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

Authors
Vishal Deshmukh, Melinda Pedraza, Lisa Tran, Karen Duong-Polk, Abdullah Ghias, Luis Dellamary, Benoit Melchior, Yusuf Yazici
Samumed, LLC, San Diego, CA

Background:
Psoriasis (PSO) is an autoimmune disease causing patches of thick, inflamed, scaly skin due to excessive proliferation of skin cells. 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. 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.

Methods:
Peripheral blood mononuclear cells were isolated from F2 (BALB/c x 129/SvJ) mice and analyzed by flow cytometry to identify H-2Dd haplotype donor mice. CD4+/CD45RBhi 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 topical SM04755 (400 μg/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 μg/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