Apremilast Reduces IL-17F, IL-17A, IL-22, and TNF-α Plasma Protein Levels in Patients With Moderate to Severe Plaque Psoriasis: Pharmacodynamic and Correlative Results From Phase 2/3 Studies

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Introduction

Psoriasis is a complex inflammatory disease mediated by proinflammatory cytokines including tumor necrosis factor (TNF)-α, interleukin (IL)-17, and IL-22. Apremilast (APR) is an oral, small-molecule phosphodiesterase 4 inhibitor that regulates inflammatory mediators including TNF-α, IL-23, IL-17A, and IL-22. APR has been shown to be effective in the treatment of moderate to severe plaque psoriasis in phase 3, randomized, placebo (PBO)-controlled trials (Efficacy and Safety Trial Evaluating the Effects of Apremilast in Psoriasis [ESTEEM] 1 and 2; NCT01194219 and NCT01232283). In the ESTEEM studies, patients receiving APR 30 mg twice daily (APR30) demonstrated statistically significant and clinically meaningful improvement, as measured by a ≥75% reduction from baseline in Psoriasis Area and Severity Index (PASI) score (PASI-75) at Week 16, the primary end point. In a phase 2b study (NCT01988103), APR also demonstrated statistically significant and clinically meaningful efficacy at Week 16 compared with PBO in Japanese patients with moderate to severe plaque psoriasis. We evaluated the pharmacodynamic effects of APR on systemic IL-17 and IL-22 cytokine levels and their correlation with clinical efficacy.

Methods

• Plasma samples were collected from a subset of patients in the ESTEEM 2 phase 3 study (PBO n=47; APR30 n=83) conducted in North America and Europe, and the PSOR-011 phase 2b study (PBO n=23; APR 20 mg twice daily [APR20] n=22; APR30 n=22) conducted in Japan.

• The Singulex Erenna® single molecule counting immunoassay (EMD Millipore) was used to quantify IL-17A, IL-17F, IL-22, and TNF-α.

• Univariate association between each biomarker and Week 16 PASI improvement was measured by the Spearman correlation coefficient.

• Multivariate associations and nonlinear relationships were analyzed using the Classification and Regression Trees (CART) and Multivariate Adaptive Regression Splines (MARS) supervised machine learning algorithms.1,2

• In ESTEEM 2, treatment with APR30 vs. PBO was associated with significant median percentage reductions from baseline to Week 4 in IL-17F (−49.8% vs. −1.4%), IL-17A (−44.4% vs. −2.7%), IL-22 (−36.3% vs. −0.8%), and TNF-α (−9.0% vs. +3.5%) (all $P<0.01$).

*Patients initially randomized to PBO switched to APR30 after Week 16. $P$-value is calculated based on Wilcoxon test to investigate the % change difference between PBO and APR30 groups.
In PSOR-011, treatment with APR30 vs. PBO was associated with significant median percentage reductions from baseline to Week 4 in IL-17F (−56.7% vs. +19.0%), IL-17A (−42.8% vs. +26.7%), and IL-22 (−27.2% vs. +7.1%) (all \( P<0.01 \)), and a nonsignificant reduction in TNF-\( \alpha \) (−3.5% vs. +3.4%).

*Patients initially randomized to PBO were re-randomized to APR20 or APR30 after Week 16. \( P \)-value is calculated based on Wilcoxon test to investigate the % change difference between PBO and APR groups.
• In ESTEEM 2, the percentage change in IL-17F, IL-17A, and IL-22 levels from baseline to Week 4 significantly correlated with the percentage improvement in PASI score at Week 16 (all $P<0.001$).

Rs=Spearman correlation coefficient. $P$-values were obtained from testing significant correlation (H1: Rs$>0$).
The CART decision tree revealed that IL-17F is the most important predictor of PASI response to APR and identified synergies between IL-17F, TNF-α, and IL-22 in predicting likelihood of response to APR in patients with psoriasis. The findings from the CART decision tree suggest that synergistic effects of IL-17F, TNF-α, and IL-22 could explain 72% of the variation in PASI improvement.

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IL-17F
Percent change from BL to Wk4 < -18.85%?
yes
no

TNF-α
Percent change from BL to Wk4 < -6.93%?

yes

-61.51%

no

-42.31%

TNF-α
Percent change from BL to Wk4 > -2.85%?

yes

1.72%

no

IL-22
Percent change from BL to Wk4 < 5.1%?

yes

-41.24%

no

-16.47%

PASI Improvement at Week 16 (%)

BL=baseline. Percentages are on a linear scale.
Additionally, the MARS algorithm identified nonlinear associations between PASI and percentage change from baseline in the levels of IL-17F and TNF-α cytokines.

All cytokines were included in the models as percentage change from baseline to Week 4 (log scale).
Conclusions

• These findings indicate that APR reduces systemic IL-17 and IL-22 cytokine levels in psoriasis patients from North America, Europe, and Japan in a similar manner.
• Reductions in IL-17F, IL-17A, and IL-22 levels at Week 4 correlated with PASI improvement at Week 16.
• Findings from 2 independent algorithms show that reducing IL-17F is the most important predictor of PASI response to APR in patients with psoriasis.
• Both models found that synergistic cytokine effects at Week 4 were predictive of PASI improvement with APR at Week 16 in patients from ESTEEM 2.
• These data suggest that reductions in IL-17 and IL-22 cytokine levels are an important mechanism through which APR exerts its anti-inflammatory effects in psoriasis.