Neutralizing interleukin-13 increases skin microbial diversity: results from a Phase 3, randomized, double-blind, placebo-controlled trial of tralokinumab in adult patients with atopic dermatitis


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Introduction

A healthy skin barrier supports the growth of commensal bacteria that protect the host from pathogenic bacteria and their virulence factors.

In atopic dermatitis (AD), recent studies have pointed to a loss of microbial diversity in lesions and non-lesional skin.

People with AD have high levels of Staphylococcus aureus colonizing both lesional and non-lesional skin.

Dysregulation of the skin microbiota in AD is believed to be influenced by epidermal barrier disruption and T helper 2-driven inflammation, in which the IL-13 cytokine plays a major role.

Tralokinumab is a fully human, high-affinity monoclonal antibody that neutralizes the IL-13 cytokine, and has been shown to improve signs and symptoms in adults with moderate-to-severe AD.\(^1\)

Objective

To examine the impact of tralokinumab treatment on microbial diversity in lesional skin of adults with moderate-to-severe AD from the Phase 3 ECZTRA 1 trial (NCT03131648).

Study design (Figure 1)

- Bacteria were collected from areas 15 ± 10 mm of lesional skin.
- A swab and overall bacterial abundance was assessed in subjects in ECZTRA 1 at Baseline and Week 16 using qPCR for the 16S rRNA and the 16S rRNA using the Ba04230906 primer set.
- Positive samples were further analyzed for dysbiosis using the BIOMATRIX software.
- Microbiome profiling was done in 6 subjects (3 on tralokinumab and 3 on placebo) at selected sites from ECZTRA 1 at Baseline, Week 8, and Week 16.

Methods

- Relative microbial abundance and Shannon diversity were assessed based on DNA sequencing of 16S ribosomal RNA V4-V5 regions.
- A total of 30,266 sequence variants (SVs) representing known taxa were identified from 208 samples. After filtering SVs found in more than one sample, a total of 3,630 SVs were used for analysis representing 21 phyla, 178 genera and 71 species.
- Serum biomarkers were also measured at baseline, and 32-42 in Singleton Eerola Array, CCL17 by ELISA.

Baseline characteristics

<table>
<thead>
<tr>
<th>Characteristic</th>
<th>Placebo</th>
<th>Tralokinumab</th>
<th>p Value</th>
</tr>
</thead>
<tbody>
<tr>
<td>Age (years)</td>
<td>15.6 (4.4)</td>
<td>14.6 (4.5)</td>
<td>0.096</td>
</tr>
<tr>
<td>Sex</td>
<td>Female 58%</td>
<td>Female 61%</td>
<td>0.493</td>
</tr>
<tr>
<td>Race</td>
<td>White 95%</td>
<td>White 96%</td>
<td>0.177</td>
</tr>
<tr>
<td>Baseline EASI</td>
<td>Mean (SD) 38.8 (14.1)</td>
<td>Mean (SD) 39.9 (13.8)</td>
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<tr>
<td>Inclusion</td>
<td>99%</td>
<td>100%</td>
<td></td>
</tr>
<tr>
<td>Patients not achieving IGA=0/1 or EASI-75 at 16 weeks</td>
<td>74.2 (13.1)</td>
<td>72.1 (10.5)</td>
<td>0.228</td>
</tr>
</tbody>
</table>

Results

A 10-fold greater reduction in S. aureus abundance was observed from Baseline to Week 16 in the population (Figures 3 and 6).

S. aureus abundance was moderately correlated with IL-13, IL-22, and CCL17/TARC (Table 1).

The tralokinumab group showed a significant increase in microbial diversity over time and across treatment groups (Figure 3).

Conclusions

- Tralokinumab treatment was associated with decreased abundance of S. aureus and increased microbial diversity in lesional skin.
- The results support neutralization of the IL-13 cytokine contributes to improving the hallmark of AD by shifting the microbial diversity on AD lesional towards commensal flora.

References


Figure 1: EcZTRA 1 trial design and microbiome sample collection.

Figure 2: S. aureus abundance correlates with select biomarkers at Baseline (Figure 2).

Figure 3: Correlation of change in S. aureus abundance with change in SAD score (Figure 3).

Figure 4: Relative abundance of the major dermatomic phyla and genes over time.

Figure 5: Treatment with tralokinumab led to a greater reduction in S. aureus abundance in lesional skin relative to placebo at Week 16.

Figure 6: Treatment with tralokinumab led to increased Shannon diversity.

Figure 7: Relative abundance of the most dominant Staphylococcus species over time.