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Effect of etrasimod on circulating lymphocyte subsets in atopic dermatitis patients

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Background: Etrasimod, a selective sphingosine 1-phosphate receptor 1,4,5 modulator that reduces peripheral lymphocytes and subsequent infiltration inflammation sites, is in development for chronic immune-mediated diseases. In the Phase 2 ADVISE trial(NCT04162769), etrasimod demonstrated efficacy in key secondary outcomes in patients with atopic dermatitis(AD). Previous data support differential effects of etrasimod on immune cell subsets in healthy volunteers; however, the impact is unknown in patients with AD. This immunophenotyping biomarker analysis of ADVISE was designed to further evaluate the effect of etrasimod on circulating immune subsets. Methods: 140 subjects were treated once-daily with etrasimod 1 mg, 2 mg, or matching placebo for 12 weeks, followed by a 4-week washout(Week 16). In a subset (n=104), immune cells were assayed by flow cytometry from isolated peripheral blood mononuclear cells, and by EpiontisID, an epigenetic immunophenotyping method, from whole blood collected pre-dose on Day 0, Week 4, Week 12, and Week 16. Significant immune cell subset modulations were evaluated in etrasimod-treated groups versus placebo at Weeks 4 and 12. Results: Significant dose-dependent reductions were seen with total CD4 and CD8 T cells, including naïve, central memory, and Th2 subsets, and B cells($P < 0.05$, etrasimod vs placebo at Weeks 4 and 12). Notably, there were also trends of reductions of skin-homing T cell subsets, including CLA^+CD4^+ central memory T cells. Monocytes, conventional dendritic cells(DC), and natural killer cells were increased($P<0.05$ at Weeks 4 and 12). Affected subsets recovered at Week 16. No meaningful treatment effects were observed on effector memory T cells(Tem), Th1, Th17, natural killer T, and plasmacytoid DCs. Conclusions: Etrasimod treatment lowered select lymphocyte subsets, including Th2 and skin-infiltrating T cell subsets. In contrast, cells involved with maintaining immune surveillance, such as Tem cells, were relatively preserved. These data suggest that etrasimod may act as a selective immunomodulator that warrants further investigation.

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A novel expression based, non-invasive method to differentiate atopic dermatitis and psoriasis

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Psoriasis and atopic dermatitis (AD) are two of the most prevalent chronic inflammatory skin diseases in the world. Currently, diagnosis of psoriasis and AD is conferred based on the combination of a visual exam and a review of medical history. In some instances, the overlapping clinical characteristics and disease manifestations make it difficult to distinguish between psoriasis and AD, so a skin biopsy is collected for pathological analysis. While effective, skin biopsies are invasive and have the potential for complications in dermatological diseases already characterized by abnormalities in the skin barrier. Here, we describe a non-invasive method to differentiate AD and psoriasis by comparing the expression of key genes involved in disease pathogenesis in AD and psoriasis. Epidermal skin samples were non-invasively collected from the skin of the patients with moderate to severe AD (n=20) or moderate to severe psoriasis (n=20) using the DermTech Smart Sticker™. RNA was isolated and analyzed by quantitative real-time PCR for the expression of IL-13, IL-23, IL-17A, S100A8, S100A9, CXCL9, CXCL10, CCL17, CCL18, CCL27, TLSP, and NOS2. Upregulation of IL-13, CCL17, IL-17A, and NOS2 exhibited the greatest differences between psoriasis and AD. When combined, Receiver Operating Characteristic (ROC) Curve analysis of the data set generated an AUC of 0.94 that can be used to differentiate the two disease conditions. Overall, this study demonstrates the potential utility of non-invasive skin sampling to differentiate AD and psoriasis patients based on a molecular signature from a set of four genes. The ability to distinguish the two disease conditions provides a valuable asset in the hands of physicians for clinical decision-making and can be utilized for the personalized treatment of AD and psoriasis patients.

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Bermekimab, anti-IL-1α antibody, inhibits skin injury induced response in healthy subjects

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Interleukin-1 alpha (IL-1α) is constitutively expressed in epithelial cells located at barrier sites, such as skin, lung and gut. Upon cellular death, injury or infection, IL-1α is released. Serum levels of IL-1α are largely undetectable in healthy volunteers (HV), or atopic dermatitis (AD) and hidradenitis suppurativa (HS) patients, while levels in the skin, especially in the epidermis and exudates from HS tunnels, are highly concentrated. Bermekimab (BMK) is a first-in-class fully human anti-IL-1α monoclonal antibody that has been tested in Ph2A AD & HS studies. To support understanding of PK/PD relationships, we developed a human skin explant model to assess proteomic & transcriptomic effects of IL-1α blockade on injury-induced inflammation. After 24-hours culture, IL-1α was detected in the media. *Ex vivo* IL-1α blockade resulted in significant decreases of CXCL1, IL-8, GCSF & IL-6 levels compared to untreated 24-hours samples ($p<0.05$ for all analytes), and consistent reduction of 73 genes (N=10 donors). Next, we utilized this model to measure post-treatment skin PD effects in HV receiving a single dose of BMK in a Ph1 study (NCT04544813). BMK exhibited linear PK following a single IV (400-1200 mg) or SC (200-800 mg) administration. Consistent with *ex vivo* blockade, CXCL1, IL-8, GCSF & IL-6 were reduced in culture media from post-dose versus pre-dose skin explants with significantly higher % reduction of IL-8 & IL-6 observed in the 800mg compared to the 200mg SC cohorts ($p<0.05$ for both analytes). Down-regulation of the same 73 genes in skin explants were also observed. These data support the relevance of IL-1α as a key skin alarmin driving tissue injury inflammation, and BMK reduces the downstream skin injury responses. Clinical research evaluating BMK in inflammatory skin diseases is ongoing.

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Cutaneous transcriptomics identifies fibroproliferative and neurovascular gene dysregulation in prurigo nodularis compared to psoriasis and atopic dermatitis

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Prurigo nodularis (PN) is a chronic inflammatory skin disease that is associated with several systemic comorbidities, suggesting dysregulation of cutaneous and systemic inflammatory processes. Th2, 17, and 22 immune signatures have been identified in PN lesions, highlighting shared cutaneous gene signatures between PN, psoriasis (PsO), and atopic dermatitis (AD). We aimed to identify pathways specific to PN by comparing the skin transcriptomes of PN, PsO, and AD. RNA-seq was performed on lesional and nonlesional biopsies from PN patients without a history of atopy or PsO. Lesional and nonlesional PsO and AD transcriptomes were obtained from the Gene Expression Omnibus. Lesional samples were compared to their respective nonlesional sample. Differentially expressed genes (DEGs) were calculated using *DESeq2* for R. Gene ontology (GO) enrichment analysis was performed using *GOseq* for R, and specific fibroproliferative and neural pathways were explored using Gene Set Variation Analysis (GSVA). We analyzed 26 PN, 26 PsO, and 26 AD samples. PN and PsO shared 3,775 DEGs, PN and AD shared 1,551 DEGs, PsO and AD shared 1,565 DEGs, and all three diseases shared 1,082 DEGs. Top GO categories for PN included epithelium development and cell adhesion, top categories for PsO included cytokine-mediated and Fc receptor signaling and top categories of AD included response to interferon gamma and myeloid differentiation. GSVA revealed upregulation of transforming growth factor beta-induced epithelial to mesenchyme transition (logFC [fold change] 0.44, $P=0.001$), epidermal acanthosis (logFC 0.61, $P<0.001$), axon regeneration (logFC 0.46, $P=0.011$), and vascular endothelial growth factor activity (logFC 0.23, $P=0.014$) in PN, but not PsO or AD lesions. In conclusion, PN is characterized by distinct fibroproliferative, neuropathic, and angiopathic signatures.

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Peripheral neuropathic changes in prurigo nodularis

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Prurigo nodularis (PN) is a chronic inflammatory skin disease characterized by intensely pruritic and hyperkeratotic nodules of unknown etiology. PN is strongly associated with peripheral neuropathies, suggesting a role for neural dysregulation in its pathogenesis. Here we study components of the cutaneous peripheral neural system, including intraepidermal nerve fiber density (IENFD), mechanoreceptors, and blood vessels in lesional and nonlesional skin of 10 patients with PN and 10 matched healthy controls. The mean age of PN patients was 57.0±16.7 years and 60% were female, with identical distributions for matched controls. No patients had an associated peripheral neuropathy. PN patients had a mean Worst Itch Numeric Rating of 8.8±1.6. Paired t-tests were used to compare lesional and nonlesional samples, while ANOVA was used to compare lesional and control samples. Tissue was processed to analyze IENFD (PGP9.5), Merkel cells (cytokeratin 20), blood vessels (CD31), and mast cell density (tryptase) by immunohistochemistry. Lesional PN skin had significantly lower IENFD compared to nonlesional ($P<0.05$) and control ($P<0.001$) skin. Nonlesional skin also had lower IENFD compared to healthy skin ($P<0.01$). Lesional skin had higher Merkel cell density ($P<0.05$), blood vessel density (13.6±0.6 vs 4.7±0.8 blood vessels/mm, $P<0.001$), and mast cell counts in the epidermis compared to nonlesional skin. Blood vessels in the upper dermis of lesional skin had an elongated pattern that paralleled the deeper dermal papillae. These findings highlight the role of neural dysregulation in the pathogenesis of PN by showing alterations in peripheral nerve structures in PN skin. These findings broaden the perception of PN from a dermatological condition to a multisystem disorder with neuropathic changes as a prominent feature. Therapeutics for PN should involve neuromodulation to address underlying cutaneous neural dysregulation.

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Racial differences in dysregulation of the renin-angiotensin-aldosterone system in patients with prurigo nodularis

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There is an unclear association between chronic kidney disease and prurigo nodularis (PN). We hypothesized that global dysregulation of the renin-angiotensin-aldosterone system (RAAS) may contribute to both the development of PN skin lesions, renal disease, and help explain observed racial disparities in PN. We thus conducted a cross-sectional analysis of renal comorbidities in PN patients using TriNetX, a global health research network providing access to medical records from approximately 69 million patients. PN patients were matched to control patients by age and sex using 1:1 propensity score matching. Epidemiological findings from this analysis provided the basis for immunoassays on blood plasma and RNA sequencing of skin biopsy samples from PN patients and healthy controls. Lesional and nonlesional skin biopsies were taken from PN patients, and from site matched locations in healthy controls. PN was associated with stages 1-5 of chronic kidney disease (CKD), end-stage renal disease, nephritic syndrome, nephrotic syndrome, glomerular disease, and tubulointerstitial disease, and the associations were significantly stronger in black patients ($P<.05$). Compared to controls, CKD progression was faster (HR 2.88, 95% CI: 1.01 − 8.26) only in black PN patients (10-year survival: 63.5% black vs. 85.5% white). Circulating plasma angiotensinogen levels were also dysregulated ($P<0.001$) only in black PN patients. Cutaneous transcriptomic analysis of genes related to RAAS also revealed dysregulation in PN lesions with greater dysregulation in black patients. Significant dysregulation of the cutaneous and systemic RAAS in black PN patients may explain the increased incidence and severity of renal disease.