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Augmentation of bronchodilator responsiveness by leukotriene modifiers in Puerto Rican and Mexican children

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Abstract

Background: Ethnic-specific interactions between different asthma medications are not well described.

Objective: To determine whether the use of leukotriene modifiers is associated with the magnitude of bronchodilator responsiveness among Mexican American and Puerto Rican children with persistent asthma.

Methods: A cross-sectional study of 84 Mexican American and 192 Puerto Rican children with persistent asthma who were aged 8 to 16 years. Within each group, bronchodilator responsiveness to albuterol, objectively assessed via spirometry, was compared between participants using leukotriene modifiers and those not using leukotriene modifiers.

Results: Leukotriene modifier use was associated with a clinically significant increase in percentage change in forced expiratory volume in 1 second of 11.8 ($P < .001$) in Puerto Rican children, but there was no significant change in percentage change in forced expiratory volume in 1 second (-3.2 , $P < .57$) in Mexican American children. This finding persisted after controlling for the use of inhaled corticosteroids. In addition, among the Puerto Rican children, the association

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between leukotriene modifier use and augmented bronchodilator responsiveness was greatest in those younger than 12 years.

Conclusions: Among children with persistent asthma, use of leukotriene modifiers is associated with augmented bronchodilator responsiveness to albuterol in Puerto Ricans, but not Mexican Americans. This ethnic-specific, drug-drug interaction highlights the need for the further understanding of asthma pharmacogenetics among children from different ethnic groups to improve asthma outcomes.

INTRODUCTION

Guidelines for asthma management recommend the use of inhaled corticosteroids (ICSs) or leukotriene modifiers as primary therapies for all patients with persistent asthma.¹ In addition to these controller therapies, short-acting β_2 -agonists are recommended for all persons with asthma as the mainstay of rescue therapy for acute asthma exacerbations; therefore, optimizing the response to short-acting β_2 -agonists is of paramount importance. Unfortunately, response to short-acting β_2 -agonists is not the same across all populations. For example, it was previously shown that Puerto Ricans with asthma have lower bronchodilator responsiveness to albuterol than Mexicans with asthma.² It is unknown whether similar ethnic-specific differences in drug responsiveness exist for controller medications.

The identification of racial and ethnic-specific differences in medication responsiveness is an important area of study, not only because certain ethnic groups (Latinos in particular) are the fastest growing population in the United States,³ but also because asthma disproportionately affects children from certain ethnic groups.^{4–6} Puerto Ricans, for example, have 1 of the highest levels of asthma-related morbidity and mortality in the country.^{4,5} Although socioeconomic and environmental factors may account for some of the disparities seen in outcomes for individuals of different ethnicities,⁷ ethnic-specific differences in drug responsiveness may be another explanation.

As part of the Genetics of Asthma in Latino Americans (GALA) study, ethnic-specific pharmacogenetic differences between Puerto Rican and Mexican persons with asthma were previously reported.^{2,8} Because ethnic-specific differences in drug responses are well documented,^{9–12} we reasoned that ethnic-specific differences in drug-drug interactions also exist between populations. The purpose of the current study was to determine whether the use of leukotriene modifiers is associated with the magnitude of bronchodilator responsiveness to albuterol in Mexican American and Puerto Rican children with persistent asthma. This was investigated in the individuals recruited for the GALA study via post hoc analysis of the collected data. A potential drug-drug interaction between leukotriene modifiers and albuterol was postulated because leukotrienes attenuate the activity of β_2 -agonists on smooth muscle cells¹³ and, therefore, leukotriene modifiers may act to block this process and augment bronchodilator responsiveness to albuterol.

METHODS

Study Participants

The participants in this study were recruited as part of the GALA study from 1998 to 2001.^{2,8} Because the goal of the current study was to identify differences among ethnic groups in the United States, only participants recruited from sites within the United States and Puerto Rico were included. Investigators recruited participants from the San Francisco Bay area (Mexican Americans) and from New York City and Puerto Rico (Puerto Ricans), as previously described.^{2,8} A total of 84 Mexican American and 192 Puerto Rican children were included in the study.

Eligible participants for the current study were between the ages of 8 and 16 years; had physician-diagnosed asthma; had symptoms of coughing, wheezing, or shortness of breath for at least 2 years; and had all biological parents and grandparents identified as Puerto Rican or Mexican American. Excluded participants had more than a 10 pack-year smoking history, smoked in the previous 12 months, and/or had a history of other lung diseases. Local institutional review boards approved the study.

Clinical Data Collection

After obtaining age-appropriate informed consent and assent, a trained interviewer administered the modified version of the 1978 American Thoracic Society–Division of Lung Diseases Epidemiology Questionnaire,¹⁴ as previously described.² The medications (montelukast, zafirlukast, and zileuton) were all categorized as “leukotriene modifiers” and were not distinguished.

Pulmonary function was evaluated using spirometry performed to American Thoracic Society standards¹⁵ before and 15 minutes after the administration of albuterol, as previously described.² Baseline forced expiratory volume in 1 second (FEV₁) is reported as pre-FEV₁, and postbronchodilator FEV₁ is reported as post-FEV₁. Bronchodilator responsiveness is reported as percentage change in FEV₁ ($\% \text{ FEV}_1$) ($[\text{post-FEV}_1 - \text{pre-FEV}_1] \times 100 / \text{pre-FEV}_1$ [all FEV₁ values given in liters]). Spirometric reference values from Hankinson et al¹⁶ were used to determine percentage predicted values. The reference values generated for Mexican Americans were also used for the Puerto Ricans because no reference values were available for this ethnic group.

Asthma Severity

Participants were classified as having either intermittent or persistent asthma based on data gathered from the 1978 American Thoracic Society–Division of Lung Diseases Epidemiology Questionnaire and pulmonary function testing. The “persistent” classification combines the “mild persistent,” “moderate persistent,” and “severe persistent” classifications of the National Asthma Education and Prevention Program¹⁷ into 1 group. Only participants who met the criteria for persistent asthma were included in this evaluation.

Participants were classified as having persistent asthma if they met 1 of the following criteria: (1) without respect to medications used, the participant has had daily asthma

symptoms for 3 or more months of the year, (2) the patient has experienced nocturnal asthma for more than 1 night per week for 3 or more months of the past year, and (3) the FEV₁ is less than 80% of the race-corrected predicted value (measured at the study visit).

Statistical Analysis

Participants were stratified by ethnicity, followed by comparison of demographic characteristics, clinical characteristics, and medication use. These comparisons were performed with the unpaired 2-tailed *t* test (continuous variables) and the χ^2 test (categorical variables).

The primary end point was the association between leukotriene modifier use and bronchodilator responsiveness to albuterol. This was evaluated by comparing mean % FEV₁ (as described in the “Clinical Data Collection” section) of participants using leukotriene modifiers with mean % FEV₁ of those not using leukotriene modifiers (% FEV₁ of leukotriene modifier users – % FEV₁ of leukotriene modifier non-users), and this difference was described as the “difference in mean % FEV₁.” This analysis was performed with multiple linear regression with inclusion of variables for pre-FEV₁ and an interaction term between leukotriene modifier use and pre-FEV₁ (medication use $\times$ pre-FEV₁). Pre-FEV₁ was included in the analysis because of the greater potential bronchodilation expected in participants with more severe airway obstruction (low pre-FEV₁). The interaction term was included because the effect of leukotriene modifier use on bronchodilator responsiveness may be more substantial in patients with severe airway obstruction (low pre-FEV₁). The following variables were included in the statistical model because of their potential confounding effects on the response to leukotriene modifiers or albuterol but were not included in the final analysis, except where noted, because none of them had statistically significant effects on the results: asthma duration, age, sex, plasma IgE levels (log-transformed values), recruitment center, allergic rhinitis, family history of atopy, tobacco smoke exposure, asthma medications, and interaction terms between specific medications used and pre-FEV₁ (medication use $\times$ pre-FEV₁). For face validity, the primary analysis was repeated with the inclusion of variables for age, sex, ICS use, and an interaction term between ICS use and pre-FEV₁. Influential data points were identified by graphically plotting DFBETA values of the regression model, and the primary analysis was repeated with exclusion of outliers. STATA V.9.1 software (STATA, College Station, Texas) was used for these analyses.

Because this study involved secondary data analysis, sample size calculations were performed to ensure that the study was adequately powered to detect a clinically meaningful difference between participants using leukotriene modifiers and those not using leukotriene modifiers. With the sample sizes and 95% confidence intervals reported later, the study was capable of identifying a 6% difference in mean % FEV₁ in the Puerto Rican participants and a 10% difference in the Mexican American participants, with an $\alpha = .05$ and a power of 0.8. Conversely, 55 Puerto Rican participants and 65 Mexican American participants would be necessary to detect a 12% difference in % FEV₁ in each group, with an α of .05 and a power of 0.8. The American Thoracic Society considers a 12% change in FEV₁ as clinically significant¹⁸; therefore, the sample sizes were determined to be adequate.

RESULTS

Participant Characteristics

A summary of variables pertinent to this analysis is presented in Table 1. A total of 443 individuals aged 8 to 16 years were recruited for the GALA study from sites within the United States. Of these individuals, 276 had persistent asthma and were included in the current analysis. Participants were categorized as having persistent asthma based on symptoms and/or a baseline FEV₁ of less than 80% of the predicted value. More Puerto Rican participants (46%) than Mexican American participants (21%) had a baseline FEV₁ of less than 80% of the predicted value ($P < .001$).

Mexican American and Puerto Rican participants were similar for all characteristics, except that Puerto Ricans had a lower baseline FEV₁ and baseline percentage predicted FEV₁, an earlier onset of asthma, and a longer duration of asthma. The lower baseline FEV₁ in Puerto Ricans persisted even after adjustment for age, sex, and body mass index. Puerto Ricans from New York City (32 [17%]) and Puerto Rico (160 [83%]) were similar, except for a lower baseline FEV₁ in the New York City participants (1.71 vs 1.98 L; $P = .03$).

The details of medication use by participants are presented in Table 2.

Lung Function Measurements and Bronchodilator Responsiveness

All participants.—Among participants not using leukotriene modifiers, the mean (95% confidence interval) % FEV₁ was greater for Mexican Americans than for Puerto Ricans (9.7 [7.0 to 12.3] vs 6.2 [4.3 to 8.1]; $P = .04$), indicating lower baseline bronchodilator responsiveness to albuterol in Puerto Ricans compared with Mexican Americans.

To determine if use of a leukotriene modifier was associated with augmented bronchodilator responsiveness to albuterol, the difference in mean % FEV₁ was compared between participants who were not using leukotriene modifiers and those who were using leukotriene modifiers. In Puerto Ricans, but not in Mexican Americans, the use of a leukotriene modifier was associated with augmented bronchodilator responsiveness (Fig 1A). The adjusted difference in mean (95% confidence interval) % FEV₁ for Puerto Ricans was 11.8 (6.2 to 17.3) ($P < .001$) compared with −3.2 (−14.4 to 8.0) ($P = .57$) for Mexican Americans. Adjusting for age, sex, and ICS use did not significantly affect the outcomes, with the difference in mean % FEV₁ (95% confidence interval) for Puerto Ricans being 11.7 (5.6 to 17.8) ($P < .001$) compared with −1.1 (−11.6 to 9.4) ($P = .84$) for Mexican Americans. Adjusting for all the potential confounders previously described yielded similar results, with a difference in mean % FEV₁ (95% confidence interval) for Puerto Ricans of 9.1 (0.1 to 18.1) ($P = .047$) compared with −14.2 (−50.0 to 21.6) ($P = .42$) for Mexican Americans. The results of the primary analysis did not differ for Puerto Ricans recruited from different sites, with Puerto Ricans from New York City having a difference in mean % FEV₁ (95% confidence interval) that was 3.5 (−8.6 to 1.7) ($P = .18$) lower than that of Puerto Ricans from Puerto Rico.

As demonstrated in Figure 2, improvements in bronchodilator responsiveness associated with leukotriene modifier use were greatest in those Puerto Rican participants who had the

lowest baseline FEV₁. Specifically, for every 200-mL decrease in baseline FEV₁, leukotriene modifier use was associated with a mean 2.9% (95% confidence interval, 1.0% to 4.8%) ($P = .003$) greater augmentation in bronchodilator responsiveness to albuterol.

Participants using corticosteroids.—It is possible that corticosteroid use may diminish or mask the ability of leukotriene modifiers to augment bronchodilator responsiveness. Because all Mexican Americans using leukotriene modifiers were also using corticosteroids, the analyses were repeated with the inclusion of only those participants in each ethnic group who were using corticosteroids.

For participants not using leukotriene modifiers but using corticosteroids of any type, the mean % FEV₁ (95% confidence interval) was again greater for Mexican Americans (10.7 [8.0 to 13.4]) than for Puerto Ricans (6.2 [3.8 to 8.6]) ($P = .01$). Figure 1B shows the association between leukotriene modifier use and bronchodilator responsiveness in individuals concomitantly using corticosteroids. In Puerto Ricans, but not in Mexican Americans, the use of a leukotriene modifier was associated with greater bronchodilator responsiveness. The adjusted difference in mean % FEV₁ (95% confidence interval) for Puerto Ricans was 11.5 (5.0 to 18.1) ($P = .001$) compared with -5.6 (-17.2 to 5.9) ($P = .33$) for Mexican Americans.

Adolescents.—Because lung function is different in childhood compared with adolescence,^{19,20} the difference in mean % FEV₁ was evaluated in Puerto Rican participants stratified by age to determine if leukotriene modifier use was associated with different degrees of bronchodilator responsiveness in young children compared with adolescents. Similar analyses were not performed for the Mexican American participants because the number of participants using leukotriene modifiers was too small to stratify into separate age groups. Twelve years of age was arbitrarily chosen as the cutoff for adolescence. Although leukotriene modifier use was associated with greater bronchodilator responsiveness in both age groups, a greater association was seen in the preadolescent participants compared with the adolescent participants (13.5 [6.8 to 20.2] vs 5.7 [-4.2 to 15.6]; $P < .001$).

DISCUSSION

This evaluation demonstrates that the use of leukotriene modifiers is associated with augmented bronchodilator responsiveness to albuterol in Puerto Rican, but not Mexican American, children with persistent asthma. The differing association between leukotriene modifier use and bronchodilator responsiveness among ethnic groups is unique and clinically important because leukotriene modifiers are recommended agents for the treatment of persistent asthma and are frequently used as first-line agents.¹ Although not addressed in the current investigation, it is possible that this ethnic-specific, drug-drug interaction is due to the differential distribution of genetic determinants in different ethnic populations.

In this same cohort of participants used for the present evaluation, we reported that Puerto Ricans have lower baseline bronchodilator responsiveness to albuterol than Mexican Americans.² The current analysis suggests that this lower responsiveness may be overcome

with the use of leukotriene modifiers as a controller therapy. If these results are confirmed in prospective studies, this may direct the choice of controller regimens for Puerto Rican children toward the addition of a leukotriene modifier.

We also found that the association between leukotriene modifier use and bronchodilator responsiveness to albuterol is age dependent. Among Puerto Rican participants, the greatest degree of association between leukotriene modifier use and augmented bronchodilator responsiveness was seen among the preadolescents, suggesting that this age group may experience a greater benefit from the use of leukotriene modifiers than older children. It is also possible that the adolescents had a greater degree of noncompliance regarding their use of leukotriene modifiers, which may have led to these findings.

Puerto Ricans had a more severe asthma phenotype than Mexican Americans, which has previously been reported.^{2,4,6,21} Puerto Ricans have some of the highest rates of asthma-related morbidity among all ethnic groups in the United States, including Latinos.^{4,21} The cause of these differences in asthma-related morbidity appears to be secondary to both genetic differences between different ethnic groups^{8,22} and external factors, such as access to medications and socioeconomic status.²³ Furthermore, suboptimal adherence to asthma guidelines by treating physicians is a well-described problem that can lead to increased asthma morbidity. This was apparent in our study as demonstrated by the fact that not all participants were using a controller medication (Table 2), but the rates of controller medication underuse were similar to or less than those reported by other investigators.^{24,25}

In the current study, Mexican Americans had a higher baseline FEV₁ and were more likely to use corticosteroids than Puerto Ricans, 2 variables that could lead to a limited ability of leukotriene modifiers to improve bronchodilator responsiveness. Nonetheless, these possibilities were accounted for in the statistical analysis by adding relevant interaction terms into the regression model, and leukotriene modifiers were still found to augment bronchodilator responsiveness only in Puerto Ricans. Furthermore, the lack of confounding effects by corticosteroids was confirmed by obtaining essentially unchanged results when the analysis was repeated with the inclusion of only those individuals using corticosteroids. The finding that leukotriene modifiers appear to have an added benefit on bronchodilator responsiveness even in the setting of concomitant corticosteroid use is consistent with previous reports, which have demonstrated that the addition of a leukotriene modifier to an ICS improves asthma outcomes.^{26–28}

Although our results are internally consistent, they are tempered by the limitations of cross-sectional study design, such as the inability to adjust for all potential confounders, including unknown and unmeasured confounders. Relevant confounders we were unable to adjust for include certain environmental exposures (such as air pollution), adherence to medications, and within-participant responses while taking and not taking leukotriene modifiers. Stemming from the latter point is the possibility that the Mexican American group was inadvertently enriched with leukotriene modifier nonresponders and that this led to the differences seen between the 2 ethnic groups. Furthermore, specific leukotriene modifiers were not differentiated from one another. As such, it is unknown whether our findings are related to 1 specific leukotriene modifier or to this class of medications as a whole. Although

duration of leukotriene modifier therapy was not ascertained, effects related to duration of use are unlikely to be of clinical significance because leukotriene modifiers have been shown to have an onset of action within 24 hours of dosing.²⁹ The use of convenience sampling may have led to a sampling bias. Because participants were not chosen in a completely random fashion for inclusion in the study, it is possible that the Puerto Rican group was inadvertently enriched with leukotriene modifier responders or that the Mexican American group was inadvertently enriched with nonresponders.

Although there was an imbalance between the number of Mexican American and Puerto Rican asthma cases and the number of Mexican Americans using leukotriene modifiers was small, the study was adequately powered to detect at least a 12% difference in FEV₁, which is the smallest difference in FEV₁ that is generally accepted as being clinically significant.¹⁸ It is interesting to speculate that the limited use of leukotriene modifiers by Mexican Americans seen in this study may be because these individuals had experienced no clinical response to these medications and had subsequently discontinued their use. Of course, this difference in leukotriene modifier use between Mexican Americans and Puerto Ricans may also have been secondary to different prescribing practices in the different centers from which the participants were recruited. Finally, there may have been misclassification of participants as leukotriene modifier users or nonusers because the degree and intensity of the use of these medications likely varied between participants.

In conclusion, this study demonstrates that the use of leukotriene modifiers is associated with augmented bronchodilator responsiveness to albuterol in Puerto Rican, but not Mexican American, children with persistent asthma. This finding was particularly significant among Puerto Rican children younger than 12 years. If these results are replicated and validated in independent cohorts, they may have important clinical significance because identification of beneficial, ethnic-specific, drug-drug interactions may improve outcomes in ethnic groups, such as Puerto Ricans, who have the highest rates of asthma-related morbidity and mortality in the country. Furthermore, these findings highlight the need for an improved understanding of how medications, ethnicity, age, and other factors interact to affect asthma outcomes, particularly in those subgroups experiencing the highest burden of asthma, such as certain ethnic groups and children.

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Figure 1.

Association between leukotriene modifier (LM) use and bronchodilator responsiveness. After adjustment for confounders, LM use was associated with increased bronchodilator responsiveness in Puerto Ricans (n = 163) but not in Mexican Americans (n = 73) (A). In only participants using corticosteroids, LM use was associated with increased bronchodilator responsiveness in Puerto Ricans (n = 128) but not in Mexican Americans (n = 35) (B). Data are given as adjusted means and corresponding 95% confidence intervals. % FEV₁ indicates percentage change of forced expiratory volume in 1 second.

Figure 2.

Effect of baseline forced expiratory volume in 1 second (FEV₁) on the association between leukotriene modifier use and bronchodilator responsiveness in Puerto Ricans. In Puerto Rican participants not using leukotriene modifiers, bronchodilator responsiveness to albuterol was independent of baseline FEV₁ (1.1% decrease in percentage change in FEV₁ for each 1-L decrease in baseline FEV₁; $P = .46$) (A). In participants using leukotriene modifiers, the mean (95% confidence interval) bronchodilator responsiveness to albuterol increased as baseline FEV₁ decreased (14.5% [5.2% to 24.0%] increase in percentage change in FEV₁ for each 1-L decrease in baseline FEV₁; $P < .001$) (B). Solid lines represent fitted regression lines; shaded areas, 95% confidence intervals of the mean.

Table 1.

Characteristics of Participants, Stratified by Ethnicity^a

Characteristic	Mexican Americans (n = 84)	Puerto Ricans (n = 192)	P value
Age, y	11.4 (9.8–13.2)	10.8 (9.3–12.8)	.15
Male sex, %	61.9	58.1	.56
Asthma onset, y	4 (2–7)	1 (0–2)	<.001
Asthma duration, y	7 (4–9)	9(7–11)	<.001
FEV ₁ value			
Baseline	2.11 (1.86–2.71)	1.91 (1.52–2.31)	<.001
Baseline % predicted	93.0(81.6–101.7)	80.5 (72.0–90.7)	<.001
Allergic rhinitis, %	82.1	80.7	.78
Serum IgE level, IU/mL	251 (106–623)	273 (89–605)	.89
Parental smoking, %			
Current	16.4	28.5	.07
Before the age of 2 y	31.1	31.8	.93
Participant ever smoked, %	0	2.4	.45

Abbreviation: FEV₁, forced expiratory volume in 1 second.

^aData are given as median (25th–75th percentile) unless otherwise indicated. Serum IgE data were available for 81 Mexican Americans and 175 Puerto Ricans. Parental smoking data were available for 61 Mexican Americans and 151 Puerto Ricans. Participant smoking data (“ever smoked”) were available for 23 Mexican Americans and 41 Puerto Ricans 13 years or older.

Table 2.

Medication Use Stratified by Ethnicity and Leukotriene Modifier Use

Medication	All participants			Non-leukotriene modifier users			Leukotriene modifier users		
	Mexican Americans (n = 84) ^a	Puerto Ricans (n = 192) ^a	P value	Mexican Americans (n = 73) ^a	Puerto Ricans (n = 142) ^a	P value	Mexican Americans (n = 11) ^a	Puerto Ricans (n = 50) ^a	P value
Leukotriene modifier	13.1	26.0	.02	0	0	NA	100.0	100.0	NA
Short-acting β_2 -agonist	98.8	96.9	.35	98.6	97.9	.70	100.0	94.0	.41
Long-acting β_2 -agonist	9.5	4.7	.12	5.5	2.8	.33	36.4	10.0	.03
Any steroid	79.8	55.7	<.001	76.7	50.0	<.001	100.0	72.0	.05
Inhaled steroid	76.2	41.7	<.001	74.0	33.1	<.001	90.9	66.0	.10
Oral steroid	8.3	22.4	.005	8.2	22.5	.009	9.1	22.0	.34
Theophylline	1.2	4.7	.15	0	5.6	.04	9.1	2.0	.24
Cromolyn	11.9	7.3	.21	13.7	7.7	.17	0	6.0	.41

Abbreviation: NA, data not applicable.

^aData are given as percentages.