

Evaluating Safety and Adverse Events Associated with Long-Acting β -Agonist in Combination Asthma Therapy Versus Inhaled Corticosteroid Alone

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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.

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Stempel DA, Szeffler SJ, Pedersen S, Zeiger RS, Yeakey AM, Lee LA, et al. Safety of adding salmeterol to fluticasone propionate in children with asthma. *N Engl J Med* 2016;375:840-9.

BACKGROUND

The long-acting β -agonist (LABA) class of medication has been an available treatment option since 1990, with current guidelines recommending initiating it as add-on therapy with inhaled corticosteroids (ICS) in patients with uncontrolled asthma with ICS alone.¹⁻³ However, concerns have been raised over the safety of this drug class, based primarily on 2 studies that showed higher rates of asthma-related death and adverse events in patients receiving salmeterol monotherapy compared with those who received short-acting β -agonist salbutamol⁴ or placebo.⁵

The Salmeterol Multicenter Asthma Research Trial (SMART) found that there were statistically significant increases in asthma-related death or life-threatening experience among those who received salmeterol when compared with placebo, and this effect was greatest in black subjects. Post hoc analyses showed no significant differences between treatments for the Caucasian group. In light of this, in 2008, the Food and Drug Administration (FDA) requested all manufacturers of LABA-containing products to conduct randomized, double-blinded, controlled studies comparing asthma therapies containing LABA with those that

did not contain LABAs. In 2011, clinical trials were begun to address this with the intention of having all of the data available by 2017. Three recently published articles comparing LABA-ICS combination therapy with ICS alone for the treatment of asthma are discussed herein.

METHODS

The AUSTRI trial⁶ was a randomized, double-blinded trial involving adolescents and adults (aged ≥ 12 years) with persistent asthma that included 710 centers in 33 countries. Inclusion and exclusion criteria are summarized in Table I. Subjects who met the inclusion criteria were randomized to one of 6 groups: fluticasone propionate-salmeterol (100 μ g-50 μ g, 250 μ g-50 μ g, or 500 μ g-50 μ g) or fluticasone propionate alone (100 μ g, 250 μ g, or 500 μ g). Medications were administered twice daily in a masked DISKUS dry-powder inhaler for a 26-week active treatment period and a 1-week follow-up period. The study's primary safety end point was the first serious asthma-related event, reviewed and confirmed by a joint adjudication committee that included death, endotracheal intubation, and hospitalization. The primary efficacy end point was the first serious asthma exacerbation, which included the use of systemic glucocorticoids for at least 3 days, or an asthma-related hospitalization or emergency department visit that led to the use of systemic glucocorticoids. The secondary efficacy measure was the use of albuterol or salbutamol for rescue therapy.

The second study⁷ was a multicenter, randomized, double-blind trial involving patients 12 years of age or older with a clinical diagnosis of asthma. The inclusion and exclusion criteria, primary safety end point, and primary and secondary efficacy end points were identical to the AUSTRI study. Subjects were randomized to receive budesonide-formoterol (80 μ g-4.5 μ g or 160 μ g-4.5 μ g) or budesonide alone (80 μ g or 160 μ g) twice daily for 26 weeks. Patients had 3 scheduled clinic visits on days 28, 84, and at the treatment end.

The third study,⁸ also known as the VESTRI trial, focused on a pediatric cohort. It was an international, randomized, double-blind, active-comparator, 26-week trial from November 2011 through November 2015 at 567 trial centers in 32 countries. The study population included children 4 to 11 years of age with inclusion/exclusion criteria as listed in Table I. Control was measured utilizing the Childhood Asthma Control Test. Subjects who met the criteria were randomized to receive 1 of 4 treatments: fluticasone

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TABLE I. Summary of studies

Study, Year (Reference)	Stempel et al, 2016 ⁶	Peters et al, 2016 ⁷	Stempel et al, 2016 ⁸
Study design	Multicenter, randomized, double-blind	Multicenter, randomized, double-blind	Multicenter, randomized, double-blind
Inclusion criteria	1-yr history of asthma - Daily asthma medications - Treated with systemic glucocorticoids or been hospitalized for an asthma exacerbation during the previous 12 mo - Age $\geq$ 12 yr	- Clinical diagnosis of asthma for at least 1 yr - Daily asthma medication - History of at least 1 asthma exacerbation in the previous year but none in the previous 4 wk - Age $\geq$ 12 yr	- Consistent use of asthma medication - Asthma exacerbation in previous 12 mo - No exacerbation in previous 30 d - Age 4-11 yr
Exclusion criteria	- History of life-threatening asthma - Cigarette smoking >10 pack-years - Unstable asthma	- History of life-threatening asthma - More than 4 separate exacerbations or more than 2 hospitalizations for asthma in the previous year - Unstable asthma within 7 d before randomization - Smoking history of more than 10 pack-years	History of life-threatening or unstable asthma
Population/subjects	11,679 total randomized: 5,834 to fluticasone propionate-salmeterol (100 μ g-50 μ g, 250 μ g-50 μ g, or 500 μ g-50 μ g) twice daily 5,845 to fluticasone propionate alone (100 μ g, 250 μ g, or 500 μ g) twice daily	11,693 total randomized: 5,846 to budesonide-formoterol (80 μ g-4.5 μ g or 160 μ g-4.5 μ g) twice daily 5,847 to budesonide alone (80 μ g or 160 μ g) twice daily	6,208 in intention-to-treat population: 3,107 to fluticasone propionate-salmeterol (100 μ g-50 μ g or 250 μ g-50 μ g) twice daily 3,101 to fluticasone propionate alone (100 μ g or 250 μ g) twice daily
Time course	26-wk active treatment and 1-wk follow-up periods	26 wk	26 wk
Results: safety/adverse outcomes	No asthma-related deaths in either group, asthma-related intubations for 2 subjects in the fluticasone-alone group, and none in the fluticasone-salmeterol group Hazard ratio for a serious asthma-related event in the fluticasone-salmeterol group was noninferior to fluticasone alone ($P = .003$) No significant differences in the rates of asthma-related hospitalization according by age or race	Two asthma-related deaths, including 1 intubation, both in the budesonide-formoterol group Addition of formoterol to budesonide did not appear to increase the risk of serious asthma-related events in adolescents and adults: 49 serious asthma-related events in 43 subjects from the budesonide-formoterol group vs 45 events in 40 subjects in the budesonide-only group	No asthma-related deaths, no asthma-related intubations Adverse effect of fluticasone-salmeterol was noninferior to fluticasone alone ($P = .006$): 27 serious asthma-related events in the fluticasone-salmeterol group vs 21 in the fluticasone-only group
Results: efficacy	Risk of an asthma exacerbation was 16% to 32% lower in the fluticasone-salmeterol group than in the fluticasone-alone group with the largest difference (35% lower risk) in adolescents	Risk of asthma exacerbation was 16.5% lower in the budesonide-formoterol group compared with the budesonide only Asthma control improvement seen in both groups, but greater improvement in the budesonide-formoterol group	Similar mean percentage of rescue therapy-free days in the fluticasone-salmeterol group (83.0%) and the fluticasone-alone group (81.9%), as well as similar C-ACT scores between groups

C-ATC, Childhood Asthma Control Test.

propionate-salmeterol 100 μ g-50 μ g or 250 μ g-50 μ g, or fluticasone alone at a dose of 100 μ g or 250 μ g. The primary safety and efficacy end points were identical to the studies described above. The secondary efficacy end point included the number of rescue therapy-free days and the number of asthma-control days. In addition, height measurements were included.

RESULTS

Study population

For the AUSTRI trial, a total of 11,751 subjects (aged $\geq$ 12 years) were randomized, and 11,679 subjects received treatment (5,834 with fluticasone-salmeterol and 5,845 with fluticasone

alone). In the trial by Peters et al,⁷ a total of 11,693 patients (aged $\geq$ 12 years) completed randomization, and 11,551 completed the study (5,846 patients received budesonide-formoterol and 5,847 received budesonide only). In the VESTRI trial, 3,107 subjects (4-11 years old) were treated with fluticasone-salmeterol and 3,101 with fluticasone alone.

Study end points

Primary safety end points

Death. There were no asthma-related deaths in either the AUSTRI⁶ or VESTRI⁸ trials. However, there were 2 asthma-related deaths in the budesonide-formoterol group in the study

by Peters et al,⁷ including 1 subject that was intubated. One of these patients was a 68-year-old woman who stopped the study medication after 104 days and died 8 weeks after being admitted to the hospital for cardiopulmonary failure. The second patient was a 22-year-old woman who stopped the study medication after 109 days, became dyspneic, cyanotic, lost consciousness, and died. The cause of death was listed as pneumonia. In terms of significance, the study was not powered for a separate analysis of asthma-related death and the authors note that these data will be pooled and evaluated once the results of these studies and 2 others currently in progress (mometasone-formoterol and fluticasone-formoterol) are completed.

Asthma-related Intubation. In the AUSTRI trial, endotracheal intubations were reported in 2 subjects in the fluticasone-alone group and in no patients in the fluticasone-salmeterol group.⁶ There was only 1 (<0.1%) asthma-related intubation in the Peters et al study,⁷ which occurred in the budesonide-formoterol group. There were no asthma-related endotracheal intubations in either treatment group in the VESTRI trial.⁸

Serious asthma-related events. Among the patients who received the study drug in the AUSTRI trial ($n = 11,679$), 36 serious asthma-related events occurred in 34 patients in the fluticasone-salmeterol group compared with 38 events in 33 patients in the fluticasone-alone group (hazard ratio 1.03; 95% confidence interval [CI], 0.64-1.66).⁶ As a result, fluticasone-salmeterol was found to be noninferior to fluticasone alone ($P = .003$). For the VESTRI trial, there were 27 serious asthma-related events (0.87%) in the fluticasone-salmeterol group versus 21 (0.68%) in the fluticasone-alone group (hazard ratio 1.28; 95% CI, 0.73-2.27), demonstrating that the risk of fluticasone-salmeterol was noninferior to fluticasone alone ($P = .006$).⁸ For the patients who received budesonide-formoterol, there were 49 serious asthma-related events in 43 subjects, compared with 45 events in 40 patients in the budesonide-only group (hazard ratio 1.07; 95% CI, 0.70-1.65), indicating statistical noninferiority between the groups.⁷

Asthma-related hospitalization. In the AUSTRI trial, 34 (0.6%) patients in the fluticasone-salmeterol group and 33 (0.6%) subjects in the fluticasone-alone group had at least 1 asthma-related hospitalization and there were no significant differences according to age or race in this group.⁶ In the budesonide-formoterol study, there were 42 (0.7%) asthma-related hospitalizations in the budesonide-formoterol group and 40 (0.7%) in the budesonide-only group, indicating no significant difference.⁷ The hospitalization rate in the VESTRI trial was 1.5 hospitalizations per 100 patient-years with each treatment that was similar to the incidence observed in children 5 to 14 years of age by the US National Surveillance of Asthma.⁸

Efficacy end points

In the AUSTRI trial, at least 1 severe asthma exacerbation was reported in 8% ($n = 480$) of patients in the fluticasone-salmeterol group and 10% ($n = 597$) in the fluticasone-alone group (hazard ratio 0.79; 95% CI, 0.70-0.89; $P < .001$). Efficacy subgroup analyses determined that the risk of an asthma exacerbation was 16% to 32% lower in the fluticasone-salmeterol

group than in the fluticasone-alone group with the largest difference (35% lower risk) seen among adolescents.⁶

In the study by Peters et al, asthma exacerbations occurred in 9.2% ($n = 539$) of subjects in the budesonide-formoterol group as opposed to 10.8% ($n = 633$) of subjects in the budesonide-only group. The risk of an asthma exacerbation was 16.5% lower with budesonide-formoterol than with budesonide alone (hazard ratio 0.84; 95% CI, 0.74-0.94; $P = .002$). There was a clinically relevant improvement in asthma control (mean average decrease from baseline Asthma Control Questionnaire (ACQ)-6 ≥ 0.5) in both treatment groups with a greater improvement observed in the budesonide-formoterol group.⁷

In the VESTRI trial, similar to the AUSTRI trial, a total of 265 patients (8.5%) in the fluticasone-salmeterol group had 1 or more severe asthma exacerbation compared with 309 (10.0%) in the fluticasone-alone group (hazard ratio 0.86; 95% CI, 0.73-1.01). The mean percentage of rescue therapy-free days for children was similar between the 2 groups, with 88.1% of the subjects in the fluticasone-salmeterol group demonstrating controlled asthma, versus 88.5% of subjects in the fluticasone-alone group.⁸

Other safety end points

The VESTRI trial, because it involved children 4 to 11 years of age, evaluated height. The group that received fluticasone 100 μg had a growth velocity of 2.712 cm per 6 months as opposed to the group that received 250 μg of fluticasone with a growth velocity of 2.657 cm per 6 months (difference, -0.055 cm per 6 months; 95% CI, -0.190 to 0.079).⁸

Black subjects

Among black subjects in the VESTRI trial, 6.7% in the fluticasone-salmeterol group versus 8.4% in the fluticasone-alone group had a severe exacerbation (hazard ratio, 0.80; 95% CI, 0.51-1.24), which was not significant.⁸ Data from the other 2 trials involving adolescents and adults also failed to show greater risk in specific age or racial groups when LABA was used with ICS.^{6,7}

CRITICAL APPRAISAL

The articles described are FDA-mandated postmarketing studies that will be pooled and analyzed when all of the data are available. However, a central theme in all 3 articles is that the addition of a LABA to an ICS is safe and effective. The AUSTRI trial and the study by Peters et al revealed that treating moderate-to-severe asthma with an ICS-LABA combination was associated with a lower risk of asthma exacerbations and serious asthma-related events than with ICS alone.

The SMART trial suggested a greater risk of exacerbation and death in the African American population on LABA therapy, and these follow-up studies tried to address this.⁵ In fact, these studies demonstrated that there was no disproportionate risk of serious adverse effects or altered efficacy (as opposed to the observations from the SMART trial). In regard to the pediatric population, the BADGER study previously showed that LABA step-up was more likely to provide best response than either ICS or leukotriene-receptor antagonist in children 6 to 17 years of age.³ These findings were consistent with the VESTRI trial, which showed that the addition of salmeterol to fluticasone was effective in children 4 to 11 years of age, and not associated with an increased risk of serious asthma-related events. Together,

these studies support the potential benefits over risks associated with the fixed-dose ICS-LABA combination for patients whose asthma is uncontrolled on ICS.

However, it is important to note that a limitation of all 3 studies is that the results may not be applicable to all patients with asthma, especially those with a history of life-threatening asthma, who were excluded in all 3 studies. This decision was made by the FDA, the study sponsors, and an independent joint oversight committee centered on patient safety. The authors for the budesonide-formoterol trial noted that those with life-threatening asthma may represent a genotypically or phenotypically distinct subgroup of all patients with asthma and they were not studied. Also, there is a high rate of adherence to the prescribed regimen in all treatment groups that is not always observed in real-life settings. Another important aspect to consider is the lower than expected intubation and mortality rates in all 3 trials, which could result in inconclusive outcomes when they are combined. However, the trials' conclusions were reinforced by their design (prospective, randomized, double-blind) and large numbers of patients across various ages, race, and gender in multiple centers and countries.

RECOMMENDATION

The body of evidence thus far supports the safety of ICS-LABA combination therapy and the reduced risk of asthma exacerbation when compared with ICS alone for patients with uncontrolled

asthma. There are 2 more FDA-mandated clinical trials to evaluate the safety of mometasone-formoterol (NCT01471340) and fluticasone-formoterol (NCT01845025) that are not yet published. The sum of these studies will be crucial to solidify recommendations regarding the safety of ICS-LABA medications.

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