Inhibition of MALT1 by mepazine acetate for the treatment of psoriasis induced by CARD14 mutations

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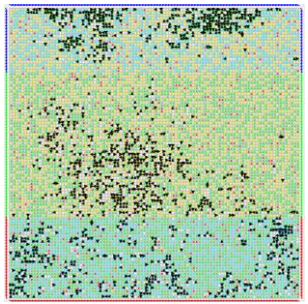
Introduction

Psoriasis is a chronic inflammatory skin disease characterized by scaly patches.[1] It is caused by genetic mutations in the caspase recruitment domain-contain protein 14 (CARD14), which amplifies the enzymatic activity of the mucosa-associated lymphoid tissue lymphoma translocation protein 1 (MALT1).[2] This CARD14-BCL10-MALT1 (CBM) complex causes NF-κB overactivation and excess chemokine production.[2] Keratinocytes are then overproduced, creating psoriatic plaques. The systemic allosteric inhibition of MALT1 by mepazine acetate may be more effective than topical therapies for severe psoriasis.[3] The objective of the study was to determine the therapeutic impact of MALT1 protease inhibitors on the proliferation of psoriatic plaques.

Methods

Psoriatic plaque development was modelled using the COBWEB simulation software. Three independently-acting agents represented keratinocytes and produced CBM complexes after activation by interferons and Th17 cytokines, rendering them "diseased".[4] Diseased agents pass on the disease by contact with other agents, resulting in psoriatic plaques on the upper epidermal layer. MALT1 inhibition by mepazine acetate was modelled using a fourth "healer" agent.



Dead keratinocytes in stratum corneum

Polygonal keratinocytes in stratum spinosum

Keratinocytes in stratum basale

Results

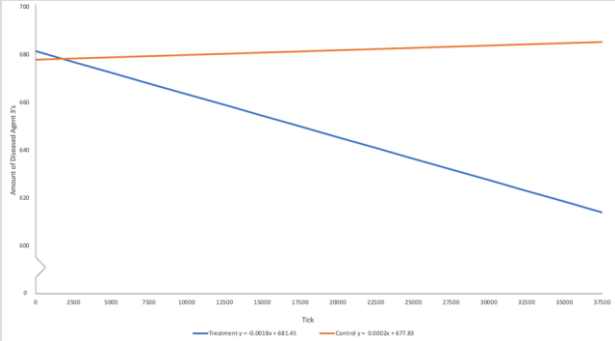


Figure 1. The average amount of CBM complex-producing dead keratinocytes on the epidermis over time between the treatment and control conditions.

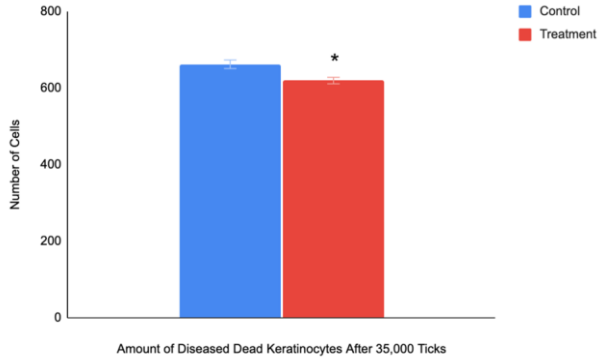


Figure 2. The mean amount of CBM complex-producing dead keratinocytes (± SE) in the stratum corneum after 35,000 ticks with and without treatment.

Discussion

The simulations with mepazine acetate treatment had a reduced accumulation of dead keratinocytes and decreased proliferation of psoriatic plaques in the upper epidermal layers, compared with control simulations after seven days.

Common treatments for psoriasis are corticosteroids, which are applied topically and as a result, have limited preventative effects. As well, topical treatments may not be feasible for patients with widely spread and severe psoriatic plaques. Due to the systemic drug delivery mechanism of transdermal patches, these may be used to more effectively treat psoriasis.

Conclusion

These results demonstrate that mepazine acetate decreases MALT1 activity, thus reducing proinflammatory responses. This model is an idealistic representation of psoriasis; variation between these results and clinical findings is likely. The next steps include building a more complex model with the ability to substantially vary responses to treatment.

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References

1. Alsholaili HA, Shahzad M, Al-Marshood A, Khalil A, Settin A, Barrimah I. Genetic background of psoriasis. *Int J Health Sci* (Qassim). 2010 Jan;4(1):23-9.
2. Van Nuffel E, Schmitt A, Afonina IS, Schulze-Osthoff K, Beyaert R, Haüfinger S. CARD14-Mediated Activation of Paracaspase MALT1 in Keratinocytes: Implications for Psoriasis. *J Invest Dermatol*. 2017;137(3):569-575. doi:10.1016/j.jid.2016.09.031.
3. Mc Guire C, Elton L, Wieghofer P, Staal J, Voet S, Demeyer A, Nagel D, Krappmann D, Pritz M, Beyaert R, van Loo G. Pharmacological inhibition of MALT1 protease activity protects mice in a mouse model of multiple sclerosis. *J Neuroinflammation*. 2014 Jul 21;11:124. doi:10.1186/1742-2094-11-124.
4. Juilland M, Thome M. Holding All the CARDs: How MALT1 Controls CARMA/CARD-Dependent Signaling. *Front Immunol*. 2018 Aug 30;9:1927. doi:10.3389/fimmu.2018.01927.