difference regarding their affinity to human IL-17A/F heterodimer. This difference may be another explanation for the efficacy of ixekizumab in secukinumab non-responder patients.

Finally, another issue of interest will be drug survival for ixekizumab. Recent reports demonstrated that secukinumab had the lowest drug survival among all the biologics [7, 8]. Differences in binding affinity are also pointed out as potential explanations. Secukinumab has a high loading dose that can lead to a rapid and convincing response. However, over time, the maintenance dose may be too low, leading to relapse at some threshold [7]. Nevertheless, these results should be interpreted with caution, as many secukinumab patients had been previously treated with more than 3 biologic agents, comprising a group of patients particularly difficult to treat. The long-term follow-up of this patient will be helpful to clarify this issue.

Owing to its high affinity to IL-17A and IL-17A/F, ixekizumab may be an interesting treatment option in difficult-to-treat patients that previously failed other biologic agents, including IL-17A inhibitors.

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