

Long-Acting Beta agonists and their relation to increased Asthma Morbidity and Mortality. The FDA Meta-Analysis

G Pesola, T Lone, R Gosala

Citation

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Abstract

INTRODUCTION

When long-acting beta-agonists (LABA) were initially introduced overseas, salmeterol was compared head to head with albuterol in a randomized, double blind study over 16 weeks (1) in addition to usual asthma care. There was a 3-fold greater probability of death with the use of salmeterol (12/16,787) compared to albuterol (2/8,393). This outcome comparison did not reach statistical significance and the results did not address the issue of the use of inhaled steroids as background treatment with LABA. In the U.S. the FDA requested GlaxoSmithKline obtain more data related to its product salmeterol, sold as Serevent or Advair and this resulted in the SMART study.

The 28 week SMART study was a randomized study of salmeterol or no salmeterol in 26,355 asthmatics on other asthma therapy that did not include a LABA. The SMART results suggested that the use of long-acting beta-agonists (LABA) had a 1.71-fold (95% C.I.; 1.01-2.89) increased risk of the combined endpoint of asthma-related death or life-threatening experiences in secondary outcome analysis relative to those asthmatics not on LABA (2). Posthoc subgroup analysis suggested that this risk was highest in African Americans with a relative risk (RR) of 4.92 (1.68-14.45). Evaluating baseline characteristics clearly revealed that the African American asthmatic population had greater asthma severity and reduced use of inhaled corticosteroids relative to Caucasians (2). Possibilities for the findings included chance (secondary analysis), increased LABA risk in asthmatics not on inhaled corticosteroids (not documented in the study) since LABA studies with concomitant inhaled steroids do not reveal such risks (3,4,5), or possibly increased prevalence of the Arg-Arg polymorphism at position 16 of the B2-receptor in those of African American descent. In any case, further evaluation

was warranted considering that these results did not fall out of any primary analytic outcome.

FDA ANALYSIS

In order to further examine whether or not LABA increase the risk of asthma morbidity and possibly mortality, the FDA did a meta-analysis of 110 asthma studies. Ninety six percent of these studies were at least 12 weeks long with at least one arm of the study including a LABA (6). All the studies were randomized, blinded, and were only included if the assigned dose of therapy was a conventional dose and was used for the approved age range of subjects (6). There was an average of 550 subjects/study and the four approved products evaluated were Advair (13,212 subjects), Serevent (43,824), Foradil (3,765) and Symbicort (1,270). Adverse outcomes were only recorded while the studies were ongoing and blinded and only the first half of randomized cross-over study designs were utilized for data analysis.

The primary objective of the analysis was to determine whether LABAs were associated with increased risks of serious asthma related events. The three serious events compiled were asthma-related death, asthma-related intubation, and asthma-related hospitalizations. These outcomes were evaluated individually and as a composite endpoint in those with and without a comparison LABA arm of a study. In addition, and of particular interest, the meta-analysis evaluated whether LABA with inhaled steroids (LABA/ICS) compared to just inhaled steroids or other asthma therapies had more serious adverse events than LABA use without inhaled steroids (LABA/noICS). In addition, demographics of age, gender, and race were evaluated to see if there were any differences.

MAIN FDA FINDINGS

Figure 1

Table 1: Major FDA Findings from Meta-Analysis of LABA in Asthmatics.

Outcome of Interest	Risk Difference. Events/1,000 subjects	Relative Risk	Baseline Risk. Events/1,000 subjects
Asthma Death	0.40 (0.11 - 0.69)	4.09 (1.37 - 12.22)	0.13
Asthma Death/Intubation	0.57 (0.01 - 1.12)	1.67 (1.03 - 2.69)	0.88
Asthma Hospitalization	2.53 (0.90 - 4.23)	1.26 (1.08 - 1.47)	9.71
Asthma Composite	2.77 (1.11 - 4.49)	1.28 (1.10 - 1.49)	9.87
LABA/ICS versus No LABA	0.39 (-1.69 - 2.18)	1.11 (0.66 - 1.87)	3.55
LABA/noICS versus No LABA	3.63 (1.51 - 5.75)	1.38 (1.18 - 1.61)	11.40
LABA versus No LABA - All	2.77 (1.11 - 4.49)	1.28 (1.10 - 1.49)	9.87

The last 3 rows of the table compare the composite outcome of asthma deaths, asthma intubations, and asthma hospitalizations. Asthma hospitalizations are the primary driving force in the composite outcome.

The results of the combined studies (n = 110 studies) reveal an increase above baseline risk for asthma death, combined death/intubations, asthma hospitalizations, and the composite endpoint of all three. Asthma intubations were not evaluated by themselves due to not enough events according to the meta-analysis. It should be noted that there were only 20 deaths in 60, 954 subjects, all in those with severe. Therefore, due to low subject number the asthma death results have more variability and are less stable estimates.

Looking at the overall results of LABA versus no LABA (last row) reveals both a 28% increase in the composite asthma endpoint above baseline risk (2.77/9.87 times 100) and a 1.28-fold greater risk of the composite endpoint in asthmatics on a LABA compared to asthmatics not on a LABA. When the LABA is combined with an inhaled steroid (LABA/ICS) there is no significant increase above baseline risk, the relative risk between treatments is not significant and LABA use appears to be very safe. However, when a LABA is not combined with an inhaled steroid (LABA/noICS versus No LABA row in table 1) there is a significant 31.8% risk of the composite outcome above baseline and a 1.38-fold greater risk of developing the composite outcome compared to not using a LABA. This suggests that it is unsafe to use a LABA without

concomitant use of an inhaled steroid.

It should also be noted that when studies were done using the combined LABA/ICS versus no LABA (usually the comparison arm was an inhaled steroid without LABA) the baseline risk of developing the composite outcome was very low at 3.55 events/1,000 subjects. This baseline risk would have been generated in those asthmatics in the comparison nonLABA arm of the study. It is unclear why the baseline risk of developing the combined outcome was so low. Possibilities include enrolling very compliant subjects (7) (selected during run-in periods of studies) that are more likely to take their medication and do other things to maximize asthma control (compliant subjects are much different than the routine often noncompliant asthmatic), studying asthmatics with more mild disease in these studies (4), or less likely the chance enrollment of less severe asthmatics. In addition, experienced, talented investigators may take very compliant moderately severe asthmatics and maintain extremely tight control in these studies (5), suggesting that most asthmatics can be controlled with minimal adverse events under the right circumstances (8). Since baseline risk was very low to begin with, better outcomes with lower adverse events would be expected. Studies evaluating subjects in the comparison arm with higher adverse events at baseline versus LABA/Inhaled Steroids combination would be interesting. This latter study could even be done sequentially, truly showing that poorly controlled asthmatics at baseline can be controlled with minimal adverse events.

DEMOGRAPHIC FDA FINDINGS

Figure 2

Table 2: Gender, Age, and Race Findings in the FDA Meta-Analysis of LABA in Asthmatics.

Outcome of Interest	Risk Difference Events/1,000 subjects	Relative Risk	Baseline Risk Events/1,000 subjects
Gender - female	4.11 (1.86 – 6.54)	1.40 (1.16 – 1.69)	10.27
Gender - male	0.99 (-1.48 – 3.40)	1.11 (0.87 – 1.41)	9.37
Age: 4 – 11	15.72 (3.24 – 26.43)	1.72 (1.16 – 2.56)	21.80
Age: 12 - 17	6.29 (0.21 – 10.92)	1.69 (1.07 – 2.65)	9.18
Age: 18 - 64	2.01 (0.34 – 3.91)	1.24 (1.03 – 1.49)	8.56
Age: 65 and above	-3.45 (-10.47 – 3.32)	0.77 (0.46 – 1.30)	15.26
Black	8.19 (1.88 – 14.38)	1.60 (1.11 – 2.29)	13.71
White	2.06 (0.09 – 3.88)	1.23 (1.02 – 1.48)	9.07

All rows of this table use the composite outcome of asthma deaths, asthma intubations, and asthma hospitalizations.

An unexpected finding was a significant 40% increase in baseline risk of the composite outcome that was present in females but not males (as seen from the data in Table 2). The gender difference maintained itself across all four medications and was statistically significant for seven, albeit the significance was undoubtedly related to the 70% contribution of seven to the meta-analysis. Except for being a smaller size for a similar dose in females that might lead to an adverse drug effect/asthma exacerbations or possibly random error, it is unclear why only females are affected by the composite endpoint when exposed to LABA. Based on this analysis, it could be argued that only females are susceptible to LABA related adverse outcomes. A gender breakdown of LABA/noICS versus LABA would be of great interest.

All ages except the elderly appear to be susceptible to increased asthma morbidity with LABAs. Children’s baseline risk (extremely high in the very young asthmatic) of asthma morbidity is increased by more than 50% when using a LABA relative to other asthma treatment. All the medication except Advair maintained this age trend.

There is a significant increase in baseline risk with LABAs in both blacks and whites, but the increase in baseline risk is increased by more than 50% in blacks, implying a race related effect of LABA. However, it was noted that there was no detectable statistical difference between races and so this increase in baseline risk is consistent with random data

variation.

Another good point brought out by the FDA analysis can be readily seen by inspecting the Kaplan-Meier cumulative incidence curve for the asthma composite. It kept on diverging over the range of the data that went out to one year in some studies. The suggestion, based on this data, is that as time marches on there will always be more asthma related adverse events on a LABA than off. In addition, there was a similar curve for asthma hospitalizations, the primary driver of the composite endpoint. Presumably, the real driver was use of a LABA without the use of an inhaled steroid but that data is not separated out.

A sensitivity analysis was done by excluding the very large SMART trial and the overall LABA versus no LABA risk difference was 3.15 (95% C.I.; 1.11-4.49), greater than inclusion of SMART. No subgroup SMART exclusion sensitivity analysis was done.

STRENGTHS OF THE FDA ANALYSIS

Length of Study. By including studies that were primarily at least 12 weeks or longer, the studies were more likely to detect adverse events that occur over time that might be missed by including studies of very short duration.

Size of Study. Inclusion of 110 studies increases the likelihood of detecting differences if they are present.

Only including RCTs. This minimizes bias since known and unknown confounders in these studies should be balanced between groups.

Including adverse events from studies only when they were blinded. This minimizes the bias that could occur if adverse events were preferentially reported only in those on LABAs.

MAJOR WEAKNESS OF THE FDA ANALYSIS

The primary weakness of this analysis was including the SMART study. The SMART study was the major impetus for considering the possibility that LABA can increase adverse events in asthmatics and stimulated a Black Box warning by the FDA that eventually included all LABA. The only way to get independent confirmation that a finding is correct is to use new results from separate studies (7). By including SMART in an analysis that will supply major data related to the hypothesis virtually guarantees that the old finding will be verified with the new meta-analysis. This is particularly true when evaluating deaths from asthma (16 of 20 deaths from the SMART study) as well as the question of

whether or not LABA cause adverse events since the SMART study supplied a very large percent of the new data. Fortunately, one sensitivity analysis found the same finding overall when excluding SMART. However, all the other findings related to age, gender, race, and the use or nonuse of steroids with LABA need to be redone without SMART to validate that the SMART findings and conclusions are indeed correct. If LABA were not used with steroids (not recorded in SMART) in many types of patients in SMART (64% of SMART patients were female) and the use of LABA alone is dangerous, all the findings generated by SMART should be replicatable without SMART.

DISCUSSION

The FDA analysis suggests that LABA without the simultaneous use of inhaled steroids will increase asthma morbidity, primarily measured by asthma hospitalizations since deaths from asthma were almost nonexistent except for the SMART trial which in a sense is old data that stimulated this meta-analysis. The purported pathophysiologic mechanism for increased asthma morbidity (and possibly mortality) with LABA monotherapy is related to masking ongoing inflammation while maintaining airway caliber until the inflammation becomes so advanced that severe asthma exacerbations finally break through (9). Monotherapy with formoterol should result in the same problems as with salmeterol. This can be gleaned from one table comparing formoterol with and without the use of an inhaled corticosteroid and noting higher adverse event rates on formoterol without the steroid versus with an inhaled steroid (10).

Given these findings, it is unlikely allergists or pulmonologists would ever use monotherapy with a LABA in asthmatics. However, considering the endless number of medications and knowledge, it is probable that well meaning physicians may forget and inadvertently employ such therapy. Therefore, in the interests of patient safety elimination of single agent salmeterol and formoterol would make the most sense for both adults and the pediatric age range. Most likely this will happen.

It is unclear why only females seemed to be at risk with monotherapy with a LABA. Except for body size, there is no obvious biologic reason why men should not be affected as well as women. Most likely this would be born out if a study compared LABA versus no LABA in men only.

One concern relates to the combination of formoterol/inhaled steroid and its possible increase in adverse events. Since the data is extremely limited with only 7 total events from 1,207 subjects, further studies are necessary to clear up this probable statistical aberration. One interesting study might compare, head to head, Advair versus Symbicort at equivalent inhaled steroid doses to see if one medication is better than another. As of now, the only drug that came out of this meta-analysis unscathed was Advair.

Last, ideally the FDA meta-analysis for all endpoints should be redone without SMART to determine if the original findings are robust. Otherwise, the analysis uses old findings along with new findings to further validate the old findings. This is sort of a *fait accompli*.

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Author Information

Gene R. Pesola, MD, MPH

Section of Pulmonary Disease, Harlem Hospital

Tahir Lone, MD

Section of Pulmonary Disease, Harlem Hospital

Ramani Gosala, MD

Section of Pulmonary Disease, Harlem Hospital