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A novel Fatty Acid Binding Protein 5 (FABP5) inhibitor shows efficacy in preclinical models of psoriasis

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Introduction & Objectives:

Fatty acid-binding protein (FABP) 5, also known as epidermal FABP, was first discovered in psoriatic lesions (Madsen et al., 1992). FABP5 regulates keratinocyte homeostasis, and is upregulated in psoriasis tissue (Takahashi-Shishido et al., 2021). Knock-out of FABP5 is beneficial in preclinical psoriasis models (Dallaglio et al., 2013). Our aim was to assess whether Artelo's novel oral FABP5 inhibitor ART26.12 is efficacious in psoriasis.

Materials & Methods:

In vitro, recombinant human epidermis was stressed with a cytokine mix (IL17, IL22, and TNFalpha) co-administered with vehicle, a JAK1 inhibitor I (CAS-No 457081-03-7; 10 μM), or ART26.12 (1, 3, or 10 μM) for 48 hrs. Change in the mRNA levels of 64 relevant genes were compared against two housekeeping genes. *In vivo*, male Balb/C mice were given either vehicle, BMS-986165 (Deucravacitinib, tyrosine kinase 2 inhibitor) (10 mg/kg p.o. QD), or ART26.12 (25 or 100 mg/kg p.o. BID) for two days prior to application of imiquimod (IMQ, 62.5 mg of a 5% cream for 7 days on their back), and throughout IMQ treatment.

Results:

In vitro, the cytokine mix upregulated genes related to innate immunity (eg DEFB4A, S100A7) and cytokine markers (especially IL8), as well as reducing differentiation markers (KRT10 and LOR)(Fig1A). The JAK1 inhibitor I largely reversed this effect. ART26.12 reduced genes related to the JAK/STAT pathway (PIAS3 and SOCS3; $p<0.001$), keratinocyte proliferation (KRT14, TP63; $p<0.001$), and chemokines and cytokines (CXCl10, TNF, IL1R1; $p<0.001$). The highest concentration of ART26.12 also upregulated genes related to anti-microbial peptides and innate immunity (eg CAMP, DEFB4A, TLR2, RNA SE7, SLP1, PI3; $p<0.01$). *In vivo*, the psoriasis area severity index (PASI) scores in the IMQ-vehicle group were near maximum by day 7 (Fig1B and C). Oral treatment with BMS-986165 attenuated PASI scores on day 6 and 7. Oral treatment with ART26.12 (25 mg/kg) reduced PASI scores on day 6 ($p<0.05$) and 7 ($p<0.001$). The higher dose of ART26.12 (100 mg/kg) reduced scores on day 7 ($p<0.05$). All drugs worked by attenuating skin scaling and thickness, with no effect on erythema. ART26.12 also reduced histopathological signs of damage (reduced hyperkeratosis, parakeratosis, inflammatory infiltrates, and epidermal acanthosis).

Conclusion:

In* models of skin inflammation, The FABP5 inhibitor ART26.12 had a positive effect on *in vitro* gene profiling and attenuated the effects of IMQ *in vivo*. These data suggest that ART26.12 shows promise as a novel oral treatment for psoriasis, and possibly other dermatological conditions where FABP5 is also known to be elevated.