Ixekizumab Is Effective in Subjects With Moderate to Severe Plaque Psoriasis With Significant Nail Involvement: Results From UNCOVER 3

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ABSTRACT

BACKGROUND: Ixekizumab, a monoclonal antibody that selectively targets interleukin-17A, has been established as safe and effective in 3 Phase 3 trials for the treatment of moderate to severe plaque psoriasis. The lifetime incidence of psoriatic nail disease is 80%-90% of patients, and approximately 50% of patients with psoriasis have nail involvement.

MATERIALS AND METHODS: The design of UNCOVER-3, a Phase 3, multicenter, double-blind, placebo- and active-controlled trial that evaluated the efficacy and safety of ixekizumab for moderate to severe psoriasis, has been published previously. Patients were randomized to receive blinded placebo, etanercept (50 mg twice weekly) or 80 mg ixekizumab every 2 weeks (IxEQ2W) or every 4 weeks (IxEQ4W) for 12 weeks. At week 12, all patients were assigned to open-label ixekizumab 80 mg every 4 weeks through week 60. In this 60-week post hoc subset analysis, we evaluated only those patients with significant baseline nail involvement, defined as fingernail NAPSI ≥16 and at least 4 fingernails involved.

RESULTS: Ixekizumab Q2W or Q4W resulted in greater improvement in nail psoriasis than placebo or etanercept by week 12 of administration, as measured by percent NAPSI reduction (IxEQ2W 39% improvement, IxEQ4W 40%, etanercept 28%, placebo -4.7%). At week 24, significantly more patients receiving ixekizumab exhibited no signs of nail involvement (IxEQ2W/Q4W 34%, IxEQ4W/Q4W 30%). Similar gains were observed at 60 weeks in all treatment groups.

CONCLUSION: Ixekizumab led to improvement in fingernail psoriasis by week 12 compared with placebo. Continued improvement in fingernail psoriasis with ixekizumab was observed, with >50% of patients achieving complete fingernail psoriasis resolution (NAPSI=0) at week 60.


INTRODUCTION

The safety and efficacy of ixekizumab, a monoclonal antibody that selectively targets interleukin-17A, have been established in 3 Phase 3 trials for the treatment of moderate to severe plaque psoriasis. We report a 60-week post hoc analysis of patients in the UNCOVER-3 trial with significant fingernail psoriasis involvement, defined as Nail Psoriasis Severity Index (NAPSI) ≥16 with ≥4 fingernails involved. Nail psoriasis is widely acknowledged to be a more difficult-to-treat manifestation of localized disease. The lifetime incidence of psoriatic nail disease is 80%-90% of patients, and approximately 50% of patients with psoriasis have nail
involvement.1-4

METHODS

The induction study design for UNCOVER-3 has been published previously.3 Briefly, UNCOVER-3 was a Phase 3, multicenter, double-blind, placebo- and active-controlled trial that evaluated the efficacy and safety of ixekizumab in patients with moderate to severe psoriasis. Patients were randomized to receive blinded placebo, etanercept (50 mg twice weekly), or 80 mg ixekizumab as 1 subcutaneous injection every 2 weeks (IXEQ2W) or every 4 weeks (IXEQ4W) for 12 weeks, following an ixekizumab 160-mg starting dose. At week 12, all patients were assigned to open-label ixekizumab 80 mg every 4 weeks through week 60. The placebo group received a 160-mg starting dose of ixekizumab while the etanercept group underwent a 4-week washout period prior to starting ixekizumab 80 mg Q4W. This trial is registered with ClinicalTrials.gov, number NCT01648177.

In this post hoc subset analysis, we evaluated only those patients with significant baseline nail involvement, defined as fingernail NAPSI ≥16 and at least 4 fingernails involved.4 Patients were analyzed according to the treatment to which they were assigned at week 0 regardless of compliance (intention-to-treat population). The primary efficacy variable was the total fingernail NAPSI score (sum of NAPSI scores of all 10 fingernails, total score 0-80). The primary objective of this analysis was to evaluate the efficacy of ixekizumab compared with placebo and etanercept on total fingernail NAPSI percent change from baseline to week 12 in patients with severe nail disease. The secondary objective was to examine the effect of ixekizumab on NAPSI percent change from baseline to week 60 in patients treated throughout the study with ixekizumab, as well as in patients who received placebo or etanercept during the first 12 weeks and were subsequently treated with ixekizumab through week 60. The NAPSI percent improvement from baseline at each post-baseline visit was analyzed using a mixed-effects model of repeated measures. The model included treatment, baseline value, visit, and interaction of treatment-by-visit as fixed factors with unstructured covariance structure. Categorical response of NAPSI score of 0 was analyzed using Fisher’s exact test in which patients who did not meet clinical response criteria or who had missing data were imputed using nonresponder imputation.

This analysis included a subset of 491 of the 1346 patients in UNCOVER 3. Treatment groups were similar in demographic and clinical characteristics (Table 1). All patients had significant nail psoriasis (NAPSI ≥16 and at least 4 fingernails involved) with overall baseline NAPSI score of 38 (mean [standard deviation], 17). The median number of fingernails involved was 10 (9 [1]).

RESULTS

Ixekizumab dosed Q2W or Q4W resulted in greater improvement in nail psoriasis than placebo or etanercept by week 12 of administration, as measured by percent NAPSI reduction. Patients treated with IXEQ2W and IXEQ4W experienced 39% and 40% improvement, respectively, in NAPSI scores at week 12 compared with 28% improvement for those treated with etanercept. Placebo-treated patients experienced worsening of NAPSI scores at week 12 (-4.7%).

Nails may take 5-7 months to regrow.5 By week 24, with continued IXEQ4W, 34% of patients initially receiving IXEQ2W and 30% who initially received IXEQ4W exhibited no signs of nail involvement.
TABLE 1
Baseline Characteristics of Patients With NAPSI ≥16 and ≥4 Fingernails Involved

<table>
<thead>
<tr>
<th></th>
<th>Placebo (n=71)</th>
<th>Etanercept (n=143)</th>
<th>Ixekizumab Every 4 Weeks (n=139)</th>
<th>Ixekizumab Every 2 Weeks (n=138)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Age, years</td>
<td>48 (11)</td>
<td>47 (13)</td>
<td>46 (11)</td>
<td>45 (12)</td>
</tr>
<tr>
<td>Males</td>
<td>58 (82%)</td>
<td>116 (81%)</td>
<td>110 (79%)</td>
<td>105 (76%)</td>
</tr>
<tr>
<td>Ethnic origin</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>White</td>
<td>70 (99%)</td>
<td>137 (98%)</td>
<td>133 (96%)</td>
<td>130 (94%)</td>
</tr>
<tr>
<td>Weight, kg</td>
<td>90 (20)</td>
<td>93 (21)</td>
<td>92 (23)</td>
<td>91 (26)</td>
</tr>
<tr>
<td>&lt;100</td>
<td>51 (7.2%)</td>
<td>56 (50%)</td>
<td>56 (71%)</td>
<td>111 (74%)</td>
</tr>
<tr>
<td>≥100</td>
<td>20 (28%)</td>
<td>48 (34%)</td>
<td>41 (30%)</td>
<td>37 (27%)</td>
</tr>
<tr>
<td>BMI, kg/m²</td>
<td>29 (5)</td>
<td>30 (8)</td>
<td>30 (7)</td>
<td>30 (7)</td>
</tr>
<tr>
<td>Psoriasis duration, years</td>
<td>22 (12)</td>
<td>21 (11)</td>
<td>20 (11)</td>
<td>18 (11)</td>
</tr>
<tr>
<td>Percentage of BSA involved</td>
<td>31 (21)</td>
<td>33 (21)</td>
<td>31 (18)</td>
<td>30 (20)</td>
</tr>
<tr>
<td>sPGA ≥4</td>
<td>41 (58%)</td>
<td>78 (55%)</td>
<td>76 (55%)</td>
<td>74 (54%)</td>
</tr>
<tr>
<td>NAPSI</td>
<td>22 (9)</td>
<td>22 (9)</td>
<td>23 (8)</td>
<td>22 (8)</td>
</tr>
<tr>
<td>Number fingernails affected</td>
<td>9.1 (1.1)</td>
<td>9.2 (1.3)</td>
<td>9.1 (1.4)</td>
<td>9.2 (1.4)</td>
</tr>
<tr>
<td>Previous therapy*</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Phototherapy</td>
<td>29 (41%)</td>
<td>66 (46%)</td>
<td>68 (49%)</td>
<td>56 (41%)</td>
</tr>
<tr>
<td>Non-biological systemic only¹</td>
<td>35 (49%)</td>
<td>59 (41%)</td>
<td>65 (47%)</td>
<td>58 (42%)</td>
</tr>
<tr>
<td>Biological only</td>
<td>4 (6%)</td>
<td>6 (4%)</td>
<td>8 (6%)</td>
<td>6 (4%)</td>
</tr>
<tr>
<td>Biological and non-biological</td>
<td>4 (6%)</td>
<td>20 (14%)</td>
<td>19 (9%)</td>
<td>7 (6%)</td>
</tr>
</tbody>
</table>

Data are mean (SD) or n (%). BMI, body mass index; BSA, body surface area; sPGA, static Physician’s Global Assessment; PASI, Psoriasis Area and Severity Index; NAPSI, Nail Psoriasis Severity Index.

*Per study entry criteria, patients with previous exposure to etanercept were excluded from the study enrollment.

¹Previous non-biologic systemic therapy included the following: methotrexate, cyclosporine, retinoids, other non-biologic systemic agents, and pсорalan combined with ultraviolet A.

This improvement persisted over the observation period, with 56% of patients initially treated with IXEQ2W and 50% of those initially treated with IXEQ4W exhibiting no nail involvement at week 60. Similar gains were observed in patients who received placebo and etanercept during the first 12 weeks and then IXEQ4W from weeks 12 to 60, with 56% of the placebo group and 47% of the etanercept group demonstrating no nail involvement at week 60 (Figure 1A).

At 60 weeks, patients initially treated with ixekizumab Q2W and Q4W both experienced an 86% reduction in NAPSI total score. Patients initially treated with placebo or etanercept who received ixekizumab Q4W treatment after 12 weeks experienced similar reductions in NAPSI by week 60 (etanercept group 83%; placebo group 89%) (Figure 1B).

This subset of patients with moderate to severe nail involvement experienced similar improvements in their psoriasis compared with the larger population observed in the UNCOVER 3 trial. At week 60, 87% (IXEQ4W/Q4W) and 89% (IXEQ2W/Q4W) of patients achieved a 75% reduction in the Psoriasis Area and Severity Index (PASI 75), 78% (IXEQ4W/Q4W) and 78% (IXEQ2W/Q4W) achieved PASI 90, and 56% (IXEQ4W/Q4W) and 57% (IXEQ2W/Q4W) achieved PASI 100.

In this post hoc subgroup analysis, ixekizumab was effective for the treatment of moderate to severe nail involvement in patients with moderate to severe psoriasis. Ixekizumab given Q2W or Q4W during the initial 12 weeks of the study was similarly effective in percent reduction of total NAPSI score as well as complete resolution of nail psoriasis (NAPSI=0). Complete resolution of nail psoriasis was evident by week 24 in more
than 30% patients treated with ixekizumab. By week 60, the mean percent reduction in NAPSI total score exceeded 80% in all groups, with patients who had initially been treated with placebo or etanercept achieving outcomes comparable with those treated continuously with ixekizumab.

The results of this post hoc subgroup analysis were similar to results from a Phase 2 trial of ixekizumab in patients with nail psoriasis. Following a 20-week dose-ranging, randomized, placebo-controlled trial, 142 patients, including 51 patients with baseline nail psoriasis, were treated with 120 mg ixekizumab Q4W in an open-label extension period. By week 48, proportions of patients achieving complete resolution of nail psoriasis were 58% in the group initially treated with placebo and 49% in the group initially treated with ixekizumab, similar to the approximately 50% of patients with complete resolution in the present analysis.

CONCLUSION

Ixekizumab led to improvement in fingernail psoriasis by week 12 compared with placebo in patients with moderate to severe psoriasis. Continued improvement in fingernail psoriasis with ixekizumab was observed, with >50% of patients achieving complete fingernail psoriasis resolution (NAPSI=0) at week 60.

**FIGURE 1.** (A) Complete resolution of nail disease (NAPSI = 0) at each visit: NAPSI ≥16 at baseline with ≥4 nails involved (n=491). (ETN, etanercept; NAPSI, Nail Psoriasis Severity Index; Q4W, ixekizumab every 4 weeks; Q2W, ixekizumab every 2 weeks.) (B) NAPSI, mean percent improvement over time: NAPSI ≥16 at baseline with ≥4 nails involved (n=491). (ETN, etanercept; NAPSI, Nail Psoriasis Severity Index; Q4W, ixekizumab every 4 weeks; Q2W, ixekizumab every 2 weeks.)
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DISCLOSURES

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REFERENCES


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