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Title: Predictors of maintained response with tralokinumab every four weeks dosing in adults with moderate-to-severe atopic dermatitis

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Introduction

Tralokinumab, a high-affinity, monoclonal antibody that specifically neutralizes IL-13, was assessed in two Phase 3 trials (ECZTRA 1 and 2) of moderate-to-severe atopic dermatitis. Tralokinumab 300 mg every two weeks (Q2W), after a 600 mg loading dose, demonstrated superiority to placebo for primary and secondary endpoints at Week (Wk) 16. Patients that met primary endpoints, Investigator's Global Assessment (IGA) 0/1 and/or Eczema Area and Severity Index (EASI)-75, were re-randomized to tralokinumab Q2W, every four weeks (Q4W), or placebo. At Wk 52, IGA 0/1 or EASI-75 was maintained without rescue use (including TCS) in 56.2% (73/130; $P<0.001$), 50.0% (67/134; $P=0.003$), and 27.4% (20/73) in the Q2W, Q4W, and placebo arms, respectively. Here potential early predictors of maintained response at Wk 52 with tralokinumab Q4W vs Q2W dosing were evaluated.

Methods

Patients from the Q2W initial treatment arm, who met primary endpoints at Wk 16, were included in *post hoc* analyses using a machine learning algorithm to identify predictors for maintained response at Wk 52. Potential predictors included baseline demographic and clinical characteristics, medical/medication history, efficacy after 16 weeks or earlier and randomized treatment (63 main factors, 52 interactions). The algorithm utilized 1000 replications for which data was randomly split into training (75% of data) and validation (25%) datasets. Per replication stepwise selection was used to systematically search combinations of significant ($P<0.05$) predictive variables for IGA 0/1 without rescue use at Wk 52 based on logistic regression. These predictors were ranked by percentage of times identified by the algorithm in the final predictive model for IGA 0/1 at Wk 52; a higher value indicates greater predictive ability. Top predictors were then assessed individually and in combination to determine maintained efficacy equivalency between Q4W and Q2W at Wk 52. Treatment differences were estimated with a Mantel-Haenszel analysis stratified by baseline IGA, region, and trial.

Results

The top two predictors for maintaining IGA 0/1 at Wk 52 regardless of dose frequency were IGA score (identified 76.1% of times) and Worst Daily Pruritus Numerical Rating Scale (NRS) <3 (56.6%) at Wk 16. When assessing efficacy equivalency between Q2W and Q4W, a numerically higher proportion of patients with IGA 0/1 at Wk 16 maintained response with Q2W relative to Q4W at Wk 52 (**Fig. 1A**). Rates of maintained response at Wk 52 were higher in patients with both of the top two predictors at Wk 16 relative to those with IGA 0/1 only (**Fig. 1B**). For patients who met both top two predictors at Wks 12/14/16 (4 weeks stable response) Q2W and Q4W maintained response comparably well at Wk 52 (**Fig. 1C**); similar equivalence between Q2W and Q4W for these patients was observed for EASI-75 and in the ECZTRA 3 trial.

Discussion

Regardless of dose frequency, IGA score and Worst Daily Pruritus NRS <3 at Wk 16 were the top two predictors of maintained treatment response at Wk 52 with tralokinumab monotherapy. Stable achievement at consecutive timepoints of clear or almost clear skin and mild or no itch symptoms with tralokinumab Q2W over 4 consecutive weeks was identified as a positive predictor of maintained long-term response with the Q4W dosing regimen. Future studies are needed to confirm these results and consider time points beyond Wk 16 to account for patients with progressive improvements achieving disease control after Wk 16.

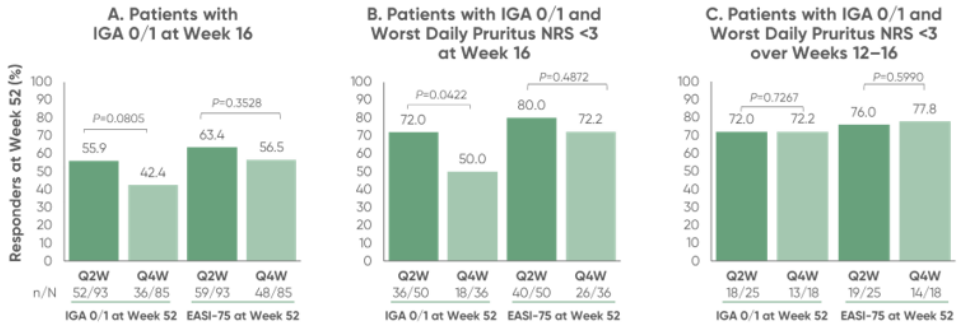

Figure 1. Percentage that maintained response (IGA 0/1 or EASI-75) at Week 52 with tralokinumab monotherapy using the top two predictors (IGA score and Worst Daily Pruritus NRS <3) with (A) IGA 0/1 at Week 16, (B) IGA 0/1 and Worst Daily Pruritus NRS <3 at Week 16, or (C) IGA 0/1 and Worst Daily Pruritus NRS <3 over Weeks 12–16. Use of rescue medication (including TCS) and missing data imputed as nonresponse. *P* values represent the difference between Q2W and Q4W groups.

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