Comparative Safety and Efficacy Assessment of Single and Concurrent Topical Therapeutics in an IMQ-Induced Murine Model of Psoriasis

V. Naageshwaran, T. Jackson, A. Alavi, I. Ruiz, S. Smith
Absorption Systems Inc, San Diego, California

Introduction
Psoriasis vulgaris is a human autoimmune disease that manifests as an inflammatory skin condition characterized by focal and coalescing cutaneous plaques with consistent scaling and variable erythema. Approximately 80% of patients affected with psoriasis have mild to moderate disease that can be treated with topical agents that are efficacious. However, the use of topical agents as monotherapy in the setting of extensive or recalcitrant disease is typically limited. Topical medications can sometimes be used concurrently to take advantage of varied mechanisms of action. In this study an IMQ induced mouse model that recapitulates the phenotype of the clinical disease was utilized to determine the efficacy and safety of single and combined therapies.

Materials and Methods

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Pre-Study Procedures:
One day prior to the start of IMQ pre-treatment, animals were anesthetized using an induction chamber and inhalation anesthetic. The back of the animals was clipped free of hair.

IMQ Pre-Treatment:
IMQ (5%) (Aldara; 3M Pharmaceuticals) was applied to the back and to the right ear daily (QD) on days 1 through 9 for all animals in Groups 1-4. Ear thickness in both the right and left ears was measured and recorded for all animals on days 3 and 5. Animals were then randomized into groups based on the thickness of the IMQ treated ear.

Test Article Treatment:
On Days 10 – 18, animals from Groups 1 – 4 had various test articles or saline applied topically singly or in combination to the back and right ear. Ear thickness in both the right and left ears and dorsal skin thickness were measured and recorded for all animals. Photographs were taken of each animal’s back on representative study days.

Terminal Procedures:
At the conclusion of the study, Study Day 19, all animals were anesthetized and euthanized. The animal’s dorsal skin and both ears were collected into 10% NBF for histopathology.

Results
IMQ treatment resulted in onset and development of phenotypic symptoms of psoriasis including inflammation and increased thickness of the dorsal skin and ears. Topical application of the different therapeutic agents singly and concurrently showed efficacy with the greatest differences observed in the animals treated with the corticosteroid clobetasol. The efficacy of calcineurin inhibitor tacrolimus, however, could not be demonstrated in this model, presumably due to a different mechanism of action. The use of concurrent therapies did appear to have the potential to enhance reduction of skin lesions and dermal inflammation.

Histopathology Results
Treatment of mice with IMQ results in hyperproliferation of keratinocytes and a disturbed epidermal differentiation.

Fig 1: Right ear thickness increases for all groups with IMQ treatment
Fig 2: Ear thickness of the right ear compared between naive (untreated) group with the IMQ/clobetasol group shows efficacy of the clobetasol treatment

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Conclusions
The IMQ-induced mouse psoriasis model presents hyperproliferation and differentiation of epidermal cells and the presence of inflammatory cells. While several models of psoriasis have been developed over the years, many do not resemble the clinical phenotype or are too complex and expensive to use as a screening tool. The study provides the framework to establish a preclinical model that can be used to show the safety and efficacy of singly and concurrently used topical medications that may have varied mechanisms of action.

Acknowledgements
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