Once-Daily Therapy for Asthma?

Two new medications have been approved for the treatment of COPD. One combines a once-daily, ultra-long-acting beta-agonist bronchodilator with an inhaled steroid effective when taken once daily. Thus, it is a beta-agonist and inhaled steroid combination – like salmeterol plus fluticasone propionate (Advair), formoterol plus budesonide (Symbicort), and formoterol plus mometasone (Dulera) -- but it is recommended for once-daily administration. The novel medications, called vilanterol and fluticasone furoate, are available in a single, fixed-dose combination (Breo). The delivery device is a dry-powder inhaler, somewhat similar to the Diskus device, called Ellipta. One inhalation delivers the full dose of medication.

The other new medication is made by the same company (GlaxoSmithKline) using the same delivery system (the Ellipta). In it are combined the same ultra-long-acting beta agonist (vilanterol) with a once-a-day anticholinergic bronchodilator, umeclidinium. It is a once-a-day, long-acting beta agonist/long-acting muscarinic antagonist (LABA/LAMA) combination, called Anoro. The appeal of both of these new combination medicines for a chronic disease like COPD is their simplicity of use. One imagines that a treatment regimen that calls for one inhalation once a day will have a high rate of patient adherence.

The question that we wish to pose in this article is the following: if you were a member of the appropriate FDA advisory panel, would you vote in favor or against approval of these medications for use in asthma? (Neither medication is currently approved for use in asthma.)

Let’s together dismiss the idea of recommending the LABA/LAMA combination for the treatment of asthma. Strong evidence points to an increased risk of asthma exacerbations when long-acting bronchodilators are used without concomitant inhaled corticosteroid. Even if it were prescribed with a simultaneous prescription for an inhaled steroid, one could never be sure whether the patient might discontinue use of the inhaled steroid while continuing to take the LABA/LAMA combination. The trend in recent years for asthma care has been to encourage prescription of long-acting bronchodilators like salmeterol and formoterol only when made available in a combination device that ensures that the patient will simultaneously receive an inhaled steroid with the LABA. In fact, salmeterol (Serevent), formoterol (Foradil), and an ultra-long acting beta-agonist, indacaterol (Arca2ta) are all available as stand-alone medications, and we rarely prescribe them in this formulation for our patients with asthma. They can be safely used without an inhaled steroid in the treatment of COPD, and that’s how the vilanterol/umeclidinium combination (Anoro) is approved to be used as well.

Our recommendation regarding the use of vilanterol/fluticasone furoate will require more thought.

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This combination, currently offered in the fixed combination of vilanterol 25 mcg and fluticasone furoate 100 mcg, meets our requirement for combining the LABA with an inhaled steroid in a single delivery device. Its efficacy has been tested in asthma among persons >12 years old, and it has been found non-inferior to twice-daily fluticasone propionate/salmeterol (Advair 250/50). It improves lung function and symptom-free days in poorly controlled asthma more than use of fluticasone furoate alone, and it reduces the frequency of severe exacerbations (requiring ≥3 days of oral steroids, urgent care, or hospitalization) by approximately 25% compared to inhaled steroids alone. It can be taken once daily in the morning or evening with equal efficacy, and observed side effects have been few (rare tachyarrhythmias reported) over 12 months of therapy.

Why would a committee member hesitate to recommend an effective, once-daily therapy such as this? Many of our patients have a hard time adhering to twice-daily dosing of their medications. Who wouldn’t want to take their asthma medication – like their aspirin, beta-blocker, or anti-hypertensive – once-daily if possible?

The “fly in the ointment” is the lingering uncertainty about the safety of LABA bronchodilators in asthma, even when they are taken together with an inhaled steroid. The Salmeterol Multicenter Asthma Research Trial, nicknamed SMART, found that the risk of fatal and near-fatal asthma was greater when persons with asthma were randomly assigned in addition to their “usual care” to receive 6 months of therapy with the LABA, salmeterol, compared to placebo; and it did not have the power (despite enrolling 26,000 subjects) to determine whether concomitant use of an inhaled steroid protected against these rare fatal and life-threatening asthmatic attacks. Is the danger from LABAs limited to bronchodilator therapy being used without anti-inflammatory therapy, with resultant dangerous airway wall swelling and mucus plugging, or is there another, currently unidentified, inherent pharmacologic risk to this class of medication?

The answer to this question will be forthcoming. Currently underway are multiple, simultaneous, large-scale clinical trials in which asthmatic patients, both children and adults, are being randomly assigned to receive a LABA or placebo in addition to an inhaled steroid. All subjects will be treated with an inhaled steroid. We will at last have data to address the danger or safety of LABAs among persons simultaneously receiving an inhaled steroid for treatment of their asthma.

In the meantime, if you are asked to cast your ballot – yay or nay – for vilanterol/fluticasone furoate for the indication of asthma, how would you vote? It is unlikely that there is uniformity of opinion among providers at Partners Asthma Center. Speaking only for myself, I would vote yes to approve, believing in the safety of the LABA/inhaled steroid combination and convinced that improved medication adherence would greatly improve asthma outcomes. We would welcome your vote along with your thinking on this subject: you can send it to asthma@partners.org, and we will plan to share it in our next issue of Breath of Fresh Air.

NOTE: We do not receive financial support from GlaxoSmithKline or any other pharmaceutical company.
Irreversible Airflow Obstruction in Asthma

On the surface of things, asthma and emphysema are polar opposites. Asthma is a disease that typically begins in early childhood and is closely linked to allergies; emphysema starts in middle-age and is usually caused by decades of cigarette smoking. Asthma is a disease of the bronchial tubes, characterized by inflammatory changes that we typically associate with allergic reactions and by hyperreactivity of airway smooth muscle; emphysema involves tissue destruction of the alveolar walls with resultant loss of lung elasticity. A chest CT can reveal the low-attenuation areas of emphysematous lung tissue; in asthma the lung parenchyma is normal, although one may see bronchial wall thickening or other abnormalities associated with airway disease (e.g., bronchiectasis; mosaic attenuation reflecting regional non-homogeneity of ventilation and consequently of perfusion).

However, long-term cigarette smokers are also at risk for airway disease. They may develop chronic bronchitis (mucous gland hyperplasia with mucus hypersecretion) and small airway obstruction due to neutrophilic inflammation and trapped secretions (a respiratory bronchiolitis). Airflow obstruction that develops in cigarette smokers is partly due to their emphysema and partly due to their bronchitis/bronchiolitis, leading to use of the umbrella term, chronic obstructive pulmonary disease (COPD), to describe the mixture of forms of lung injury that can emerge. It is, of course, the airway aspects of COPD that we target when we treat our patients with inhaled bronchodilators and/or corticosteroids to improve their breathing. Still, our expectation is that persons with asthma will have mostly reversible airflow obstruction (returns to normal with treatment), whereas persons with COPD will have some component of irreversible airflow obstruction (that persists despite maximal treatment).

Sadly, persons with asthma may also smoke cigarettes, the ultimate “double jeopardy” for developing persistent airflow obstruction. By some estimates, 20-30% of persons with asthma are or have been smokers, similar to the general population. After decades of cigarette smoking, one would not be surprised to find that persons with asthma might develop persistent, irreversible airflow obstruction on pulmonary function testing. Even on a good day, when their asthma is under perfect control, they have reduced expiratory flow. If the persistent airflow obstruction is severe enough, they will experience exertional breathlessness … all the time. This group of patients may be described as having “Asthma-COPD Overlap syndrome,” an area of considerable on-going research (use the following link, for example, to view the Asthma Grand Rounds lecture on the topic by Dr. Craig Hersh, member of the Pulmonary and Critical Care Medicine Division and Channing Division of Network Medicine at Brigham and Women’s Hospital: [PAC Asthma Grand Rounds videorecording June, 2014](#)).

Now, here’s the rub with our current taxonomy: what do we make of the person with asthma who never smoked cigarettes and yet continues with persistent, irreversible airflow obstruction despite intense anti-asthmatic treatment? We have escalated treatment according to asthma guidelines. Perhaps we have even given a two-week course of oral steroids to ensure maximal treatment. And yet, when we measure lung function following bronchodilator administration, our asthmatic patient continues to have a reduced FEV1 and peak expiratory flow and evidence for expiratory airflow obstruction. At

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some point along the course of illness, he or she has developed irreversible obstructive lung disease. We would not call it COPD, which we reserve to describe chronic bronchitis and emphysema from long-term cigarette smoking, but asthma with persistent airflow obstruction or perhaps chronic irreversible asthma. We might check for alpha-1 antitrypsin deficiency, to be sure that this patient does not have a genetic predisposition to develop obstructive lung disease even in the absence of cigarette smoking, but in this example the blood test returns normal. What happened to this patient? Why has his/her asthma developed a component of permanent airway narrowing?

The short answer is that we know very little about why some patients with asthma develop permanent airway narrowing. Among a large, general population of persons with asthma, this phenomenon appears to be uncommon, perhaps occurring fewer than 5% of the time. However, among a group of patients selected for the severity of their disease, the figure may rise closer to 50%. Some evidence suggests that long duration of disease may be a factor; other studies point to recurrent severe asthmatic attacks potentially triggering step-wise decreases in lung function. One had hoped that treatment with inhaled steroids, by damping asthmatic inflammation, might prevent irreversible airway scarring and narrowing, but to date no evidence is available to support this wished-for outcome. More likely, the pathobiology of irreversible airway narrowing in asthma involves pathways that are largely steroid-resistant, as in many other fibroproliferative disease processes.

At what age this permanent loss of lung function occurs; whether the mechanism is part of the usual asthmatic pathology or another superimposed process; exactly what the airway pathology looks like; and how best to prevent its development or progression are all unanswered questions. For now, we are left to recognize and characterize it and attempt to optimize the reversible component of our patient’s airflow obstruction. And, of course, no cigarette smoking!