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Combination Long-Acting Beta-Agonist and Inhaled Corticosteroid Therapy for Asthma: New Safety Concerns, Summary of Clinical Evidence and Drug Utilization Evaluation

By Dan Hartung, Pharm.D., M.P.H and Kathy Sentena, Pharm.D. both from OSU College of Pharmacy-Drug Use Research & Management

Currently, there are three Food and Drug Administration (FDA) approved combination long-acting beta agonist (LABA) inhaled corticosteroid (ICS) products on the market: salmeterol / fluticasone propionate (Advair Diskus®, Advair HFA®), formoterol fumarate dehydrate / budesonide (Symbicort®), formoterol fumarate dihydrate / mometasone (Dulera®). New evidence is raising safety concerns and practitioners need to reexamine the role of LABAs in the treatment of asthma.

Safety: Controversy over the safety of treating asthma patients with LABAs has been on ongoing discussion for 20 years. The 2007 Salmeterol Multicenter Asthma Research Trial (SMART) study included 6,112 patients over 3 years. Salmeterol plus fluticasone propionate was compared to placebo, salmeterol alone or fluticasone propionate alone. Patients taking salmeterol were noted to have a fourfold increase risk of mortality.[1] Additional analysis suggests that the risk may be mitigated by the use of inhaled corticosteroids. Safety risks associated with LABAs were also evaluated in meta-analysis of 19 trials including over 33,000 patients. LABA use was associated with an increased risk of exacerbations requiring hospitalizations and life-threatening exacerbations.[2] A second meta-analysis of data from the GlaxoSmithKline Clinical Trial Registry, comparing LABA-ICS use to ICS, failed to demonstrated a statistically significant increased risk of asthma related hospitalization, however the median trial length was only 12 weeks.[3] The Cochrane collaborative published several meta-analysis of the safety of formoterol and salmeterol when combined with ICS relative to ICS monotherapy.[4,5] In their studies, significant risks of fatal or non-fatal adverse events associated with LABA use were not observed. However, the number of subjects having an event was too small to rule out the possibility that ICS do not completely mitigate the increased risks of LABA.

In response to the study data suggesting an increased risk of severe asthma exacerbations and even death in patients using LABA therapy, the FDA issued a Public Health Advisory notice in November 2005, followed by a Black Box Warning in March 2006. In February 2010 the FDA released an updated warning including the following key points:[6]

1. The use of LABAs is contraindicated without the use of an asthma controller medication such as inhaled corticosteroid. Single-ingredient LABAs should only be used in combination with asthma controller medication; they should not be used alone.

2. LABAs should only be used long-term in patients whose asthma cannot be adequately controlled on asthma controller medications.

3. LABAs should be used for the shortest duration of time required to achieve control of asthma symptoms and discontinued, if possible, once asthma control is achieved. Patients should then be maintained on an asthma controller medication.

4. Pediatric and adolescent patients who require the addition of a LABA to an inhaled corticosteroid should use a combination product containing both an inhaled corticosteroid and a LABA to ensure compliance with both medications.

Included in this warning were labeling changes that require LABA products to be a part of a Risk Evaluation and Mitigation Strategy, including a revised Medication Guide for patients and education on appropriate prescribing for health care providers.

Place in Therapy: Long-term control medications are recommended by the National Heart Lung and Blood Institute (NHLBI) Guidelines for the Diagnosis and Management of Asthma Expert Panel Report 3 (EPR3) for the control of persistent asthma.[7] ICS are the most potent and effective long-term control treatment and have been documented to reduce asthma severity, symptoms and control, improve quality of life, improve lung function, prevent exacerbations, reduce emergent health services utilization, and reduce the risk of death due to asthma. They are shown to more effectively improve asthma control compared to any other single controller agent.

Accordingly, NHLBI guidelines state that LABA are the preferred adjunctive therapy, when combined with an ICS, in adults and children ≥12 years old. When added to ICS, LABA are more effective at improving lung function, symptoms, and short-acting beta2-agonist (SABA) use compared to increased ICS or leukotriene receptor antagonist addition. However, the new safety data for LABA suggests that the addition of a LABA or increasing the ICS dose from low to medium should be given equal consideration in patients ≥12 years old with moderate persistent asthma or those whom are not adequately controlled on a low–dose ICS. For patients ≥5 years old with severe persistent asthma (step 4 or higher) LABA-ICS is recommended. If asthma is well controlled for at least 3 months, consideration should be given to step down therapy, including reducing or discontinuing LABA treatment.[7]

Several large systematic reviews and meta-analyses have been preformed to further delineate the appropriate role of LABA and LABA/ICS combination therapy in the treatment of asthma (Table 1). Overall, this data, along with treatment guidelines, consistently demonstrate that adding LABA to ICS in adults and children with persistent asthma will improve airway function, asthma symptoms, quality of life, reduce short-acting rescue inhaler use compared to ICS dose escalation. The benefit of adding LABA to ICS for preventing severe exacerbations and mortality is not supported or clear.

Table 1: Efficacy Review of LABA Studies in Asthma

Study	Patients/ Medications	Results
Cochrane Collaborative Systematic Review[8]	• 42,333 adults & children with asthma / 67 studies • LABA vs. Placebo (67% on ICS)	• LABA associated with improvements in measures of airway flow (e.g. morning PEF, FEV1), improved symptoms, and less use of rescue medication
Cochrane Collaborative Systematic Review[9]	• 9509 adults & children with asthma / 30 clinical trials • Addition of LABA to ICS vs. increasing ICS dose	• LABA-ICS associated with improved measures of airway function, symptom –free days, and reduced use of rescue inhalers • LABA-ICS not found to lower exacerbation rate requiring systematic corticosteroids
Drug Effectiveness Review Project (DERP) Systematic Review[10]	• 1676 adult patients / 10 clinical trials • 156 chidren / 1 open-label trial • Comparison of controller medications within and across classes	• Moderate evidence of inconsistent data to support LABA-ICS vs. ICS alone as first line therapy • High evidence supportomg LABA-ICS vs. ICS dose escalation for improvements in symptom-free days, asthma symptoms, rescue – free days, and rescue inhaler use
Canadian Agency for Drugs and Technology in Health (CADTH) Meta-analysis[11]	• 31 Randomized, controlled trials • LABA-ICS vs ICS	• LABA-ICS may have benefit over higher-dose ICS in improving peak expiratory flow (PEF), reducing the risk of an exacerbation & increasing the number of symptom free days (SFD) and days with optimal control • LABA-ICS vs. similar dose ICS found the LABA-ICS of benefit

Drug Utilization Evaluation (DUE)

Rational: While controversy exists about the presence and magnitude of risk associated with LABA use, professional guidance and product labeling clearly indicate that combination therapy should be researved for individuals who cannot be managed with ICS alone. The goal of this DUE was to describe characteristics of incident users of LABA-ICS combination products in the Oregon fee-for-service (FFS) Medicaid population. A more detailed report of this DUE is available online.[12]

Methods: Patients were required to have six months of FFS Medicaid enrollment in the year prior to the incident prescription (index fill) for a LABA-ICS and continuous enrollment in the 3 months immediately prior to their index fill. Only subjects with valid demographic data between the ages of 5 through 64 on their index fill date were included. The age restriction was applied to limit the analysis to adolescents and adults, where the evidence and guidelines are more clearly defined. Diagnosis of asthma was determined in three ways. First, all medical encounter data were screened for an ICD9 code for asthma during the previous year. We also used established NCQA/HEDIS measures of asthma to ascertain disease status as recommended by the Oregon Asthma Program Data Workgroup.[13] Similarly, the presence of COPD was defined as any medical encounter with an ICD9 code for COPD in the year previous. Additionally, we created another definition of COPD which excluded individuals who also meet the HEDIS criteria for asthma.

Table 2: Characteristics of ICS-LABA combination product users

n	583	
	mean	**SD**
Age	35.27	16.86
ED visits per year	0.28	1.11
Hospitalizations per year	0.06	0.45
Oral steroid Rx per year	0.22	0.71
	count	**%**
Sex (female)	396	67.9%
Race (non-white)	130	22.3%
Asthma (any dx)	303	52.0%
Asthma (HEDIS)	170	29.2%
Persistent Asthma (HEDIS)	89	15.3%
COPD (any dx)	97	16.6%
Severity (controller ratio <50% or >1 oral steroid or ED/Hosp)	101	17.3%
Index Drug Advair	553	94.9%
Index Dose (high versus other)	408	70.0%
Index Prescriber Specialty		
Pulmonary	21	3.6%
Pediatrics	51	8.7%
General practice	270	46.3%
Other	241	41.3%

The index fill dose for Advair® or Symbicort® was classified as high if it was for the 230/21 (HFA), 250/50 (diskus), 500/50 (diskus) or 160 / 4.5 dosage strengths respectively. Physician specialty was determined for the index drug claim: pulmonary - physician with an allergy, immunology, pediatric allergy, or pulmonary disease specialty; general practice - clinician with family practice, internal medicine, general practice, or nurse practitioner designation; or pediatrics. Medication history was established using pharmacy claims which documented a fill or evidence of medication availability (fill date plus day supply) in the 3 months (93 days) prior to index fill. Medication history was subdivided into drug classes for analysis and included ICS, LABA, and anticholinergics. An asthma controller indicator was created that included use of ICS, LABA, leukotriene agent, omalizumab, mast cell stabilizer, or theophylline in the 93 days prior to index fill. A COPD controller variable was created which included inhaled anticholinergic or LABA. Finally, a combined controller variable was developed and included agents contained in asthma and COPD controller variables.

A combined disease severity variable was created to provide the greatest sensitivity for any history of asthma exacerbation. The asthma severity variable was defined by any of the following: a controller to total asthma drug ratio <50%, or >1 oral steroid prescription in the previous year, or ED visit or hospitalization related for asthma or COPD in the previous year. This utilization review primarily presents descriptive statistics for patients meeting inclusion and exclusion criteria. We explored the relationship between use of controller agents prior to initiating ICS-LABA and study subject characteristics (e.g. disease severity) in a series of chi-squared tests of proportion.

Results: Table 2 reports characteristics of 583 incident ICS-LABA users who met the selection criteria. The predominate product used was Advair®. A majority of new users started on a higher doses. Initial treatment was linked to pulmonary, allergy, or immunology prescribers in 4% of patients. Nearly half of all new prescriptions were linked to family practice or internal medicine prescribers. Overall, while 52% had a diagnosis for asthma in the previous year, only 30% met the HEDIS criteria for asthma. Only 15% of new users met the HEDIS criteria for persistent asthma. We found that 17% of individuals had a diagnosis for COPD

Table 3 shows pharmacotherapy history in the 93 days prior to incident ICS-LABA fill among study subjects. Only 70 (12%) had pharmacy claim evidence of using an asthma controller agent in the 3 months prior to their initial ICS-LABA prescription. The use of ICS in the overall study population was low at 35 (6%). When the definition of controller was expanded to include anticholinergics, the percentage using a controller increases to 22%.

Table 3: Pharmacotherapy history

	All Users n=583		**HEDIS Asthma n=170**		**COPD (no asthma) n=76**	
	count	%	count	%	count	%
ICS	35	6.0%	23	13.5%	5	6.6%
LABA	5	0.9%	5	2.9%	0	0.0%
Anticholinergic	71	12.2%	18	10.6%	33	43.4%
Asthma Controller	70	12.0%	47	27.6%	7	9.2%
COPD Controller	76	13.0%	23	13.5%	33	43.4%
Any Controller	129	22.1%	57	33.5%	38	50.0%

A diagnosis of asthma, using any criteria, was significantly associated with having prior use of an asthma controller agent. Similarly, having a diagnosis of COPD was associated with using a COPD controller agent prior to starting an ICS-LABA drug. Subjects meeting the asthma/COPD severity measure were significantly more likely to have used a controller agent compared to subjects without the severity of disease indicator (41.6% versus 18.1%). Choice of initial ICS-LABA and prescription by a specialist was not associated with having a controller agent prescribed prior to ICS-LABA initiation.

Conclusions: The DUE suggests that utilization patterns are not consistent with asthma practice recommendations. Depending on the denominator, between 6% and 14% of asthma patients were using ICS prior to starting LABA-ICS. Using a less conservative definition of controller increased the proportion of users to between 22% to 50%. COPD patients may represent a significant proportion (n=76 or 13%) where LABA is clearly recommended.

The Oregon Drug Use Review Board recommended a prior authorization of LABA-ICS products to promote utilization more consistent with asthma practice recommendations.[14] The Division of Medical Assistance Programs will implement the policy January 1, 2011.

Reviewed by: Tom D. Yan, M,D Kaiser Permanente, Pulmonary/Critical Care and Stacy Eria, R.Ph., Regence Pharmacy Services

References posted to:
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