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Long-Acting β_2-Agonists in Asthma
Not so SMART?

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Abstract

Asthma is a worldwide chronic disorder that is characterised by airway inflammation and hyper-responsiveness, which results in intermittent airflow obstruction and subsequent perception of symptoms and exacerbations. Inhaled corticosteroids are a fundamental component in the prevention of the short- and long-term complications associated with inadequately controlled asthma. However, many individuals experience persistent symptoms and exacerbations despite receiving low-to-medium doses of an inhaled corticosteroid (400–800 μg/day of beclometasone or equivalent). In these symptomatic asthmatic patients, guidelines advocate the initiation of a long-acting β_2-adrenoceptor agonist (LABA) as additional second-line controller therapy.

The recent SMART (Salmeterol Multi-centre Asthma Research Trial) study was designed to compare the effects of add-on salmeterol 42μg (ex-actuator) twice daily with placebo over 28 weeks in a randomised, double-blind, parallel-group fashion, with the intention to enrol 60 000 asthmatic patients. However, the study was halted prematurely because preliminary data revealed an increased mortality associated with regular use of salmeterol. Moreover, concerning rates of respiratory-related deaths, asthma-related deaths and life-threatening events were observed among African Americans, who constituted up to 18% of the study population. This in turn prompted the US FDA to announce important safety information regarding inhalers containing LABAs and advise that new labelling be produced outlining the "small but significant risk in asthma-related deaths" associated with their regular use. This evidence-based review discusses the data from SMART and highlights potentially important drawbacks with regular use of LABAs in persistent asthma.

Many studies have demonstrated the benefits of adding a long-acting β_2-adrenoceptor agonist (LABA) to the treatment regimen of symptomatic asthmatic patients uncontrolled on inhaled corticosteroids in terms of lung function, symptoms, quality of life and exacerbations.[1] As a consequence, LABAs are widely advocated as suitable add-on therapy in adult patients with persistent asthma using a low-to-medium dose of inhaled corticosteroid (400–800 μg/day of beclometasone or equivalent).[2,3] This article reappraises the benefit-risk assessment of LABAs in the context of a recent study, in which increased mortality with regular use of salmeterol was observed.[4]

Table I. Relative risks and number at risk using life-table analysis for primary and secondary outcomes for salmeterol versus placebo for the whole SMART (Salmeterol Multi-centre Asthma Research Trial) population and African Americans[4,5]

Study population	Endpoint	Relative risk (95% CI[a])	Actual numbers (salmeterol vs placebo)
Total SMART population	Combined respiratory-related death or respiratory-related, life-threatening experience	1.40 (0.91, 2.14)	50 vs 36
	Respiratory-related death	2.16 (1.06, 4.41)	24 vs 11
	Combined asthma-related death or life-threatening experience	1.71 (1.01, 2.89)	37 vs 22
	Asthma-related death	4.37 (1.25, 15.34)	13 vs 3
African Americans	Combined respiratory-related death or respiratory-related, life-threatening experience	4.10 (1.54, 10.90)	20 vs 5
	Combined asthma-related death or life-threatening experience	4.92 (1.68, 14.45)	19 vs 4

a The 95% CI, which excludes unity, denotes a significant difference between salmeterol and placebo.

In November 2005, the US FDA announced important safety information regarding inhalers containing the LABA salmeterol. The FDA advised that new labelling be produced, outlining the "small but significant risk in asthma-related deaths" with regular use of LABAs. This concern arose following preliminary data from the GlaxoSmithKline-sponsored SMART (Salmeterol Multi-centre Asthma Research Trial) study,[5] which has now been fully published.[4] This phase IV study compared add-on salmeterol 42μg (ex-actuator) twice daily with placebo over 28 weeks in a randomised, double-blind, parallel-group design, with the intention to enrol 60 000 patients. The primary outcome variable was either respiratory-related death or life-threatening experience, e.g. the need for intubation and/or mechanical ventilation. Secondary outcomes included all-cause death, asthma-related death and asthma-related death or life-threatening experience.

An interim analysis involving data from 13 174 patients treated with salmeterol and 13 179 patients treated with placebo revealed no significant difference for the primary outcome variable,[4] although a significant increase with salmeterol versus placebo in secondary outcomes was observed (table I). Although the study was not designed to detect *post hoc* subgroup differences according to ethnic backgrounds, there were significantly greater differences in African Americans, who constituted up to 18% of the study population.

Inhaled corticosteroids were used in 47% of the total population at baseline, with 50% use in Caucasians and 38% use in African Americans. For the total population who were not using inhaled corticosteroids in terms of the secondary outcome of combined asthma-related death or life-threatening experience, the relative risk was 2.39 (95% CI 1.09, 5.22), indicating a significant difference. For the same parameter in those using inhaled corticosteroids, the relative risk was 1.24 (95% CI 0.59, 2.58). There was a significant increase in relative risk for the primary outcome and for combined asthma-related death or life-threatening experience in African American patients who were not using inhaled corticosteroids, which amounted to a relative risk of 5.61 (95% CI 1.25, 25.26) and 10.46 (95% CI 1.34, 81.58), respectively. For the primary outcome in African Americans using inhaled corticosteroids, the differences were non-significant.

Based on these results, the study was prematurely halted in January 2003. In collaboration with the FDA, GlaxoSmithKline communicated these findings to healthcare providers, made them accessible on the Internet and created a boxed warning on the prescribing information sheets of Serevent® [1] Inhalation Aerosols, Serevent® Diskus® and Advair (Seretide™) Diskus®, all of which contain salmeterol as an active ingredient. The paper by Nelson et al.[4] also raises the question as to whether the same risk of death and adverse events with the use of the

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combination inhaler (fluticasone propionate plus salmeterol) would be observed when concomitant inhaled-corticosteroid compliance is enforced.

1. A Class Effect?

The FDA decided that similar warnings should be created on the prescribing sheets of inhalers containing formoterol as an active ingredient. Whether these findings are a class effect or peculiar to salmeterol alone is currently uncertain, although data have suggested some untoward effects with formoterol. In a review of three randomised, double-blind, placebo-controlled trials, more patients receiving the maximum recommended daily dose of formoterol (24μg twice daily) had a greater risk of serious asthma exacerbation than those receiving placebo.[6]

2. Problems with Long Acting β2-Adrenoceptor Agonists (LABAs)

Several plausible mechanisms support the hypothesis that regular use of LABAs may lead to a heightened risk of worsening asthma or respiratory-related death in certain susceptible individuals. The following sections highlight some of these mechanisms in addition to outlining problems arising with the use of LABAs in persistent asthma.

2.1 Subsensitivity

Regular use of LABAs results in β2-adrenoceptor down-regulation, receptor internalisation and the uncoupling of the G-protein-adenyl cyclase unit, with subsequent subsensitivity (or tachyphylaxis) of response to effects upon airway smooth muscle and inflammatory cells. This phenomenon is generally more apparent for bronchoprotective than bronchodilator effects.[7] Even when using inhaled corticosteroids, subsensitivity occurs to the bronchoprotective effects of LABAs following exposure to direct and indirect bronchoconstrictor stimuli.[8,9] For example, in a randomised, double-blind, crossover, placebo-controlled, double-dummy study, patients with mild-to-moderate persistent asthma using inhaled corticosteroids received add-on therapy for 1 week with formoterol 24μg twice daily, formoterol 24μg once daily or placebo.[9] An adenosine monophosphate (AMP) bronchial challenge was performed 12 hours after the first and last doses of each treatment. A significant loss of protection was observed with formoterol twice daily between the first and last doses (3.7-fold difference, $p = 0.006$) and with formoterol once daily (2.9-fold difference, $p = 0.005$), whereas no difference was observed with placebo.

Furthermore, there was a significant difference between active treatments and placebo for first-dose protection; however, following the last dose, the residual degree of protection between active treatments and placebo was not significant. This suggests that, even with a 24-hour administration regimen, pronounced subsensitivity develops to formoterol by prolonged occupancy of airway β2-adrenoceptors. Subsensitivity to methacholine chloride bronchial challenge has been also reported with varying doses of formoterol, either once or twice daily, as add-on therapy to inhaled corticosteroids.[8] Similar results have also been observed with add-on salmeterol in terms of subsensitivity against methacholine chloride and histamine challenge.[10,11]

In a meta-analysis of 13 randomised controlled trials (n = 596 asthmatic patients) evaluating bronchoprotection with LABAs (either salmeterol or formoterol) as add-on therapy, the overall residual protection after the last dose amounted to only 0.79 (95% CI 0.63, 0.96) doubling dose/dilution from placebo.[12] All these data indicate that, despite the development of predictable subsensitivity of response, adding a LABA does confer a small but significant degree of protection against bronchoconstrictor stimuli over and above that conferred by inhaled corticosteroids alone.

2.2 Genotype Predisposing to Subsensitivity

Specific polymorphisms of the β2-adrenoceptor can influence receptor regulation and agonist coupling. Initially, it was considered that the homozygous glycine amino acid polymorphism at position 16 predisposed to greater receptor down-regulation and subsensitivity of response to LABAs compared

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with the arginine polymorphism.[13] This was supported by *in vivo* retrospective data, which showed that the homozygous glycine-16 compared with the arginine-16 genotype exhibited a less-marked response to regular formoterol as add-on therapy in asthmatic patients.[14] Moreover, in asthmatic patients with the homozygous glycine-16 genotype using inhaled corticosteroids, add-on salmeterol and formoterol were significantly superior to placebo after the first but not the last doses.[15]

However, more recent data suggest that relative to individuals homozygous for glycine at the 16th position of the β_2-adrenoceptor, those who are homozygous for arginine may have an impaired therapeutic response (in terms of symptom scores and lung function) to salmeterol regardless of whether concomitant inhaled corticosteroids are used.[16] In a meta-analysis of six randomised controlled trials in which regular LABAs or placebo were given as add-on therapy to inhaled corticosteroids, a comparison was made of responses in asthmatic patients who were either homozygous or heterozygous for the arginine-16 genotype versus a group with the homozygous glycine-16 genotype.[17] For the composite endpoint of either bronchoprotection to methacholine chloride or AMP, the protection conferred by LABA was not significantly different from placebo after the first or last doses in the glycine-16 group (n = 100). However, in the arginine-16 group (n = 52), the protection was significantly worse than placebo after the last but not the first doses. It is therefore tempting to speculate that the paradoxical worsening in bronchoprotection in susceptible individuals with the homozygous arginine-16 genotype might be a possible explanation for the adverse effects of salmeterol observed in SMART, particularly in the setting of acute asthma when airway tone would be increased.

These data indicate the need for a large, multicentre, prospective, genotype-enriched study, powered to assess the effects of LABAs as add-on therapy to inhaled corticosteroids on exacerbation frequency. Moreover, some data do suggest that polymorphisms of the β_2-adrenoceptor are found more commonly in patients of different ethnic backgrounds, which in turn suggests that a defined group of asthmatic patients may be further predisposed to the development of subsensitivity.[18] Unfortunately, no genotype data were available from SMART to suggest whether this might provide an explanation for the increased risk found in African Americans.

2.3 LABAs and Inflammation

There has been debate regarding the ability of LABAs to 'mask' underlying airway inflammation, despite the preservation of airway calibre due to smooth muscle stabilisation. In this scenario, asthmatic patients who use regular inhaled LABAs for a 'bronchodilator boost', but adhere less stringently to inhaled corticosteroids, could conceivably have few day-to-day symptoms because of the sustained bronchodilation provided. Such individuals could be predisposed to chronic 'grumbling' underlying airway inflammation, leading to an exacerbation or, over many years, airway remodelling.

In a small study,[19] regular salmeterol controlled symptoms and maintained airway calibre but was associated with an increase of sputum eosinophil counts when inhaled corticosteroid administration was tapered. Prior to an exacerbation, these patients who had preserved lung function had no warning symptoms despite increased airway eosinophilia.

LABAs suppress the release of inflammatory mediators from primed mast cells in the airway,[20,21] reduce plasma exudation from airway endothelium[22,23] and block bronchoconstricting sensory nerve activation in guinea pig bronchi.[24] However, there are conflicting *in vivo* and *ex vivo* data from asthmatic patients regarding any relevant anti-inflammatory activity of LABAs.[25-30] For example, 175 patients with moderate, persistent asthma were randomised, after a 6-week run-in not controlled on triamcinolone 800 μg/day, to receive either salmeterol or placebo.[31] Over the next 4 months, inhaled corticosteroids were reduced and discontinued in the entire placebo group and in one-half of the salmeterol group (the other half had an unchanged corticosteroid dose). The primary endpoint of the overall number of treatment failures over 4 months with either salmeterol (43.2%) or placebo (47.4%) was

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similar in both groups during corticosteroid reduction and elimination; however, it was significantly lower in the group with an unchanged corticosteroid dose in the presence of salmeterol (12.2%). In other words, adding salmeterol had no appreciable anti-inflammatory or disease-modifying effects during corticosteroid tapering and elimination.

Several studies have demonstrated that synergism may occur with concomitant use of LABAs and inhaled corticosteroids on a histological and molecular basis.[32,33] In asthmatic patients, the combination of fluticasone propionate plus salmeterol compared with either component alone resulted in greater *ex vivo* glucocorticoid receptor activation in induced sputum epithelial cells.[34] In a placebo-controlled study involving symptomatic asthmatic patients receiving inhaled corticosteroids, the effects of supplemental salmeterol was examined by way of changes in bronchial biopsy material.[35] It was demonstrated that individuals treated with salmeterol experienced a significant reduction in blood vessel density in the lamina propria. Corticosteroids have also been shown to positively influence the effects of LABAs in terms of activity upon the glucocorticoid response on the β_2-adrenergic gene. For example, corticosteroids can regulate β_2-adrenergic receptor function by increasing its expression through gene transcription[36] and demonstrate inhibitory effects upon G-protein coupling and β_2-adrenergic receptor down-regulation.[37]

There is less convincing evidence that interplay between inhaled corticosteroids and LABAs actually translates into 'real-life' benefit. The term 'synergy' is often used incorrectly and refers to the response of corticosteroid and LABA together being greater than the sum of their individual parts. In the studies of Kavuru et al.[38] and Shapiro et al.,[39] the salmeterol/fluticasone propionate combination inhaler produced greater effects on the forced expiratory volume in 1 second (FEV_1) than either drug alone at the same dose; the effects were clearly additive but not synergistic.

In a randomised crossover study in patients with mild-to-moderate persistent asthma, fluticasone propionate 500 μg/day plus salmeterol was compared with a double dose of fluticasone propionate, with each treatment given over 2 weeks.[40] The higher fluticasone propionate dose conferred significant superiority compared with add-on salmeterol in effects upon inflammatory biomarkers. In another study of mild-to-moderate asthmatic patients that compared combined fluticasone propionate 500 μg/day plus salmeterol with fluticasone propionate 500 μg/day alone, no differences were observed in exhaled nitric oxide levels, AMP threshold concentration and blood eosinophil counts.[41]

Adding formoterol to either low- or medium-dose budesonide did not potentiate anti-inflammatory effects in terms of AMP threshold concentration or exhaled nitric oxide levels.[42] Similar results were obtained by Lee et al.,[43] where no difference in inflammatory biomarkers was observed when comparing salmeterol/fluticasone propionate or budesonide/formoterol combination inhalers with their respective corticosteroid inhaler alone, despite better lung function outcomes with the combination inhalers. These data imply that interactions between both moieties observed *in vitro* cannot necessarily be extrapolated into clinically relevant, enhanced anti-inflammatory effects. However, LABAs and corticosteroids do exhibit complementary effects on separate pathways of smooth muscle and inflammation, respectively, resulting in additive although not synergistic effects.

2.4 Reliever Effect in Acute Asthma

During an exacerbation of asthma, inhaled short-acting bronchodilators are a fundamental component for immediate treatment. Several studies have shown that salmeterol or formoterol as add-on therapy to inhaled corticosteroids results in blunting of the reliever response to salbutamol (albuterol) after acute bronchoconstriction.[10,43-47] This implies that in the clinical setting of acute asthma occurring in individuals regularly using LABAs, benefits may not occur when even high doses of inhaled salbutamol are used. For example, to investigate the acute effects of high-dose inhaled salbutamol on methacholine chloride-induced bronchoconstriction, corticosteroid-treated asthmatic patients re-

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ceived add-on therapy with either placebo, salmeterol 50μg twice daily or formoterol 12μg twice daily in a randomised crossover period.[48] After an initial 1-week run-in period, individuals underwent three separate treatment periods each of 9 days (separated by a washout period). A methacholine chloride challenge was performed 1 hour after the first dose of LABA and after 7 days of treatment. After 9 days of treatment, a third methacholine chloride challenge was performed 1 hour after inhalation of a single 1600μg dose of salbutamol. Bronchoprotection diminished over 7 days of regular treatment with either LABA, with the subsensitivity not overcome by administering a high dose of salbutamol.

In another study, significant tolerance to the acute bronchodilator effects of salbutamol was present after 36 hours of discontinuing regular formoterol.[49] Similar results were found in a prospective, randomised, crossover trial in patients with moderate, persistent asthma, in which adding salmeterol or placebo to inhaled corticosteroids for 4 weeks resulted in persistent β_2-adrenoceptor down-regulation on peripheral blood lymphocytes at 36 hours after stopping salmeterol. In turn, this was associated with blunting of the acute reliever response to cumulative doses of inhaled salbutamol.[11] In another study, the time taken to recover after administration of salbutamol was significantly delayed in patients using regular formoterol plus budesonide versus budesonide alone.[43]

2.5 When Should LABAs be Prescribed?

Add-on therapy with LABAs are generally superior to an increased dose of inhaled corticosteroid in terms of 'bronchodilator sensitive' endpoints such as lung function, symptoms and reliever use.[50-52] For example, in a meta-analysis of nine parallel-group studies (n = 3685 asthmatic patients),[53] add-on salmeterol was significantly superior at improving lung function and reducing symptoms and reliever use compared with a higher inhaled corticosteroid dose. In the same study, add-on salmeterol only conferred a 2.4% (p = 0.03) reduction in moderate or severe exacerbations compared with an increased inhaled corticosteroid dose. This suggests that, when compared with increasing the dose of inhaled corticosteroid, the addition of salmeterol in 41 symptomatic patients would prevent a single exacerbation.

Add-on treatment with a LABA has been shown to be useful in asthmatic patients using even low inhaled corticosteroid doses. For instance, a meta-analysis incorporating 12 studies (n = 4576 patients) concluded that fluticasone propionate 200 μg/day (or equivalent) was a reasonable corticosteroid dose at which to start treatment with a LABA in patients with persistent asthma.[54] These findings were based on the fact that in individuals using fluticasone propionate 200 μg/day, add-on salmeterol was superior to at least a 2-fold increase in inhaled corticosteroid dose. This was in terms of endpoints such as exacerbation frequency, lung function and reliever use. The number needed to treat in this meta-analysis was 37 in terms of preventing a moderate-to-severe exacerbation in one additional patient,[55] which is similar to the number needed to treat in the study by Shrewsbury et al.[53]

Bateman et al.[50] reported on adding salmeterol to fluticasone propionate compared with increasing the dose of fluticasone propionate in a multicentre study of 3421 patients with persistent asthma, looking at achievement of guideline-defined optimal control outcomes – the 'GOAL' (Gaining Optimal Asthma ControL) study. The combination inhaler was significantly better in achieving optimal control than corticosteroid alone across all severities of asthma. Although the results also reported statistically significant superiority in favour of the combination product for reducing severe exacerbations over 12 months, one has to question the clinical relevance of these observations. In patients with mild-to-moderate asthma, it would take 25 years for a patient receiving fluticasone propionate alone to experience an additional exacerbation versus salmeterol/fluticasone propionate combination. In contrast, for patients with severe asthma, it would take 9 years for a patient receiving fluticasone propionate alone to experience an additional exacerbation versus salmeterol/fluticasone propionate combination.

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The additive effects of LABAs on exacerbations probably reflect 'stabilising effects' on airway smooth muscle rather than any anti-inflammatory potentiation of concomitant inhaled corticosteroid *per se*.

In another study, optimising the inhaled corticosteroid dosage to 800 μg/day of budesonide and then adding formoterol resulted in a significantly reduced number of severe exacerbations compared with adding formoterol to 200 μg/day of budesonide (49% vs 26% reduction, respectively).[56] Adding formoterol to budesonide 800 μg/day did confer a small additive reduction in exacerbations, which amounted to a difference of 0.12 exacerbations per patient per year. In other words, adding formoterol to higher-dose budesonide conferred a reduction in severe exacerbations, which was statistically significant although unlikely to be clinically relevant.

There are a paucity of data comparing the long-term effects of a lower dose of an inhaled corticosteroid plus LABA with a higher inhaled corticosteroid dose. In one study,[57] significant reductions in basement membrane thickness did not occur until after 3 months of therapy with high-dose (1500 μg/day) fluticasone propionate. Moreover, Reddel et al.[58] demonstrated that patients starting with 3200 μg/day of budesonide had greater normalisation in airway hyper-responsiveness and fewer exacerbations than even 1600 μg/day of budesonide. Thus, it is vital to ensure that untoward long-term sequelae of suboptimal anti-inflammatory treatment do not occur at the expense of short-term superior bronchodilation with the widespread use of LABAs, although the potential for long-term systemic adverse effects with higher doses of inhaled corticosteroids does exist.[59]

Clinicians should be aware that since asthmatic patients constitute a heterogeneous population in terms of disease severity, natural history and response to treatment, it also stands to reason that different patients will require different inhaled corticosteroid doses to adequately suppress underlying airway inflammation and prevent longer-term structural changes.[60] The dose-response curve in terms of FEV_1 becomes relatively flat at daily fluticasone propionate doses of 100–250μg (or equivalent).[61] Clinicians therefore encounter difficulties in deciding when inflammation has been adequately suppressed and airway hyper-responsiveness adequately attenuated if conventional measures of assessing control, such as lung function, are employed. In terms of suppressing airway hyper-responsiveness, a dose-response effect has in fact been demonstrated between the effects of high (>1000μg) versus low-to-medium (<1000μg) daily doses of beclometasone or equivalent.[62] This in turn implies that it can be difficult in everyday practice to gauge when in fact a LABA should be initiated.

3. Conclusion

Guidelines advocate low-to-medium doses of inhaled corticosteroids in all but the mildest asthma, and the initiation of a LABA is widely advocated in patients with persistent symptoms (step 3 of the pharmacological treatment escalator).[2,3] Data from SMART have raised important concerns regarding the safety of long-term treatment with salmeterol in terms of an increased frequency of asthma- and respiratory-related deaths and life-threatening experiences.[4] Among the African American population, there was an increase in the rates of respiratory- and asthma-related deaths and life-threatening experiences compared with placebo. In this respect, it is of particular concern that suggestions have been made that the initial presentation and dissemination of the interim data from SMART was misleading and lacking complete transparency.[63] Furthermore, <50% of the total enrolled study population in SMART were receiving regular inhaled corticosteroids (and, therefore, many were using salmeterol or placebo as monotherapy), with as few as 38% of African Americans using inhaled corticosteroids at baseline. This must surely raise serious doubts regarding the ethical basis of the trial since the majority of participants were not receiving the most basic and cost-effective treatment for persistent asthma. Indeed, one could perhaps conclude from SMART that the role of fixed-dose combination inhalers is highlighted and that taking more LABA is always

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associated with greater inhaled corticosteroid intake, in addition to issues of better compliance.

Although it is tempting to interpret subgroup data from SMART according to inhaled corticosteroid use, the trial was never intended to examine the *a priori* effects of concomitant inhaled corticosteroid use in terms of salmeterol-related adverse effects.

So where does this leave us in the post-SMART era, in which the data from the GOAL study[50] tend to point prescribers towards using combination inhalers at step 2 of the pharmacological treatment escalator rather than step 3? To go down this route would have major implications for healthcare providers given the relatively low cost of generic inhaled corticosteroid formulations. Moreover, for a large proportion of patients with mild-to-moderate asthma, the use of low to medium doses of inhaled corticosteroids will produce adequate control.[56,64,65] For patients with moderate-to-severe asthma, especially those with impaired lung function (i.e. FEV_1 <80%), frequent exacerbations, persistent symptoms or frequent-reliever use, there would appear to be logical reasons for adding in a LABA to an optimised inhaled corticosteroid dose, in which case it is more convenient to use a single combination inhaler.

The data from SMART raise questions as to what should be done for patients who experience severe life-threatening exacerbations despite using a LABA plus inhaled corticosteroid. In such individuals, perhaps LABAs should be avoided and alternative controllers, such as leukotriene receptor antagonists,[66] which would confer further anti-inflammatory effects, should be used instead.[67] It would be interesting to know whether such patients who fare poorly on LABAs are genetically susceptible towards the development of down-regulation and subsensitivity, particularly in terms of blunting of the acute-reliever response to salbutamol. In this respect, crucial data from SMART or future studies would be the consumption of reliever therapy prior to and during an acute attack. Until such information becomes available, it may be prudent to err on the side of safety and discontinue concomitant LABA use in patients who either have increasing short-acting β_2-agonist use or who do not derive effective relief of symptoms from short-acting β_2-agonists. Perhaps in these patients, alternative second-line therapy, such as a leukotriene receptor antagonist, may be the smartest pharmacological adjunct.

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