Development of a skin inflammation model with imiquimod in healthy volunteers

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INTRODUCTION

Imiquimod (IMQ) is a known TLR7/8 agonist that causes psoriasis like skin inflammation. Mouse models have been developed and are widely implemented. No fully characterized healthy volunteer model for dermatological drug development programs currently exists.

AIM

To develop and refine a temporary human skin inflammation model with IMQ for application in clinical drug development.

METHODS

- Randomized, vehicle-controlled, open-label, dose ranging study
- 16 healthy male subjects
- 1:1 randomization to receive tape stripping (TS) or not prior to the first dose administration
- IMQ (5 mg) QD for 72h under occlusion to the back by a 12 mm Finn Chamber
- Erythema by visual erythema grading, colorimetry and 2D photo analysis
- Perfusion by laser speckle contrast imaging (LSCI)
- Skin punch biopsies for histology and immunohistochemistry assessment

RESULTS

- IMQ application to tape stripped skin induced statistical significant ($p<0.05$), dose-dependent hyper perfused erythematous lesions
- Infiltrates consisted of CD4+ T-cells, CD8+ T-cells, CD11c+ dendritic cells and HLA-DR plasmacytoid cells
- mRNA expression of CXCL10, hBD-2, ICAM-1 and MXA was induced relative to ABL
- Maximum effect at 48h (Figure 1,2,3)
- Effects less pronounced without TS
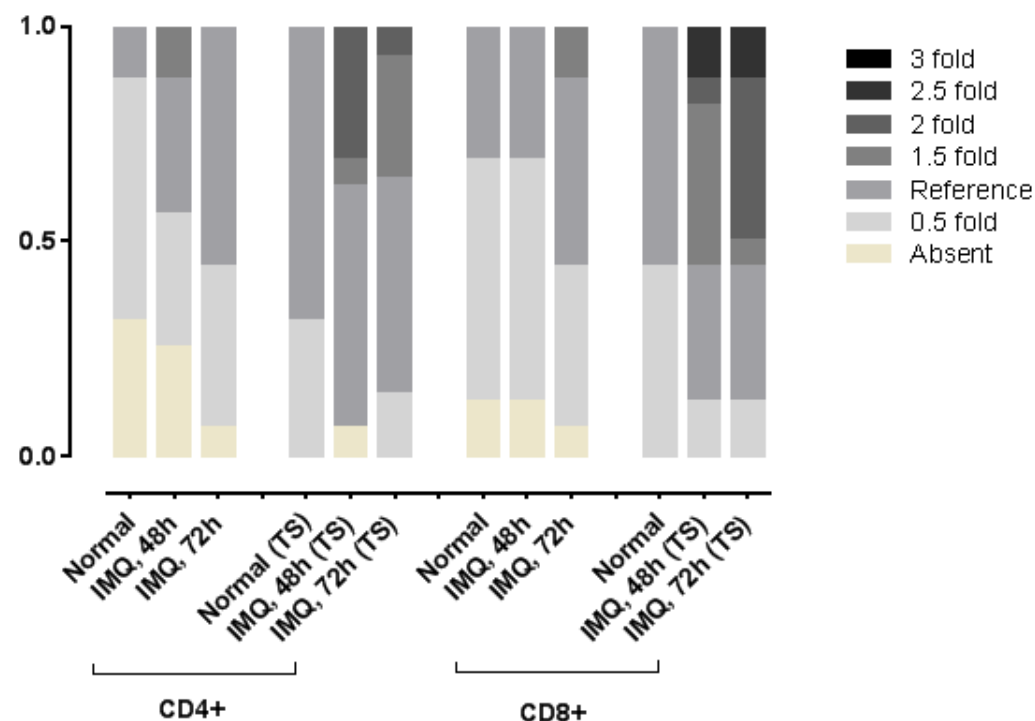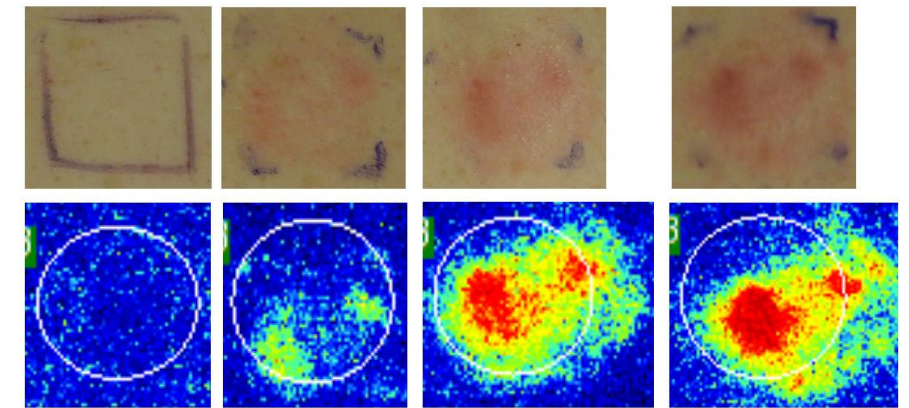- Effects were fully reversible

Figure 1. Effect of IMQ on erythema and perfusion on tape stripped skin after 24h, 48h and 72h.

Figure 2. Number of CD4+ and CD8+ cells compared to the reference biopsy in subjects treated with IMQ.
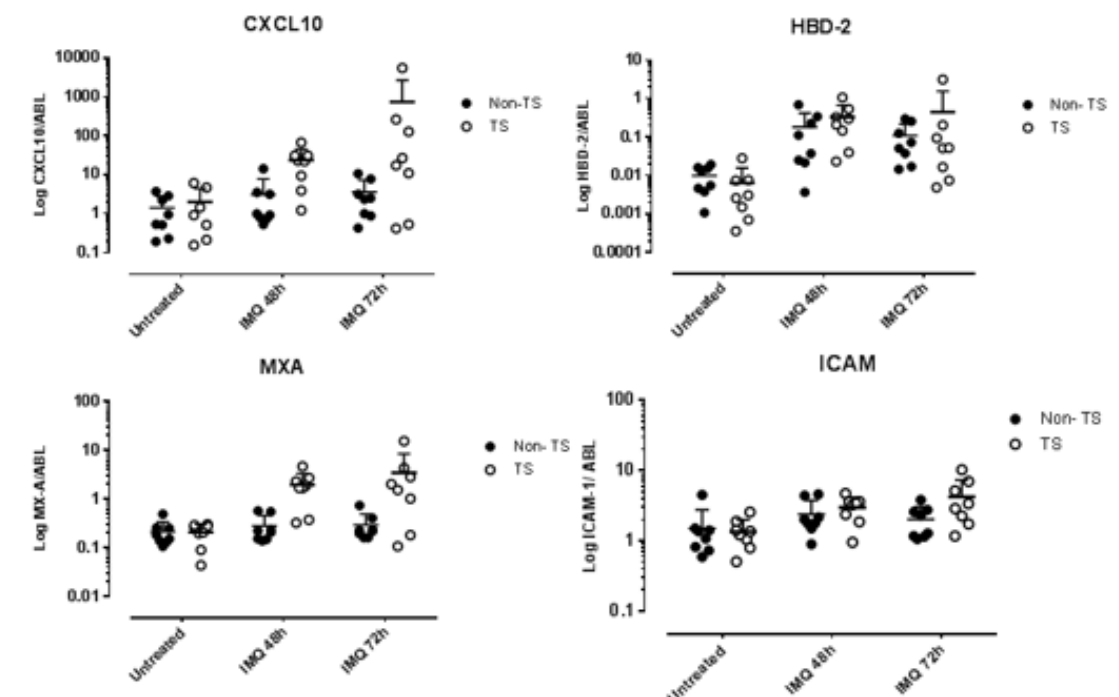

Figure 3. Effect of IMQ on mRNA expression of CXCL10, HBD-2, MXA and ICAM

CONCLUSIONS

This study validates the IMQ skin challenge model, with 48h of application and TS prior to the first dose administration. Future interaction studies will enable proof pharmacology of novel compounds targeting the innate immune system.