

Gly/Gly and Arg/Arg genotype responses to albuterol differed in mild asthma

Israel E, Chinchilli VM, Ford JG, et al. Use of regularly scheduled albuterol treatment in asthma: genotype-stratified, randomised, placebo-controlled cross-over trial. *Lancet*. 2004;364:1505-12.

QUESTION

In patients with mild asthma, does a genotype-dependent effect of regularly scheduled albuterol exist?

METHODS

Design: Randomized, placebo-controlled, cross-over trial (Beta-Adrenergic Response by Genotype [BARGE] trial).

Allocation: Concealed.*

Blinding: Blinded (clinicians and patients).*

Follow-up period: 24 weeks.

Setting: {6 centers in the United States.}†

Patients: 78 patients who were 18 to 55 years of age (mean age 31 y, 68% women) and had physician-diagnosed mild asthma, who reported use of as-needed inhaled β -agonist < 56 puffs/wk as their only treatment, whose FEV₁ was \geq 70% of the predicted value, and who had either the Arg/Arg or Gly/Gly genotype as the locus encoding the 16th amino acid residue of the β_2 -adrenergic receptor.

Intervention: Each patient with the Arg/Arg genotype was matched with a patient with the Gly/Gly genotype by FEV₁ (within 10% of predicted) and study center. During a 6-week, single-blind, run-in period, they received 2 puffs 4 times/d of a placebo metered-dose inhaler and open-label ipratropium bromide as rescue medication. Patients were allocated to the active-to-placebo ($n = 37$) or placebo-to-active ($n = 41$) cross-over sequence and received inhaled albuterol

or placebo, 2 puffs, 90 μ g/puff, 4 times/d. An 8-week placebo run-out period occurred between and after the 2 treatment periods.

Outcomes: Morning PEFR. Secondary outcomes were spirometric values, evening PEFR, morning/evening PEFR variability, asthma symptoms, use of rescue medication, and adverse asthma control episodes.

Patient follow-up: 86% (intention-to-treat analysis).

MAIN RESULTS

In patients with Gly/Gly genotype, morning PEFR improved with albuterol and no significant change was seen with placebo (Table). The difference persisted through the 8-week run-out period. In patients with the Arg/Arg genotype, greater improvement in morning PEFR occurred with placebo (Table) and the difference persisted through the 8-week run-out period. During the run-in period, when all patients received an albuterol placebo and ipratropium bromide as rescue medication, patients with the

Arg/Arg genotype increased morning PEFR by 23 L/min compared with 2 L/min in patients with the Gly/Gly genotype. Significant genotype-related differences were also seen for FEV₁, FVC, evening PEFR, and rescue inhaler use; and for asthma symptoms (Table). No differences were seen by treatment or genotype for adverse asthma control episodes.

CONCLUSION

In mild asthma, patients with the Gly/Gly genotype had better asthma control with albuterol than when it was withdrawn, and patients with the Arg/Arg genotype had worse asthma control with albuterol than when it was withdrawn.

Source of funding: National Institutes of Health.

For correspondence: Dr. E. Israel, Brigham and Women's Hospital and Harvard Medical School, Boston, MA, USA. E-mail eisraelast@partners.org. ■

*See Glossary.

†Information provided by author.

Albuterol vs placebo by genotype for mild asthma at 16 weeks‡

Outcomes	Genotype	Albuterol	Placebo	Difference (95% CI)
Change in morning PEFR (L/min)	Gly/Gly	13	-1	14 (3 to 25) [§]
	Arg/Arg	2	12	-10 (-19 to -2)
Change in morning symptom score¶	Gly/Gly	-0.1	0	-0.1 (-0.2 to -0.1) [§]
	Arg/Arg	0.1	0	0.1 (0 to 0.1)

‡CI defined in Glossary.

[§]Difference favors albuterol.

||Difference favors placebo.

¶Asthma symptom score (range 0 = no symptoms to 3 = incapacitating symptoms)†.

COMMENTARY

Pharmacogenomics promises physicians the ability to customize therapy for individual patients. The well-done multicenter trial by Israel and colleagues reports some interesting findings for highly selected patients with mild asthma. The repeated measures analysis indicates that the apparent differences between genotypes are not due to random error. Whether they are clinically important is less certain. The differences in changes in morning PEFR and FEV₁ are modest. They compare with weighted mean differences of 50 L/min and 340 mL, respectively, attributable to inhaled beclomethasone in a systematic review of 52 trials (1). However, there are also consistent changes in symptoms and requirements for rescue medication. The study was underpowered to detect a statistically significant effect on exacerbations in patients with mild asthma. Although many respiratory studies focus on lung function, it is unfortunate that health-related quality of life or other patient-important outcomes were not assessed.

Physicians should not and cannot yet routinely request genotyping of their asthma patients' β_2 -receptors. The study used 3 methods of

genotyping, which are not all widely available. Almost half the patients screened were ineligible, presumably because they were heterozygous for this polymorphism. The prevalence of the Arg/Arg genotype is lower in some other populations (2).

Interest is increasing in the effect of β_2 -receptor haplotypes on lung function and response to therapy. The design of this study precluded the investigation of the conjoint effects of other polymorphisms.

Mild asthma is relatively simple to manage in accordance with published clinical practice guidelines. Thus, for almost all patients and physicians, an individual trial of β_2 -agonist is likely to remain much simpler than genotyping for the foreseeable future.

*Michael J. Abramson, MB BS, BMedSc, PhD, FRACP, FAFPHM
Monash University
Melbourne, Victoria, Australia*

References

- Adams NP, Bestall JB, Jones PW. *Cochrane Database Syst Rev*. 2000;(4): CD002738.
- Hopes E, McDougall C, Christie G, et al. *BMJ*. 1998;316:664.