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Rapid and Sustained Improvement in a Patient With Plaque Psoriasis Switched to Brodalumab After Failing Treatment Clearance on Six Other Biologic Therapies

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ABSTRACT

Psoriasis is a chronic, inflammatory, remitting/relapsing autoimmune condition involving a dysregulated inflammatory response of the interleukin (IL) 23/T-helper (Th)-17 pathway. Greater understanding of the immune-mediated pathology of the disease has led to the development of numerous biological therapies and biosimilars that target the various inflammatory pathways. Each biologic has a unique mechanism of action, pharmacodynamics, and pharmacokinetics resulting in different clinical efficacy and tolerability. This case describes a 64-year-old female with a nine-year history of plaque psoriasis, predominantly affecting her feet, who was successfully treated with brodalumab having previously failed multiple topical and systemic therapies including six other biologicals.

To date, there are few guidelines to help physicians select the optimal biology agent and none that have looked specifically at plantar psoriasis. For this patient, finding a biologic that worked and was tolerable was a process of trial and error that took four years. The results achieved in this previously refractory patient with difficult-to-treat psoriasis may be due to the unique mechanism of action of brodalumab, though this will need to be confirmed in larger studies.

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INTRODUCTION

Psoriasis is a T-cell meditated disease involving a dysregulated IL-23/Th-17 inflammatory response. With greater understanding of the pathogenesis of the disease, biologic agents that target specific cytokines have been developed. To date, 10 monoclonal antibody drugs and 6 biosimilars that target 3 main pathways: tumor necrosis factor α, IL-23, and IL-17 have been approved for the treatment of plaque psoriasis.[1] While most of these biologics demonstrate similar efficacy in clinical trials, patient response in real-world settings is unpredictable and highly variable.[2]

Psoriasis involving the hands and feet affects only about 30% of patients with plaque psoriasis but is a uniquely problematic form of the disease.[3] Although the total body surface area (BSA) may be small, the impact of hand or foot psoriasis on a patients' quality of life can be significant. The location of the lesions often prevents patients from participating in activities of daily living. Patients with hand and foot involvement are affected to a greater degree by physical aspects of the disease, such as pain, discomfort, cracking, and bleeding of the skin.[4] Furthermore, as this case demonstrates, hand and foot psoriasis is difficult to treat and often refractory to multiple therapies. The toll that hand and foot involvement can take on a patient physically, psychosocially, and even economically requires that the bar for treatment success be raised when treating this specific subpopulation.

CASE

A 64-year-old Caucasian female was first seen in our office in October 2014 for evaluation of bilateral plantar psoriasis. Other than psoriasis for the past five years, she had no past medical or surgical history, no known allergies, and was a former smoker. Prior psoriasis treatments included calcipotriene cream, fluticinonide cream, calcipotriene and betamethasone dipropionate (Taclonex®, Leo Pharma) topical suspension 0.005%/ 0.064%, Tazarotene (Tazorac®) cream, clobetasol propionate cream and lotion, methotrexate 20 mg once a week for a total life time dose of 1120 mg, adalimumab (Humira®, Abbvie) 40 mg subcutaneous every other week, and flurandrenolide tape.

At her initial consult, inspection of both feet revealed erythematous plaques with thick adherent silvery scale (Figure 1).

FIGURE 1. Plantar plaque psoriasis initial consult.

Inspection of skin outside of affected area showed no abnormalities. The patient was being treated with subcutaneous ustekinumab (Stelara®, Janssen) injections every 12 weeks and advised to perform twice weekly bleach water soaks to decrease

infection risk. Over time, the duration of efficacy of ustekinumab waned and the patient began to experience flare ups in her feet between injections and the development of new psoriasis plaques on her hands and elbows, despite doubling the dose, and decreasing the injection interval to 10 weeks. In July 2015, apremilast (Otezla®, Celgene) 30 mg twice daily was added to her treatment regimen. At 3-month follow-up, although there was improvement in her feet and right palm, she had developed new erythematous plaque with thick adherent silvery scale on her right and left elbows and right and left legs. Despite ongoing treatment with ustekinumab and apreminlast, she continued to have intermittent flares and was advised to apply calcipotriene and betamethasone dipropionate (Enstilar®, Leo Pharma) foam, 0.005%/0.064% twice daily when flared.

In March 2016, she developed culture proven methicillin-resistant staphylococcus aureus (MRSA) on both feet which was treated with doxycycline.

In May 2016, she was switched from ustekinumab to secukinumab (Cosentyx®, Novartis) 300 mg subcutaneous injections weekly for 5 weeks and then every 4 weeks and advised to use UVB at least twice weekly. Apremilast was discontinued as patient did not feel it was helping. At this time, she was also diagnosed with psoriasiform dermatitis on the right lower leg and was complaining of flaring, tingling in her feet and pain when walking.

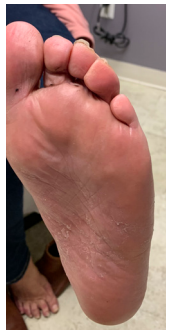
In June 2016, she developed another persistent MRSA infection in her feet, which was treated with multiple 30-day courses of doxycycline. In July, she was switched from secukinumab to ixekizumab (Taltz®, Lilly) due to constant flaring and increased foot itch and pain. She returned for follow-up after three ixekizumab injections, complaining of worsening symptoms and foot pain. Inspection of left lower leg, right lower leg, right plantar foot, and left plantar foot showed deep, seated vesicles with overlying erythematic, fissures, scaling, and honey crusting.

In June 2017, apremilast was added to ixekizumab due to continued worsening symptoms and the patient was advised to use betamethasone cream and flurandrenolide tape daily. At two-month follow-up, the patient stated that she had seen minimal improvement since adding apremilast and that she did not like ixekizumab injections because they caused "stabbing pain, redness, and a baseball-size knot at the injection site."

Both biologics were discontinued, and she was started on guselkumab (Tremfya®, Janssen). At 1 and 3-month follow-up of the first injection, the patient stated that her symptoms were no better and that her feet hurt continuously, and that she would flare five days before injections became due.

In February 2018, she presented in our office with severe foot pain and a recurrence of culture proven MRSA, which was treated with bleach baths and doxycycline and we initiated the process to switch her from guselkumab to brodalumab (Siliq®, Ortho Dermatologics). Brodalumab injections were started in March 2018 and she was seen for follow-up in August at which time her plantar psoriasis showed significant improvement. The patient indicated that her psoriasis was the best it had been in years, despite increased emotional stress due to the sudden death of her husband. On examination both feet showed improving, erythematous plaque with thick adherent silvery scale with decreased cracking of the plantar foot. Inspection of skin outside of affected area revealed no abnormalities (Figure 2).

FIGURE 2. After treatment with brodalumab



At the time of writing, the patient has been on brodalumab 210 mg subcutaneous injections every other week for 15 months and her condition continues to improve. We will follow her every three months.

DISCUSSION

Difficult-to-treat areas of plaque psoriasis, such as the palms and feet, may not respond well to traditional treatment algorithms and may be associated with disproportionately high physical and psychosocial burdens.[5-7] Additionally, the management of patients with recalcitrant disease is a challenge for even the most experienced dermatologists. While the availability of biologic medications for psoriasis has reduced the challenge considerably, as this case shows, they have not eliminated it.

And although emerging evidence from head-to-head randomized clinical trials provides pertinent information regarding the safety and efficacy of biologic agents in the treatment of moderate-to-severe psoriasis, and clues as to which agents may work best for patients with certain disease related factors and comorbid conditions, this case underscores the importance of providing personalized therapy for each patient based on individual clinical outcomes and tolerance of specific treatments.

To date, there are few guidelines to help physicians select the optimal biology agent for their patient and none that have looked specifically at plantar psoriasis. For this patient, finding a biologic that proved to have both efficacy and safety was a process of trial and error that took four years. Prior to starting treatment with brodalumab, the patient had previously tried and failed treatment clearance with adalimumab, apremilast, gusel-

kumab, ixekizumab, secukinumab, and ustekinumab.

Additionally, she had experienced severe injection site reactions to ixelizumab. This is consistent with the adverse events reported in the plaque psoriasis pivotal clinical trials through week 12. According to the ixekizumab prescribing information,[8] injection site reactions occurred in 17% of patients and were the most frequently reported adverse event. The worsening symptoms our patient experienced while on ixekizumab could have been due to immunogenicity. Data from clinical studies showed that 22% of subjects, treated at the recommended dosing regimen developed antibodies to ixekizumab during a 60-week treatment period, which was associated with reduced clinical response and 10% of these were classified as neutralizing antibodies which was associated with loss of efficacy.[8]

Could immunogenicity have been the problem with other agents and could immunotolerance to brodalumab be the reason why is she responding to one biologic when so many others failed? We may never know with absolute certainty, but in the meantime, we speculate that it could also be due to differences in the mechanism of action of these agents.

In psoriatic skin, immune triggers activate a signaling cascade. At the beginning of the cascade, dendritic cells create the inflammatory cytokines IL-12and IL-23. IL-12 activates Th1 cells, while IL-23 activates Th17 cells. Th1 has long been linked with immunological conditions, but the Th17 pathway has only recently been identified as one of the key culprits in psoriasis; since it's a source of IL-17 cytokines, including IL-17A. Further downstream, on the surface of the keratinocyte, these cytokines bind to, and activate, signaling through the IL-17 receptor. IL-17 receptor activation results in the release of pro-inflammatory factors and additional IL-17 cytokines driving further inflammatory processes in the skin.

Several of the biologics approved for plaque psoriasis inhibit upstream cytokines such as TNF-α, IL-12, and IL-23, which can reduce production of IL-17 cytokines. Other biologics inhibit IL-17 downstream, by essentially gathering up cytokines and slowing the process before they bind with the receptor, whereas brodalumab is the only biologic that blocks the signaling of the IL-17 Receptor A (IL-17RA), thus inhibiting further downstream pro-inflammatory effects. Doing so affects several IL-17 cytokines including IL17A, IL-17F, IL-17C, IL-17A/F, and IL-25, interfering with transmission of the pro-inflammatory signs that lead to psoriasis.

Studies have shown that IL-17F contributes to skin manifestations and comorbidities of psoriasis in a tissue-specific fashion and is increased in both psoriatic lesional skin and the sera of psoriatic patients.[9-11] IL-17C has been linked to skin inflammation and is also over-expressed in lesional skin of psoriatic patients.[12-13] In murine models, IL-17C injections leads to epidermal thickening and psoriasiform dermatitis.

Given that brodalumab is the only licensed agent that can block IL-17 C and F, this may also account for the clinical improvements seen in this patient.

The results observed in this single patient need to be confirmed in larger Phase 4 studies of recalcitrant patients.

DISCLOSURES

Kathleen Haycraft has participated in Advisory Boards for Pfizer, Lilly, Celgene, Abbvie, Valeant, Sanofi Aventis/ Regeneron, Maui Dermatology Conferences, and Johnson and Johnson; additionally, she has received Consultancy Payments from Bausch Health.

Dr. Cooke has no relevant disclosures or conflicts of interest.

REFERENCES

1. von Csiky-Sessoms S, Lebwohl M. What's New in Psoriasis. *Dermatol Clin.* 2019;37(2):129-136.
2. Amin M, No DJ, Egeberg A et al. Choosing First-Line Biologic Treatment for Moderate-to-Severe Psoriasis: What Does the Evidence Say? *Am J Clin Dermatol.* 2018;19:1-13.
3. Fretzin S, Crowley J, Jones L, Young, M, Sobell, J. Successful treatment of hand and foot psoriasis with efalizumab therapy. J *Drugs Dermatol.* 2006;5(9):838-846.
4. Pettey AA, Balkrishnan R, Rapp SR, Fleischer AB, Feldman SR. Patients with palmoplantar psoriasis have more physical disability and discomfort than patients with other forms of psoriasis: Implications for clinical practice. *J Am Acad Dermatol.* 2003;49(2):271-275.
5. Menter A, Griffiths CE. Current and future management of psoriasis. Lancet. 2007;370(9583):272.
6. Pettey A.A, Balkrishnan R, Rapp SR, Fleischer AB, Feldman SR. Patients with palmoplantar psoriasis have more physical disability and discomfort than patients with other forms of psoriasis: Implications for clinical practice. *J Am Acad Dermatol.* 2003;49(2):271-275.
7. Rapp SR, Exum ML, Reboussin DM, Feldman SR, Fleischer A, Clark A. The physical, psychological and social impact of psoriasis. *Journal of Health Psychology.* 1997;2(4):525-537.
8. Ixekizumab injection Prescribing Information. Eli Lilly and Company, Indianapolis, IN. April 2018.
9. Johansen C, Usher PA, Kjellerup RB, Lundsgaard D, Iversen L et al. Characterization of the interleukin-17 isoforms and receptors in lesional psoriatic skin. *Br J Dermatol.* 2009;160(2):319-324.
10. Soderstrom C, Berstein G, Zhang W, Valdez H, Fitz L, et al. Ultra-sensitive measurement of IL-17A and IL-17F in psoriasis patient serum and skin. *AAPS* J. 2017;19(4):1218-22.
11. Park YA, Kim YH, Sol IS, Yoon SH, Hong JY et al. Relationship between serum interleukin-17F level and severity of atopic dermatitis in children. *Pediatr Allergy Immunol Pulmonol.* 2015;28(2):112-6.
12. Johansen C, Vinter H, Soegaard-Madsen L, Olsen LR, Steiniche T, et al. Preferential inhibition of the mRNA expression of p38 mitogen-activated protein kinase regulated cytokines in psoriatic skin by anti-TNFalpha therapy. *Br J Dermatol.* 2010;163(6):1194-1204.
13. Johnston A, Fritz Y, Dawes SM, Diaconu D, Al-Attar PM, et al. Keratinocyte overexpression of IL-17C promotes psoriasiform skin inflammation. *J Immunol.* 2013;190(5):2252–62.

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