Safety of Fluticasone plus Salmeterol in Asthma — Reassuring Data, but No Final Answer

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After the introduction of the long-acting beta-agonist (LABA) salmeterol for the treatment of asthma, two large trials — the Salmeterol Multicenter Asthma Research Trial (SMART),[1] which was mandated by the Food and Drug Administration (FDA) and involved 26,000 patients, and the Serevent Nationwide Surveillance (SNS) trial[2] in the United Kingdom, which involved 25,000 patients — showed a higher risk of asthma-related death among patients receiving salmeterol than among those receiving placebo. A second LABA, formoterol, was introduced some years later, and although no such large studies were available for this drug, the aggregate evidence showed that patients taking this drug had an increased risk of severe asthma-related adverse events.[3]

These results seemed paradoxical, since LABAs have repeatedly been shown to be very effective in decreasing asthma exacerbations as add-on therapy among patients who have not had an adequate response to inhaled glucocorticoids.[4] To explain this apparent contradiction, it was argued that in the SMART and SNS trials, salmeterol was delivered in a separate inhaler and the observed adverse events could be attributed to the use of this class of drug without concomitant protective administration of inhaled glucocorticoids.[5] However, in the absence of indisputable evidence of such a protective effect, the FDA mandated the inclusion of a black-box warning in the package insert for these products. In addition, and to clarify this issue, the FDA required that the manufacturers of LABAs conduct randomized, double-blind, controlled clinical trials comparing the combination of these drugs with inhaled glucocorticoids in a single inhaler, as compared with inhaled glucocorticoids alone. A composite of serious asthma outcomes (i.e., asthma-related death, intubation, or hospitalization) was mandated as the primary end point. The results of the first of these trials, which was conducted in patients as young as 12 years of age by GlaxoSmithKline (the manufacturer of salmeterol) and reported by eight of its employees or associates, are now described in the *Journal*.[6]

At first glance, these results appear to be quite reassuring. The rate of the composite outcome (as observed during a 6-month treatment period) was not significantly higher among the 5834 patients who received fluticasone–salmeterol than among the 5845 patients who received fluticasone alone, and noninferiority of fluticasone–salmeterol was achieved.

However, in order to determine to which patients these results apply, it is important to understand the criteria that were used to identify suitable trial participants. The presence of asthma was apparently ascertained from history alone, since no diagnostic testing was required, and a major inclusion criterion was a history of asthma exacerbation requiring the use of inhaled glucocorticoids or hospitalization in the previous year (with the exclusion of the month before randomization). Strictly speaking, these criteria could apply to the whole spectrum of patients with persistent asthma, from mild to severe. However, patients were excluded from the trial if they had a history of life-threatening or unstable asthma. Why this decision was made is never explained, but it is bewildering that the patients at highest risk for the composite primary outcome were purposely left out. It has been shown, for example, that almost two thirds of patients who were hospitalized with life-threatening asthma had a history of admission to an intensive care unit, as compared with only 11% of patients who were admitted with severe but not life-threatening asthma.[7] Thus, it is not surprising that only two patients in the trial had life-threatening asthma and that adherence to study medication was 95%, a rate of success unheard of in clinical practice and even in highly controlled clinical trials. The exclusion of patients with unstable asthma probably selected those who were prone to be highly adherent to their usual therapy.

What practical conclusions can be drawn from this study? It is clear that among patients

with asthma who have not had life-threatening episodes in the past and are highly adherent to their drug regimen, it is likely that the use of salmeterol together with fluticasone in a single inhaler is safe. For these patients and this combination, the black-box warning should be lifted. This is an important result, and it stresses once again that most patients with asthma, and especially those without serious episodes, can reach high levels of symptom control and avoid frequent exacerbations by simply using their inhalers every day.

What remains unanswered is whether this conclusion applies to patients who have the most severe and unstable disease, since these are the patients for whom all guidelines still recommend the use of LABAs combined with inhaled glucocorticoids as first-line treatment. For these patients, the safe clinical approach is to maintain the same precautions in using fluticasone–salmeterol that have been recommended until now for all patients with asthma. In addition, the current trial evaluated patients 12 years of age or older. In one of the ongoing trials that are assessing adverse events associated with fluticasone–salmeterol (ClinicalTrials.gov number, NCT01462344), investigators are studying children between the ages of 4 years and 11 years. The results of this trial should provide much-needed data on the effect of these drugs in young children. It is also imperative to further explore the possibility that the presence of rare variants in genes associated with the response to beta-agonists may increase the risk of severe exacerbations when these drug combinations are administered to patients with the most severe asthma.[8]

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MAGE-D2 and the Regulation of Renal Salt Transporters

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Bartter's syndrome is a rare, genetically heterogeneous disorder characterized by renal salt wasting, hypokalemic metabolic alkalosis, and secondary hyperaldosteronism with normal to low blood pressure. Two distinct presentations of the syndrome exist: antenatal Bartter's syndrome and classical Bartter's syndrome. Both forms are inherited as autosomal recessive traits.

Patients with antenatal Bartter's syndrome may carry loss-of-function mutations in the genes encoding the furosemide-sensitive sodium–potassium–chloride cotransporter NKCC2, the inwardly rectifying potassium channel ROMK, or the chloride channel β-subunit barttin.[1] The concerted action of these transporters in the renal thick ascending limb of the loop of Henle ensures transcellular sodium chloride reabsorption in this nephron segment, which accounts for up to 20 to 25% of the total amount of filtered sodium chloride. In most persons with