BET inhibitor OTX015 reduces imiquimod-induced mouse psoriasis dermatitis

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Bromodomain and extra-terminal (BET) proteins perform a key role in epigenetic control of gene expression that is involved in malignant and inflammatory diseases. Recently, therapeutic targeting of BET bromodomains has been proposed to have utility in TH17-mediated pathology, including autoimmune diseases such as psoriasis. Herein, we used a BET inhibitor, OTX015, in a mouse model of imiquimod (IMQ)-induced psoriasis dermatitis (PD): to determine immunological changes and therapeutic efficacy in this IL-17-dependent preclinical model of psoriasis. Mice were topically treated with IMQ over 6 days and either orally administered OTX015 at 25 mg/kg/day or control, starting from day 1 of IMQ treatment. After 6 days of treatment, OTX015-treated mouse skin showed decreased skin disease severity, scale, ear thickness, and periwound epithelial thickness when compared to vehicle-treated mice. Flow cytometric analysis of OTX015-treated ear skin revealed a ~50% decrease of neutrophil (CD11b+Ly6G+) infiltration. In addition, cervical lymph nodes in OTX015-treated mice contained significantly fewer CD45+ γδ T cells (i.e., major producers of IL-17A in murine PD models). Spermine was observed in IMQ-treated mice, and systemic OTX015 treatment almost completely normalized spermine size and weight. Of note, mice did not show significant activity change or weight loss vs. control-treated mice after 6 days of OTX015 treatment. In summary, our results suggest that OTX015 can be safely administered in mice and may provide significant anti-inflammatory benefit that derives clinical and immunological signs of PD in IMQ-treated mice. Further investigation of BET proteins as treatment for psoriasis in humans is thus warranted.

Selectively targeting JAK1 or JAK3 pathway is sufficient to reverse alopoeica areata

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Disregulation of the Janus kinase/signal transducers and activators of transcription (JAK-STAT) pathway has pathological implications in autoimmune diseases. We found that therapeutic targeting of JAK-STAT pathways using first-generation JAK1/2 inhibitor (ruxolitinib) or pan-JAK inhibitor (tolakitinib) were effective in the treatment of human AA and in the C3H/HeJ mouse model. To further understand the role of individual JAK in AA and to produce the desired anti-inflammatory effects without unnecessary inhibition of other JAK pathways, we used JAK-selective inhibitors (JAK1-selective inhibitor filgotinib, JAK2-selective inhibitor CEPI3779 and JAK3-selective inhibitor PF06611600 to treat C3H/HeJ mice with AA. We demonstrate that JAK1-selective inhibitors as well as JAK3-selective inhibitors are effective in reversal of alopecia in C3H/HeJ mice with AA. In contrast, JAK2-selective inhibitor failed to restore hair growth. JAK1-selective inhibition and JAK2-selective inhibition was associated with decreased skin inflammation, cell infiltration, reduced pathogenic cell responses and analysis of RNAseq data of whole skin biopsies taken from the JAK1 inhibitors-treated mice revealed statistically independent (orthogonal at FDR<0.05) molecular responses reflecting the variable efficacy of each JAK1 inhibitor type. JAK1 and JAK3 inhibitors (but not JAK2 inhibitors or controls) exhibited normalized gene expression patterns similar to unaffected C3H/HeJ mice, indicating JAK1 and JAK3 inhibition suppressed the dermal inflammatory/ cytotoxic T cell signature for AA reversal. Our results contribute to a more refined understanding of JAK1 or JAK3 as therapeutic targets and suggest that inhibition of JAK2 is not required for treatment efficacy in AA.

Real-world effectiveness of dupilumab based on Investigator Global Assessment (IGA) and peak Pruritus Numerical Rating Scale (PNRS) scores

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Psoriasis is a multifactorial skin disease involving abnormal cell proliferation and inflammation; an efficacious topical treatment is yet to be identified. A topical formulation containing 1% naltrexone HCI in xematop base was compounded, characterized and evaluated in vitro as a possible treatment for psoriasis. A three-dimensional porous tissue model was exposed to the formulation for 2 or 5 days and analyzed for the level of markers of cellular proliferation, and inflammatory cytokine IL-6. Using immunohistochemical staining, the level of Ki67 protein significantly decreased in the drug-treated tissues. Western blot analysis showed 86% and 53% down-regulation of other proliferation markers PCNA and CYCLIN D1, respectively, after 5-day exposure. The pro-survival Wnt/beta-catenin pathway was compromised as indicated by 57% decrease in the level of betacatenin and down-regulation of its downstream targets CYCLIN D1 (decreased by 53%), c-MYC (63%), c-Jun (92%) and MET (96%) proteins. Likewise, the PKL4/ALK1/SMAD7 pathway was significantly inhibited by 1% naltrexone HCI in xematop, suggesting protein synthesis was affected. The production of IL-6 was inhibited by 70% in drug-treated tissues. These results suggest that the compounded drug is efficacious in down-regulating molecular markers associated with the pathogenesis of psoriasis. Low-dose naltrexone in xematop was stable within 180 days when stored under refrigerated or ambient conditions. These results provide a basis for a clinical evaluation of 1% naltrexone HCI in xematop in psoriasis patients.