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

Paola Facheris, MD
Laboratory of Inflammatory Skin Diseases
Icahn School of Medicine at Mount Sinai, New York, NY, USA
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DISCLOSURES
I do not have any relevant relationships with industry.
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Kappa Opioid Receptors and Oral Difelikefalin

- Kappa opioid receptors (KORs) are located primarily in the nervous system but are also expressed in immune cells and in human skin\(^1\-^4\)
- Dynorphin A, an endogenous KOR ligand, was identified in the epidermis\(^2\)
- An imbalanced epidermal kappa-opioid system has been implicated in pruritus in patients with atopic dermatitis (AD)\(^2\)
- Reduction in itch intensity in patients with AD has been linked to a restored KOR system\(^2\)

- Difelikefalin (DFK) is a selective KOR agonist
- DFK was recently approved by the FDA for the treatment of moderate-to-severe pruritus in adults undergoing hemodialysis\(^5\) and is under investigation for the treatment of other chronic pruritic conditions, including pruritus associated with AD

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DFK for Moderate-to-Severe Pruritus in AD

- In an MC903 AD mouse model, DFK reduced scratching independently of skin inflammation\(^1\)

- In the phase 2 clinical study, DFK demonstrated a significant reduction in pruritus in subjects with **mild-to-moderate AD (BSA <10%)**, measured as a ≥4-point improvement in I-NRS at week 12\(^1\)

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BSA, body surface area; I-NRS, Itch Numeric Rating Scale.

A sub-study of 40 subjects evaluated the effect of DFK on AD- and pruritus-related gene profiles using baseline (LS, NL) and week 12 (LS) skin biopsies.

**Methods:**
- Gene expression was measured using RNA-seq and RT-PCR.
- Pathway analysis was performed using GSVA and Spearman correlations were used to correlate biomarkers and clinical scores.
- Data from all DFK treatment groups were pooled.

GSVA, gene set variation analysis; LS, lesional; NL, non-lesional; RT-PCR, reverse transcriptase polymerase chain reaction.
Baseline Demographics and Disease Characteristics of Study Subjects

<table>
<thead>
<tr>
<th>Characteristic</th>
<th>Placebo (n=11)</th>
<th>DFK 0.25 mg (n=9)</th>
<th>DFK 0.5 mg (n=10)</th>
<th>DFK 1.0 mg (n=10)</th>
<th>P value</th>
</tr>
</thead>
<tbody>
<tr>
<td>Female, n (%)</td>
<td>7 (63.6)</td>
<td>7 (77.8)</td>
<td>5 (50.0)</td>
<td>4 (40.0)</td>
<td>0.37</td>
</tr>
<tr>
<td>Race, n (%)</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td>0.70</td>
</tr>
<tr>
<td>• Black or AA</td>
<td>4 (36.4)</td>
<td>5 (55.6)</td>
<td>4 (40.0)</td>
<td>6 (60.0)</td>
<td>-</td>
</tr>
<tr>
<td>• White</td>
<td>5 (45.5)</td>
<td>3 (33.3)</td>
<td>6 (60.0)</td>
<td>4 (40.0)</td>
<td>-</td>
</tr>
<tr>
<td>• Other</td>
<td>2 (18.2)</td>
<td>1 (11.1)</td>
<td>0 (0.0)</td>
<td>0 (0.0)</td>
<td>-</td>
</tr>
<tr>
<td>Mean age, years</td>
<td>47.7</td>
<td>44.6</td>
<td>44.6</td>
<td>35.9</td>
<td>0.33</td>
</tr>
<tr>
<td>Mean I-NRS score</td>
<td>8.0</td>
<td>8.2</td>
<td>8.6</td>
<td>9.1</td>
<td>0.21</td>
</tr>
<tr>
<td>Mean EASI score</td>
<td>6.7</td>
<td>7.3</td>
<td>4.8</td>
<td>6.9</td>
<td>0.76</td>
</tr>
<tr>
<td>Mean BSA (%)</td>
<td>8.1</td>
<td>7.7</td>
<td>8.1</td>
<td>9.3</td>
<td>0.97</td>
</tr>
<tr>
<td>Mean AD duration, years</td>
<td>21.8</td>
<td>18.2</td>
<td>26.5</td>
<td>11.6</td>
<td>0.31</td>
</tr>
</tbody>
</table>

- Study groups were balanced by I-NRS score

I-NRS scores range from 0 to 10 (0 = no itch, 10 = worst itching imaginable); EASI scores range from 0 to 72.
AA, African American; EASI, Eczema Area and Severity Index.
Oral DFK, but Not Placebo, Downregulated the Overall Expression of Pruritus-Related Genes at Week 12

GSVA analysis

**Pruritus-related genes**

![Graph showing change in Z-score (Week 12 vs Baseline)]

- **Placebo**
- **DFK**

- **Log2FCH (Week 12 vs Baseline)**

- **IL-31**
- **NGF**
- **OSM**

- **Substance P**
- **CGRP**

***P<0.001; **P<0.01; *P<0.05; +P<0.1.

Red symbols indicate significance vs placebo.
Black symbols indicate significance vs baseline.

FCH, fold change; IL, interleukin; CGRP, calcitonin gene-related peptide; NGF, nerve growth factor; OSM, oncostatin M.
Oral DFK Significantly Modulated the Th2 Pathway

GSVA analysis

**Th2 pathway**

Red symbols indicate significance vs placebo.
Black symbols indicate significance vs baseline.

CCL, C-C motif chemokine ligand; Th, T helper; TSLP, thymic stromal lymphopoietin; TSLPR, thymic stromal lymphopoietin receptor.

***P<0.001; **P<0.01; *P<0.05; +P<0.1.
Oral DFK, but Not Placebo, Significantly Modulated Th17/Th22 and Other Inflammation Markers

**Th17/Th22**

- **IL-19**
  - Placebo: -2.5 ± 0.5
  - DFK: 4.0 ± 1.0
- **IL-22**
  - Placebo: 0.0 ± 0.5
  - DFK: 3.0 ± 1.0

**DEFB4**

- Placebo: 2.5 ± 0.5
- DFK: 4.5 ± 1.0

**S100A12**

- Placebo: 0.0 ± 0.5
- DFK: 3.0 ± 1.0

**Th9**

- **IL-9**
  - Placebo: -2.0 ± 0.5
  - DFK: 2.0 ± 1.0

**Negative Regulators**

- **IL-34**
  - Placebo: 0.0 ± 0.5
  - DFK: 1.0 ± 1.0
- **IL-37**
  - Placebo: 0.0 ± 0.5
  - DFK: 1.0 ± 1.0

Red symbols indicate significance vs placebo. Black symbols indicate significance vs baseline.

DEFB4, defensin beta 4; S100A2, S100 calcium-binding protein A2.

***P<0.001; **P<0.01; *P<0.05; +P<0.1.
Oral DFK, but Not Placebo, Significantly Improved the Skin Barrier

GSVA analysis

Skin barrier genes

Red symbols indicate significance vs placebo. Black symbols indicate significance vs baseline.

CLDN, Claudin; FLG, filaggrin; GJB3, gap junction protein beta 3; K16, keratin 16; TJP3, tight junction protein 3.
Pruritus- and Inflammation-Related Markers Correlate With Changes in EASI

MMP12, matrix metalloproteinase 12; TRPA1, transient receptor potential cation channel A1.
Conclusions

• As expected from the preclinical data in the MC903 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