Small Molecule Inhibitor of the Wnt Pathway (SM04755) as a Potential Topical Treatment for Psoriasis

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Background:

Psoriasis (PSO) is an autoimmune disease causing patches of thick, inflamed, scaly skin due to excessive proliferation of skin cells[1]. Wnt signaling plays an important role in PSO, regulating inflammation and keratinocyte proliferation. SM04755, a novel, topical small-molecule Wnt pathway inhibitor was previously shown to inhibit inflammation and keratinocyte proliferation *in vitro* and in an IMQ-induced mouse PSO model[2]. In this study, the effects of SM04755 on inflammation and skin health were evaluated in a model using reconstitution of ICR *scid* mice with minor histocompatibility mismatched naïve $CD4^+$ T lymphocytes, which more closely resembles human PSO pathophysiology[3].

Methods:

Peripheral blood mononuclear cells were isolated from F_2 (BALB/c x 129/SvJ) mice and analyzed by flow cytometry to identify H-$2D^d$ haplotype donor mice. $CD4^+$/$CD45RB^{Hi}$ cells from donor mice spleens were purified and injected intravenously into CB17/ICR-Tac Prkdc/*scid* (ICR *scid*) mice ($5x10^5$ cells/mouse). Skin appearance and ear thickness were evaluated weekly. At the first signs of PSO (lesions and increased thickness), psoriatic mice were randomized and treated with SM04755 (400 $\mu g/cm^2$) or vehicle. After 14 weeks, body and spleen weights were measured, and inflammation was evaluated by measuring cytokines (IL-1β, TNF-α, IL-6, CXCL11, IL-17 and IL-23) in tissues from skin, ears, spleen and plasma using ELISA. Epidermal thickness and infiltrating cells in the skin were histologically evaluated.

Results:

Immune reconstitution of ICR *scid* mice resulted in PSO-like signs, with lesions and increased thickness of the skin and ears. Treatment with topical SM04755 (400 $\mu g/cm^2$) significantly ($p<0.01$) decreased skin and ear thicknesses and improved skin appearance Body weights were significantly ($p<0.05$) higher in treated compared to vehicle mice. SM04755 significantly reduced histologically measured epidermal thickness ($p<0.05$) and immune infiltration in the skin compared to vehicle. Further, inflammatory cytokine levels in the skin, ears, spleen and plasma and spleen weight were significantly ($p<0.05$) reduced in SM04755 treated animals compared with vehicle.

Conclusion:

In a mouse model of minor histocompatibility mismatched T lymphocyte reconstitution-induced PSO, topically applied SM04755 inhibited inflammation and decreased skin and

ear thicknesses compared to vehicle. SM04755 has potential as a topical therapy for PSO. Clinical trials are on-going.

References:

1. National PSO Foundation
2. Deshmukh et.al., Arthritis Rheumatol. 2016; 68 (suppl 10)
3. Schon et.al., Nature Medicine, Feb 1997