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Evaluation 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].

OBJECTIVE

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 control site,** left back: No topical treatment, i.e. non-lesional skin
- Day 1-8, oral treatment, 2 groups each n=12:
  - **Group A: Oral placebo/vehicle** or no oral treatment as control
  - **Group B: Oral dexamethasone** once daily to inhibit inflammation (1-2 mg/kg)
- Day 9, dermal interstitial fluid sampling by dOFM
  - dOFM probes for sampling from IMQ+ skin
  - 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).

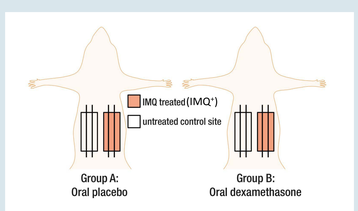

Fig. 1: Daily treatment with IMQ (IMQ+) for 8 days on right back of the rats to induce skin inflammation. On day 9 six dOFM probes (3 in treated skin, 3 in untreated skin) delivered interstitial fluid for analysis.

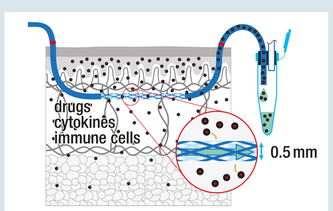

Fig. 2: dOFM sampling working principle. dOFM continuously delivers unfiltered dermal interstitial fluid for analysis of biomarkers, drugs, and immune cells.

RESULTS

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:

- that IMQ had induced psoriasis-like skin inflammation: Increased erythema, skinfold-thickness, histopathology scores (Figs. 3, 4 and Table 1)
- that IMQ had significantly increased release of a number of cytokines in treated vs. untreated skin (Table 2).
- 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 (data not shown)

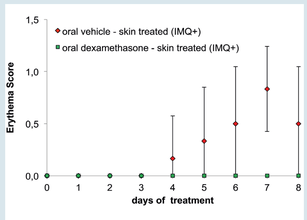

Fig. 3: Effect of topical IMQ treatment on erythema in rats receiving oral vehicle or dexamethasone. Data for scaling and skinfold thickness are similar. Oral dexamethasone successfully inhibits the inflammatory effect of IMQ.

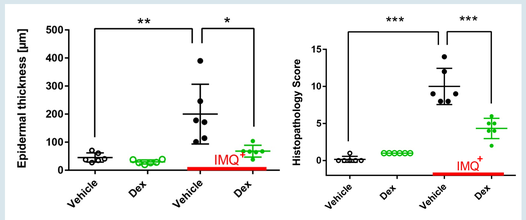

Fig. 4: Epidermal thickness (left panel) and histopathology scores (HPS, right panel) from skin biopsies on day 9. The HPS score was adapted from Kim et. al. 2015. [5]

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] IL17A was ns but 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).

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.**

REFERENCES

[1] C. Dragatin et al. “Secukinumab distributes into dermal interstitial fluid of psoriasis patients as demonstrated by open flow microperfusion.,” Exp. Dermatol., 2016.

[2] F. Kolbinger et al. “ß-defensin-2 is a responsive biomarker of IL-17A-driven skin pathology in psoriasis,” J Allergy Clin Immunol, 2016.

[3] M. Bodenlenz et al. “Open Flow Microperfusion as Dermal Pharmacokinetic Approach to Evaluate Topical Bioequivalence”, Clin. Pharmacokinet., 2016.

[4] L. van der Fits et al. “Imiquimod induced psoriasis-like skin inflammation in mice is mediated via the IL-23/IL-17 axis”, J Immunol., 2009.

[5] B.Y. Kim et al. “Histopathological findings are associated with the clinical types of psoriasis but not with the corresponding lesional psoriasis severity index.” Ann Dermatol. 2015.

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