12–15, severe). An age-specific score of 1 to 3 was assigned to 5 variables (oxygen saturation, respiratory rate, work of breathing, auscultation, and ability to talk). Response to inhaled β₂ agonist was measured by determining the time taken to reduce the frequency of β₂ agonists from 20-minute intervals to administration at 1, 2, and 4 hourly intervals, with longer times indicating poorer response to treatment. Polymerase chain reaction was used on peripheral blood samples to amplify the 2 polymorphisms of interest (Arg16Gly and Gln27Glu).

RESULTS. There were 58 (39.2%) patients who were homozygous Gln27Gln, 69 (46.6%) patients who were heterozygous Gln27Glu, and 21 (14.2%) patients who were homozygous Glu27Glu. Subjects homozygous for Gln were slowest to respond to inhaled β₂ agonists and took the longest to reach 1, 2, and 4 hourly β₂-agonist treatments (time to 1 hourly: 2.6 ± 2.9 hours; time to 2 hourly: 10.6 ± 9.3 hours; time to 4 hourly: 29.8 ± 23.5 hours). Heterozygotes for Gln had an intermediate response (time to 1 hourly: 2.0 ± 2.8 hours; time to 2 hourly: 10.7 ± 18.1 hours; time to 4 hourly: 28.5 ± 26.2 hours). Homozygotes for Glu had the most rapid response (time to 1 hourly: 1.4 ± 1.2 hours; time to 2 hourly: 6.8 ± 8.9 hours; time to 4 hourly: 24.3 ± 22.2 hours). No significant associations were found between Arg16Gly and response to treatment. After controlling for asthma severity score, previous use of asthma medications, age, gender, and concurrent upper respiratory infection symptoms, homozygotes for Gln were still more likely to have the slowest response to treatment. No associations were found between β₂-adrenoreceptor genotype and asthma severity scores or asthma patterns.

CONCLUSIONS. This study demonstrates an association between single-nucleotide polymorphisms and response to β₂-agonist treatment for children during an acute asthma exacerbation as compared with stable nonacute disease. Children who are homozygous for β₂-adrenoceptor Gln27Gln respond less effectively to inhaled β₂-agonist therapy.

REVIEWER COMMENTS. As the authors pointed out in the report, most children are treated effectively during an acute asthma exacerbation. The length of treatment with inhaled β₂ agonists, however, can be variable and unpredictable. The results of this study explain, at least in part, this variability. In the future, knowledge of a patient’s β₂-adrenoreceptor genotype can possibly guide decisions about duration and need for additional therapies during an acute asthma exacerbation.

Effect of ADRB2 Polymorphisms on Response to Longacting β₂-Agonist Therapy: A Pharmacogenetic Analysis of Two Randomised Studies


PURPOSE OF THE STUDY. To determine if polymorphisms at amino acid 16 of the β₂-adrenergic receptor (ADRB2) affect response to long-acting β₂-agonists in combination with inhaled corticosteroids (ICSs).

STUDY POPULATION. The study included individuals at least 12 years old (2225 in study 1 and 405 in study 2) who had asthma for at least 6 months and used ICSs.

METHODS. In study 1, individuals with at least 12% reversibility of their forced expiratory volume in 1 second received 6 months of double-blind treatment with budesonide plus formoterol for maintenance and reliever therapy, fixed-dose budesonide plus formoterol, or fixed-dose fluticasone plus salmeterol. The primary outcome was the time to first severe asthma exacerbation. In study 2, participants received 7 months of open-label treatment with an adjustable regimen of budesonide plus formoterol, fixed-dose budesonide plus formoterol, or fixed-dose fluticasone plus salmeterol. Primary outcomes included the number of asthma exacerbations, time to first exacerbation, and percentage of participants with at least 1 exacerbation. Participants were stratified according to ADRB2 genotype, and the relation between genotype and asthma outcome was determined.

RESULTS. Baseline characteristics were similar among all Gly16Arg genotypes, and the genotypes were equally distributed across treatment groups. A combination of the 3 treatment groups showed a similar likelihood of having >1 severe asthma exacerbation for each genotype in study 1 (Gly/Gly, 12%; Gly/Arg, 11%; and Arg/Arg, 9%) and study 2 (Gly/Gly, 9%; Gly/Arg, 8%; and Arg/Arg, 9%). The time to first exacerbation was similar among genotype groups (study 1 P = .31, study 2 P = .94). In study 1, there was no interaction among treatment group, genotype, and time to first severe exacerbation (P = .88). Improvement of morning peak expiratory flow and other secondary end points was similar for all genotypes in both studies. In study 2, differences in response according to genotype were not seen between participants with and without baseline reversibility of forced expiratory volume in 1 second.

CONCLUSIONS. Individuals with asthma may continue to receive ICSs plus long-acting bronchodilators regardless of their Gly16Arg genotype.

REVIEWER COMMENTS. Study results have varied regarding the effectiveness of long-acting β₂-agonists, with or without
the concomitant use of ICSs, in individuals with the Arg/Arg genotype relative to the Gly/Gly genotype. This large and long-term randomized study, including participants taking different long-acting β₂-agonists, adds to the evidence suggesting that combination ICS/long-acting bronchodilator therapy may be equally effective in people with the Arg/Arg genotype. Given the overall effectiveness and prevalence of ICS/long-acting bronchodilator use and the increasing focus on individualization of asthma management, responses of subgroups of people with asthma to these medications will continue to be an important area of research.

Montelukast as Add-on Therapy to β-Agonists and Late Airway Response

PURPOSE OF THE STUDY. To evaluate montelukast’s ability to inhibit the late-phase airway response after allergen exposure in adults with house dust mite–induced asthma.

STUDY POPULATION. Thirty-five adults (19 men, 16 women) aged 18 to 31 with mild, stable asthma and sensitivity to house dust mites were included.

METHODS. This study was designed as a randomized, double-blind, single-dose, placebo-controlled, crossover trial. Subjects underwent serum testing for antigen-specific immunoglobulin E (IgE) to house dust mite. Sensitive subjects were then examined for airway infections and underwent spirometry and determination of their fraction of nitric oxide in exhaled air (FeNO). They were then challenged with increasing concentrations of inhaled Dermatophagoides farinae via a nebulizer system. Testing was stopped when the patient’s forced expiratory volume in 1 second (FEV₁) decreased at least 20% (early airway response [EAR]), they experienced significant clinical symptoms, or they received a cumulative dose of 1270 mg. Patients were then given 1 puff of salbutamol (0.1 mg) and either montelukast (10 mg) or a placebo. FEV₁ was measured for the following 8 hours with a decrease of at least 20% demonstrating a late airway response (LAR). Formoterol (12 μg) was then given to treat those patients. Subjects returned at least 2 weeks later and were crossed-over into the other group.

RESULTS. Of the 35 subjects in the study, 12 showed no significant EAR on 1 or both study days, 11 showed only an EAR, and 12 demonstrated both an EAR and LAR. This last group was analyzed further. The difference in FEV₁ from baseline values 3 to 8 hours after challenge was expressed as the area under the FEV₁ time-response curve (FEV₁-AUC). The FEV₁-AUC of patients on placebo was $-2.47 \pm 1.32$ vs $-0.768 \pm 1.68$ for the patients on montelukast ($P < .005$). Subjects with a dual response had a significantly higher baseline FeNO than those with no response ($56.4 \pm 21.0$ ppb; $P < .05$).

CONCLUSIONS. Montelukast was able to block the late-phase airway response in subjects who responded dually to the allergen challenge. In addition, patients with a higher baseline FeNO seemed more likely to develop an LAR than those with lower ones.

Reviewer Comments. The results of this study implicate a role for montelukast as an “add-on,” therapeutic option for symptomatic relief after allergen exposure in subjects with mild asthma. It also suggests a rapid onset of action that allows for its usage in such a setting. This study supports existing ones that have demonstrated the effect of montelukast within 2 to 3 hours for up to 24 hours. There was also a “trend toward significance” showing subjects on montelukast with higher FEV₁ values than those on placebo. However, this study was limited in its sample size and should be expanded to fully elicit montelukast’s role in acute exacerbations. It would also be worthwhile to investigate its effects on subjects with moderate-to-severe asthma in the same setting. Last, this study also alluded to the fact that a patient’s baseline FeNO may be a predictor of whether he or she develops an LAR. This should also be explored further in expanded studies and in children.

Attenuation of the September Epidemic of Asthma Exacerbations in Children: A Randomized, Controlled Trial of Montelukast Added to Usual Therapy

PURPOSE OF THE STUDY. To evaluate whether montelukast, when added to usual asthma therapy, would affect the asthma symptoms experienced during the annual asthma epidemic occurring each year when school resumes after summer vacation.

STUDY POPULATION. Participants included 194 subjects from 2 to 14 years of age with physician-diagnosed asthma. More than 90% of the children had prescriptions for an inhaled corticosteroid (ICS).

METHODS. Children were randomly assigned to receive either an age-appropriate dose of montelukast ($n = 98$) or
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Elinor Simons

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