Letter to the Editor

Synergistic cytokine effects as apremilast response predictors in patients with psoriasis

To the Editor:

Psoriasis is a complex inflammatory disease regulated by proinflammatory cytokines including TNF-α, IL-17, and IL-22.[1,2] The observed effects of combinations suggest that these cytokines act synergistically, as evidenced by combination effects that are greater than the sum of the effects of separate components.[3] In a similar manner, cytokine interactions may play a role in therapeutic response to a given treatment that modulates 1 or more psoriasis-related cytokine effector substances.

Apremilast, an oral phosphodiesterase 4 (PDE4) inhibitor, regulates the expression of genes in a broad array of proinflammatory and anti-inflammatory cytokine pathways, including TNF-α, IL-10, IL-23, and IL-17A.[4-7] Apremilast 30 mg twice a day treatment has been shown to be effective in phase 3, randomized, placebo-controlled studies assessing the treatment of moderate to severe plaque psoriasis in North America and Europe (Efficacy and Safety Trial Evaluating the Effects of Apremilast in Psoriasis [ESTEEM] 1 and 2).[8,9] Similar positive clinical findings have recently been demonstrated with apremilast 30 mg twice a day treatment (vs placebo) in the phase 2b PSOR-011 trial conducted in Japanese patients with moderate to severe plaque psoriasis.[E1]

Pharmacodynamic substudies of ESTEEM 2 and PSOR-011 were performed to describe proinflammatory cytokine levels and explore whether cytokine synergies may be used to predict response to apremilast after 16 weeks in patients with moderate to severe psoriasis. Patient selection and study methods for both trials have been described previously.[9,E1]

Plasma samples were collected from a subset of ESTEEM 2 patients (n = 83 apremilast, n = 47 placebo) at weeks 4, 16, 32, 36, 40, and 44 and a subset of PSOR-011 patients (n = 24 apremilast 30 mg twice a day, n = 22 apremilast 20 mg twice a day, n = 23 placebo) at weeks 2, 4, 16, 24, and 52. A cytometric bead array measuring 47 protein analytes associated with inflammation (Inflammation Multi-Analyte Profile version 1.0, Myriad Rules Based Medicine, Austin, Tex) was used for the initial proteomic analysis of ESTEEM 2 plasma samples. Table E1 in this article's Online Repository at www.jacionline.org lists the 47 protein analytes included in the initial proteomic analysis. Significant percentage changes from baseline were observed at week 16 in patients receiving apremilast 30 mg twice a day versus placebo for 4 of 47 proteins: IL-17A ($P = .0454$), alpha-2 macroglobulin ($P = .0389$), chemokine CC-motif ligand 5 ($P = .0102$), and tissue inhibitor of metalloproteinase-1 ($P = .0073$) (data not shown). Logistic regression analysis showed no significant associations between changes in these 4 biomarkers and a ≥75% reduction in Psoriasis Area and Severity Index (PASI) score. Therefore, a more sensitive assay was used to measure the low-abundance cytokines important in psoriasis pathogenesis. Samples were analyzed for IL-17A, IL-17F, IL-22, and TNF-α proteins using an ultrasensitive immunoassay (Erenna, Singulex, Alameda, Calif). The relationship between changes in psoriasis-related cytokine levels and clinical efficacy (ie, percentage change from baseline in PASI score at week 16) was examined among patients included in the pharmacodynamics subset in ESTEEM 2 using Spearman correlation coefficients, and classification and regression trees (CART)[E2] and multivariate adaptive regression splines (MARS)[E3] supervised machine learning algorithms. The CART algorithm enables complex interactions to be interpreted as a sequence of rules in a decision tree, with the result typically presented in the format of a tree growing from the root node to the decision nodes. This algorithm is designed only to describe interactions as products of binary variables, not taking into account the main effects.[E4] At a high level, MARS approximates complex relationships by a series of linear regressions on different ranges of the predictor variables. In contrast to the CART algorithm, these relationships can be first-order (main effects) as well as higher-order (first, second, etc) interactions.[E3] Instead of a binary function, the MARS algorithm uses a hinge function, as described by Friedman.[E3] For the predictive algorithm, each biomarker was defined as a potential predictor of PASI improvement at week 16; biomarker values (IL-17A, IL-17F, IL-22, and TNF-α) entered into the model were defined as percentage change in expression from baseline to week 4. CART and MARS algorithms have used the functions available in R libraries (recursive partitioning [or rpart] and earth, respectively) to select optimal combinations of biomarker values. When using the CART algorithm, the ANOVA method was specified as the splitting rule and a minimum number of 10 observations per terminal node was specified as the stopping rule. The parameters for the MARS algorithm under the earth package were linear models and first-order interactions for the hinge functions. The search for the optimal model was based on 5-fold cross-validation and an exhaustive pruning method. Additional information about CART and MARS is included in this article's Online Repository at www.jacionline.org.

In both ESTEEM 2 and PSOR-011, the observed baseline median IL-17A, IL-17F, and IL-22 levels in the current subsets of patients with psoriasis were all elevated compared with median or mean values in healthy individuals, based on previous reports that used the same Erenna assays.[E4-E6] Median TNF-α levels were similar to those previously reported in healthy control subjects.[E4]

In ESTEEM 2, apremilast treatment was associated with significant reductions from baseline (vs placebo) in plasma levels of IL-17F, IL-17A, IL-22, and TNF-α at week 4, the first time point measured, and at week 16 (Fig 1, *A*). These observations were independently confirmed in PSOR-011, wherein treatment with apremilast was associated with significant reductions in plasma IL-17A, IL-17F, and IL-22 at week 4, and for IL-17F and IL-22 at week 16. There was a trend for a reduction in TNF-α in the PSOR-011 study at the apremilast 20 mg twice a day and 30 mg twice a day doses, which was statistically significant for the 20 mg twice a day dose but not the 30 mg twice a day dose (Fig 1, *B*). In general, the magnitudes of the decreases in plasma IL-17A, IL-17F, and IL-22 levels in the apremilast 30 mg twice a day groups were similar between the ESTEEM 2 and PSOR-011 studies. Decreases in cytokine levels were sustained through week 44 in ESTEEM 2 patients and through week 52 in PSOR-011 patients receiving apremilast; these reductions emerged in patients initially randomized to placebo and switched to apremilast at week 16 (Fig 1).

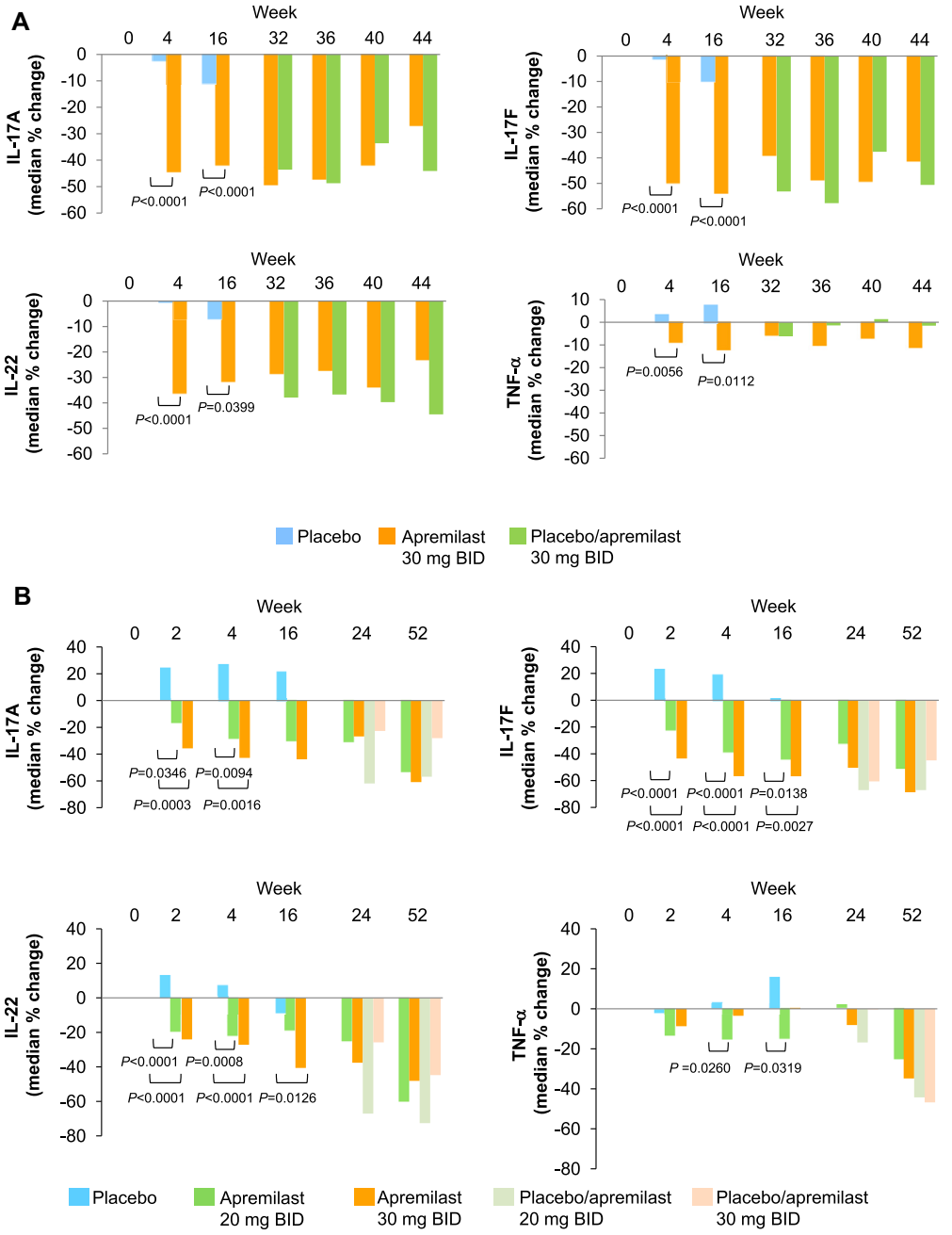

FIG 1. A, Changes from baseline in plasma IL-17A, IL-17F, IL-22, and TNF-α levels by apremilast treatment in North American and European patients with psoriasis in ESTEEM 2. Treatment of patients with moderate to severe psoriasis with apremilast, but not placebo, reduced plasma IL-17A, IL-17F, IL-22, and TNF-α levels in 2 independent clinical trials. Blood samples drawn at the indicated time points were assayed for these cytokines using ultrasensitive immunoassays. Patients initially randomized to placebo were switched to apremilast after week 16; all patients received apremilast treatment at later time points as indicated. *P* values are based on Wilcoxon tests to investigate percentage change difference between the placebo and apremilast treatment groups. **B,** Changes from baseline in plasma IL-17A, IL-17F, IL-22, and TNF-α levels by apremilast treatment in Japanese patients with psoriasis in PSOR-011. Treatment of patients with moderate to severe psoriasis with apremilast, but not placebo, reduced plasma IL-17A, IL-17F, IL-22, and TNF-α levels in 2 independent clinical trials. Blood samples drawn at the indicated time points were assayed for these cytokines using ultrasensitive immunoassays. Patients initially randomized to placebo were switched to apremilast after week 16; all patients received apremilast treatment at later time points as indicated. *P* values are based on Wilcoxon tests to investigate percentage change difference between the placebo and apremilast treatment groups. *BID,* Twice a day.

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