Characterization of the Psoriasis-like Inflammation in the Imiquimod Rat Model using Dermal Open Flow Microperfusion

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Purpose

Topically applied imiquimod has been shown to induce psoriasis-like skin inflammation in mice. The use of larger animals such as rats would enable the use of clinical research techniques such as dermal Open-Flow Microperfusion (dOFM). This minimally-invasive clinical method has proven to enable continuous sampling of different drugs and cytokines in inflamed and healthy skin in humans in vivo in PK-PD as well as topical bioequivalence trials [1–3]. We tested whether psoriasis-like inflammation can be induced by using imiquimod in a rat model and characterized any effects of imiquimod and a known immunosuppressant by using clinical skin scores and cytokine profiles from dOFM sampling of inflamed and healthy skin.

Methods

- Sprague-Dawley rats, n=24
- Day 1-8, topical treatment, n=24:
 - ➔ **IMQ-treated (IMQ⁺)**, right back: Once daily topical imiquimod (IMQ) cream to introduce psoriasis-like skin inflammation
 - ➔ **Untreated (IMQ⁻)**, left back: No topical treatment, i.e. non-lesional skin
- Day 1-8, oral treatment, 2 groups each n=12:
 - ➔ **Dex**: Once daily oral dexamethasone to inhibit inflammation (1 - 2 mg/kg)
 - ➔ **Vehicle**: Vehicle (placebo) or no oral treatment as control group
- Day 9, dermal interstitial fluid sampling by dOFM
 - ➔ 3 dOFM probes for sampling from IMQ⁺ skin
 - ➔ 3 dOFM probes for sampling from untreated skin
 - ➔ **Fig. 1** shows the dOFM protocol
 - ➔ **Fig. 2** shows the dOFM principle
 - ➔ Skin evaluation: erythema, skinfold thickness, scaling, histopathology scores (HPS) [5]
 - ➔ Dermal interstitial fluid (dOFM): Forty cytokines using rodent panels (MSD rodent panel, Ampersand rodent panel)

Results & Discussion

The daily topical IMQ dose induced visible skin inflammation in all rats within 4 days (**Fig. 3**) which is similar to mice [4]. After 8 days, the lesions were fully developed. Day 9 data demonstrated (**Fig. 4, Table 1**):

- that IMQ had induced psoriasis-like skin inflammation: Increased erythema, skinfold-thickness, histopathology scores, and significantly increased release of a number of cytokines in treated vs. untreated skin. IL-17A was only quantifiable in IMQ-treated skin. Still, IL17A and IL17F levels were very low on day 9, however, these low levels are in agreement with the reduced expression of IL-23, IL-17A, and IL-17F in the IMQ model in mice after 8 days [4] as IMQ only transiently induces cytokines of the IL-23/IL-17 axis in skin.
- **the efficacy of dexamethasone** to inhibit the inflammatory effect of topical IMQ.
- an effect of IMQ and dexamethasone on the **dermal immune cell population** – see poster # 488

Conclusions

- Topical imiquimod rapidly induces psoriasis-like skin inflammation in rats.
- Oral dexamethasone inhibits the inflammatory effect in rats.
- This imiquimod rat model can be used to screen novel psoriasis drugs.
- dOFM enabled cytokine and immune cell sampling from rat skin in-vivo. This study demonstrates that this clinical tool is also highly informative in preclinical research.

Figure 1: Daily treatment with imiquimod and sampling in the skin on day 9. Rats were IMQ-treated (IMQ⁺) for 8 days on their right back to induce skin inflammation. dOFM probes (3 in treated skin, 3 in untreated skin) deliver interstitial fluid for FACS-analysis.

Figure 2: dOFM sampling working principle. dOFM continuously delivers unfiltered dermal interstitial fluid for analysis of biomarkers, drugs, and immune cells.

Figure 3: Effect of topical IMQ treatment on erythema in rats receiving oral dexamethasone or vehicle. The effect of topical IMQ gets obvious after 4 days. Oral dexamethasone successfully inhibits the inflammatory effect of topical IMQ. Data for scaling and skinfold thickness are similar. Table 1 provides all parameters for day 9.

Figure 4: Epidermal thickness (left panel) and histopathology scores (HPS, right panel) from skin biopsies on day 9. The HPS score was adapted from Kim et. al. 2015. [5]

References

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Table 1: Effect of treatments on skin appearance on day 9

	IMQ effect (IMQ ⁺ vs. untreated skin)	Dex efficacy (Oral Dex vs. vehicle)
	N=12 rats	N=12 rats
Skinfold thickness	P<0.05	P<0.05
Erythema	P<0.05	P<0.05
Scaling	P<0.05	P<0.05
Epidermal thickness ¹	P<0.05	P<0.05
HPS ¹	P<0.05	P<0.05

¹ Epidermal thickness and Histopathology Score (HPS) available from 6 rats only.

Table 2: Effects of treatments on intradermal cytokines/markers on day 9

	IMQ effect (IMQ ⁺ vs. untreated skin)	Dex efficacy (Oral Dex vs. vehicle)
	N=12 rats	N=12 rats
IL-10	P<0.05	P<0.05
IL-12p70	P<0.05	P<0.05
IFNβ	P<0.05	P<0.05
IL-1α	ns	P<0.05
IL-6	ns	P<0.05
IL-17A	ns ²	p<0.10
IL-17F	ns	ns

ns: not statistically significant. ² IL-17A was not quantifiable in IMQ treated skin only. Further 25 cytokines were analysed in dOFM samples, some of which also showing significant changes following topical IMQ and/or oral dexamethasone treatment (data not shown).