Treatment of Palmoplantar Pustulosis with the Combination of Ustekinumab and Apremilast: A Case Report

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Case Report

A 58-year-old female patient presented with a rash on her feet and ankles that had been present for over one year. She had developed pustular lesions on the plantar surfaces and some on her palms. For treatment, she was using a combination of betamethasone valerate and calcipotriol without improvement. Her past medical history was significant for hypertension and hyperthyroidism. Her social history was positive for smoking.

For three months the patient received 50 mg twice-weekly injections of etanercept. However, the patient did not notice significant improvement and continued getting pustules on her feet. She wanted to try a different biologic, so she was switched to Adalimumab.

The patient was administered Adalimumab 40 mg SC every two weeks for six months after a loading dose of 80 mg. Initially, she experienced 50% improvement, but eventually stopped responding and started worsening. Consequently, she switched to ustekinumab 45 mg q12 weeks, which was gradually titrated up to 90 mg q8 weeks. For two years she remained on ustekinumab 90 mg q8 weeks, again with initial improvement and eventual worsening. She was still not satisfied and wanted another treatment option.

She then tried secukinumab 300 mg SC weekly for one month; however this immediately worsened her plantar involvement. Subsequently, given the severity of her flare, she restarted ustekinumab at a dose of 90 mg q8 weeks with the simultaneous addition of apremilast 30 mg PO BID. She initially experienced some loose stools, consistent with apremilast treatment [6], however they subsequently resolved. Within two months of returning to ustekinumab and adding apremilast, her PPP was almost completely clear. The patient has remained on this combination for six months with excellent results and treatment has been well tolerated.

Of all the previous therapies tried within the past five years, the combination of ustekinumab 90 mg every 8 weeks and apremilast 30 mg PO BID has provided the greatest clinical improvement, even though ustekinumab at 90mg q8 weeks was insufficient as monotherapy.

Discussion

Treatment of PPP is notoriously difficult, as it tends to be resistant to therapy and frequently relapses. Clinicians have used essentially all therapeutic modalities for psoriasis and other autoimmune diseases to treat PPP [3]. The standard treatments include topical corticosteroids and topical retinoids, systemic retinoids, phototherapy, cyclosporine and colchicines [7]. A systematic review on PPP found that only topical corticosteroids under occlusion, acitretin, psoralen plus ultraviolet A and the combination of both (Re-PUVA) were of proven benefit [4].

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However, therapeutic recommendations on treating PPP are heavily reliant on case reports and personal experience [3]. This is especially true when assessing the efficacy of biological therapies. For instance, in a small trial of five patients with severe refractory PPP, ustekinumab was an effective and safe therapeutic option in PPP, with complete or almost complete resolution of lesions [1]. Such results were not observed in our patient. Another clinical

Introduction

Palmoplanter pustulosis (PPP) is characterized by sterile pustules on the palms and soles along with hyperkeratosis, scaling and fissuring [1]. PPP can present by itself, or along with plaque psoriasis where it is considered Palmoplanter pustular psoriasis (PPP) [1,2]. Genetic studies indicate that PPP may not be related to psoriasis, possibly accounting for their different responses to certain treatments, namely TNF-α antagonists [3]. Gene expression microarray analysis has shown that PPP and PPPP are not distinct clinical entities and differ from psoriasis based on increased expression of GPRIN1 and ADAM23 at the gene and protein level [2]. PPP is more common in middle-aged women, diabetics and smokers [1]. PPP may also be associated with thyroid dysfunction [4] and is part of the clinical SAPHO syndrome, where it may occur with one or more of the following: synovitis, acne, pustulosis, hyperostosis, osteitis.

Abbreviations

PPP: Palmoplantar Pustulosis; PPPP: Palmoplantar Pustular Psoriasis; PUVA: Psoralen Plus Ultraviolet A; Re-PUVA: Retinoid plus Psoralen Plus Ultraviolet A PUVA; PPPASI-50: 50% improvement in palmoplantar pustular area and severity index; PDE4: Phosphodiesterase 4; SAPHO: Synovitis, Acne, Pustulosis, Hyperostosis, Osteitis.

Ustekinumab and Apremilast: A Case Report

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trial of 33 patients with PPP and PPPP did not support clinical efficacy of PPP treatment with Ustekinumab. Patients treated with ustekinumab 45 mg did not show a statistically significant difference in achieving a 50% improvement in their palmoplantar pustular area and severity index (PPPASI-50) compared to patients treated with placebo [8].

Because ustekinumab and apremilast were started together simultaneously in our patient, there is the possibility that apremilast alone is treating her PPP, as our patient experienced insufficient response to ustekinumab as monotherapy. Although no studies have investigated retreatment with ustekinumab after loss of efficacy in psoriasis, other studies have shown that the risk of loss of response is higher in treatment-experienced patients when retreating inflammatory diseases with biologic therapy [9]. Consequently, apremilast monotherapy could be investigated in order to potentially remove unnecessary treatment with ustekinumab.

A noteworthy point in this case was the patient’s initial lack of response to etanercept and secondary loss of response to adalimumab. This is consistent with other reports that have shown that TNF-α antagonists have limited value for PPP therapy [3]. Although infliximab has been reported to be effective in treating palmoplantar psoriasis, it has not proven to be the case with PPP [10]. Nonetheless, etanercept has been shown to be effective in reducing the severity of PPP in certain patients [11].

Another molecular similarity between PPP and PPPP patients includes increased expression of IL-17A in the skin of palms/soles, compared to normal subjects [8]. The possibility of targeting IL-17A for the treatment of PPP and PPP has been proposed. However, our patient worsened soon after initiation of anti-IL 17A therapy with secukinumab.

With respect to the role of apremilast in treating PPP, a literature search did not reveal any accounts of apremilast as a treatment modality for PPP, although it has been reported to be effective for palmoplantar psoriasis [12]. The improvement noted after the addition of apremilast in our patient may be due to the fact that phosphodiesterase 4 (PDE4) inhibition is less targeted than abiotic and may provide a wider range of immunomodulation. On the other hand, ustekinumab is a human monoclonal antibody that binds to the human interleukins 12 and 23, which prevents interaction with their cell surface IL12Rβ1 receptor [13]. As such, both apremilast and ustekinumab inhibit inflammatory pathways that are critical in the pathogenesis of psoriasis, but in different ways.

Although the simultaneous use of apremilast and ustekinumab may raise concerns over significant inhibition of the immune system, apremilast monotherapy has not shown signs of clinical immunosuppression [14]. Thus, the addition of apremilast to ustekinumab is not likely to increase the immunosuppression by ustekinumab. Nonetheless, such combination therapy should only be considered after failure of monotherapy and with careful consideration of the risk to benefit ratio. Furthermore, retrospective observational data has indicated that apremilast in combination with biologic agents has shown improved treatment efficacy with no additional safety concerns [15].

Another concern regarding the combination of ustekinumab and apremilast treatment for PPP is the cost associated with this treatment regimen. Once treatment success is achieved, one could taper therapy to find the most cost-effective dose required to maintain effect. It is important to recognize that cost may be a significant barrier for this combination treatment and therefore, may only be considered in the most severe and refractory patients with this debilitating condition.

Overall, it is clear that some of the only evidence on the treatment of PPP is derived from case reports and small clinical trials. By presenting this case report we hope to shine a light on another potentially useful treatment for severe refractory PPP. Although there is a lack of evidence on the efficacy of biological treatment for PPP in general, and particularly for ustekinumab in combination with a PDE4 inhibitor, we hope to make practitioners aware of this potentially life changing treatment. However, more studies are necessary to determine the safety and efficacy of combination apremilast and ustekinumab, or the potential for apremilast monotherapy for the treatment of PPP.

References
