Oral Difelikefalin Improves Itch and Inflammatory Biomarkers in Atopic Dermatitis Subjects With Moderate-to-Severe Pruritus

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Background: Pruritus is the most frequent and burdensome atopic dermatitis (AD) symptom and can exacerbate disease via the itch-scratch cycle. Difelikefalin (DFK), a kappa-opioid receptor (KOR) agonist, was recently approved to treat moderate-to-severe pruritus in adults with chronic kidney disease undergoing hemodialysis. DFK blocks pruritus signaling through peripheral sensory neurons. KOR agonism may also have anti-inflammatory activity. We tested the impact of DFK on pruritus-related and inflammatory transcriptomes of subjects with AD.

Methods: In a phase 2 clinical study, subjects with AD and moderate-to-severe pruritus were randomized (1:1:1:1) to receive oral twice-daily DFK (3 different doses) or placebo for 12 weeks. A substudy of 40 subjects characterized the effect of DFK on pruritus- and AD-related gene expression using baseline and week 12 skin biopsies. Gene expression was measured using RNA-sequencing and TaqMan Low-Density Array qualitative polymerase chain reaction. Data from all DFK treatment groups were pooled.

Results: DFK treatment altered expression of multiple individual pruritus- and AD-related genes. Gene set variation analysis confirmed downregulation of pruritus-related genes (eg, IL-31, TRPV2) and the Th2 pathway following 12 weeks of treatment with DFK, but not placebo. Changes in gene expression of pruritus- and immune-related genes significantly correlated with skin improvement for DFK-treated subjects.

Conclusion: DFK downregulated expression of key genes implicated in pruritus and AD inflammation. Previous reports demonstrate an anti-pruritic effect of DFK in AD and other chronic itch conditions. DFK is a promising therapy for AD-related pruritus and may provide additional anti-inflammatory benefit by impacting the itch-scratch cycle.

References

KARE Biomarker

**Disclosures**

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