

Safety of Long-Acting Beta-Agonists in Asthma

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Practice Options from Beyond Our Pages focuses on identifying, critiquing, and placing into context research studies published in other journals that have the potential to change our clinical practices. It is written by Allergy-Immunology Fellows partnered with faculty members, and does not require an invitation for submission. This feature is coordinated by Editorial Board members Matthew Rank, MD and Julie Wang, MD.

REFERENCE

Busse WW, Bateman ED, Caplan AL, William Kelly H, O'Byrne PM, Rabe KF, et al. Combined analysis of asthma safety trials on long-acting β_2 -agonists. *N Engl J Med* 2018;378:2497-505.

BACKGROUND

Current asthma guidelines recommend step-up therapy with an inhaled corticosteroid (ICS) combined with a long-acting β -agonist (LABA) for moderate-to-severe persistent asthma.^{1,2} However, safety concerns have loomed over LABA use since their arrival on the market. Shortly after the release of salmeterol in the 1990s, Castle et al³ raised initial concerns by demonstrating a relative risk of 3.0 ($P = 1.05$) in mortality due to respiratory/asthma-related deaths in the salmeterol group compared with the salbutamol group.³ Despite the statistically insignificant relative risk, the results prompted further investigation. Continued concern was substantiated by the 2006 Salmeterol Multi-center Asthma Research Trial (SMART), which demonstrated a significant increase in adverse asthma-related death or life-threatening events with the use of salmeterol compared with placebo.⁴ The SMART was designed to assess salmeterol safety regardless of the concomitant use of ICS. The SMART showed no difference in safety between ICS/LABA and placebo but did show the increased risk when LABA was used alone. Because of this, in 2006, the Food and Drug Administration (FDA) warned against the use of LABA medications without ICS for asthma.⁴ Subsequent meta-analyses failed to reproduce consistent findings in support of or negating those results.⁵⁻⁹ Given these inconsistencies, in 2010, the FDA required the 4 pharmaceutical companies producing LABAs in the United States (Astra-Zeneca, GlaxoSmithKline, Merck, Novartis) to perform prospective, randomized controlled trials comparing the safety of ICS/LABA therapy with ICS alone. This combined analysis reports a synthesis of the 4 trials conducted between 2011 and 2016.

METHODS

Each multicenter parallel, randomized, double-blind, noninferiority trial included patients 12 years and older with persistent asthma. Patients were randomly assigned to ICS alone or ICS/LABA for a 26-week period. Three of the sponsors (AstraZeneca, Glaxo-SmithKline, and Merck) exceeded the target enrollment of 11,664 patients and completed the trials. The fourth company, Novartis, terminated enrollment at 823 patients when their drug was removed from the market, though not for safety reasons, and those enrolled were still randomized, observed, and analyzed after the 26-week period. An intention-to-treat analysis was performed on the 4 trials. Serious asthma-related events were characterized as hospitalization, intubation, or death. Each serious asthma-related event was adjudicated by a joint committee blinded to the study group designations. The primary outcome was a composite score of asthma-related intubation or death. Secondary analyses were performed on the individual components of the composite score (hospitalization, intubation, and death) as well as analysis of at-risk subgroups based on age, race, smoking history, and obesity level. The primary statistic was the relative risk of intubation or death with an ICS/LABA compared with an ICS alone.

RESULTS

The combined analysis of the 4 trials included 36,010 total patients with 18,006 randomized to the ICS group and 18,004 randomized to the ICS/LABA group. The following combination inhalers were included: fluticasone propionate/salmeterol (Glaxo-SmithKline), budesonide/formoterol (AstraZeneca), mometasone/formoterol (Merck), and formoterol separately inhaled from fluticasone propionate (Novartis). The individual trials had nearly equal numbers of total patients and subgroups with the exception of significantly reduced numbers for the Novartis trial. There were a total of 3 asthma-related intubations (2 in the ICS group and 1 in the ICS/LABA group) and 2 asthma-related deaths (ICS/LABA group) in the intention-to-treat analysis. Asthma-related events occurred in 0.60% of the patients in the ICS group and in 0.66% of the ICS/LABA group (relative risk 1.0, 95% confidence interval [CI] 0.83-1.43, $P = .55$). A minimum of 1 asthma exacerbation was recorded in 11.7% of patients in the ICS group and 9.8% of patients in the ICS/LABA group (relative risk 0.83, 95% CI 0.78-0.89, $P < .001$). Subgroup analyses for those groups considered at higher risk than the overall population (adolescent, black, Asian, and obese populations) showed no significant increase in the relative risk of serious asthma-related events or the risk of asthma exacerbations in the ICS/LABA group. Between-group differences in the

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number of asthma exacerbations for each trial and the combined analysis demonstrated a statistically significant reduction in exacerbations in the ICS/LABA group compared with the ICS group (ICS: 11.7% vs ICS/LABA: 9.8%; $P < .001$) showing increased efficacy over ICS alone with no increased risk.

CRITICAL APPRAISAL

This combined analysis is the largest study to compare the majority of currently available LABA-containing asthma medications and the only to do so in a harmonized safety trial. The analysis exhibits strength in size and consistency in wide-ranging patient demographics amongst the trials. Despite these strengths, there were a number of limitations. First, the early withdrawal of the Novartis trial lowered the overall enrollment numbers and skewed the ability to determine whether separate LABA and ICS inhalers would be inferior to a combination inhaler. Although the available data did not show any trend toward increased exacerbations or events in the ICS/LABA group compared with ICS alone, this could not be definitively determined because of termination of their trial. Second, the low enrollment may have also contributed to the fact that the rates of asthma-related events, including intubations and death, were lower than expected based on pre-enrollment statistical power calculations. However, the study authors suggest that the anticipated event rates were already so low that any risk difference would be minimal. Third, the study is not all inclusive. New medications, such as Breo (fluticasone furoate/vilanterol), have since been released into the market, and though the overall goal of this study is to address the class of medications rather than comparison of each individual product, vilanterol was not specifically studied. In addition, this study can be extrapolated to a large adolescent and adult population, but not necessarily every asthmatic. One significant issue is the exclusion criteria. Patients who had a pre-existing history of asthma-related life-threatening events were not included; thus the results of this combined analysis cannot be extended to that high-risk population, who would typically be treated with an ICS/LABA based on current guidelines.^{1,2} Furthermore, this analysis did not include data for patients aged 4 to 11 years, a group which may require step-up therapy with an ICS/LABA medication for asthma. Limited existing studies, however, have mirrored the results demonstrated in the most recent adult studies. A meta-analysis in 2011 noted that, of all age ranges, those aged 4 to 11 years had the largest incidence difference in asthma composite index scores (including asthma-related hospitalization, intubations, and deaths) when using a LABA compared with either no baseline therapy or self-reported baseline ICS use.⁹ When ICS was assigned, there was no significant difference in risk regardless of LABA use, suggesting that with regular adherence to the ICS, there is no significant increase risk when LABA is added.⁹ Most recently, a study similarly structured to that of the adult fluticasone propionate/salmeterol trial demonstrated that this specific ICS/LABA was noninferior to fluticasone propionate alone with regard to asthma-related

adverse events in children aged 4 to 11 years.¹⁰ Lastly, a new strategy termed single maintenance and reliever therapy (SMART) using the ICS/LABA for both daily control and quick relief has been introduced as a possible regimen for patients with persistent asthma.¹¹ Given that this combined analysis addressed ICS/LABA use from a controller perspective, the safety data may not directly apply to more frequent use.

Nonetheless, evidence from this combined analysis indicates that ICS/LABA is overall noninferior to ICS alone with regard to risk for serious asthma-related events, prompting the removal of the FDA black box warning in 2018. Despite prior smaller studies showing no increased risk when ICS is added to LABA, the safety concern continues to be raised by patients and providers. A large prospective analysis such as this can help to mitigate those fears in both patient and providers and further supports the removal of the black box warning.

RECOMMENDATION

Providers should feel comfortable with following current asthma guidelines when using an ICS/LABA as indicated in step-up asthma therapy for patients 12 years and older. Use of LABA as monotherapy is not advised.

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