SKIN

BRIEF ARTICLE

The Power of Two: Effective Management of Severe Refractory Psoriasis Through Combined TYK2 and IL-23 Inhibition

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ABSTRACT

This case report highlights the clinical course of a 76-year-old male with severe, treatment-refractory psoriasis that was unresponsive to many topical and systemic therapies over many years. Prior treatments included topical corticosteroids, oral prednisone, and systemic immunosuppressants such as methotrexate, cyclosporine, and mycophenolate, all of which provided minimal or transient benefit. Biologic therapies including dupilumab, ixekizumab, and apremilast similarly did not achieve sustained disease control. Narrowband UVB phototherapy offered some temporary resolution, however symptoms promptly returned upon cessation.

The patient eventually achieved significant clinical improvement with a novel combination therapy of risankizumab, an IL-23 inhibitor, and deucravacitinib, a selective TYK2 inhibitor. Initiation of risankizumab monotherapy resulted in partial improvement, reducing body surface area (BSA) involvement from 65% to 20%. Given the incomplete response and history of refractory disease, deucravacitinib was then added, leading to further improvement and BSA involvement decreasing to 4% over this time period. The combination was well tolerated, with no adverse effects reported.

This case underscores the complexity of managing psoriasis in patients with recalcitrant disease. It also suggests the potential efficacy and safety of combining targeted biologic and oral therapies in patients who fail to respond adequately to monotherapy. The success of this dual approach may reflect complementary mechanisms of action and highlights the need for individualized, flexible treatment strategies in difficult-to-treat psoriasis cases. Further studies are warranted to evaluate the long-term efficacy and safety of this combination in broader patient populations.

INTRODUCTION

Refractory psoriasis, poses a significant challenge in dermatological practice. This case of a 76-year-old male patient demonstrates the complexity of managing refractory psoriasis with a history of partial responses to various treatments, including high-potency topical steroids, oral systemic immunosuppressants, biologics, and combination therapies. Despite multiple attempts with treatments such as cyclosporine, methotrexate, and various biologics like dupilumab, ixekizumab, and risankizumab, the patient's psoriasis remained poorly controlled until the combination of risankizumab (an IL-23

inhibitor) and deucravacitinib (a TYK2 inhibitor) was introduced.

Both risankizumab, a monoclonal antibody against IL-23, and deucravacitinib, an oral TYK2 inhibitor have been shown to significantly improve psoriasis symptoms, particularly in those who have failed prior treatment.[1-4] Combining IL-23 and TYK2 inhibition can potentially provide a more comprehensive suppression of the inflammatory pathways driving psoriasis. IL-23 inhibition directly blocks the activation of Th17 cells, while TYK2 inhibition interferes with the downstream signaling of IL-23 and other cytokines and leads to the overall suppression of inflammatory response.[5]

This case report describes a patient whose severe psoriasis was refractory to IL-4/13, IL-17, and IL-23 monotherapy, as well as combination therapy with apremilast now responding well to IL-23 inhibitor and TYK2 inhibitor combination therapy.

CASE REPORT

A 76-year-old male with history of eczema first presented to our academic dermatology department at age 69 for evaluation of dermatitis (**Figure 1**). A shave biopsy showed “a confluent parakeratosis overlying epidermis with psoriasiform hyperplasia and mild spongiosis. Within the reticular dermis there was a superficial and perivascular lymphohistiocytic infiltrate with rare dermal eosinophils and focal eosinophilic exocytosis.”

This shave biopsy led to a working diagnosis of psoriasis and triamcinolone, desonide, and clobetasol were initiated. His dermatitis continued to spread and be poorly controlled despite treatment with high potency topical steroids, oral prednisone, topical moisturizers and hydroxyzine.

At that time, the differential diagnosis expanded to include pityriasis rubra pilaris (PRP) and spongiotic drug eruption. Possible medication culprits of a drug induced eruption were discontinued (including metoprolol) which improved the rash, only for it to return several months later. A trial of mycophenolate was initiated but was discontinued due to only offering minimal improvement. Narrowband UVB (nbUVB) treatment was initiated shortly after the trial of mycophenolate and offered significant improvement. Following discontinuation of nbUVB the patient’s rash remained controlled for around 12 months before returning. Cyclosporine was initiated following the return of the rash and offered minimal improvement even after multiple dose increases. Methotrexate was trialed next, along with topical tacrolimus, both of which offered minimal improvement.

As a result of the patient’s rash being refractory to treatment, the differential diagnosis expanded to include eczematous dermatitis leading to dupilumab therapy initiation. At the time of starting dupilumab the rash had expanded to cover 65% of the patient’s body surface area. Following 16 weeks of dupilumab without significant improvement, ixekizumab was initiated for treatment of psoriasiform dermatitis. Ixekizumab led to mild, but not significant improvement, and eventually apremilast was added to the treatment regimen. The combination of ixekizumab and apremilast was discontinued due to minimal improvement in the rash, and risankizumab was then initiated. Risankizumab led to improvement in affected area of the rash as well as a decrease in itch, with the affected body surface area decreased to 20%.

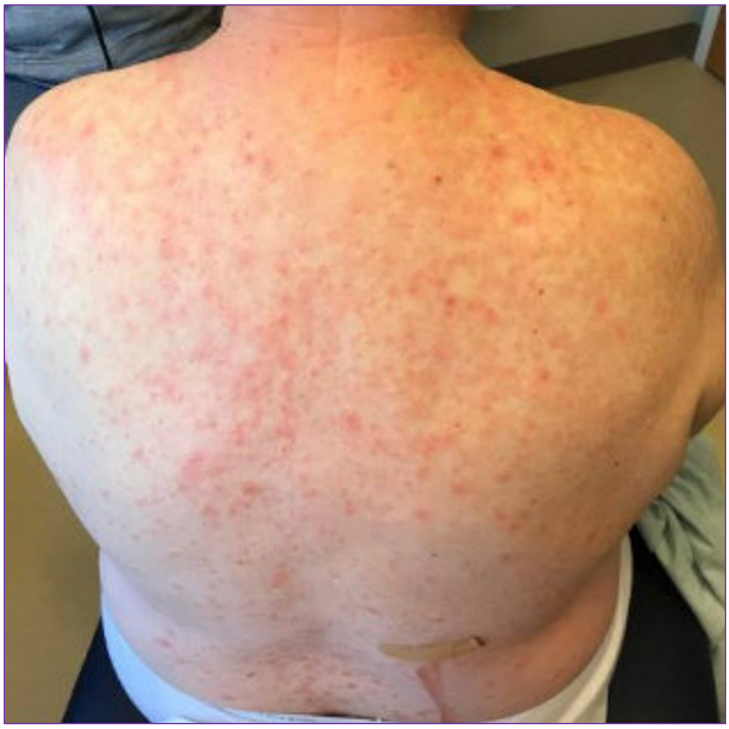

Figure 1. Clinical photo from 11/19/18

Due to this partial, but not complete skin clearance on risankizumab monotherapy, and the previous treatment failures of apremilast and methotrexate, deucravacitinib was added to offer additional improvement. Following five months of risankizumab and deucravacitinib combination treatment, the patient experienced a decrease in affected BSA to 14%. Both risankizumab and deucravacitinib were well tolerated with no reported adverse effects while the patient has been on the combination.

At follow up 10 months after initiating Risankizumab and deucravacitinib combination therapy our patient's condition continued to improve. Both medications have been tolerated without any adverse effects, and no difficulties with administration of either medication. Now 16 months after the initiation of combination risankizumab and deucravacitinib, the psoriasis continues to clear with only 4% BSA remaining involved (**Figure 2**), improved from 65% BSA when starting the regimen.

DISCUSSION

This case report highlights utilization of combination IL-23 and TYK-2 inhibition as a reasonable potential treatment for refractory psoriasis unresponsive to high potency topical corticosteroids, oral systemic immunosuppressants, biologic monotherapy, and biologic combination therapy with apremilast. Currently there is a lack of available safety and efficacy data surrounding the long-term use of combination IL-23 and TYK2 inhibition. Our report hopes to expand upon this.

The combination of a TYK2 inhibitor and IL-23 blocking biologic provided significant relief for the patient where previous treatments did not. A portion of his results may be due to an ability to dually block several steps in the inflammatory cascade involved with psoriasis

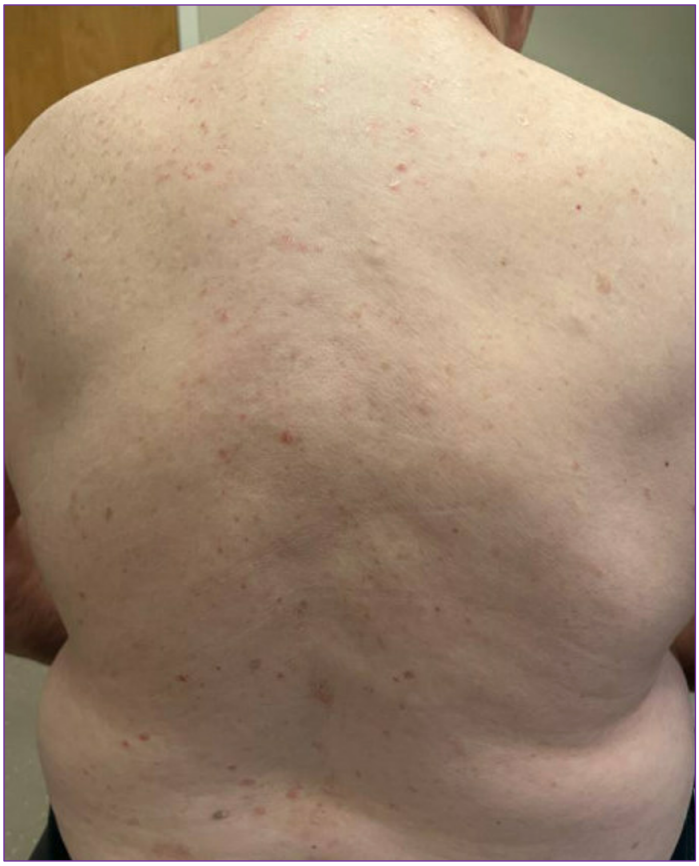

Figure 2. Clinical photo from 4/1/25

along with blocking IL-23 at multiple steps, both the receptor and downstream signaling level. New data are also emerging on the genetic role of psoriasis with variations in the HLA-Cw6 allele associated with a faster and higher clinical response to ustekinumab another biologic blocking interleukin-12/interleukin-23.[6] Although this patient was not able to be tested for variations in genetic alleles this may also have contributed to his significant response.[6] Additionally this patient did not report any side effects to medication including but not limited to infection, back/joint pain or fatigue and serves as a testament to the tolerability of the regimen.

This case provides continued support that combination therapy in psoriasis is a safe and effective option for particularly non-responsive patients. While classically there are increased concerns of infection for patients on dual therapy this has not been the case in this report. Likewise, the patient has experienced durability of the regimen with no relapses or adverse effects at his current follow up over one year after starting treatment.

CONCLUSION

The combination of psoriasis therapies, in this case risankizumab and deucravacitinib, may offer a safe and effective option for those patients who have exhausted all previous options and are still not adequately controlled.

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