

Controversies regarding long-acting β 2-agonists

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Purpose of review

This review examines the literature regarding the efficacy and safety of long-acting β 2-agonists as add-on therapy to inhaled corticosteroids.

Recent findings

The Global Initiative for Asthma (GINA) 2009 guidelines and the National Heart, Lung, and Blood Institute (NHLBI) 2007 asthma guidelines recommend adding long-acting β 2-agonists to patients inadequately controlled on inhaled corticosteroids. These recommendations must be balanced against published data which demonstrate a signal of increased morbidity and mortality with use of long-acting β 2-agonists. These conflicting data raise the question of whether or not there may be genotypic or phenotypic discriminators leading to disparate responses to long-acting β 2-agonists.

Summary

The combination of long-acting β 2-agonists and inhaled corticosteroids demonstrates improvement in asthma control and exacerbation rates; however, long-acting β 2-agonists are not recommended for use as monotherapy or without optimization of inhaled corticosteroid dose. Although the majority of asthmatic patients appear to benefit from the addition of long-acting β 2-agonists, there are concerns that a small proportion of patients, including steroid-naïve patients and African Americans, may not obtain such benefits. Thus far, studies have not clearly demonstrated genotypic or phenotypic differences explaining the variability in response.

Keywords

asthma, efficacy, long-acting β 2-agonists, safety

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Introduction

Asthma is a chronic disease characterized by airway inflammation, bronchial hyper-responsiveness, and airway remodeling [1]. The burden of asthma has been increasing over the past two decades [2]. For example, in 2003, 17 per 10 000 people were hospitalized for asthma and 1.4 per 100 000 people died from asthma in the US [2,3]. These sobering figures have resulted in modifications to the NHLBI and GINA asthma management guidelines [1,4]. Although long-acting β 2-agonists (LABAs) have been used in conjunction with inhaled corticosteroids (ICS) for many years, safety concerns have prompted the Food and Drug Administration (FDA) to issue official warnings for the use of LABAs [5,6]. In this review, we will explore the literature that addresses both the efficacy and safety of using LABAs in asthmatic patients.

Early comparative studies

Although anti-inflammatory agents such as ICSs are the mainstay of asthma treatment, prolonged use and high doses of ICSs may lead to unwanted local and systemic

side-effects [1,7]. The dose–response curve for the clinical efficacy of ICSs is relatively flat, with the majority of the clinical benefit achieved at low doses [8,9] as exemplified in a meta-analysis evaluating fluticasone propionate [10]. In contrast, the dose–response curve for side-effects with ICSs is steep [11,12].

In light of these dose–response characteristics, adding an alternative medication to attain asthma control is a reasonable consideration. Two studies from the early 1990s were the first to demonstrate the benefits of adding a LABA to an ICS [13,14]. In a randomized, double-blind, placebo-controlled (DBPC) study, Greening *et al.* [13] investigated the effect on morning peak flows (AM-PEF) after the addition of a LABA to medium-dose ICS compared to doubling the ICS dose in 429 asthmatics over a 6-month period. The increase in AM-PEF was significantly greater in the combination group compared with doubling the ICS dose ($P < 0.05$); however, there were no differences in exacerbations ($P = 0.42$). Woolcock *et al.* [14] conducted a 24-week randomized, DBPC study comparing the efficacy and safety of combining a LABA added to a medium-dose ICS vs. high-dose ICS alone in 738 asthmatic patients uncontrolled while using

medium-dose ICS. Combination therapy led to an increase in mean percentage predicted AM-PEF rates compared with high-dose ICS alone ($P < 0.001$). These early comparative studies were the catalyst for further research evaluating the addition of a LABA to an ICS.

Impact of long-acting β_2 -agonists on inhaled corticosteroids

There are currently two different LABAs available – formoterol and salmeterol. They are both highly selective and potent β_2 -adrenergic receptor agonists that demonstrate bronchial smooth muscle relaxation for up to 12 h [15]. In a guinea pig model, high doses of formoterol, a full β_2 -agonist, produce maximal smooth muscle relaxation, whereas salmeterol, a partial β_2 -agonist, demonstrated less than maximum bronchodilating effects [16,17]. Formoterol has a higher intrinsic activity than salmeterol and an onset of action of approximately 5 min, whereas salmeterol has an onset of action of approximately 15 min [18–21]. Clinical studies in humans demonstrate that formoterol and salmeterol have similar effectiveness in improving lung function, rescue medication use, and symptom scores [22,23].

ICSs primarily suppress inflammation and airway hyper-responsiveness via glucocorticoid receptors [24]. Activated glucocorticoid receptors induce anti-inflammatory mediators and inhibit certain transcription factors which ultimately result in the decreased production of pro-inflammatory mediators [24–26]. Furthermore, an in-vitro study by Eickelberg *et al.* [26] demonstrated that β_2 -agonists are potent activators of the glucocorticoid receptors, and that LABAs can up-regulate the anti-inflammatory effects of ICSs via a ligand-independent activation of the glucocorticoid receptors. Maneechote-suwan *et al.* [27] explored the effect of 4 weeks of treatment with formoterol compared with placebo, examining sputum neutrophil numbers and interleukin-8 (IL-8) levels in 15 ICS-naïve, nonsmoking patients with mild persistent asthma. The use of formoterol significantly reduced sputum IL-8 levels and neutrophil numbers compared with placebo ($P = 0.0004$ and 0.0061 , respectively). Several studies, however, demonstrated lack of anti-inflammatory effects. Overbeek *et al.* [28] performed a double-blind, parallel-group trial in 40 asthmatic patients with a FEV_1 of 50–90% of predicted with a positive methacholine challenge who had used no ICSs in the prior 4 weeks. Patients were then randomized to 8 weeks of treatment with low-dose budesonide and placebo or low-dose budesonide and formoterol. The dose of budesonide was then quadrupled for an additional 8 weeks in both treatment groups. Although low-dose budesonide reduced epithelium major basic protein levels after 8 weeks of treatment, there was no significant difference between low-dose budesonide and low-dose

Key points

- Although optimizing the inhaled corticosteroid (ICS) dose is important for asthma management, adding a long-acting β_2 -agonist (LABA) may further assist with controlling symptoms.
- LABAs should never be used as monotherapy. They should only be used in combination with ICSs in patients not adequately controlled on low-dose ICS alone.
- A small subgroup of asthmatic patients may be prone to deleterious effect from the use of LABAs. From the data available, it cannot be ascertained for certain whether this is due to a genotypic or phenotypic susceptibility to an untoward effect of these drugs.

budesonide and formoterol subgroups ($P = 0.28$). Likewise, Roberts *et al.* [29] demonstrated a lack of anti-inflammatory effect when salmeterol was used as monotherapy. In this DBPC study, 26 ICS-naïve asthmatic patients were randomized to treatment with either salmeterol or placebo, examining peak expiratory flow (PEF) and bronchoscopy with lavage (BAL) and biopsy at baseline and following 6 weeks of treatment. Although the salmeterol group demonstrated improved clinical indices of asthma control, there were no changes in biopsy or BAL indices of inflammation. Furthermore, a recent meta-analysis [30] demonstrated that LABAs do not have anti-inflammatory or pro-inflammatory properties.

Rationale for combination therapy

The efficacy of adding a LABA to an ICS likely depends on each patient's severity and historical response to therapy. As an example, in ICS-naïve asthmatic patients with mild airway obstruction, the initiation of combination therapy did not reduce the rate of exacerbations compared to ICS alone [31]. This was demonstrated in the Oxis and Pulmicort Turbuhaler in the Management of Asthma (OPTIMA) study [31], which was a randomized, DBPC study that compared the addition of a LABA to low-dose ICS in reducing time to first severe asthma exacerbation and number of poorly controlled asthma-days. In nearly 700 ICS-naïve patients with mild asthma, who were randomized to receive low-dose ICS, low-dose ICS and a LABA, or placebo for 1 year, ICS alone reduced the risk of severe exacerbations by 60% [relative risk (RR) = 0.40, 95% confidence interval (CI) 0.27, 0.59] and poorly controlled days by 48% (RR = 0.52, 95% CI 0.40, 0.67) compared with placebo. Although the addition of a LABA to an ICS provided further benefit over ICS alone such as improvement in FEV_1 ($P = 0.023$), this addition did not significantly diminish severe exacerbations ($P = 0.50$). However, in the same study, nearly 1300 uncontrolled patients, despite being treated with

low-dose ICS, were randomized to treatment with low-dose ICS, low-dose ICS and a LABA, doubling the ICS dose alone, or double ICS dose and a LABA for 1 year. In these patients, the addition of a LABA to either the low or double ICS dose demonstrated a decrease in the risk for the first severe exacerbation by 43% (RR = 0.57, 95% CI 0.46, 0.72) and the rate of poorly controlled asthma-days by 30% (RR = 0.70, 95% CI 0.60, 0.82). Adding a LABA to the lower dose of ICSs was more effective than doubling the ICS dose in terms of reducing the risk of severe exacerbations ($P=0.001$) and improving FEV₁ ($P<0.05$). Therefore, there appears to be limited benefit in adding a LABA to ICSs in ICS-naïve asthmatic patients with mild asthma. However, in uncontrolled asthmatic patients already taking an ICS, the addition of a LABA improves asthma control and reduces the rate of exacerbations compared with increasing the ICS dose. The conclusions from the OPTIMA study were further reinforced in a recent meta-analysis [32].

The Formoterol and Corticosteroids Establishing Therapy (FACET) study was sentinel in establishing the utility of combining a LABA with an ICS in asthmatic patients not controlled with an ICS alone [33]. This randomized, DBPC study examined the exacerbation rate in 852 adult asthmatic patients, comparing low-dose ICS, with or without a LABA, with quadruple-dose ICS, with or without a LABA. In this year-long study, there were 425 severe exacerbations. The rate of severe exacerbations was reduced by 26% when the LABA was added to low-dose ICS, by 49% when the quadruple-dose ICS was given alone, and by 63% when LABA and quadruple-dose ICS was given ($P<0.001$). These data illustrate the importance of treatment with the optimal ICS dose, as it is essential for achieving asthma control, but also emphasizes the fact that the addition of a LABA may further aid in reducing asthma exacerbations [33,34].

Although the addition of a LABA may control symptoms and maintain stable lung function, there has been concern that chronic use could delay awareness of progressive inflammation, a phenomenon known as 'masking' [35,36]. This 'masking' effect was demonstrated in a randomized, DBPC, cross-over study [36], in which salmeterol or placebo was added to 13 asthmatic patients on high-dose ICS while the ICS was reduced in a step-wise fashion until a clinical exacerbation was seen. Mean ICS dose was reduced by 87% during salmeterol treatment vs. 69% with placebo ($P=0.04$). In the week before clinical exacerbation, eosinophil counts were significantly higher in the salmeterol treatment arm compared with placebo ($P=0.006$). It should be noted, however, that at the time of exacerbation, six out of 13 patients in the LABA arm were not on any ICSs. These outcomes reinforce the importance of not discontinuing the ICS when starting a LABA, as this may not only worsen

inflammation but also result in a diminished awareness of potentially worsening inflammation [6,36].

The clinical implications of 'masking' were evaluated in an extension of the original FACET study [37] which examined the 425 severe exacerbations occurring during the study. In this study, Tattersfield *et al.* [37] found that increased rescue medication use, change in PEF, nocturnal awakenings, or prolongation of the exacerbations were not affected by the addition of a LABA. This descriptive analysis diminished fear that a LABA could 'mask' inflammation. Furthermore, numerous meta-analyses have shown that the use of a LABA in the management of asthma is effective not only in improving pulmonary function, increasing symptom-free days, and decreasing the need for rescue β 2-agonists [32,38] but also in reducing asthma exacerbation rates [39].

Asthma control may be especially challenging in more severe asthmatic patients. The Gaining Optimal Asthma Control (GOAL) study [40], a 1-year randomized, double-blind, parallel-group study of 3421 patients with uncontrolled asthma, compared combination therapy with an ICS and a LABA vs. an ICS alone in achieving asthma control. On the basis of their previous ICS exposure, patients were randomized into three strata: 1, ICS-naïve; 2, low-dose ICS; or 3, moderate/high-dose ICS. The primary endpoints, 'total control' and 'well control', were based upon composite scores. 'Total control' was defined as no symptoms, exacerbations, or rescue β 2-agonists use, whereas 'well control' was defined as infrequent daytime symptoms and rescue β 2-agonists use. Treatment was 'stepped up' until 'total control' was achieved or until patients received the maximum ICS dose. 'Total control' was achieved across all strata in 31 vs. 19% of patients after dose escalation ($P<0.001$) for combination therapy vs. ICS alone, respectively. Asthma became 'well controlled' in 63% of patients receiving combination therapy vs. 50% of patients using ICSs alone after maximal dose escalation ($P<0.001$). For each stratum, the proportion of patients achieving 'total control' and 'well control' status was significantly greater with use of combination therapy compared with ICS alone. Unfortunately, 'total control' was only achieved in 19% of the patients in stratum 3 despite receiving the maximum ICS dose with concomitant LABA [40,41]. Forty-nine percent of ICS-naïve patients achieved 'total control' with combination therapy compared with 19% of patients who previously required high-dose ICS. These outcomes indicate that severe asthmatic patients may not completely improve even while using combination therapy with maximum-dose ICS; however, they still attain better control with combination therapy than ICSs alone.

Asthma control is also complicated by patient variability in response. The Best Add-on Therapy Giving Effective

Responses (BADGER) study [42*] evaluated which step-up asthma therapy was most beneficial in asthmatic children who were uncontrolled on an ICS alone. In this randomized, DBPC, three-period cross-over trial, 182 asthmatic children (aged 6–17) receiving low to medium-dose ICS were randomized to receive each of three step-up therapies for 16 weeks: 1, high-dose ICS (ICS step-up); 2, medium-dose ICS and a LABA (LABA step-up); or 3, medium-dose ICS and a leukotriene receptor antagonist (LTRA) (LTRA step-up). A composite outcome which included exacerbations, asthma-control days, and FEV₁ was used to determine whether the likelihood of a differential response to the step-up regimens was more than 25%. The study found that 95% of participants had a

differential response to each of the three treatments ($P < 0.001$). Despite the fact that LABA step-up therapy was more than 1.5 times as likely to produce the best overall response compared with the responses to either LTRA (relative probability 1.6; 95% CI 1.1, 2.3; $P = 0.004$) or ICS step-up therapy (relative probability 1.7; 95% CI 1.2, 2.4; $P = 0.002$), many children in fact responded best to one of the other two treatments. Therefore, asthma control is an iterative and patient-specific process with the need for frequent monitoring of medication response and appropriate therapy modification.

A summary of these studies investigating the efficacy of combination therapy is shown in Table 1.

Table 1 Summary of efficacy studies

Study, year, (reference), duration	Design	Patients: <i>N</i> , age, description	Study group/intervention	Outcome measure(s)
OPTIMA, 2001, [31], 1 year	R, DBPC	<i>N</i> = 1970 (group A <i>n</i> = 698, group B <i>n</i> = 1272) Age ≥ 12 with mild asthma Group A – ICS-naïve Group B – ICS-treated	Group A: 200 µg/day BUD vs. 200 µg/day BUD + 9 µg/day F Group B: 200 µg/day BUD vs. 200 µg/day BUD + 9 µg/day F vs. 400 µg/day BUD vs. 400 µg/day BUD + 9 µg/day F	Time to first severe asthma exacerbation Poorly controlled asthma days
FACET, 1997, [33], 1 year	R, DBPC	<i>N</i> = 852 Adults (age ≥ 18) with uncontrolled asthma on ICS	200 µg/day BUD vs. 200 µg/day BUD + 24 µg/day F vs. 800 µg/day BUD vs. 800 µg/day BUD + 24 µg/day F	Asthma exacerbation rate
GOAL, 2004, [40], 1 year	R, double-blind, parallel group	<i>N</i> = 3421 Age ≥ 12 years with uncontrolled asthma Stratum 1 – ICS-naïve Stratum 2 – low-dose ICS (≤ 500 µg/day BDP) Stratum 3 – medium-dose ICS (>500 to ≤ 1000 µg/day BDP)	Strata 1 and 2 – maximum FP/S (100/50 µg b.i.d., 250/50 µg b.i.d. or 500/50 µg b.i.d.) vs. FP alone (100, 250, 500 µg b.i.d.) Stratum 3 – maximum FP/S (250/50 µg b.i.d., 500/50 µg b.i.d.) vs. FP (250 or 500 µg b.i.d.)	'Total control' 'Well control'
BADGER, 2010, [42*], 48 weeks	R, DBPC, triple cross-over	<i>N</i> = 182 Children (aged 6–17) Uncontrolled on ICS	ICS step-up – 500 µg/day FP vs. LABA step-up – 200 µg/day FP + 100 µg/day S vs. LTRA step-up – 200 µg/day FP + 5 mg/day or 10 mg/day LTRA	Frequency of differential response $>25\%$ based on exacerbations, asthma-control days and FEV ₁

BDP, beclomethasone dipropionate; b.i.d., twice daily; BUD, budesonide; DBPC, double-blind, placebo-controlled; F, formoterol; FEV₁, forced expiratory volume in 1 s; FP, fluticasone propionate; ICS, inhaled corticosteroid; LABA, long-acting β_2 -agonist; LTRA, leukotriene receptor antagonist; R, randomized; S, salmeterol.

Safety concerns regarding long-acting β 2-agonists

As noted prior, LABAs are often useful adjuncts to ICSs in asthma treatment providing relief of symptoms and improving lung function. However, concerns regarding their risk of increasing severity of asthma exacerbations and death surfaced soon after they became available [43–46]. In a letter to the editor in the *New England Journal of Medicine* in 1994, Finkelstein [47] described two elderly asthmatic patients who had fatal respiratory arrests while ‘clutching their (salmeterol) inhalers’.

Although the addition of a LABA may yield a reduction in the ICS dose, LABAs should not be used alone to treat asthma. This is well illustrated in the Salmeterol or Corticosteroids (SOCS) study [44] which demonstrated that the use of a LABA without an ICS increases the risk of asthma exacerbations and treatment failures in patients previously receiving ICSs. In this randomized, DBPC, parallel-group study, 164 participants with persistent asthma, previously controlled with low-dose ICS during a 6-week run-in period, were randomly assigned to continue treatment with their ICS or switch to a LABA or placebo for 16 weeks. During the active treatment period, the LABA arm had significantly more treatment failures compared with ICS (24 vs. 6%, $P=0.004$) and asthma exacerbations (20 vs. 7%, $P=0.04$) compared with the ICS. The Salmeterol $\pm$ Inhaled Corticosteroids (SLIC) study [43] went on to examine whether ICS therapy can be reduced or eliminated after adding a LABA. One hundred and seventy-five patients, uncontrolled on low-dose ICSs, were randomized to receive a LABA or placebo with their ICS in this 24-week DBPC trial. Half the patients in the subgroup started on a LABA were randomly assigned to maintain their ICS dose throughout the trial, whereas the other half underwent a blinded reduction with subsequent discontinuation of their ICS. The relative risk of treatment failure in the subgroup in which the ICS was completely eliminated was 4.3 (95% CI 2.0, 9.2) compared with the ICS and LABA combination subgroup ($P<0.001$). These studies provide further support against the discontinuation of an ICS when initiating a LABA.

The FDA warnings regarding LABAs stem from several published studies including the Serevent National Survey (SNS) and the Salmeterol Multicenter Asthma Research Trial (SMART) [48–50]. Soon after salmeterol was released in the UK in 1993, the role of LABAs as a maintenance medication in treating asthma raised concerns. The first study to demonstrate a possible signal of poor outcome with the use of a LABA was SNS which compared the safety of salmeterol to albuterol [48]. This was a randomized, DBPC, 16-week study [48] which examined approximately 25 000 asthmatic patients who

were given salmeterol (twice-daily) or albuterol (four times daily) while prior asthma medications were continued. The co-primary outcomes were serious events and withdrawals. There were significantly fewer withdrawals in the salmeterol group compared with the albuterol group (2.91 vs. 3.79%, $P=0.0002$), yet there was a small, nonsignificant increase in asthma-related deaths in the salmeterol group compared with the albuterol group (0.07 vs. 0.02%, $P=0.105$) [48]. It is important to note that 31% of patients randomized to both arms of this study were on no ICSs at baseline, and that there was no measure of adherence to ICSs. The latter issue is potentially quite important as patients may have discontinued their ICS and used LABAs as monotherapy [50].

SMART was designed to evaluate the safety of salmeterol in asthmatic patients who had no prior exposure to a LABA [49]. This was a 7-month, multicenter, randomized, DBPC, observational surveillance study. There were 50 000 participants anticipated to be in the study, but enrollment in the study was terminated following an interim analysis of 26 355 patients which demonstrated a signal of increase in mortality. In this study, patients were randomly assigned to receive salmeterol or placebo for 28 weeks while continuing their baseline medications, including ICSs. There was a small but significant increase in respiratory-related deaths (24 vs. 11; RR = 2.16; 95% CI 1.06, 4.41), asthma-related deaths (13 vs. 3; RR = 4.37; 95% CI 1.25, 15.34), and combined asthma-related deaths or life-threatening experiences (37 vs. 22; RR = 1.71; 95% CI 1.01, 2.89) in patients receiving salmeterol compared with placebo. Furthermore, post-hoc analyses revealed that there was a small but significant increase in respiratory-related deaths or life-threatening experiences (20 vs. 5; RR = 4.10; 95% CI 1.54, 10.90) and combined asthma-related deaths or life-threatening experiences (19 vs. 4; RR = 4.92; 95% CI 1.68, 14.45) in African Americans treated with salmeterol compared with placebo [49]. Although very large, there are several significant limitations to this study. To begin with, investigators obtained only minimal baseline demographics. Additionally, there was no monitoring of symptoms, lung function, or adherence with controller medications. Since over one-half of patients did not receive concomitant ICS therapy despite having unstable asthma, the increase in mortality observed in SMART could possibly be attributed to the use of LABAs as monotherapy. However, the study was not designed to compare subgroups that did or did not receive an ICS [50].

Further concern was expressed following a study by Mann *et al.* [51] who demonstrated that at higher than recommended doses LABAs were associated with an increase in morbidity. The investigators reviewed three prospective, randomized, DBPC clinical studies of formoterol at 12 and 24 μ g twice-daily for the treatment of

patients with asthma. In all three randomized studies, serious asthma exacerbations occurred more frequently in the formoterol 24 µg twice-daily arm compared with the placebo arm or formoterol 12 µg twice-daily arm. However, none of these studies was primarily designed nor geared to address serious asthma exacerbations or the potential protection with concomitant use of ICS.

In a meta-analysis, Salpeter *et al.* [52] performed a database search through 2005 to assess the risk of severe, life-threatening, or fatal asthma exacerbations associated with the use of LABAs. They demonstrated that LABAs increased severe and life-threatening asthma exacerbations, as well as asthma-related deaths. The analysis was largely influenced by data from SMART, and the majority of the reviewed studies did not require concomitant use of an ICS nor was there verification of ICS adherence [35,52]. Salpeter *et al.* [53] recently published results from a separate meta-analysis which included clinical trial data from 4039 patients treated with a LABA and an ICS compared with 3214 patients treated with an ICS alone. They reported that a LABA, with or without an ICS, doubled deaths and intubations. There are several flaws with this analysis. These include that the majority of included studies evaluated LABA as monotherapy, the use of an ICS was not always controlled, the dose of the ICS varied between the combination and ICS alone groups, and studies with no asthma-related deaths or intubations were excluded from the meta-analysis [54]. Once again this brings into question whether this signal is due to LABA monotherapy use. Weatherall *et al.* [55•] conducted a meta-analysis of asthma-related deaths in randomized controlled trials comparing salmeterol with non-LABA therapies in which they stratified with ICS use. Although the odds ratio (OR) for risk of asthma mortality in patients not prescribed an ICS was 7.3 (95% CI 1.8, 29.4), in studies in which patients were randomized to receive combination salmeterol and fluticasone propionate, there were no asthma deaths or intubations and no increase in risk of hospital admissions for asthma. And finally, in another meta-analysis, Nelson *et al.* [56•] did not demonstrate any evidence of increased risk of asthma-related hospitalizations or asthma-related deaths with formoterol vs. nonformoterol treatment.

A summary of the studies investigating the safety of LABAs is shown in Table 2.

The role of genetic polymorphisms

The response to β₂-agonists may be influenced by β₂ receptor polymorphisms (ADRB2) [57]. The β₂ adrenergic receptor's most common homozygous genotype found at the 16th amino acid position is glycine/glycine (Gly/Gly). The arginine to glycine substitution leading to

the arginine/arginine (Arg/Arg) genotype is found in one-sixth of the white North American population and one-fifth of the African American North American population [50,58].

Several retrospective analyses [59,60] demonstrated that asthmatic patients with the Arg/Arg polymorphism may carry an increased risk of adverse outcomes related to regular use of short-acting β₂-agonists (SABAs). Following these retrospective studies, Israel *et al.* [61] reported the results of the Beta-Agonist Response by Genotype (BARGE) study, which was a prospective, randomized, DBPC study of 78 ICS-naïve adults with mild asthma. Patients were treated with regularly scheduled albuterol (four times a day) or placebo for 8 weeks and then crossed over for an additional 8 weeks. The primary outcome was the change in AM-PEF. Whereas the Arg/Arg group experienced a small but significant reduction in AM-PEF during regular treatment with albuterol vs. placebo, the Gly/Gly group demonstrated a rise in AM-PEF vs. placebo with a genotype attributable difference of -24 l/min ($P=0.0003$). In light of these pharmacogenomic data regarding the use of SABAs, Wechsler *et al.* [62] retrospectively evaluated the SOCS and SLIC studies, comparing response to salmeterol based upon ADRB2. The study found a signal of worsening asthma control (based on AM-PEF and FEV₁) in patients with the Arg/Arg genotype. Notably though, the data were derived from a small sample size and thus required replication in a larger population (number using salmeterol $n=25$ in SOCS and $n=30$ in SLIC).

Bleecker *et al.* [63,64] performed retrospective analyses evaluating the effects of variation in ADRB2 on clinical response to salmeterol or formoterol in combination with ICSs. These analyses failed to demonstrate a decline in lung function in asthmatic patients when stratified by genotype. Following this lack of signal of deteriorating function, further comfort can be gleaned from the recent prospective trial, the Long-Acting Beta Agonist Response by Genotype (LARGE) study [65]. The LARGE study demonstrated that patients with either the Arg/Arg or Gly/Gly genotype respond equally to combination treatment. In this randomized, DBPC, cross-over trial, patients with moderate asthma were enrolled in matched pairs according to Arg/Arg genotype ($n=42$) or Gly/Gly genotype ($n=45$). Patients in a matched pair were randomly assigned to receive salmeterol or placebo in addition to moderate-dose ICS for two 18-week periods. The primary endpoint was mean AM-PEF. The mean AM-PEF improved in both Arg/Arg and Gly/Gly participants, and the improvement in AM-PEF did not differ significantly between genotypes ($P=0.9$). It should be noted, however, that although there was no loss in bronchodilatory effect between genotypes, there was a disparity in methacholine PC₂₀. The PC₂₀ in Gly/Gly

Table 2 Summary of safety studies

Study, year, (reference), duration	Design	Patients: <i>N</i> , age, description	Study group/intervention	Outcome measure(s)	Results/comments
SNS, 1993, [48], 16 weeks	R, DBPC	<i>N</i> = 25 180 Age >12 Requiring regular BD use	50 μ g b.i.d. S vs. Alb q.i.d.	Serious events Asthma-related deaths Withdrawals	<i>P</i> = 0.105 (asthma-related deaths) <i>P</i> = 0.0002 (withdrawals)
SMART, 2006, [49], 28 weeks	R, DBPC observational	<i>N</i> = 26 355 Age >12 No prior LABA use	42 μ g b.i.d. S vs. placebo	Respiratory-related deaths Asthma-related deaths Combined asthma-related deaths or life-threatening experiences	(24 vs. 11; RR, 2.16; 95% CI 1.06, 4.41) (13 vs. 3; RR, 4.37; 95% CI 1.25, 15.34) (37 vs. 22; RR, 1.71; 95% CI 1.01, 2.89) £
SOCS, 2001, [44], 28 weeks (6-week run-in, 16-week treatment, 6-week placebo)	R, DBPC, parallel group	<i>N</i> = 164 Age >12 Controlled on 800 μ g/day T during run-in Switched to S, <i>n</i> = 54 Continued T, <i>n</i> = 54 Placebo, <i>n</i> = 56	84 μ g/d S vs. 800 μ g/d T vs. placebo	Treatment failures Asthma exacerbations	(24 vs. 6%, <i>P</i> = 0.004) S compared to T (20 vs. 7% <i>P</i> = 0.04) S compared to T
SLIC, 2001, [43], 24 weeks (6-week run-in, then 2-week add-on S or placebo, then 16-week reduction and elimination)	R, blinded, double dummy, parallel group	<i>N</i> = 175 Age >12 Suboptimal on 800 μ g/day T during run-in Placebo minus (<i>n</i> = 21); add-on placebo S minus (<i>n</i> = 77); add-on 84 μ g/day S for 2 weeks then reduce and eliminate T S plus (<i>n</i> = 77); add-on 84 μ g/day S for 2 weeks and continue T	S minus vs. S plus	Time to asthma treatment failure in patients receiving S at end of T elimination	RR, 4.3 (95% CI 2.0, 9.2) in S minus compared to the S plus subgroup (<i>P</i> < 0.001)

Alb, albuterol; BD, bronchodilator; b.i.d., twice daily; BUD, budesonide; DBPC, double-blind, placebo-controlled; F, formoterol; ICS, inhaled corticosteroid; LABA, long-acting β_2 -agonist; q.i.d., four times daily; R, randomized; S, salmeterol; T, triamcinolone acetonide. £: post-hoc analysis data from SMART study not included.

patients was 2–4 times higher with the use of a LABA compared with placebo ($P < 0.0001$), whereas there was no difference in responsiveness between use of LABA and placebo in Arg/Arg participants ($P = 0.87$). This 2.5 times higher genotype-specific difference in responsiveness to methacholine was significant ($P = 0.0038$). Further studies may be needed to establish the importance of this genotype-specific difference in responsiveness to methacholine.

In summary, patients with the Arg/Arg genotype may suffer deleterious effects with regular use of SABAs, but the published data have not as convincingly demonstrated evidence of a pharmacogenetic effect of the ADRB2 with use of LABAs.

Distinct clinical outcomes in asthma may depend upon phenotypes such as race or ethnic group. African Americans experience greater asthma prevalence and morbidity compared with whites [2]. Whereas the asthma mortality rate has been decreasing since 1994 in whites, it has been increasing in African Americans over a similar time period [2,66]. In a post-hoc subgroup analysis of African American individuals in the LARGE study [65] (20% of the cohort), there was a genotype-specific difference in morning and evening PEF. Although these subgroups were small ($n = 9$ with Arg/Arg genotype and $n = 8$ Gly/Gly genotype), the genotype-specific differences approached significance (morning PEF, $P = 0.09$ and evening PEF, $P = 0.07$). Furthermore, in the post-hoc analysis of SMART [49], the African American subpopulation treated with salmeterol demonstrated a small but significant increase in respiratory-related deaths or life-threatening experiences compared with placebo (20 vs. 5; RR = 4.10; 95% CI 1.54, 10.90) and combined asthma-related deaths or life-threatening experiences compared with placebo (19 vs. 4; RR = 4.92; 95% CI 1.68, 14.45). To explore this potential cause, Bailey *et al.* [66] examined the safety and efficacy of combination ICS and LABA compared with ICS alone in African Americans. In this randomized, double-blind, parallel-group prospective study, nearly 500 African American adolescents (age > 12) and adults with uncontrolled asthma on low-dose ICS were randomized to low-dose ICS or to low-dose ICS and salmeterol for 52 weeks. The primary outcome was the annualized exacerbation rate. There was no significant difference in the rate of asthma exacerbations between the ICS and LABA vs. ICS monotherapy group ($P = 0.169$).

These exploratory studies evaluating genotype and phenotype-attributable adverse effects have not yielded consistent results. Differences may be related to study design, sample size, ICS dose, and the severity of asthma in target populations.

Conclusion

As clinicians, we are left to grapple with several issues when considering the addition of a LABA to an ICS. Although improvements in several asthma control measures are seen with LABA use, this add-on therapy is not anti-inflammatory. This efficacy must be weighed against a potential signal of increased morbidity and mortality with the use of a LABA. Although the majority of patients appear to benefit from the addition of a LABA, the main question remaining is whether this negative signal is a reflection of its use as monotherapy or a potential subgroup of asthmatics that are at risk when using this add-on agent. Further complicating this issue is the fact that not all patients respond equally to the addition of a LABA. It is hoped that in the future, through enhanced understanding of asthma phenotypes as well as pharmacogenomics, clinicians will be better able to decide which patients will most likely benefit from the addition of a LABA. Until this has been resolved, clinicians are left to balance this ever growing literature.

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Papers of particular interest, published within the annual period of review, have been highlighted as:

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Additional references related to this topic can also be found in the Current World Literature section in this issue (pp. 000–000).

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