

Genetics, Ethics, and the Use of Long-acting β -Adrenergics to Treat Asthma

Long-acting β -agonists (LABAs) improve control of persistent asthma that is not well controlled with inhaled corticosteroids (ICS) in adults (1) and children (2), but there are safety concerns related to their continuous use (3–4). Initial pharmacogenetic studies suggested that, during long-term use of short-acting β -agonists, individuals with asthma that are homozygotes for the arginine (Arg) allele at codon 16 of the β 2-adrenergic receptor gene (ADRB2) were at increased risk of adverse outcomes when compared with homozygotes for the glycine (Gly) allele or Arg/Gly heterozygotes (5, 6). Retrospective analyses of clinical trials using LABAs, either alone or in combination with ICS, revealed similar adverse outcomes in relation to the Arg/Arg genotype (7). However, other analyses of large LABA clinical trials were unable to reproduce these findings (8).

These contradictory results prompted Bleecker and coworkers, in this issue of the *Journal* (pp. 676–687), to perform a large, prospective, genotype-stratified, randomized trial comparing a LABA (salmeterol) alone or combined with ICS for 16 weeks (9). This elegant study shows that the polymorphism at codon 16 of ADRB2 has little or no effect on clinical responses to salmeterol alone or combined with ICS. This finding confirms and extends the results of a study published recently showing that the combination of salmeterol and ICS improves airway function irrespective of ADRB2 genotype (10).

The lack of replication of the results of the original studies showing a relationship between ADRB2 genotype and adverse events associated with LABA use would suggest that the observations from earlier clinical trials should be considered spurious. Alternatively, the effects of functional common genetic variants, such as that in codon 16 of the ADRB2 gene, may be weak and context-dependent. Thus, what is true for one population may not be true for all. In the case of the study by Bleecker and colleagues (11), subjects may have differed in certain unknown phenotypic characteristics from those enrolled in the conflicting studies, suggesting that it is too early to rule out a functional polymorphism at codon 16 of the ADRB2 that might play a role in modulating responses to LABAs. However, as is not uncommon in asthma genetics studies (11), neither this polymorphism nor any of the other common variants reported for ADRB2 have pharmacogenetic effects that can be generalized to all patients with asthma.

Two other results of the study by Bleecker and coworkers are worth mentioning. First, Arg/Arg homozygotes, who by design made up approximately one third of the subjects enrolled, had 55% of the exacerbations observed during the run-in phases of the trial, confirming a recent report by Palmer and colleagues (12). Second, Bleecker and coworkers (9) confirmed that the use of salmeterol significantly increases the risk of loss of asthma control (13), as suggested by the

observation that 10 of 272 subjects receiving salmeterol had an exacerbation, compared with only 1 of 272 patients receiving the ICS+LABA combination. Unfortunately, one of the patients randomized to salmeterol alone died of asthma during the treatment period. While we do not know whether the death was caused by salmeterol, we need to see it in the context of the SMART study (14), in which four times as many asthma deaths occurred among subjects in whom salmeterol alone was added to usual therapy. Thus, although the study by Bleecker and colleagues (9) was approved by the appropriate institutional review boards, difficult and contentious ethical issues are raised that are not fully addressed in the manuscript.

According to the number assigned to the clinical trial (NCT00102882), the study began in 2004, well after it was known that salmeterol is associated with loss of asthma control (13). Moreover, the run-in period showed that the subjects were using a mean of 1.3–1.5 puffs per day of reliever medication when not taking controllers, suggesting that most of them were not adequately controlled (15). It is thus crucial to determine if, in the face of an obvious lack of equipoise in safety and efficacy between study arms, it was justifiable to expose subjects to the risk of being randomized to a treatment (salmeterol alone) known to be inferior to the alternative one (i.e., the use of combination therapy with ICS+LABA). We believe that this approach was not justifiable. Although from a scientific point of view it could have been interesting to determine if Arg/Arg homozygotes show worse outcomes when receiving LABA alone than when receiving ICS+LABA, all current guidelines state that the use of LABA without concomitant use of ICS is clearly not recommended and actually contraindicated in patients with asthma. Thus, acquiring knowledge about the use of LABA alone would have had no practical application.

As others have stressed (16), these issues are particularly important for the children aged 12 and older who participated in the trial. Even assuming equipoise between arms (which we have argued was lacking), children should not have been allowed to participate. According to all currently accepted standards and federal regulations, the participation of children is permitted in research associated with a “minor increase over minimal risk” only if the research “is likely to yield generalizable knowledge about the subject’s disorder that is of vital importance” (16). Given the results of the SMART study (14), we do not believe that the risk associated with the use of salmeterol alone is a *minor* increase over minimal risk. But even if one were to accept that assertion, the lack of any practical use for findings related to a treatment that is contraindicated in asthma eliminates all expectation that the results of this study could have yielded “generalizable knowledge . . . of vital importance.”

In summary, the study by Bleecker and coworkers raises very important scientific and ethical issues that we believe should be a matter for discussion in the research community. From a scientific point of view, genetic studies have provided new and valuable information about the mechanisms involved in determining the heterogeneity of responses to pharmacotherapy—but few of the results obtained have yielded information that can be used in a practical way to predict which treatments should

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or should not be prescribed for which patients. Perhaps the time has come to acknowledge that the study of genetic variants without concomitant consideration of other determinants of therapeutic efficacy (e.g., specific phenotypic characteristics, race, sex, exposures that trigger symptoms) will provide few results that are useful for our patients. From an ethical point of view, it is imperative for scientists, ethicists, and patient advocates to reach a consensus as to how to apply regulations in a way that will enhance progress in scientific knowledge but also respect and protect the rights of study participants, especially children. This will not be an easy task, given the divergence of opinion among well-intentioned practitioners. Reaching such consensus is, however, mandatory if we expect the public to support and participate in research that is essential for the discovery of new medicines to treat and cure debilitating diseases such as asthma.

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Meeting the Obligation to Balance Bioethics and Clinical Trial Design in Asthma

The above editorial by Dr. Martinez and Dr. Fabbri in this issue of the *Journal* (pp. 647–648 [1]) commenting on our article (pp. 676–687 [2]) raises complex issues relevant to the use of long-acting bronchodilators (LABA) in the treatment of asthma and states that “acquiring knowledge about the use of LABA alone would have no practical application.” We respectfully disagree with this statement.

Previous studies have suggested that ADRB2 Arg16Gly polymorphisms may alter clinical responses to short- and long-acting β -agonists (SABA, LABA). Several studies supporting this finding were conducted with SABAs in the absence of inhaled

corticosteroids (ICS) (2, 3), or when ICS were permitted but not required (5–7).

Results of pharmacogenetic studies assessing LABA responses based on Arg16Gly polymorphisms have been mixed since initial small retrospective studies using salmeterol suggested that clinical responses may be affected by Arg16Gly polymorphisms with or without concomitant ICS (8), whereas larger retrospective studies with salmeterol or formoterol found no pharmacogenetic associations in the presence of ICS (5, 9, 10). The editorial by Taylor and Hall in the *Lancet*, which accompanied the latter study, pointed out that it was unknown