Impact of the Arg 16 allele of the B2AR gene on the effect of withdrawal of LABA in patients with moderate to severe asthma

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Abstract

Introduction: Long-acting beta agonists (LABAs) are effective for controlling asthma, however questions about their safety have led to concerns over use. Genetic polymorphisms at the 16 amino acid position of the beta-2 adrenergic receptor gene (B2AR) may be associated with increased risk. Methods: A randomized, double blind study was conducted in patients with moderate to severe asthma being treated with combined inhaled corticosteroids/LABA (ICS/LABA), comparing the effect of LABA continuation versus withdrawal on asthma outcomes among patients stratified by B2AR genotype (Arg/Arg vs. Gly/Gly at the 16th amino acid position). Results: 67 participants (31 Arg/Arg, 36 Gly/Gly) were randomized to receive fluticasone alone (F) or continue combined fluticasone/salmeterol (F/S) after a run-in period on F/S. Among Gly/Gly subjects, those in the F/S treatment group showed improvement in AM PEFR (+8.4 L/s) whereas those receiving F alone experienced a reduction in AM PEFR over the study period (−14.4 L/s), (p = 0.06). There was no significant difference in morning peak expiratory flow rate (AM PEFR) in Arg/Arg participants randomized to receive F/S (−15.7 L/s) vs F alone (−5.6 L/s) (p = 0.61). There was no significant difference in exacerbations in the Arg/Arg subjectstreated with F/S compared with those treated with F (p = 0.65). Conclusions: Withdrawal of LABA therapy in asthmatics with the Arg/Arg genotype at the 16th amino acid position of B2AR did not lead to significant improvement in AM PEFR. LABA withdrawal in the Gly/Gly genotype however led to a borderline significant decline in AM PEFR.

Introduction

Beta-2 agonists are the most commonly used bronchodilators for the treatment of asthma. There are several functional variants of the gene encoding the beta-2 adrenergic receptor (B2AR), including one distinguished by a single nucleotide polymorphism (SNP) encoding a substitution of arginine for glycine at the 16th amino acid position of the receptor. Asthma patients homozygous for this arginine variant (Arg/Arg) have been shown in some studies to experience a decline in lung function [1] or increase in asthma exacerbations [2] when treated with daily short acting beta agonists (SABAs). The safety of long-acting beta agonists (LABAs) has also been called into question. One large prospective study demonstrated that asthmatics randomized to the LABA salmeterol had increased asthma morbidity and mortality compared with a control group not taking salmeterol [3]. Subsequent studies have identified genotype-attributable detrimental effects on outcomes associated with LABA use [4,5]. Wechsler, in a retrospective study, found that asthmatics with the Arg/Arg genotype demonstrated a lack of benefit from LABA treatment, with or without concomitant inhaled corticosteroids (ICS), compared to Gly/Gly participants [5].

Risks associated with LABA use have not been consistently demonstrated [6, 7]. In a large genotype-stratified prospective trial, gains in lung function associated with salmeterol use were equivalent for Arg/Arg and Gly/Gly participants, with no difference in rates of asthma exacerbation [7]. The need for additional studies to clarify the safety of LABAs in asthma has been raised by experts in the field [8–10] and by the FDA [11]. The FDA has recommended ‘LABAs should be used for the shortest duration of time required to achieve control of asthma symptoms and discontinued, if possible, once asthma control is achieved.’ However, a number of studies have demonstrated that asthma control can be jeopardized by discontinuation of the LABA component of ICS/LABA combination regimens [12–14].

A prospective study examining the effect of LABA discontinuation on asthma outcomes among patients stratified by
B2AR genotype (Arg/Arg vs. Gly/Gly at the 16th amino acid position) is particularly important in light of genotype specific findings and recommended guidelines. In the randomized, double blind clinical trial reported here, adults with moderate or severe persistent asthma with either the Arg/Arg or Gly/Gly genotype and receiving combination ICS/LABA therapy were randomized to continue treatment with an ICS/LABA combination or step down to the equivalent dose of ICS with removal of LABA. Objective measures of lung function, asthma quality of life, asthma control and exacerbations were evaluated in each of the four groups.

Methods

Study participants were recruited from Columbia University Medical Center affiliated faculty practices and clinics in allergy and asthma in New York City and New Jersey, and Hackensack University Medical Center in Hackensack, New Jersey between July 2007 and July 2010. The study was approved by both Institutional Review Boards (ClinicalTrials.gov number, NCT00521222). All participants were age 18 years or older with physician diagnosed moderate or severe persistent asthma and were receiving treatment with combined ICS/LABA. Severity was based on NAEPP criteria. After providing informed consent, all potential study participants underwent genetic screening for beta-2 adrenergic receptor genotype, and those homozygous for the arginine or glycine variant at the 16th amino acid position (Arg/Arg or Gly/Gly) were eligible to participate. (For exclusion criteria see Selected Methods in the Supplementary Appendix).

Study design and procedures

Following screening, participants entered a 6-week run-in phase during which they continued treatment with an ICS/LABA (Advair HFA®, 45 mcg, 115 mcg or 230 mcg of fluticasone propionate with 21 mcg of salmeterol, 2 puffs every 12 hours) with dose matched to the subject’s medical regimen at enrollment (Figure 1). Ipratropium bromide was provided for use as rescue therapy with instructions to use albuterol only if asthma symptoms were not responsive to ipratropium. Beginning with the run-in phase, participants were asked to complete daily diary cards which included daily reporting of morning and evening peak expiratory flow rate (PEFR), use of rescue medication, daily dose of controller therapy, absence from school or work, nocturnal awakenings, unscheduled health care visits, and daily asthma symptom score on a scale of 0–3 (Table S1).

At completion of the run-in phase, participants with FEV1 ≥ 70% predicted were randomized to either continuation of combination therapy with fluticasone/salmeterol (F/S) at the same dose used during the run-in or fluticasone (F) alone at a comparable corticosteroid dose (Flovent HFA®, 44 mcg, 110 mcg or 220 mcg/fluticasone propionate spray) for a 16-week treatment period (Figure 1). Randomization was stratified by genotype (Arg/Arg or Gly/Gly) and FEV1% predicted (≥ 85% or < 85%). Randomization was carried out by the Columbia University Research Pharmacy using the Microsoft Excel random number generator. Investigators and research staff were kept blinded to the genotype and study drug assignment. HFA devices were blinded and distributed by the Columbia University Research Pharmacy.

Baseline measures collected at randomization included Juniper Mini Asthma Quality of Life Questionnaire score (MiniAQLQ)[15], Juniper Asthma Control Questionnaire score (ACQ) [16] and Asthma Symptom Utility Index (ASUI)[17]. Baseline morning and evening peak flow, rescue therapy use, and asthma symptom score were assessed by calculating the mean values for each parameter reported over the final two weeks of the run-in period. Serum specific IgE against 12 selected inhalants were measured using the ImmunoCap® system (Phadia) [18]. (See list in Selected Methods of the Supplementary Appendix.)

Participants were assessed by a study investigator every 4 weeks during the 16-week treatment period. At each visit, mean AM and PM PEFR was calculated using participant self-reported values provided on the diary cards for the two weeks prior to each visit. The best of three attempts was used for the AM and PM PEFR with the Micro Direct Peak Flow Meter which was provided. MiniAQLQ, ACQ and ASUI were reassessed at the 8-week and 16-week visits. Forced spirometry was performed at each visit after holding study medication for >12 hours, with pre- and post-bronchodilator (albuterol) assessments at baseline, 8 weeks, and 16 weeks.
Participants who experienced more than two exacerbations during the course of the study were withdrawn according to pre-determined safety parameters. (Exacerbation is defined in Selected Methods of the Supplementary Appendix.) Adverse events were defined as any untoward events or symptoms reported by the patient whether related to the study drug or not.

Genotype determination
Participant genomic DNA was extracted from 200 µL of whole blood using the QIAGEN QIAampDNA Mini Kit (QIAGEN Sciences, Germantown MD). Extracted DNA (2 µL, approximately 50 ng) was used to identify the SNP encoding the B2AR 16Arg/Gly polymorphism (dbSNP rs1042713; NM_000024.5 c46A>G [pArg16Gly]), using previously published methods [19]. Each sample was also analyzed in parallel with a commercially available TaqMan® assay kit (Applied Biosystems, Foster City, CA)[20]. Samples were classified as AA, AG or GG and there was perfect concordance between the two assays. The genotype of coded patient samples for subjects with the Arg/Arg and Gly/Gly genotypes was conveyed to the research pharmacist for randomization.

Statistical analyses
The primary outcome variable was the change in morning peak expiratory flow rate (AM PEFR) between the beginning and end of the 16-week treatment period within each genotype and compared between genotypes. Secondary endpoints included change in pre and post bronchodilator FEV1, FEV1 % predicted, evening PEFR, Mini AQLQ, ACQ, and ASUI, rescue therapy use, asthma symptom score and asthma exacerbations. Longitudinal data analysis was performed following a modified intention-to-treat (MITT) principle in which all available data was included in the analysis from randomized participants who took at least one dose of study drug. For participants who were withdrawn or were lost to follow-up after randomization, longitudinal analyses compared each value at the start of the 16-week treatment period to the last observed value carried forward (LOCF) for each variable examined. (See Selected Methods in the Supplementary Appendix for additional details.)

Results
One hundred and fifty-six participants were screened by genetic testing at the B2AR site. The genotype distributions within the screened population were 25% Arg/Arg (39/156), 33% Gly/Gly (51/156) and 42% Arg/Gly (66/156) (Table S2). Among African Americans who were screened, 24% were Arg/Arg and 42% were Gly/Gly; whereas, among Caucasians 23% were Arg/Arg and 28% were Gly/Gly. The prevalence of the Arg/Arg genotype did not vary significantly by race (p ≥ 0.25) or Hispanic ethnicity (p ≥ 0.83). African American subjects constituted 21% of the Arg/Arg and 27% of the Gly/Gly groups (Table S2). Of those subjects who self-identified as Hispanic, 28% were Arg/Arg. Fifteen of the 19 participants who described their race as “other” indicated they were of Hispanic ethnicity.

Of the 90 participants homozygous at the B2AR site, 67 participants (31 Arg/Arg and 36 Gly/Gly) were randomized to receive either fluticasone (F) alone, or fluticasone/salmeterol (F/S) via metered dose inhaler (Figure 2). Six participants who were randomized were withdrawn prior to receiving study drug. Endpoint analysis included 28 randomized participants with the Arg/Arg genotype (13 F, 15 F/S) and 33 with the Gly/Gly genotype (16 F, 17 F/S).

The mean age was 47.2 (+15.5) years among Arg/Arg and 43.1 (+14.5) years among Gly/Gly participants (Table 1). Study subjects reported a duration of asthma ranging from one to 61 years with a mean duration of 23.5 years. Asthma duration for each of the 4 study groups was comparable. A majority of participants (77%) were women. Baseline characteristics of the Arg/Arg and Gly/Gly groups did not differ significantly except for history of hospitalizations for asthma. The number of subjects reporting ever being hospitalized for asthma was greater among Gly/Gly participants (42% vs. 8%, p = 0.003). The report of prior hospitalization for asthma remained significantly different among the four treatment/genotype groups following randomization (Table S3). BMI was higher in the Arg/Arg group with near statistical significance (p = 0.07). The BMI was comparable in both Arg/Arg treatment groups and both Gly/Gly treatment groups (Table S3). Overall, the majority of participants had well controlled asthma at study entry, with 57% of Arg/Arg subjects and 69% of Gly/Gly subjects reporting a mean symptom score of zero for the 14 days preceding the randomization visit.

Each treatment group experienced a reduction from baseline morning (AM) PEFR over the course of the study period except for the Gly/Gly subjects receiving F/S (Figure 3, Table 2). None of these changes from baseline reached statistical significance. The Gly/Gly participants randomized to receive F/S showed improvement in AM PEFR (+8.4 L/s) in contrast to those receiving F alone, who experienced a reduction in AM PEFR over the study period (−14.4 L/s) (p = 0.06). The Arg/Arg subjects showed no significant difference in the AM PEFR in the group randomized to F/S vs those randomized to F alone. The F/S treatment groups differed across genotypes, with Gly/Gly participants improving in AM PEFR over the study period (+8.4 L/s) and Arg/Arg participants declining (−15.7 L/s), but this inter-genotype difference did not reach statistical significance (p = 0.20).

Pre-BD FEV1 declined significantly from baseline to end of treatment period only for the Arg/Arg group randomized to fluticasone (FEV1, p = 0.02). There was also a significant decline in FEV1 % predicted in the Arg/Arg group treated with fluticasone alone (p = 0.03).

Gly/Gly subjects randomized to F/S experienced an improvement in asthma symptom score (−1.2), whereas those randomized to F had a worsened score (+0.5) (Table 2). That difference approached significance (p = 0.07). There was no significant change in asthma symptom score in other groups (Table 2).

Mini-AQLQ, ASUI, and ACQ scores trended toward improvement during the treatment period in all four participant groups (Table S4), although no statistically significant changes were observed. There was a clinically meaningful improvement in the AQLQ score (15) of ≥ 0.5 (+0.55 in Arg/Arg subjects and +0.50 in Gly/Gly subjects) when treated with F alone that was not seen in the F/S treatment groups.
Twenty-three percent of study subjects experienced an asthma exacerbation during the treatment period. No subjects were withdrawn due to the pre-defined exacerbation criteria. There were more exacerbations in the Arg/Arg subjects being treated with F/S (27%) than in those on F (15%) and fewer exacerbations in the Gly/Gly subjects being treated with F/S (18%) than in those on F (31%), but numbers were small and not significantly different \( (p = 0.65 \text{ and } 0.44) \) (Table S5). African Americans did have a statistically higher rate of exacerbations than non-African Americans \( (p = 0.02) \). However, there was no statistically significant association between exacerbation rate and gender or treatment group.

There were 14 adverse events among 12 participants during the treatment period with no serious adverse events. There was no significant difference among the 4 treatment groups with regard to adverse event incidence. Only one of the 14 events was considered potentially related to study participation and this occurred in a Gly/Gly subject randomized to F/S (Table S6).

**Discussion**

The current study was designed to compare the effects of continuation of combination therapy (ICS/LABA) with step down therapy through discontinuation of LABA in asthmatic subjects with the Arg/Arg and Gly/Gly genotypes.

In our cohort of asthmatic subjects living in the New York City area, the prevalence of Arg/Arg at B2ABR was 25% (Table S2), higher than that reported in some previous studies [6, 21]. We did not find the significant racial or ethnic differences reported in prior studies, likely a reflection of the diverse ethnic population in the area. Specifically, the prevalence of the Arg/Arg genotype among screened study candidates was 24% among African Americans and 23% among Caucasians. The methodology we used for genotyping has been shown to have a high level of accuracy [22,23]; two independent methods were used for each sample and results were identical in every case.

For the primary endpoint, AM PEFR, among Gly/Gly participants, LABA continuation in the treatment regimen was associated with a near significant benefit compared to LABA withdrawal. This finding suggests a beneficial effect of LABA use in Gly/Gly subjects and is consistent with Wechsler’s data showing similar benefit [5]. In contrast, among Arg/Arg participants, LABA continuation was not associated with a significantly better outcome in AM PEFR when compared with LABA withdrawal. As shown in Figure 3, AM PEFR was not found to decrease in the Arg/Arg subjects on F/S until their 8 week study visit despite 6 prior weeks of F/S during the treatment period.
Table 1. Study population.

| Characteristic               | Arg/Arg (n = 28) | Gly/Gly (n = 33) | P Value |
|-----------------------------|------------------|------------------|---------|
| Age – mean (range)          | 47.2 (15.5)      | 43.1 (14.5)      | 0.29    |
| Female Sex – no. (%)        | 23 (82)          | 24 (73)          | 0.54    |
| Ethnic Origin – no. (%)     |                  |                  |         |
| White                       | 15 (53.6)        | 17 (51.5)        | 0.98f   |
| African-American            | 8 (28.6)         | 10 (30.3)        |         |
| Asian                       | 2 (7.1)          | 3 (9.1)          |         |
| Other                       | 3 (10.7)         | 3 (9.1)          |         |
| Hispanic*                   | 4 (14.2)         | 5 (15.1)         | 0.92    |
| Mean Height – inches (sd)   | 65.3 (3.2)       | 65.5 (3.0)       | 0.80    |
| BMI – mean (sd)             | 33.2 (10.8)      | 28.7 (7.3)       | 0.07    |
| Age of Asthma Onset – yrs (sd) | 21.0 (14.3)   | 18.6 (18.5)      | 0.56    |
| Allergies Trigger           |                  |                  |         |
| Asthma – no. (%)            | 20 (71.4)        | 24 (72.7)        | 1.00    |
| Hospitalized for Asthma – no. (%) | 2 (8.1)  | 14 (42.4)        | 0.003   |
| Mean Mini AQLQ score (sd)   | 2.77 (1.97)      | 3.23 (2.81)      | 0.20    |
| Mean ACQ Score (sd)         | 0.66 (0.659)     | 0.59 (0.571)     | 0.51    |
| Mean ASUI Score (sd)        | 0.88 (0.101)     | 0.89 (0.089)     | 1.00    |
| Mean FEV1% Predicted        |                  |                  |         |
| Pre-bronchodilator          | 2.50 (0.72)      | 2.68 (0.61)      | 0.30    |
| Post-bronchodilator         | 2.54 (0.76)      | 2.78 (0.63)      | 0.20    |
| Mean PEF – L/min (sd)       | 84.6 (11.9)      | 87.0 (12.1)      | 0.44    |
| Specific IgE ≥ 0.35 IU/ml At least one allergen – no. (%) | 15 (53.6) | 18 (54.5) | 1.00 |
| Number of allergens – mean (sd) | 3.5 (2.74) | 4.0 (3.60) | 1.00 |

* Differences in ethnic origin among White, African American, Asian and other participants were evaluated by Pearson Chi-Square test for the group as a whole.

** Hispanic was defined independently of other categories (that is, participants could classify themselves as Hispanic in addition to any other category); differences evaluated by Pearson Chi-Square test.

** Pre-bronchodilator FEV1% predicted.

Table 2. Outcome measures.

| Fluticasone-Salmeterol Treatment Group | Fluticasone Treatment Group | P(geno) | P(Rx group) |
|---------------------------------------|-----------------------------|---------|-------------|
| Arg-Arg Genotype                      |                             |         |             |
| AM PEFR, L/min                        | 411.1 (109.4)               | 395.4 (109.8) | 0.39 |
| PM PEFR, L/min                        | 410.1 (113.4)               | 397.8 (115.1) | 0.31 |
| FEV1 Pre-BD, L                        | 2.36 (0.70)                 | 2.35 (0.70) | 0.52 |
| FEV1 Post-BD, L                       | 2.40 (0.73)                 | 2.40 (0.73) | 0.24 |
| FEV1% Predicted                       | 94.6 (10.9)                 | 94.5 (10.9) | 0.92 |
| Symptom Score                         | 2.2 (3.5)                   | 1.9 (3.0) | 0.30 |
| | | | |
| Gly-Gly Genotype                      |                             |         |             |
| AM PEFR, L/min                        | 431.4 (85.3)                | 439.8 (104.8) | 0.26 |
| PM PEFR, L/min                        | 426.5 (101.6)               | 446.5 (101.6) | 0.17 |
| FEV1 Pre-BD, L                        | 2.78 (0.71)                 | 2.70 (0.74) | 0.13 |
| FEV1 Post-BD, L                       | 2.87 (0.77)                 | 2.80 (0.74) | 0.13 |
| FEV1% Predicted                       | 88.8 (11.6)                 | 86.3 (13.9) | 0.19 |
| Symptom Score                         | 2.2 (3.9)                   | 1.0 (3.0) | 0.15 |

Outcome measures are provided for baseline and the last observation carried forward (LOCF). Each value represents the mean for the indicated participant groups, standard deviation provided in parentheses. Fluticasone-Salmeterol (F+S) represents the mean for the daily reported values for the 2-week period preceding the study visit. Fluticasone alone (% F) represents the mean for the daily reported values for the 2-week period preceding the study visit. The change (delta) between baseline and LOCF values compared across treatment groups, that is fluticasone/salmeterol compared with fluticasone alone within each genotype [P(Rx group)]. P(geno) refers to the comparison of the change between baseline and LOCF values compared across genotypes, that is fluticasone/salmeterol compared with fluticasone alone within each genotype. Fluticasone-Salmeterol (F+S) represents the mean for the daily reported values for the 2-week period preceding the study visit. The change (delta) between baseline and LOCF values compared across treatment groups, that is fluticasone/salmeterol compared with fluticasone alone within each genotype [P(Rx group)]. P(geno) refers to the comparison of the change between baseline and LOCF values compared across genotypes, that is fluticasone/salmeterol compared with fluticasone alone within each genotype.

Figure 3. Mean morning peak expiratory flow rate for the 2-week period preceding each study visit between randomization (treatment week 0) and study completion (treatment week 16) are depicted for each of the four participant groups: Arg/Arg receiving fluticasone (Arg/Arg-F), Arg/Arg receiving fluticasone/salmeterol (Arg/Arg-F/S), Gly/Gly receiving fluticasone (Gly/Gly-F), and Gly/Gly receiving fluticasone/salmeterol (Gly/Gly-F/S). No statistically significant differences were found between the four groups shown. Note that mean PEF values shown here at V6 are distinct from the LOCF mean values provided in Table 2.
run in period, consistent with the delayed response previously reported with beta agonists [1].

The contribution of genotype to the potential negative effect of LABA use on AM PEF is suggested by the finding that Arg/Arg participants who continued LABA treatment (with ICS) during the study experienced a decrease in PEF (−15.7 L/min) compared with Gly/Gly subjects who experienced an increase (8.4 L/m), but this difference was not statistically significant. In general there were no major changes in lung function seen in the course of the study, likely a reflection of the fact that patients were on appropriate asthma therapy prior to randomization [24]. Although AM PEF did not change significantly in either Arg/Arg treatment group, FEV₁ and FEV₁% predicted did decline in the Arg/Arg group randomized to ICS treatment alone. Discordance between PEFR and spirometry results has been described previously by Hegewald et al. [25]. The trends in PEF in the two Gly/Gly treatment groups is supported by self-reported asthma symptom scores, which improved when continued on F/S, but worsened with borderline significance (p = 0.07) when LABA was withdrawn (Table 2).

Both Gly/Gly and Arg/Arg subjects randomized to withdrawal of LABA experienced a clinically meaningful improvement in asthma quality of life (AQLQ) despite the fact that Gly/Gly participants experienced a decline in AM PEF with LABA withdrawal. This was not seen in those subjects of either genotype who were continued on ICS/LABA combination therapy. Therefore, treatment with LABA may have a detrimental effect on quality of life that is not genotype related. In a study of children with asthma who had the Arg/Arg genotype it was found that quality of life was improved when those children on ICS therapy received montelukast as a second controller compared to those children who received a LABA [26].

Demonstration of asthma control by ACQ was not a requirement for randomization in this study. Nevertheless the ACQ score showed optimal control (≤0.75) in 3 of the 4 treatment groups at baseline (Table S4). The exception, the Arg/Arg group later randomized to ICS alone, was characterized by a baseline ACQ value of 0.87, still well below the threshold indicator for suboptimal control [16].

A principal weakness of the current study is the relatively small sample size, but racial and ethnic diversity was maintained. Baseline data was collected and was comparable for the two genotypes and 4 treatment groups with the exception of hospitalizations and BMI. It is known that BMI can affect asthma severity and a high BMI has been shown to have a genetic basis [27]. History of prior antibiotic use was not collected. Although antibiotic use early in life can contribute to the incidence of asthma [28], it is not known to affect asthma severity or response to therapy.

Still, it may be of interest to collect this data in future studies. A near significant difference was seen in the primary end point for Gly/Gly subjects and significant or near significant changes in a number of outcome measures. The relatively small or limited effects of LABA withdrawal may be a reflection of the fact that most patients were well controlled prior to enrollment. If they were not well controlled, then step down therapy could be questionable. Asthma exacerbations were equally distributed among the 4 treatment groups; however, African Americans overall had a higher rate of exacerbations, consistent with other published works. Finally, our study analyzed the effect of polymorphisms at a single locus of the B2AR gene. Ortega et al. recently identified rare variants of the B2AR gene that were associated with increased risk of exacerbations in patients being treated with LABAs [29]. In general there is increasing interest in the role of genetics in all aspects of asthma [30].

Conclusions

The current study demonstrates that Gly/Gly subjects have a borderline significantly higher AM PEF when continued on ICS/LABA compared with ICS alone. Arg/Arg subjects with asthma being treated with ICS/LABA therapy however showed no significant difference in AM PEF compared with those in whom LABA is discontinued. Discontinuation of LABA led to clinically meaningful improvement in asthma-related quality of life in both Gly/Gly and Arg/Arg participants. Discontinuation of LABA treatment in both Arg/Arg and Gly/Gly subjects in this study population was safe and did not result in an increase in asthma exacerbations.

Patients homozygous for the Arg16 variant of the beta 2 adrenergic receptor have been reported by others to represent 13% of the white population and 24% of the black population [21]. In our study, there was an even greater prevalence of Arg/Arg overall without a racial difference. Because 34 million Americans and an estimated 300 million people worldwide have asthma, the potential adverse effect of beta-2 agonists on lung function may affect over 5 million asthmatics in the United States and 45 million worldwide.

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Declaration of interest

The authors report no conflicts of interests and have no relevant disclosures. The authors are responsible for the content and the writing of this article.

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