Published in final edited form as:

J Allergy Clin Immunol. 2012 August ; 130(2): 516–22.e4. doi:10.1016/j.jaci.2012.03.030.

IL-4 receptor polymorphisms predict reduction in asthma exacerbations during response to an anti-IL-4 receptor α antagonist

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Abstract

Background—This is the first large pharmacogenetic investigation of the inflammatory IL-4/IL-13 pathway in patients with moderate-to-severe asthma. We analyzed genomic DNA from participants in a 12-week placebo-controlled efficacy trial of pitrakinra (1, 3, or 10 mg twice daily), a novel IL-4/IL-13 pathway antagonist (Clinicaltrials.gov NCT00801853).

Objectives—The primary hypothesis for this analysis is that amino acid changes in the 3' end of the IL-4 receptor α gene (*IL4RA*) or closely proximal variants would predict reductions in asthma exacerbations for subjects randomized to pitrakinra therapy.

Methods—Nineteen *IL4RA* single nucleotide polymorphisms (SNPs) were tested in 407 non-Hispanic white subjects for association with the primary clinical end point of asthma exacerbations and changes in secondary end points for asthma symptom scores.

Results—The most consistent pharmacogenetic associations were observed for the correlated tagging SNPs rs8832 and rs1029489 in the *IL4RA* 3' untranslated and proximal regions, respectively. Subjects homozygous for the rs8832 common G allele randomized to pitrakinra (placebo group nonsignificant) had decreased asthma exacerbations and decreased nocturnal awakenings and activities limited by asthma. There was also a significant pitrakinra dose-response relationship (placebo/1 mg/3 mg/10 mg) for exacerbations in subjects homozygous for the

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Disclosure of potential conflict of interest: R. E. Slager has received grants from the National Institutes of Health (NIH) and research support from Aerovance. B. A. Otulana and Y. P. Yen are employees of Aerovance. G. A. Hawkins has received research support from Aerovance. S. P. Peters has received research support from the NIH. S. E. Wenzel has consulted for Genentech, and has received research support from Aerovance, GlaxoSmithKline, and Sanofi-Aventis. D. A. Meyers and E. R. Bleeker have consulted for and received research support from Aerovance.

common allele in rs1029489 ($P = .005$) and rs8832 ($P = .009$) and the intronic SNPs rs3024585, rs3024622, and rs4787956 ($P = .03$).

Conclusion—This study demonstrates a significant pharmacogenetic interaction between anti-IL-4 receptor α therapy and *IL4RA* gene variation, identifying an asthma subgroup that is more responsive to therapy with this antagonist.

Keywords

Pharmacogenetics; pitrakinra; IL-4 receptor; asthma therapy; IL-4 receptor antagonist

Allergic asthma is characterized by chronic inflammation and, in some subjects, airway remodeling, which is often accompanied by increased eosinophil and CD4⁺ T_H2 cell counts.^{1,2} Previous human and animal studies have shown that T_H2 cytokines are critical mediators in chronic allergic airway inflammation,³ and in murine models T_H2-type inflammation can also enhance bronchial hyperresponsiveness.^{4,5} Because of the important role for this pathway in the pathogenesis of asthma, there is growing interest in asthma therapies based on modulation of T_H2 cytokines, including IL-4 and IL-13. However, clinical results for drugs targeting this pathway in adults with asthma were initially disappointing, possibly because of T_H2 pathway redundancy or the inclusion of subjects with differential therapeutic responsiveness to modulation of this pathway.^{6–9} There have been recent trials that show promising results, especially in subgroups of patients. For instance, an antibody blocking IL-13 has been effective at reducing airway symptoms and improving lung function in a subset of subjects with T_H2-specific inflammatory asthma.¹⁰

Another therapeutic approach for asthma is to target the α subunit of the IL-4 receptor, the signaling component of the heterodimeric receptor complex for both IL-4 and IL-13. Pitrakinra is a recombinant form of IL-4 that blocks IL-4 receptor α complexes and inhibits downstream signaling.¹¹ Detailed pharmacology of pitrakinra is presented in an article by Burmeister et al.¹¹ Previous studies provided evidence that this antagonist targets T_H2 inflammation in subjects with allergic asthma and preliminary evidence that pitrakinra therapy decreases severe adverse events requiring β -agonist reliever medications.¹² Therefore this current clinical trial testing the efficacy of a novel biologic on clinically relevant asthma outcome was warranted. Our research group previously completed a preliminary pharmacogenetic analysis using data from an earlier phase 2 placebo-controlled trial of pitrakinra¹³ in patients with allergic asthma ([Clinicaltrials.gov](https://clinicaltrials.gov/ct2/show/study/NCT00535431) NCT00535431).¹² In a phase 2a allergen challenge study, we demonstrated that variation in the human IL-4 receptor α gene (*IL4RA*) was associated with therapeutic responses to pitrakinra treatment.¹³ The nonsynonymous *IL4RA* single nucleotide polymorphisms (SNPs) rs1805011 (E400A, also called E375A) and rs1801275 (Q576R, also called Q551R), as well as several other *IL4RA* tagging SNPs, were significantly associated with a reduction in FEV₁ that occurs during the late antigen response in the pitrakinra-treated group only.¹³ In a separate line of evidence, we also performed a genetic analysis of cynomolgus monkeys treated with an IL-4/IL-13 antagonist similar to pitrakinra¹⁴ and identified novel cynomolgus *IL4RA* polymorphisms significantly associated with a therapeutic reduction in bronchial hyperresponsiveness, eosinophilia, or both.¹³

In this phase 2b clinical trial of pitrakinra's efficacy and safety ([Clinicaltrials.gov](https://clinicaltrials.gov/ct2/show/study/NCT00801853) NCT00801853), participants with moderate-to-severe asthma were evaluated for the primary clinical end point of asthma exacerbations in a double-blind, randomized, placebo-controlled study. Subjects were randomized to pitrakinra or placebo by means of inhalation twice daily for 12 weeks. For the global intent-to-treat study population ($n = 534$), there was no statistically significant difference between pitrakinra and placebo in the incidence of asthma exacerbations; however, there was a significant reduction in exacerbations (10 mg of pitrakinra compared with placebo, $P = .004$) in a prespecified subset of subjects ($n = 125$) with evidence of increased blood eosinophil counts.^{15,16} We performed a pharmacogenetic analysis of *IL4RA* polymorphisms in 407 non-Hispanic white subjects with available DNA from the global trial to identify potential genetic modifiers of the pitrakinra treatment response.

Although there is limited published information regarding genetic predictors of asthma exacerbations, our group previously reported that the minor alleles of *IL4RA* E400A and Q576R variants were related to asthma exacerbations and lower lung function.¹⁷ On the basis of our initial pharmacogenetic results and reported *IL4RA* associations with exacerbations, the primary hypothesis for this analysis is that *IL4RA* amino acid changes E400A and Q576R or closely proximal genetic variants in the 3' end of this gene will predict reductions in asthma exacerbations in participants randomized to anti-IL-4 receptor α (IL-4R α) therapy.

METHODS

Clinical trial population

A pharmacogenetic analysis was performed in a phase 2b clinical trial of pitrakinra, an IL-4R α antagonist. In this trial 534 participants with moderate-to-severe asthma from the intent-to-treat population were enrolled in a 12-week randomized, placebo-controlled, multicenter (sites in the United States and Europe), double-blind, dose-ranging study (1, 3, or 10 mg twice daily) to test the safety and efficacy of pitrakinra. Subjects were evaluated for the primary end point of incidence of asthma exacerbation and several secondary clinical end points. Patients were stabilized for 4 weeks of run-in on inhaled corticosteroids and long-acting β -agonists (LABAs) and then randomized to pitrakinra or placebo for a 12-week treatment period. LABAs were withdrawn at 4 weeks (study day 28), and inhaled corticosteroid withdrawal began 6 weeks after initiation of blinded treatment (stepped down on study days 42 and 56 and stopped on day 70).¹⁵ Complete participant inclusion and exclusion criteria can be viewed at [Clinicaltrials.gov](https://clinicaltrials.gov/ct2/show/study/NCT00801853) NCT00801853. Briefly, inclusion criteria defined a population of nonsmoking male and female subjects 18 years of age and older who had moderate-to-severe asthma and whose symptoms were not well controlled with current asthma therapy. All subjects had experienced an asthma exacerbation requiring oral corticosteroid treatment at least once within the preceding 2 years. Because the majority of participants reported non-Hispanic white ethnicity, genetic analysis was performed in 407 non-Hispanic white subjects from the intent-to-treat population, who provided genomic DNA and consent to participate in a genetic study. Although DNA was available from a total of 465 subjects, we analyzed non-Hispanic white subjects only because of the small

numbers of subjects with other ethnic backgrounds. Characteristics of participants in the global clinical trial and non-Hispanic white subjects analyzed at study entry (after the 4-week run-in period on combination 250/50 µg fluticasone propionate/salmeterol therapy) are reported in Table I. The safety profile for pitrakinra based on adverse events and laboratory measurements was satisfactory.¹⁵ All subjects provided informed consent, and this pharmacogenetic analysis was approved by the Wake Forest School of Medicine Institutional Review Board.

Outcome definitions

The primary end point of incidence of asthma exacerbation was defined according to the following criteria: a morning peak flow of at least 30% below baseline for 2 or more consecutive days and 6 or more additional uses of short acting β-agonist reliever medication (1 puff = 1 reliever occasion) in a 24-hour period over baseline levels for 2 or more consecutive days; deterioration of asthma requiring treatment with oral corticosteroids; deterioration of asthma requiring treatment increase of 4 or more times the baseline dose of inhaled corticosteroids; deterioration of asthma requiring hospitalization; or deterioration, in the opinion of the investigator, of the patient's condition significant enough to be considered an asthma exacerbation. When a subject experienced an asthma exacerbation, he or she had completed the primary end point and was withdrawn from the study.¹⁵ This definition of exacerbation is consistent with other relatively short-duration clinical trials performed by the National Heart, Lung, and Blood Institute's Asthma Clinical Research Network (www.acrn.org).^{18,19}

Additional secondary end points analyzed in this genetic analysis included time (in days) to an asthma exacerbation and changes from baseline in pulmonary function and asthma symptom scores. Pulmonary function, including measurement of FEV₁ percent predicted, forced vital capacity percent predicted, and FEV₁/forced vital capacity ratio, were performed according to standard procedures by using Vitalograph, Inc (Buckinghamshire, United Kingdom), spirometric equipment according to American Thoracic Society guidelines.²⁰ Asthma symptom scores ranged from 0 to 4 and were reported by the participants in a daily diary. Questions used in this analysis are available in Table E1 in this article's Online Repository at www.jacionline.org. For all secondary end points, the weekly average change from baseline was evaluated at study completion for participants who finished the study (week 11 for diary symptom scores and visit 8 for in-clinic measurements) or the week before exacerbation or study withdrawal.

Genotyping and quality control methods

Twenty-one tagging and nonsynonymous SNPs in *IL4RA* were genotyped in 407 non-Hispanic white subjects. SNPs that tagged blocks of correlated *IL4RA* polymorphisms ($r^2 > 0.8$) were selected based on available genomic information (hapmap.org and ncbi.nih.gov/snp) to provide maximum coverage of common polymorphisms in the primarily non-Hispanic white participants who comprised the global clinical trial population. Genomic DNA was isolated and purified by PPD Central Laboratories (Richland Heights, Ky) and then shipped to Wake Forest for genotyping with the Sequenom MassARRAY iPLEX platform (Sequenom, Inc, San Diego, Calif). Standard genotyping quality control procedures

were performed by using the publicly available programs Plink version 1.07²¹ and Haploview version 4.2.²² On the basis of the quality control criteria of minor allele frequency (MAF) of greater than 5%, genotyping efficiency of greater than 80%, and consistency with Hardy-Weinberg equilibrium ($P > .01$, Fisher exact test), 19 *IL4RA* SNPs were included in genetic association tests. For all SNPs tested, MAFs were consistent across treatment groups. For example, the MAF for rs8832 in the placebo, 1-mg, 3-mg, and 10-mg treatment groups was 0.43, 0.41, 0.48, and 0.42, respectively. A list of *IL4RA* SNPs analyzed is presented in Table E2 in this article's Online Repository at www.jacionline.org, and a linkage disequilibrium plot and map of these SNPs is included as Fig E1 in this article's Online Repository at www.jacionline.org.

Statistical analysis

Pharmacogenetic analyses were performed by using *IL4RA* SNP genotype by exacerbation status contingency tables stratified by treatment status with an additive test for trend. An additive model is consistent with outcome values for heterozygotes intermediate to subjects homozygous for major and minor alleles. We tested the SNP association with the primary clinical outcome: exacerbations in subjects randomized to placebo and all doses of pitrakinra both pooled and each dose separately. To evaluate the pitrakinra dose response (placebo/1 mg/3 mg/10 mg), we developed contingency tables with exacerbation status by treatment assignment stratified by SNP genotypes (heterozygotes and subjects homozygous for minor allele combined). On the basis of these results, we also performed a subgroup analysis of subjects randomized to the 3- and 10-mg doses of pitrakinra.

Because participants with high blood eosinophil counts responded more effectively to pitrakinra,^{15,16} we tested SNP associations with exacerbations stratified by eosinophil counts (using designations of >350 cells/mm³ as high and ≤ 350 cells/mm³ as low). For continuous variables, general linear models were developed to test change from baseline by treatment assignment, adjusting for region and baseline values and stratified by genotype, as described above. We also used Kaplan-Meier plots with a log-rank test (each dose compared with placebo) to evaluate differences in time to exacerbation by treatment assignment stratified by SNP genotype. Statistical analyses were performed with Plink version 1.07,²¹ Haploview version 4.2,²² and SPSS/PASW version 18 (SPSS, Inc, Chicago, Ill). A 2-sided P value of less than .05 was considered statistically significant, and we adjusted for multiple comparisons by using Bonferroni correction based on our primary hypothesis.

RESULTS

Demographics

Demographic and baseline clinical characteristics, including lung function, total serum IgE levels, and fraction of exhaled nitric oxide (FENO) levels, of participants were similar for subjects in the overall intent-to-treat trial population ($n = 534$) and the genotyped non-Hispanic white subjects ($n = 407$) analyzed in this study (Table I).

Asthma exacerbations

In this pitrakinra 2b clinical trial the frequency of asthma exacerbations was 19.9% overall, and there were no significant differences in exacerbations in participants assigned to active pitrakinra doses compared with those assigned to placebo.¹⁵ In 407 genotyped non-Hispanic white subjects, exacerbations occurred in 80 participants (overall, 19.7%), and there were also no statistically significant differences in exacerbations by treatment assignment: 22 (20.6%) exacerbations in the placebo group, 20 (19.6%) exacerbations in the 1-mg group, 24 (23.3%) exacerbations in the 3-mg treatment group, and 14 (14.7%) exacerbations in the 10-mg treatment group. To test for significant differences in exacerbations by genotype, we analyzed *IL4RA* SNP genotype associations with asthma exacerbations stratified by treatment assignment (placebo and all doses of pitrakinra pooled). The frequency of exacerbations in subjects with the common GG genotype in the tagging SNP rs8832 who were receiving active pitrakinra (11%) was significantly reduced compared with that of subjects with the AG (22%) or AA genotypes (25%, $P = .03$), and this SNP was not associated with exacerbations in the placebo group.

Because there was evidence that *IL4RA* tagging SNPs might interact with pitrakinra treatment and identify a therapeutically responsive subpopulation, we then investigated a pitrakinra dose-response relationship (placebo/1 mg/3 mg/10 mg). The correlated SNPs ($r^2 = 0.75$) rs8832 (Fig 1, A) and rs1029489 (Fig 1, B) showed a similar dose-response relationship for subjects with the common GG genotype for either SNP ($P = .005-.009$). When individual doses of pitrakinra were compared with placebo within the rs8832GG genotype, there was a significant decrease in exacerbations at the 10-mg dose ($P = .03$), corresponding to a 22% overall reduction and an 88% relative reduction. Significant dose-response trends for subjects homozygous for the major allele were also observed for rs3024585, rs3024622, and rs4787956 ($P = .03$, data not shown). There were also no significant differences in baseline demographic or clinical characteristics between subjects with the rs8832GG genotype and subjects with AG/AA genotypes, which would confound these therapeutic associations with asthma exacerbations (see Table E3 in this article's Online Repository at www.jacionline.org).

In a subgroup analysis of participants randomized to 3- and 10-mg doses of pitrakinra only, subjects homozygous for the common alleles in 6 *IL4RA* SNPs were significantly less likely to have an asthma exacerbation than subjects with the minor allele, including rs8832 and rs3024530, which had the lowest P values (Fig 2, $P = .007$). Inversely, participants with the rs1110470 minor allele were less likely to experience exacerbations compared with subjects with the common allele (Fig 2). These SNPs were not associated with exacerbations in the placebo group. Additionally, a lower P value for association with asthma exacerbations in the combined 3- and 10-mg treatment groups was observed for 4 haplotypes that contain the rs8832 G allele (3, 4, 6, and 7 listed in Table II). As indicated by an odds ratio of less than 1, subjects with these haplotypes were less likely to experience exacerbations.

Secondary outcomes

Although there was little overlap between subgroups of participants with high blood eosinophil counts and the *IL4RA*/rs8832GG genotype,¹⁶ we explored the relationship

between the rs8832 genotype and exacerbations, as stratified by eosinophil counts. Subjects with the GG genotype receiving active pitrakinra (all doses combined) in the low-eosinophil-count group only were less likely to have an exacerbation (11%) than subjects with the AG (16%) or AA (24%) genotype ($P = .04$). There was no association with this SNP and asthma exacerbations in subjects with high blood eosinophil counts, although the number of subjects were smaller, and therefore our power to detect associations was lower in this group.

For subjects in the intent-to-treat population with high blood eosinophil counts, there was also a favorable pitrakinra treatment response for secondary end points related to increased time to exacerbations and asthma symptom scores.¹⁵ Therefore we explored these clinical end points in our pharmacogenetic analysis in all genotyped non-Hispanic white subjects. Kaplan-Meier plots were developed to test for significant differences in time to asthma exacerbation by treatment assignment stratified by *IL4RA* SNP genotypes. As shown in Fig 3, for subjects with the rs8832GG genotype, there were significant differences in time to asthma exacerbation for the subjects randomized to 10 mg of pitrakinra compared with those receiving placebo ($P = .02$, log-rank test). Similar results were noted for subjects homozygous for the common alleles in rs1029489 ($P = .005$, placebo vs 10-mg log-rank test) and rs4787956 ($P = .02$).

We also investigated *IL4RA* variation and changes in asthma symptoms. There was a dose-dependent reduction in nocturnal awakenings in subjects with the rs8832GG (Fig 4, A) and rs3024622CC (Fig 4, B) genotypes. Furthermore, activities limited by asthma remained similar to baseline or improved in subjects randomized to pitrakinra with the rs8832GG ($P = .009$), rs1029489GG ($P = .01$), and rs4787956AA ($P = .01$) genotypes.

Our primary hypothesis was that *IL4RA* amino acid changes or closely proximal SNPs at the 3' end of this gene would interact with responses to pitrakinra therapy (including rs1805011, rs1801275, rs8832, rs1029489, rs12102586, and rs4797956; see Fig E1). For our primary dose-response relationship analysis, rs8832 (adjusted $P = .05$) and rs1029489 (adjusted $P = .03$) were associated with a therapeutic response to this intervention after this correction.

DISCUSSION

This is the first large pharmacogenetic analysis of the T_H2-related IL-4/IL-13 inflammatory receptor in subjects with moderate-to-severe asthma. In this relatively short (12-week) trial, LABAs were tapered 4 weeks after initiation of blinded IL-4R α antagonist or placebo treatment, and inhaled corticosteroids were tapered and withdrawn subsequently. Although there was no overall significant difference between active IL-4R α therapy and placebo,^{15,16} therapeutic efficacy was observed by *IL4RA* genotype in this pharmacogenetic analysis. Consistent with our hypothesis that *IL4RA* variants were associated with a specific reduction in asthma exacerbations in subjects randomized to anti-IL-4R α receptor antagonist, the most consistent pharmacogenetic association was observed for the tagging SNP rs8832. Non-Hispanic white subjects homozygous for the rs8832GG common allele randomized to active pitrakinra experienced fewer exacerbations ($P = .03$), nocturnal

awakenings ($P = .04$), and asthma limitations in activities ($P = .009$) compared with subjects with the rs8832 A minor allele. More importantly, there was a significant dose-response relationship to this IL-4R α inhibitor for asthma exacerbations in subjects with the rs8832GG genotype, which was also observed for the correlated SNP rs1029489 (which remained significant after adjustment for multiple testing). A significant clinical response was observed for 4 haplotypes that contained the rs8832 common G allele associated with decreased exacerbations ($P = .0003-.0006$) in subjects randomized to 3 and 10 mg of pitrakinra. These results provide evidence that IL-4R α variation modulates therapeutic responses in asthmatic subjects and identifies a subgroup of subjects with moderate-to-severe persistent asthma who respond with reduced asthma exacerbations and symptoms. On the basis of extrapolation from the survival curve in Fig 3, we speculate that there might be a long-term positive effect for subjects with the rs8832GG genotype receiving active therapy compared with those receiving placebo.

This analysis is based on an earlier pharmacogenetic analysis that we performed on IL-4R α inhibition with pitrakinra to reduce late-phase allergen responses.¹² In this prior smaller allergen challenge study of 28 subjects, we identified 2 nonsynonymous variants in *IL4RA* (E400A and Q576R) and several other tagging SNPs that were associated with a reduction in delayed allergen responses. In addition, we supplemented these preliminary pharmacogenetic responses with an analysis of late-phase allergen responses in nonhuman primates, showing that IL-4R α inhibition reduces bronchial hyperresponsiveness and eosinophilia after antigen airway challenge.¹³ In this current analysis E400A and Q576R polymorphisms were not associated with asthma exacerbations and treatment responses, possibly because of small numbers of subjects in the previous analysis or differences in study design and primary outcome. However, in this pharmacogenetic analysis significant results were noted for the tagging SNPs rs2239347 and rs3024622, which were statistically associated with reduced late-phase antigen response and therapeutic pitra-kinra responses previously¹³ and were also predictors of reduction in exacerbations in subjects randomized to 3- and 10-mg doses of pitrakinra in this study. The most important pharmacogenetic associations were observed for the correlated SNPs rs8832 and rs1029489 ($r^2 = 0.75$), which were not associated with a therapeutic pitrakinra response in our previous small antigen-challenge studies.¹³ Although differences in the 2 studies can be caused by different therapeutic end points, our primary hypothesis that *IL4RA* variation identifies a subset of asthmatic subjects more responsive to IL-4R α inhibition was confirmed.

The pharmacologic mechanism for modulation of pitrakinra by rs8832 and rs1029489 is unknown because these tagging SNPs have no known function and reside in the *IL4RA* 3' untranslated region and the proximal gene region, respectively (see Fig E1). Additionally, because *IL4RA* SNPs significantly associated with clinical outcomes were common in the non-Hispanic white population (approximately 10% to 45% MAFs) and were chosen to "tag" correlated *IL4RA* variants, these SNPs might only be markers for a different functional variant, and further in-depth sequencing of the *IL4RA* 3' region might provide additional information regarding the functional mechanism of *IL4RA* interaction with pitrakinra. We speculate that genetic variants in the 3' untranslated region of the receptor might affect RNA stability or processing that could potentially interact to modulate T_H2 inflammation.

However, an important concept of this analysis is that it identifies a subset of subjects with severe persistent asthma who are responsive (33% of subjects with the rs8832GG genotype) to anti-IL-4R α therapy and also shows that the other 67% were not responsive. Without this genetic biomarker, these responsive subjects are not easily identified. Other approaches that include use of blood biomarkers, such as eosinophil counts, characterize a somewhat more responsive subset that is not as specific as these pharmacogenetic findings. For example, subjects with the rs8832GG genotype had a greater relative reduction in asthma exacerbations at the 10-mg level compared with placebo than the group with high blood eosinophil counts.^{15,16} This genetic variant might potentially represent an excellent predictive genetic marker for therapeutic responses to anti-IL-4R α receptor intervention. However, the predictive value of variation in *IL4RA* needs to be further replicated in additional studies with either pitrakinra or other biologic therapies that target IL-4, IL-13, or their receptor, perhaps by using a genotyped stratified trial design.^{23,24} These pharmacogenetic approaches could lead to targeted therapies in this pathway. A similar method has been recently proposed for anti-IL-13 treatment and predictive responses in asthmatic patients with higher serum periostin levels or higher levels of FENO.¹⁰ These biomarkers identify a subset of asthmatic subjects more responsive to an IL-13 antibody.⁵ Periostin, FENO, and other biomarkers also require replication and could potentially be used in conjunction with pharmacogenetic analysis.

In this important pharmacogenetic study, we were able to take advantage of comprehensive pharmacologic and phenotype information to evaluate the therapeutic interaction between *IL4RA* variants and different doses of pitrakinra, an IL-4 receptor antagonist. These results provide novel evidence that in non-Hispanic white subjects with moderate-to-severe asthma with a common genotype, the rs8832GG genotype treated with this anti-IL-4R α inhibitor demonstrates a significant dose-dependent reduction in asthma exacerbations and improved outcomes for several other asthma-related clinical end points. Thus these results represent one of the first examples of a pharmacogenetic effect based on receptor variation that identifies a subset of subjects with severe asthma who respond to a new biologic intervention. These analyses provide a basis for understanding therapeutic heterogeneity in asthmatic subjects and are an important step toward paradigms that are based in individualized or stratified treatments in subjects with asthma and other common disorders.

Supplementary Material

Refer to Web version on PubMed Central for supplementary material.

Acknowledgments

We thank Carla Martin, Shelly Smith, and Siqun (Lilly) Zheng at the Wake Forest Center for Genomics and Personalized Medicine Research for genotyping assistance.

Supported by Aerovance, Bayer Healthcare, and the National Institute of Heart, Lung, and Blood grants HL065899, HL101487, and HL089992.

Abbreviations used

FENO	Fraction of exhaled nitric oxide
IL4RA	IL-4 receptor α gene
LABA	Long-acting β -agonist
MAF	Minor allele frequency
SNP	Single nucleotide polymorphism

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Clinical implications: Pharmacogenetic analysis of the *IL4RA* gene identified a subgroup of asthmatic subjects by genotype who were more responsive to therapy with an IL-4/IL-13 pathway antagonist.

FIG 1.

Exacerbations by treatment assignment stratified by *IL4RA* SNP genotype. There was a significant dose-response trend for treatment response to exacerbations in subjects homozygous for the rs8832GG genotype (**A**) and the GG genotype in the correlated SNP rs1029489 (**B**).

FIG 2.

IL4RA variants associated with exacerbations. Seven *IL4RA* SNPs were significantly associated with asthma exacerbations by genotype in participants randomized to 3- and 10-mg doses of pitrakinra. The dashed line indicates overall exacerbation frequency (19.7%) in genotyped non-Hispanic white subjects.

FIG 3.

Kaplan-Meier plot for time to exacerbation by treatment assignment for subjects with the rs8832GG genotype. On study day 28, LABAs were withdrawn, and inhaled corticosteroids were stepped down on study days 42 and 56 and stopped completely on day 70. There was a significant difference in time to exacerbation by survival time analysis for subjects with the rs8832GG genotype randomized to 10 mg of pitrakinra compared with placebo. *P* values are from log-rank tests.

FIG 4.

IL4RA polymorphisms predict change in nighttime awakenings caused by asthma. There was a significant dose-response trend for change in nighttime awakenings by treatment assignment (placebo/1 mg/3 mg/10 mg) observed for subjects with the common rs8832GG genotype (**A**) and participants with the common rs3024622CC genotype (**B**). There was no significant trend for participants with the minor allele in these SNPs. CFB, Change from baseline.

TABLE I

Baseline characteristics of the global intent-to-treat pitrakinra clinical trial population and genotyped non-Hispanic white participants analyzed in this study

Characteristic	Non-Hispanic white genotyped subjects (n = 407)	Global intent-to-treat population (n = 534)
Sex (% female)	59	59
Ethnicity (% non-Hispanic white/African American/Hispanic/other)	—	88/8/3/2
Recruitment country (% United States/Europe)	41/59	48/52
Age at enrollment (y)	45.1 ± 13.8	45.4 ± 13.7
Body mass index (kg/m ²)	29.4 ± 6.3	30.0 ± 7.5
Baseline lung function		
FEV ₁ (% predicted)	72.3 ± 11.3	72.9 ± 11.5
FVC (% predicted)	84.4 ± 12.3	85.3 ± 12.6
FEV ₁ /FVC ratio	69.0 ± 10.3	68.9 ± 10.2
Blood eosinophils (cells/mm ³)	265 ± 216	265 ± 210
Total serum IgE (IU/mL [*])	356.5 ± 733	405.3 ± 850.1
FENO (ppb)	19.3 ± 15.6	18.9 ± 14.7

FVC, Forced vital capacity.

* One outlier removed.

TABLE II

IL4RA 5-SNP sliding window haplotypes and association with asthma exacerbations in non-Hispanic white subjects randomized to 3 and 10 mg of piritakinra treatment

Haplotype	rs3024585	rs3024622	rs4787423	rs1805011 (E400A)	rs1801275 (Q576R)	rs8832	rs1029489	rs12102586	rs4787956	Frequency	Odds ratio	P value*
1	G	C	T	A	A					0.4	0.35	.001
2		G	T	A	A	A				0.25	1.34	.35
3		C	T	A	A	G				0.38	0.30	.0003
4			T	A	A	G	G			0.4	0.33	.0006
5				A	A	A	A	C		0.34	1.65	.07
6				A	A	G	G	C		0.43	0.34	.0006
7					A	G	G	C	A	0.42	0.38	.001

Selected *IL4RA* haplotypes from the 3' end and the proximal gene region with frequencies of greater than 10% are shown, with *P* values and odds ratios for association with asthma exacerbations. An odds ratio of greater than 1 indicates a haplotype is associated with increased exacerbations.

* *P* values adjusted for geographic region in logistic regression models.