Tralokinumab prevents flares in moderate-to-severe atopic dermatitis; post hoc analyses of a randomized phase 3 clinical trial (ECZTRA 3)

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Introduction

• Atopic dermatitis (AD) is a chronic, inflammatory skin disease characterized by periods of acute symptomatic worsening (flares)1.
• Tralokinumab is a fully human, high-affinity, monoclonal antibody that specifically neutralizes interleukin (IL)-13, a key driver of cutaneous barrier dysfunction, inflammation and dysbiosis in AD2.
• Severe AD flares prompt rescue therapy with high-potency topical corticosteroids (TCS), systemic steroids, and antibiotics, and can lead to emergency room visits and hospitalizations3.
• Flare prevention is one of the primary goals for long-term control of AD. Flares are commonly defined as worsening of AD requiring treatment intensification or escalation that leads to an increase in the flares frequency measured, particularly in moderate-to-severe AD4,5.

Objective

To assess the impact of tralokinumab treatment on flare prevention in adults with moderate-to-severe AD from the ECZTRA 3 trial (NCT0333854).

Methods

Study design (Figure 1)

• Patients were randomly assigned 2:1 to receive either subcutaneous tralokinumab 300 mg + TCS or placebo + TCS every 2 weeks (Q2W) for an initial treatment period of 16 weeks.
• The treatment during the continuation period depended on the regimen received in the initial treatment period and on the subject's clinical response:
  - BSA ≥ 10% or IGA 2/3 at Week 16.
• During the initial and continuation treatment periods, all subjects applied a thin film of a supplied TCS (mometasone furoate, US: Class 4 [mid-strength]; Europe: Class 3 [potent]) once daily to areas with active lesions, as needed, lower potency TCS or topical calcineurin inhibitors could be prescribed if needed on body areas where the supplied TCS was not advisable or on areas where continued treatment with TCS was considered unsafe.
• Topical therapy was discontinued when skin lesions were cleared.
• All tralokinumab arms during Weeks 16-32 were pooled together for these post hoc analyses.

Endpoints and analyses

• Time to first flare from Week 0 to 16 according to the following definitions:
  o Rescue flare*: treatment intensification to either high-potency TCS, oral corticosteroids, and other systemic treatments
  o All flare: adverse event (AE) reporting of "dermatitis acuta or dermatitis infected" was analyzed to reflect AD worsening to a degree beyond minimal fluctuation
  o Rescue+AE flare: combined analysis of Rescue flare and AE flare, whichever occurred first
  o Per protocol AE flare: AD flares, defined as worsening of the disease that required escalation/intensification of AD treatment including addition or intensification of the supplied TCS
• Proportion of patients with flares from Week 0 to 32
• Time to first flare during a Cochrane proportional hazard model stratified by region and baseline IGA with planned treatment as covariate

Results

Patient characteristics

Patients had a long duration of AD and nearly 50% had severe AD (IGA 4-6) at baseline (Table 1).

Table 1. Baseline characteristics

<table>
<thead>
<tr>
<th>Arm</th>
<th>n=253</th>
<th>Placebo Q2W + TCS (n=126)</th>
<th>Placebo Q4W + TCS (n=129)</th>
<th>Tralokinumab Q2W + TCS (n=107)</th>
<th>Tralokinumab Q4W + TCS (n=106)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Mean age, years</td>
<td>37.7</td>
<td>36.8</td>
<td>36.0</td>
<td>36.7</td>
<td>36.5</td>
</tr>
<tr>
<td>Male%</td>
<td>66.0</td>
<td>65.6</td>
<td>68.0</td>
<td>66.1</td>
<td>68.5</td>
</tr>
<tr>
<td>Mean duration of AD, years</td>
<td>28.7</td>
<td>28.0</td>
<td>29.0</td>
<td>28.2</td>
<td>28.9</td>
</tr>
<tr>
<td>Median age of AD onset, years</td>
<td>2.0</td>
<td>2.0</td>
<td>2.0</td>
<td>2.0</td>
<td>2.0</td>
</tr>
<tr>
<td>Mean IGA involvement at AD, %</td>
<td>60.0</td>
<td>61.4</td>
<td>61.2</td>
<td>60.9</td>
<td>61.1</td>
</tr>
<tr>
<td>Mean EASI</td>
<td>34.6</td>
<td>36.2</td>
<td>36.0</td>
<td>34.8</td>
<td>36.4</td>
</tr>
<tr>
<td>Mean weekly percent daily pruritus NRS</td>
<td>7.9</td>
<td>7.7</td>
<td>7.5</td>
<td>7.7</td>
<td>7.6</td>
</tr>
</tbody>
</table>

*All randomized subjects (S) subjects were not dosed and therefore not included in the analyses.

AD flare analyses (Week 0 to 16)

• Overall, 7 (2.8%) patients experienced a rescue flare in the tralokinumab + TCS group compared to 13 (10%) in the placebo + TCS group during the first 16 weeks, corresponding to a 78% risk reduction with tralokinumab
• Similarly, 6 (2.4%) patients experienced an ‘All flare’ in the tralokinumab + TCS group versus 16 (12%) with placebo + TCS during the first 16 weeks, corresponding to an 80% risk reduction with tralokinumab
• The risk of a ‘Rescue+AE flare’ was 7% lower with tralokinumab
• The proportion of patients with a ‘per protocol flare’ during the initial 16-week treatment period was numerically lower in the tralokinumab + TCS group (8.9%) compared to the placebo + TCS group (14.6%)

TCS use by the end of the initial treatment period (Week 0 to 16)

• Mean amount of TCS used during Weeks 16-32 was significantly lower in the placebo + TCS group (50%) compared to the tralokinumab + TCS group (96%)
• The cumulative amount of TCS used over 16 weeks was approximately 32% lower in tralokinumab + TCS group compared to the placebo + TCS group (p=0.0001). TCS use with continued tralokinumab treatment (Week 16 to 32)

• Estimated use of TCS among patients continuing on tralokinumab (Q2W) remained low, 9.2-13.6% vs 52.1-61.4% per each 2-week period

Conclusions

• Tralokinumab treatment reduced the risk of ‘rescue flare’ by 78% relative to placebo when used in combination with TCS in adults with moderate-to-severe AD
• Nearly all patients (96%) remained free of ‘rescue flare’ with tralokinumab + TCS during the entire 32-week treatment period
• We propose ‘rescue flare’ as a clinically relevant flares outcome measure in moderate-to-severe AD that highlights flares where moderate potency TCS treatment is insufficient

References


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• The authors thank the UCB, Genzyme, Pfizer, and Leo Pharma for their support in conducting this trial

Note: All authors were involved in the design of the study, data collection, analysis, and interpretation of the results, and in writing the manuscript.

Figure 1. ECZTRA study design (modified)

Figure 2. Time to first flare (Week 0 to 32) according to the following window definitions: A: Rescue flare; B: AE flare; C: Rescue+AE flare; D: Per protocol flare.