KAPPA OPIOID RECEPTORS AND ORAL DIFELIKEFALIN

- Kappa opioid receptors (KORs) are located primarily in the nervous system and in human skin.1
- Dynorphin A, an endogenous KOR ligand, was identified in the epidermis.2
- An enhanced epidermal kappa opioid system has been implicated in pruritus in patients with atopic dermatitis (AD).3
- Reduction in itch intensity in patients with AD has been linked to a restored KOR system.4
- Dihydromorphine (DHY) is a selective KOR agonist.
- DFK was recently approved by the US Food and Drug Administration for the treatment of moderate-to-severe pruritus in adults undergoing hemodialysis and is under investigation for the treatment of other chronic pruritic conditions, including pruritus associated with AD.5

DFK FOR MODERATE-TO-SEVERE PRURITUS IN AD

- In an M2MO AD mouse model, DFK reduced scratching independently of skin inflammation.6
- In the phase 2 clinical study, DFK demonstrated a significant reduction in pruritus in subjects with mild-to-moderate AD (study surface area <$15%). Measured as a 4-point improvement in itch Numeric Rating Scale (NRS) at week 12. (Figure 2c)

RESULTS

- Baseline demographics and disease characteristics are shown in Table 1.
- Study groups were balanced by I-NRS score.

| Characteristic | Placebo (n=10) | DFK 0.25 mg BID (n=11) | DFK 1.0 mg BID (n=9) | DFK 0.5 mg (n=8) | P
<table>
<thead>
<tr>
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</thead>
<tbody>
<tr>
<td>Age, years</td>
<td>35.5 (18.6)</td>
<td>34.9 (20.7)</td>
<td>35.6 (18.2)</td>
<td>34.8 (20.9)</td>
<td>.70</td>
</tr>
<tr>
<td>Sex, % female</td>
<td>5 (50.0)</td>
<td>5 (45.5)</td>
<td>5 (55.6)</td>
<td>6 (75.0)</td>
<td>.31</td>
</tr>
<tr>
<td>Skin type</td>
<td>60% (6)</td>
<td>55% (5)</td>
<td>60% (5)</td>
<td>70% (6)</td>
<td>.59</td>
</tr>
<tr>
<td>Mean BSA (%)</td>
<td>43.1 (21.0)</td>
<td>48.6 (20.7)</td>
<td>48.6 (20.9)</td>
<td>43.7 (22.1)</td>
<td>.41</td>
</tr>
<tr>
<td>Mean I-NRS score</td>
<td>7.8 (1.6)</td>
<td>6.7 (1.9)</td>
<td>6.7 (1.9)</td>
<td>7.8 (1.6)</td>
<td>.70</td>
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Figure 3. I-NRS Response in a Phase 2 Study

- Oral DFK, but not placebo, downregulated the overall expression of pruritus-related genes at week 12 (Figure 4).
- Oral DFK significantly modulated the Th17 (Th17)2 pathway (Figure 5).
- Oral DFK, but not placebo, significantly modulated Th17/Th22 and other inflammation markers (Figure 6).
- Oral DFK, but not placebo, significantly improved the skin barrier (Figure 7).

CONCLUSIONS

- Consistent with the preclinical data in the M2MO AD mouse model, DFK significantly modulated the expression of pruritus-related genes in subjects with AD.
- In addition, oral DFK significantly modulated the expression of AD-related inflammatory genes and pathways (Th2, Th22, Th17, Th9) and epidermal barrier products.
- Oral DFK is a promising therapy for AD-related pruritus and may provide additional anti-inflammatory benefit by impacting the itch-scratch cycle.

REFERENCES


ACKNOWLEDGMENTS

The authors thank all the clinical investigators and patients who participated in this study. We also acknowledge colleagues at Eli Lilly, Phil and Linda, Cara Therapeutics, Inc., and Ventyx Biosciences – consultant, for medical writing and editorial services, which was funded by Cara Therapeutics, under the direction of the authors.

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DISCLOSURES

All authors disclose no conflicts of interest. Financial disclosures associated with participation in this study are via the following resources: Abbott, AbbVie, Amgen, Arcutis, Avotres, Boehringer Ingelheim, Cara Therapeutics, Inc., Dermavant Sciences, Eli Lilly, Incyte, Janssen Research & Development, Janssen Biotech, Kyowa Kirin, LEO Pharma, Pandion Therapeutics, Pfizer, Shire, Sun Pharma, Takeda, Teva, Ventyx Biosciences – consultant. JG & KN: Ventyx Biosciences – consultant.

Presented at: the 4th Annual Revolutionizing Atopic Dermatitis (RAD) Conference; April 9–11, 2022; Baltimore, MD

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

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INTRODUCTION

OBJECTIVE

INTRODUCTION

RESULTS

CONCLUSIONS

ACKNOWLEDGMENTS

REFERENCES

Figure 1. DK2 in House Model AD

Figure 2. AD-like Skin Lesions Scratching

Figure 3. I-NRS Sub-study

Figure 4. Th17 Pathway

Figure 5. Inflammation Markers

Figure 6. Skin Barrier Genes

Figure 8. Correlations Between Biomarkers and Clinical Scores

Figure 7. Skin Barrier Genes

Table 1. Baseline Demographics and Disease Characteristics

Table 2. Change in EASI

Figure 1. AD-like Skin Lesions Scratching

Figure 2. I-NRS Response in a Phase 2 Study