Immune Modulation by Topical PH-10 Aqueous Hydrogel (Rose Bengal Disodium) in Psoriasis Lesions

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INTRODUCTION: PH-10 is a topical hydrogel formulation that yields selective delivery of Rose Bengal Disodium (RB) to epithelial tissues (Figure 1A). RB is a fluorescent derivative capable of producing singlet oxygen upon photo-activation, but its therapeutic mechanism in psoriasis vulgaris is not established.

METHODS: We thus conducted a mechanically-focused study of PH-10 in 30 patients with psoriasis vulgaris using sequential vehicle and active drug treatment for 4 weeks each (registered clinical trial NCT02232086). Skin biopsies were collected before treatment (baseline) and at the end of vehicle (day 29) and PH-10 treatment (day 64) (Figure 1C and Figure 2). Effects of vehicle vs PH-10 treatment were assessed on cellular immune infiltrates, driver cytokines of psoriasis and the overall disease transcriptome using immunohistochemistry and gene-expression profiling with Affymetrix U133A 2.0Plus arrays and RT-PCR (Figures 3-7).

RESULTS: Vehicle treatment for 4 weeks did not significantly alter expression of core IL-23/IL-17-modulated genes or the overall disease transcriptome (using a principle component analysis, PCA). However, 4 weeks of treatment with PH-10 significantly (FC >1.5, p < 0.05) downregulated IL-17A, IL-22, IL-26, IL-36, and keratin 16 mRNAs as assessed by RT-PCR, while a PCA analysis of gene array results showed a shift towards non-lesional skin with some post-treatment biopsies clustering within the non-lesional skin profile (Figure 4). Pathways that were significantly improved by PH-10 included published psoriasis transcriptomes and cellular responses mediated by IL-17, IL-22, and interferons. To strengthen analysis of immune and psoriasis-related gene modulation by PH-10, we divided patients into responders vs. non-responders based on the PCA analysis after 4 weeks of treatment (comparing to non-lesional skin at baseline) (Figure 5). Using this approach, more than 500 disease-related genes were down-regulated after 4 weeks of treatment with PH-10 and expression of a wide-range of central “psoriasis-related” genes including IL-23, IL-17, IL-22, S100A7, IL-19, IL-36, and CXCL1 were effectively normalized—treated lesional skin had values in the same range as baseline non-lesional skin (Figure 6). We also measured decreased expression of T-cell activation markers including ICOS and CTLA4, changes that were paralleled by decreases in myeloid (CD11c+) dendritic cells and T-cells using IHC measures (Figure 7).

CONCLUSIONS: The results of this study establish that PH-10 has highly significant ability to modulate psoriatic inflammation, having key cytokine drivers of this disease, but only a subset of patients revert the lesional phenotype to that of non-lesional skin. This type of “mixed” response outcome occurs with other topical or systemic drugs now approved for psoriasis, highlighting a need to personalize treatments and potentially to have predictive response biomarkers for individual drugs.

Figure 1. Confocal fluorescence micrographs of normal human skin: topical PH-10 (A) vs H&E staining (B). From Wachtter et al., Laser Surg Med 2003; 33, 101. Sequential biopsy locations (C) for assessment of effect of 28 consecutive days of vehicle (second biopsy, on study day 29) and PH-10 (third biopsy, on day 64) vc baseline (first biopsy) in a skin assay using normal skin collected concurrently with first biopsy at day -7 baseline.

Figure 2. Target plaque at baseline (A), after vehicle (B) and after PH-10 (C). Subject O311.

Figure 3. IHC staining of non-lesional (NL) and lesional (LS) psoriasis skin at baseline (BL), after vehicle (D29) and after PH-10 (D64). Subjects O203 (left) and O317 (right).

Figure 4. RT-PCR of KRT16 (A), all available patients. PLA of gene array results (B) for non-lesional (NL) skin and lesional (LS) psoriasis skin at baseline (BL), day 29 and day 64, DEG FC>2 and fdr<0.05, all available patients.

Figure 5. Microarray PCA data for all genes in the dataset was used to identify a cohort of “Molecular Responders”, patients with PC-1 values for D64/ID5 lower than the 90th percentile for PC-1 values for BL/ID5. For these Responders, gene expression in LS tissue after PH-10 treatment is similar to NL skin at baseline. Data shown for DEG FC>2 and fdr<0.05.

Figure 6. Neutrophil activity of least squares linear regression (LASSO) levels (RT-PCR) by molecular response cohort in non-lesional (NL) skin and lesional (LS) psoriasis skin at baseline (BL), day 29 (D29) and day 64 (D64).

Figure 7. ICOS expression by molecular response cohort in non-lesional (NL) skin and lesional (LS) psoriasis skin at baseline (BL), day 29 (D29) and day 64 (D64).