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Meeting Report

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Guest Editors: Lawrence Yu, Sau L. Lee, Guenther Hochhaus, Lana Lyapustina, Martin Oliver, and Craig Davies-Cutting

Safety of β2-Agonists in Asthma: Linking Mechanisms, Meta-Analyses and Regulatory Practice

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Abstract. An epidemic of asthma fatalities in the 1970s prompted a series of case-control studies which indicated that short acting β-agonists increased the risk of death. Subsequent mechanistic and pharmacodynamic studies have suggested that β-agonist monotherapy facilitates airway inflammation, although when co-administered with inhaled corticosteroids (ICSs), similar evidence is lacking. The Salmeterol Multicenter Asthma Research Trial, which revealed a fourfold increase in asthma-related deaths in salmeterol-treated patients, prompted a paradigm shift in the evidential assessment of β-agonist safety. The FDA's meta-analysis of over 60,000 patients ultimately concluded that long-acting β-agonist (LABA) therapy increased the risk of serious asthma-related events. However, this meta-analysis itself raised questions given a large body of omitted data and a limited emphasis on the risk of ICS-LABA co-administration. Subsequently, the FDA mandated the conduct of five large studies to definitively ascertain whether ICS-LABAs increase asthma-related risk. Whether this ambitious programme will provide certainty remains to be seen given issues of multiplicity, the very low frequency of fatal and near-fatal asthma, and the administration of a free combination of ICS and LABA in one trial. The FDA's *de facto* use of FEV1 as a safety parameter, based on findings from the Foradil NDA, is a further topical issue: subsequent clinical study data, considerations relating to regional pulmonary drug deposition and pharmacological differences between different β-agonists suggest that FEV1 may be a suboptimal safety metric. Models evaluating airway inflammation and bronchial reactivity may be more appropriate to assess the relative risk of asthma-related events.

KEY WORDS: FDA; FEV1; long-acting β-agonists; meta-analyses; safety.

INTRODUCTION

This paper relates to a presentation on β-agonist safety given at the "Orlando Inhalation Conference—Approaches in International Regulation" in March 2014. The presentation provided an overview of major events in the ongoing β-agonist safety debate and examined the relationship between mechanistic findings and clinical trial data. The FDA's LABA safety meta-analysis, the post-market safety studies mandated by FDA, and the use of FEV1 as a *de facto* safety metric were also discussed.

MAIN TEXT

An increase in asthma mortality was reported in England and Wales (1,2), Australia and New Zealand (2) in the mid-1960s. No adequate studies were undertaken to identify a cause for this trend. However, the (over)use of β-agonists was circumstantially implicated by the temporal association between increasing sales and an increase in asthma-related death, followed by a reduction in mortality once warnings as to the potential role of these drugs were disseminated (1,3). A second epidemic of asthma deaths in New Zealand, commencing the year after the local launch of fenoterol and reaching an unprecedented peak of 4.1 asthma deaths per 100,000 per annum amongst those aged 5 to 34 years in 1979 (4), prompted a series of case-control studies which indicated that excessive use of fenoterol (5–7), and to a lesser extent salbutamol (8) (albuterol), increased the risk of asthma death. Several authors subsequently examined how β-agonists might lead to increased asthma mortality, if not via delaying presentation for appropriate medical care. In the absence of concomitant inhaled corticosteroids (ICS), a variety of potentially deleterious mechanistic effects of β-2 agonists were shown, albeit not invariably so. A near-doubling in sputum eosinophil levels (9), an increase in airways hyperresponsiveness (AHR) to both direct (10) and indirect (9) stimuli and an increase in the allergen-induced late asthmatic response (11) and allergen-induced AHR (11) have all been reported with regular β-agonist monotherapy. It has been suggested that the precursor to these effects may be an

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adverse β-agonist-induced shift in the Th1/Th2 cytokine milieu (12–14). When β-agonists are used in conjunction with inhaled corticosteroids, mechanistic data suggestive of an increased risk are, however, less compelling. Although some authors have reported lesser bronchoprotection to AMP (9) or allergen challenge (11) with combination ICS and β-agonist than with ICS monotherapy, others have reported similar bronchoprotective effects with these treatments (15) whilst in most cases, bronchoprotection with regular combination therapy remains at clinically relevant level (15,16). There is also little evidence of inflammatory cellular change with combination therapy (9,15).

The seminal Salmeterol Multicenter Asthma Research Trial (SMART) which reported a fourfold increase in asthma mortality in patients randomised to salmeterol *versus* placebo (17) led to a shift in focus in the β-agonist debate, towards much larger datasets and serious event-based outcomes, and prompted the Food and Drug Administration (FDA) to request comprehensive pooled safety analyses from manufacturers of LABAs for further evaluation. The FDA's re-analysis of these Sponsor data (from approximately 61,000 subjects) determined that the risk of a serious asthma-related event (i.e., death, intubation or hospitalisation) was significantly increased in subjects receiving *versus* not receiving LABA (risk difference 2.80 per 1000 subjects) (18). Although many of the FDA's secondary analyses supported its overall conclusion, a number of important issues received little prominence in the FDA's review. Firstly, approximately 95% of the data provided by AstraZeneca appear to have been omitted from the FDA's meta-analysis. The grounds for exclusion of these data are not clear, although the use of the Turbohaler device in many AstraZeneca trials may be implicated since this inhaler device is not approved in the USA. Given the extent of the AstraZeneca database (approximately 24,000 subjects) and the fact that AstraZeneca's analyses showed no increase in risk of serious asthma-related events with formoterol (19), the almost complete omission of these data from the FDA analysis was potentially critical. Secondly, the FDA's analysis demonstrated that where patients were randomised to LABA and ICS *combination* therapy, there was no increase in risk *versus* ICS monotherapy (risk difference 0.25 per 1000 subjects). Unfortunately, these data (based on approximately 15,000 patients) constituted only one quarter of the total FDA dataset and were thus subsumed by the much greater volume of data in subjects not specifically assigned ICS alongside their LABA study treatment. A third key finding was that no asthma-related deaths or intubations occurred in subjects treated with Advair or Symbicort; the only products included in the FDA review with which co-administration of ICS and LABA was assured (18).

The FDA has subsequently mandated that four manufacturers of LABA-containing products undertake five large-scale safety studies (four adult/adolescent, one paediatric—see Table I). In each trial, 11,700 asthmatics (6200 in the paediatric trial) with a history of exacerbations will be randomised to 6-month treatment with either ICS-LABA or ICS monotherapy at a fixed dose (20).

Whether this extensive programme of studies will provide definitive resolution remains uncertain (26). If 7 deaths are seen with ICS-LABA *versus* 1 with ICS in the 46,800 patients enrolled across these trials (a plausible if pessimistic estimate) that will still fail to exclude the possibility that the true difference is zero since the 95% confidence interval will straddle unity (relative risk 7.0; 95% confidence interval (CI), 0.9–56.9) (26). Additionally, whilst each individual study is appropriately (90%) powered, across five separately assessed, essentially replicate studies, the risk of failing to exclude a difference where none exists in at least one study, thereby wrongly deeming one treatment 'unsafe', is 41% ($1–0.9^4$) (26). The comparison of a combination of formoterol (Foradil DPI) and fluticasone via separate inhalers to fluticasone monotherapy in one trial is also of concern: GSK's salmeterol meta-analysis revealed a monotonic trend whereby the relative risk of serious asthma-related events increased from fixed combination Advair (no increase in risk *versus* ICS monotherapy) to salmeterol plus ICS as randomised study treatment via separate inhalers to salmeterol added to background (non-study treatment) ICS (a definite increase in risk *versus* ICS monotherapy) (27). This trend is most plausibly explained by incomplete ICS adherence when non-single inhaler combinations are used, illustrating an important potential confounding influence in the Foradil trial.

Table I. FDA-mandated LABA Safety Trials

Trial	Treatment arms			Age group	Sample size
1 (21)	Advair	*vs*	Flovent	≥12 years	11,700
2 (22)	Symbicort	*vs*	Pulmicort	≥12 years	11,700
3 (23)	Dulera	*vs*	Asmanex	≥12 years	11,700
4 (24)	Foradil + Flovent	*vs*	Flovent	≥12 years	11,700
5 (25)	Advair	*vs*	Flovent	4–<12 years	6200

An unresolved and intriguing question is whether all LABAs confer the same risk. When effects upon asthma-related hospitalisation were assessed in the GSK and AZ meta-analyses, Advair had a neutral effect on risk *versus* fluticasone monotherapy (27), whereas formoterol plus budesonide (as single or separate inhalers) reduced the odds of hospitalisation by 32% *versus* budesonide monotherapy (19). Data from the FDA-mandated studies (summarised in Table I) may elucidate whether this difference is real.

A further issue is that of dose-related safety. A possible dose-related safety signal was seen in the Foradil New Drug Application (NDA) clinical programme (28,29) with 2.0% *versus* 4.5% serious asthma exacerbations with Foradil 12 μg *versus* 24 μg, respectively. The FDA has cited these data during subsequent NDA reviews (30,31) as a basis for its 'lowest effective dose' philosophy. Interestingly, in a large Foradil phase IV study, conducted in response to the Foradil NDA data, there was no evidence of a dose-related safety signal (32). AstraZeneca's subsequent formoterol meta-analysis also showed no elevation in the risk of asthma-related hospitalisation across regular formoterol (metered) daily doses up to 48 μg or with adjustable maintenance dosing (19). The totality of these data query the regulatory use of FEV1 with established LABAs to define 'safe' doses of novel LABAs (30,31), an approach seemingly based on the observation that Foradil 24 μg demonstrated greater

bronchodilation than 12 μg in the NDA studies in which a putative dose-related safety signal was seen (30,31).

The notion that safe doses of new LABAs should be identified by closely matching the bronchodilation attained with existing, approved products is further challenged by pharmacological considerations, and the relationship between pulmonary deposition pattern and clinical effect. Greater bronchodilatory effect (FEV1) has been attained with a large particle salbutamol monodisperse formulation exhibiting a more central deposition pattern despite a relatively lower total pulmonary dose than a small particle monodisperse formulation with a more peripheral deposition pattern (33)—implying that the larger particle formulation is both more efficacious and safer. With respect to pharmacological characteristics of inhaled LABAs (near-)complete agonists, such as formoterol or indacaterol, occupy fewer receptors than partial agonists, such as salmeterol, to elicit a given smooth muscle relaxant effect. Thus, with the use of a complete agonist, more 'spare' receptors are available which can subsequently be bound and further relax smooth muscle. The maximal bronchodilatory effect that a partial agonist may generate is thus less than a complete agonist (34). Differences in β1/β2 selectivity are also relevant. For example, in a rhesus monkey model at doses conferring similar (formoterol) or lesser (salmeterol) bronchoprotection *versus* indacaterol, both formoterol and salmeterol had greater and substantially more prolonged effects upon heart rate than indacaterol (35). These data imply that indacaterol may be dosed closer to its Emax, at least from a cardiovascular safety perspective, than salmeterol or formoterol allow. Overall, these pharmacological nuances illustrate the limitations of applying FEV1, a unidimensional efficacy metric, to adjudicate comparative asthma-related safety risk.

CONCLUSION

β-agonist monotherapy may have a 'permissive' effect upon airway inflammation. Similar, consistent data are lacking for ICS-LABA combination therapy. This distinction explains the increased risk of serious asthma-related events with LABA monotherapy, whilst the available data supports the safety of ICS-LABA fixed combination therapy. Based on its own meta-analysis, however, the FDA reached somewhat different conclusions and has mandated a series of large, replicate studies to further evaluate the risk of serious asthma events with ICS-LABAs. This programme of studies contains certain inherent limitations which, it is hoped, the FDA will consider before data from these potentially landmark studies become available. Might these data additionally alter the FDA's 'lowest effective dose' philosophy and use of FEV1 as a *de facto* safety benchmark? Differences in regional pulmonary deposition pattern and pharmacology between different LABAs suggest potential limitations of the current regulatory approach. The use of models evaluating airway inflammation and bronchial reactivity which are more plausibly related to any putative increase in risk could offer an alternative approach with which to assess the relative safety risks and appropriate doses of novel LABAs.

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