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Review

Successful use of the excimer laser for generalized psoriasis in an ustekinumab non-responder

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Abstract

Effective treatments for moderate to severe psoriasis are phototherapy and biologics. These treatments are similar in that they both decrease cutaneous immune system hyperactivity, yet do so through different mechanisms. Our patient, a 63-year-old man, had a rapid response to treatment with the high dose excimer laser, having previously failed treatment with 28 weeks of ustekinumab therapy. A pre-treatment biopsy of a psoriatic plaque was found to contain relatively low levels of IFN-γ (Th1) and IL-17 (Th17) secreting T cells. Following treatment with the excimer laser, the patient had quick improvement in Psoriasis Area and Severity Index that was reflected by a 3-fold reduction in the number of live T cells found in the post-treatment biopsy. Although ustekinumab and the excimer laser both result in decreased levels of these cytokines, the excimer laser directly causes apoptosis of T cells and induces DNA damage in antigen presenting cells. Thus, the broader effects of phototherapy on immune cells compared to the targeted inhibition of IL-12 and IL-23 by ustekinumab likely account for the superior response observed.

Keywords: Psoriasis, Excimer, Ustekinumab, Treatment Failure

Introduction

Psoriasis is a chronic, immune-mediated disease that manifests as red silvery plaques on the skin [1]. Both phototherapy and biologic agents are very effective for the treatment of psoriasis, although they have differing mechanisms of action. Phototherapy acts more broadly on the immune cells in the skin, whereas biologics target specific cytokines thought to play a significant role in the pathogenesis of psoriasis, such as TNF-α, IL-23, and IL-17 [2].

These variable mechanisms of action may help explain the different clinical responses to these treatment modalities. Even though biologics are very efficacious, primary treatment failures have been observed in certain patients [3-5]. Treatment failures may be primary if there is a lack of initial efficacy or secondary if patients lose efficacy over time as with biologic fatigue [5, 6]. Primary treatment failures and varied clinical responses to the same treatment have resulted in efforts to identify biomarkers and genetic

polymorphisms that could have the potential of predicting clinical response.[7-10]. Although phototherapy is less convenient than biologics, it remains an effective and relatively safe treatment option for psoriasis [11].

Herein, we describe the clinical and immunologic response of a patient who sequentially underwent two unrelated investigator-initiated trials, receiving treatment with ustekinumab, followed by treatment with high dose excimer laser in combination with topical treatment. This case highlights the utility of phototherapy in a patient who had a poor response to ustekinumab, supported by supplemental data from lesional biopsies collected before and after treatment with excimer laser.

Case synopsis

A 63-year-old man with Fitzpatrick skin type IV and a six-year history of generalized plaque psoriasis covering 20% of his body was enrolled in a clinical trial and was treated with ustekinumab, 45 mg, for 28 weeks. The dosing schedule was as per USFDA labeling with 45 mg of ustekinumab given at week 0, 4, 16, and 28. Previous to the study, the patient used only topical steroids. At his baseline study visit, his Psoriasis Area and Severity Index (PASI) was 13.7. Throughout the course of the ustekinumab trial, the patient showed minimal improvement with just a 13% PASI improvement from baseline (13.7 to 12) after 28 weeks of treatment. Given his lack of improvement, the patient was deemed a nonresponder to ustekinumab [12, 13].

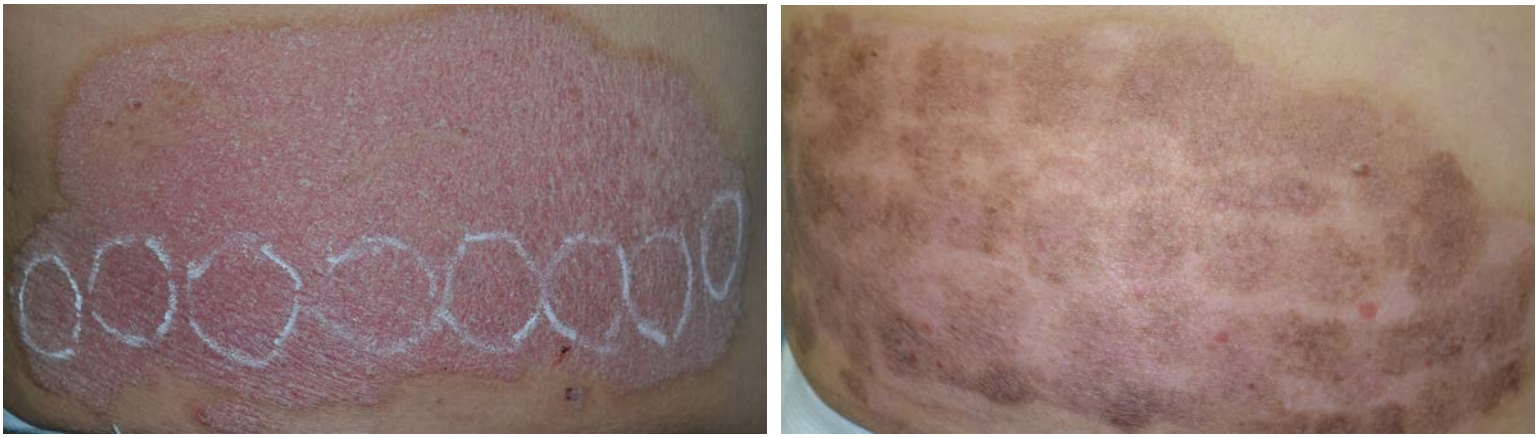

Figure 1. A) Patient photograph prior to treatment with the 308-nm excimer laser. White circles illustrate MBD testing protocol used to determine an optimally high dose that could be delivered without causing cutaneous blistering. B) Patient photograph at week 6 after treatment with high dose excimer laser. Residual, subsiding laser erythema and hyperpigmentation observed.

Six months after completing the ustekinumab trial, the patient again presented to our office with untreated, thick confluent psoriatic plaques on the trunk and extremities (Figure1A). The patient chose to enroll in a second clinical trial investigating the use of excimer laser 1-2 x per week combined with topical therapy clobetasol propionate spray and calcitriol ointment for the treatment of generalized psoriasis [14]. With the patient's consent, two 4 mm punch biopsies were taken before and after treatment of a psoriatic plaque located on the patient's back. Treatment with the excimer laser was given according to our previously published plaque-based sub-blistering dosimetry protocol, whereby plaques are directly tested for maximum tolerance. This maximal dose is defined as the minimal blistering dose (MBD). A dose ~20% below the MBD is then selected as the starting dose. Target plaques on the trunk and legs were tested with a range of doses from 700-2100 mj/cm2, in increments of 200 mj (Figure1A). Based on his MBD testing results, the trunk, arms and gluteal region were treated with 700 mj/cm2, and the legs were treated at 1500 mj/cm2.

After only two laser sessions, the patient's PASI score decreased by 50%, from 14.7 to 6.3. Clinically, the plaques on the upper extremities and trunk had less induration and scale**.** The lesions remained red as expected, since the laser itself can induce erythema and also hyperpigmentation that subsides over time (Figure1B). By week 6, the patient's PASI score had improved by more than 80% (14.7 to 2.7). This robust response was maintained through the end of the 12-week study when his PASI score was 3.4. The patient received a total of 12 treatments during the duration of the study.

In order to further investigate the mechanism of response to sub-blistering dose excimer laser therapy, the pre and post treatment biopsy specimens were analyzed for functional differentiation of lymphocytes using immune-flow cytometry (Figure2). In panel A, an example of a complete responder to ustekinumab from unpublished data is illustrated to show the typical Th1 (IFN-gamma) and Th17 (IL-17) cytokine signature found in psoriatic lesions responsive to this treatment. At baseline, our patient only had 15% of T cells that secreted IL-17 and/or IFN- γ (Figure2B) compared to 46% observed in the complete ustekinumab responder

(Figure2A). After treatment with the excimer laser, an absolute three-fold reduction was observed in the percentage of live T cells in his treated skin (Figure2B).

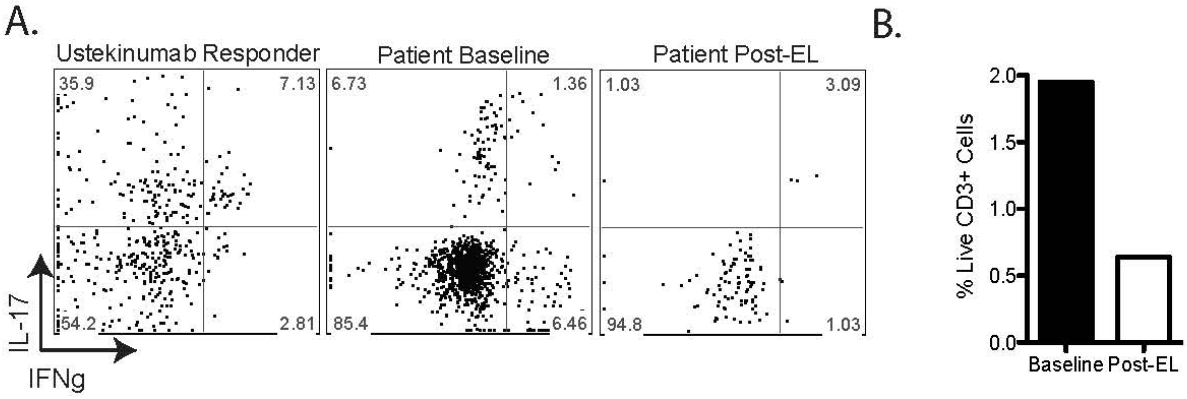

Figure 2. A) All plots are from lesional skin & gated on live CD3+ cells. Results from the pre-treatment biopsy compared to an example of a complete responder to treatment with ustekinumab. B) Chart illustrating the absolute reduction of the total percentage of live CD3+ cells before (baseline/black) and after treatment with excimer laser (post-EL/white)

Discussion

This 63-year-old man with severe generalized psoriasis failed to respond to a 28 week course of ustekinumab yet had a robust response to high dose excimer laser in combination with topical therapy, reaching PASI 75 after just 6 weeks of treatment. The cutaneous immune profile of this patient marked by relatively low levels of IFN-gamma (Th1) and IL-17 (Th17) secreting T cells may account for his poor response to ustekinumab, an IL-12 and IL-23 targeted agent that blocks the downstream effects of Th1 and Th17 cells. His superior response to excimer laser as reflected by his three-fold reduction in absolute live T cells after treatment could be explained by the broad and direct effect of UV light on T cell apoptosis and DNA damage to antigen presenting cells [2].

Key cytokines in the pathogenesis of psoriasis are TNF-α, IL-23, IL-17 and IL-22. By targeting these cytokines, biologic therapy has greatly advanced the treatment of psoriasis. Yet, some patients do not respond to certain biologic agents. Although primary failure with ustekinumab is uncommon compared to other biologics, it has been estimated to occur in 19% of cases within a published meta-analysis [3]. Because every biologic agent targets a specific cytokine, the dominant pathogenic cytokine in each individual's lesional skin may be an important determinant of therapeutic outcome. In contrast, phototherapy results in broad cutaneous immunosuppression that could be advantageous as monotherapy or adjunctive therapy in patients unresponsive to biologics.

Moreover, treatment with the excimer laser offers the advantage of sparing non-involved skin while aggressively delivering higher doses of light to diseased skin when compared to whole-body UVB therapy [15]. The greatest barrier to the treatment of phototherapy is convenience. With high dose excimer laser therapy, patients receive greater results in less time [14, 16, 17]. Our patient's superior and rapid clinical response to high dose excimer laser coupled with the flow cytometry data from his lesional biopsy illustrate phototherapy can be more effective and convenient when given using sub-blistering plaque-based dosimetry.

Conclusion

Even with the advent of more highly targeted therapeutic agents such as biologics, phototherapy modalities remain a safe and effective treatment option that may produce superior results in certain patient subsets. Immune flow-cytometry of lesional skin in this case provided a possible reason for our patient's poor response to therapy with ustekinumab and remarkable clinical response with high dose excimer laser. Identifying biomarkers to predict clinical response and determine optimal treatment choices for patients would be both time saving and cost effective. Future studies are needed to better predict the clinical response of patients as the treatment armamentarium for psoriasis expands.

References

1. Malakouti M, Brown GE, Wang E, Koo J, Levin EC. The role of IL-17 in psoriasis. The Journal of dermatological treatment. 2014.

2. Tartar D, Bhutani T, Huynh M, Berger T, Koo J. Update on the immunological mechanism of action behind phototherapy. Journal of drugs in dermatology : JDD. 2014;13(5):564-8.
3. Puig L. Induction phase, primary endpoint, time to decide on primary failure, and therapeutic goals in biologic treatment of psoriasis. Journal of the European Academy of Dermatology and Venereology : JEADV. 2013;27(2):e257-60.
4. Levin AA, Gottlieb AB, Au SC. A comparison of psoriasis drug failure rates and reasons for discontinuation in biologics vs conventional systemic therapies. Journal of drugs in dermatology : JDD. 2014;13(7):848-53.
5. Leman J, Burden AD. Sequential use of biologics in the treatment of moderate-to-severe plaque psoriasis. The British journal of dermatology. 2012;167 Suppl 3:12-20.
6. Levin EC, Gupta R, Brown G, Malakouti M, Koo J. Biologic fatigue in psoriasis. The Journal of dermatological treatment. 2013.
7. Kaur J, Sharma VK, Sethuraman G, Tejasvi T. Comparison of the efficacy of psoralen ultraviolet A with narrowband ultraviolet B phototherapy for the treatment of chronic plaque psoriasis in patients with skin types IV and V. Clin Exp Dermatol. 2008;33(4):513-5.
8. Chong HT, Kopecki Z, Cowin AJ. Lifting the silver flakes: the pathogenesis and management of chronic plaque psoriasis. BioMed research international. 2013;2013:168321.
9. Prieto-Perez R, Cabaleiro T, Dauden E, Ochoa D, Roman M, Abad-Santos F. Genetics of psoriasis and pharmacogenetics of biological drugs. Autoimmune diseases. 2013;2013:613086.
10. Al-Hoqail IA. Personalized medicine in psoriasis: concept and applications. Current vascular pharmacology. 2010;8(3):432-6.
11. Richard EG, Hoenigsmann H. Phototherapy, psoriasis, and the age of biologics. Photodermatology Photoimmunology & Photomedicine. 2014;30(1):3-7.
12. Kimball AB, Papp KA, Wasfi Y, Chan D, Bissonnette R, Sofen H, et al. Long-term efficacy of ustekinumab in patients with moderate-to-severe psoriasis treated for up to 5 years in the PHOENIX 1 study. Journal of the European Academy of Dermatology and Venereology : JEADV. 2013;27(12):1535-45.
13. Papp KA, Langley RG, Lebwohl M, Krueger GG, Szapary P, Yeilding N, et al. Efficacy and safety of ustekinumab, a human interleukin-12/23 monoclonal antibody, in patients with psoriasis: 52-week results from a randomised, double-blind, placebo-controlled trial (PHOENIX 2). Lancet. 2008;371(9625):1675-84.
14. Levin E, Debbaneh M, Malakouti M, Brown G, Wang E, Gupta R, et al. Supraerythemogenic excimer laser in combination with clobetasol spray and calcitriol ointment for the treatment of generalized plaque psoriasis: Interim results of an open label pilot study. The Journal of dermatological treatment. 2014.
15. Mudigonda T, Feldman S, Dabade T. 308-nm excimer laser versus nontargeted phototherapy for localized psoriasis: A review. Journal of the American Academy of Dermatology. 2012;66(4):AB181-AB.
16. Kagen M, Yan C, Shah G, McCormick TS, Cooper KD. Turbo UVB treatment of psoriatic plaques with excimer laser: single dose efficacy associated with both epidermal and dermal T cell apoptosis. Journal of Investigative Dermatology. 2005;124(4):A46-A.
17. Debbaneh MG, Levin E, Sanchez Rodriguez R, Leon A, Koo J, Rosenblum MD. Plaque-based sub-blistering dosimetry: Reaching PASI-75 after two treatments with 308-nm excimer laser in a generalized psoriasis patient. The Journal of dermatological treatment. 2014.

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