The Role of Short- and Long-acting β-agonists and Inhaled Corticosteroids in the Management of Asthma and COPD—A Review of the Guidelines

a report by
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Asthma and chronic obstructive pulmonary disease (COPD) are major health problems in the US and affect 20 million and 11.2 million people, respectively. The small airways play a significant role in the pathophysiology of both diseases. In asthma, inflammation can occur anywhere from the large central airways to the smaller peripheral, or distal, airways. Airflow limitation in COPD patients occurs mainly in the small airways.

Bronchodilators are central to the management of asthma and COPD, and comprise inhaled short- and long-acting β2-agonists (SABAs and LABAs, respectively) and inhaled anticholinergics. Inhaled SABAs are indicated for all children and adults with asthma and COPD. Inhaled corticosteroids (ICS) are prescribed for patients with persistent asthma symptoms. However, long-term administration of ICS does not control symptoms completely in all cases. A combination of drug classes with different mechanisms of action improves outcomes compared with monotherapy in patients with moderate or more severe disease. This paper will review the current guidelines and discuss the relative roles of SABAs, LABAs, and ICS, and complications thereof, in the treatment of asthma and COPD, and explore the evidence for the efficacy of therapies in the distal airways.

Rescue Medications
Rescue medications are used as and when required for short-term relief of episodic wheezing and shortness of breath. All patients with asthma or COPD receive an inhaler containing a SABA. SABAs act on β2 receptors in the airways, causing smooth-muscle relaxation, which results in bronchodilation within 30 minutes of inhalation. The bronchodilatory effect of SABAs lasts for up to six hours. Side effects of β-agonist use can include headache, restlessness, anxiety, and tachycardia with premature contractions.

Anticholinergics such as ipratropium are also used in short-acting inhalers, often in combination with β-agonists. Anticholinergics are competitive inhibitors of acetylcholine at M3 muscarinic receptors, reducing the contraction of airway smooth muscle. A systematic review of randomized controlled trials examining the effectiveness of an inhaled short-acting anticholinergic in asthma patients demonstrated that the drug can be helpful in certain individuals. The most common side effect in clinical trials has been dry mouth, which has generally been mild and resolved during the course of the therapy.

There has been little controversy about the use of SABAs for preventing exercise-induced bronchospasm and relieving acute symptoms of asthma, or the use of short-acting anticholinergics in COPD. However, such short-acting medications would have to be used three or four times daily in order to control symptoms, and such frequent use of SABAs has been associated with an increased risk for asthma-related death. Thus, long-acting agents for β-agonists and anticholinergics have been developed to provide pharmacological advantages over short-acting drugs for both chronic asthma and COPD patients; examples of such long-acting β-adrenergics are salmeterol and formoterol, which have activity spanning 12 hours, while the long-acting anti-cholinergic teotropium has activity over a 24-hour time interval.

Long-term-control Medications

Long-acting β2-agonists—Asthma
LABAs such as salmeterol and formoterol are smooth-muscle relaxants administered to patients with chronic asthma who have moderate to severe disease. The effects of currently available LABAs last for approximately 12 hours. Monotherapy with LABAs has been shown to be inferior to the use of ICS, which are the recommended first-line treatment for asthma. Results from the Salmeterol Multi-Centre Asthma Research Trial (SMART) study, which included more than 26,000 participants, showed a small but significant increased risk for asthma-related death and an increase in life-threatening exacerbations with salmeterol monotherapy, affecting African-Americans at a greater incidence than Caucasians. This study resulted in the US Food and Drug Administration (FDA) mandating label warnings on all LABAs.

In addition, a meta-analysis of pooled results from 19 trials including 33,826 people with asthma was conducted to evaluate the use of LABAs. An overall increased risk for fatal exacerbations in the β-agonist-treated group was found compared with placebo. The authors of the meta-analysis concluded that use of LABAs can increase the risk for hospitalization, life-threatening asthma attacks, and asthma-related deaths compared with placebo.
Inhaled Corticosteroids—Asthma

All current guidelines state that ICS should be used as a first-line treatment in patients with persistent asthma symptoms. In the US, ICS can be used in the combination of beclomethasone dipropionate, budesonide, flunisolide, fluticasone propionate, mometasone furoate, and triamcinolone acetonide. ICS are considered to be the most potent and effective anti-inflammatory and preventive treatment currently available for chronic asthma. The clinical effects of corticosteroids include improvements in quality of life, diminished airway hyper-responsiveness, reduction in hospitalizations, and a decreased need for systemic corticosteroids.

In both children and adults, ICS have been shown to greatly increase forced expiratory volume in one second (FEV1), exacerbation rates, frequency of symptoms, and airway hyper-responsiveness in patients with mild to moderate persistent asthma compared with other single long-term control medications. Prolonged use of ICS can have systemic effects, including suppression of the hypothalamic-pituitary-adrenal axis, growth retardation in children, disturbed glucose tolerance, decreased mineralization of bone, and cataracts and glaucoma.

Inhaled Corticosteroids—COPD

In contrast to asthma guidelines, the Global initiative for Chronic Obstructive Lung Disease (GOLD) guidelines state that ICS should be administered only in severe COPD. A systematic review published in 2006 revealed that the use of ICS in COPD patients reduced the risk for exacerbations by 33% compared with placebo, but this positive treatment effect was seen only in patients with moderate to severe COPD. However, there is evidence that long-term use of ICS does not improve lung function in COPD; several studies of COPD have demonstrated that the use of ICS does not affect the long-term decline in FEV1. Long-term use can also lead to side effects such as oropharyngeal candidiasis and hoarseness, as well as possibly increasing susceptibility to pneumonia.

Combination Therapy—Asthma

Both bronchodilators and anti-inflammatory drugs are able to reduce symptoms in chronic asthma and COPD patients. The possibility of a complementary effect between these two drug classes has also been investigated. Studies have demonstrated that patients treated with a combination of a LABA and an ICS have a significantly reduced need for systemic steroids in comparison with other treatments. Benefits were also noted in FEV1, symptom-free survival days, and withdrawal rates when LABAs were used as add-on treatment compared with using corticosteroids alone. Importantly, the addition of a LABA was not associated with any increase in adverse effects over those seen with corticosteroids alone.

A Cochrane review of 26 trials examined the effectiveness of LABAs plus ICS compared with ICS alone in patients with chronic asthma. The study confirmed the beneficial effects of adding a LABA to an ICS, and stated that the strength of evidence from the trials was strong enough to recommend this approach in adult asthma patients. The authors also concluded that current data are insufficient to draw conclusions on the use of LABAs in children, the optimal dose of ICS at which LABAs should be added, the use of two single drugs or a combined device, or the best type of LABA to administer.

Combination Therapy—COPD

The use of combined ICS and LABAs has additionally been examined in patients with COPD. The efficacy and safety of corticosteroids alongside a LABA was examined in moderate to severe COPD patients in a randomized, double-blind, placebo-controlled trial over one year. The combined treatment resulted in improvements in all disease characteristics of COPD, including lung function and quality of life, with a reduction in exacerbations.

The Towards a Revolution in COPD Health (TORCH) trial had the primary objective of examining the difference in survival rates between COPD patients treated with an ICS in combination with a LABA versus a LABA alone, an ICS alone, or placebo over a three-year period. Treatment with the combined regimen resulted in a significant decrease in exacerbations and an improvement in health status compared with placebo. However, overall mortality was comparable between the two groups, suggesting that the combination had no effect on survival. Larger and longer-term randomized trials are needed to confirm this finding.

Another Cochrane review in COPD evaluated results from 11 randomized clinical trials to examine the effectiveness of a combined corticosteroid and LABA inhaler. Co-administration of the two drugs appeared to be beneficial in terms of the number of exacerbations and quality of life compared with placebo. However, side effects were more frequent in the treatment arm. Pneumonia was the most common adverse effect, which is of particular concern in the elderly because it can lead to hospitalization. In one of the studies included in the review, combination treatment resulted in...
a 70% increase in the rate of hospitalization with pneumonia compared with placebo.18 Future studies are required to evaluate whether the addition of a corticosteroid to a LABA is beneficial for patients with COPD.

Recent data have suggested that corticosteroids boost β-agonists by slowing their disposal.19 Horvath et al. discovered a novel mechanism by which corticosteroids rapidly improve bronchodilatation due to a β-agonist. The authors concluded that corticosteroids increase airway tissue retention of inhaled drugs and thus improve pharmacological responses to β-agonists. Similar complementary effects have been noted in COPD patients,20 when ICS were used in conjunction with β-agonists, there was a more marked reduction in bronchial CD8+ T-cells and sputum neutrophils, both of which are indicative of the degree of severity and disease progression.

A Focus on Small Airways
Sophisticated imaging21 and immunohistochemical techniques22 have shown that a significant amount of inflammation occurs at the distal airways in asthma; this distal airway inflammation is proposed to take part in many of asthma’s pathological processes. In a study comparing patients with mild asthma versus unafflicted individuals, pulmonary functions were similar, but patients with asthma exhibited an increase in peripheral lung resistance by over seven-fold.53 This increased peripheral lung resistance was also demonstrated in a study comparing 20 patients with bronchial asthma versus five healthy non-smoking subjects: the researchers found that patients who had suffered from asthma for over 20 years and who had more severe airflow obstruction also had increased peripheral resistance.23 The inflammatory response in nocturnal asthma has also been shown through endobronchial and transbronchial biopsies to involve small airways units, largely in alveolar tissue.24 Previously, the distal airways were overshadowed by their larger proximal counterparts as a drug target, likely because they are more difficult to observe in comparison, the typical physiological measures of pulmonary function lean toward measuring large airways, and to date no single test exists for small airway function that can reflect airflow obstructions. Furthermore, physiological measures have not been shown to be any better at correlating small airways with respiratory symptoms than any other current tests of airway function.54

Recent years have seen the development of drugs designed to reach the smaller airways, such as hydrofluoroalkane (HFA)-beclomethasone, HFA-ciclesonide, and HFA-flunisolide. Because they are drug solutions rather than the suspensions used in most metered-dose inhalers, the mass median aerodynamic diameter (MMAD) of 1.1µm is much smaller than that of other products, ranging anywhere from 2.5 to 4.0µm. This size difference therefore allows for different depositions and a wider area of distribution. In a single-blind study comparing a suspension-based ICS with a solution-based ICS, patients received either HFA-beclomethasone 320µg/day or chlorofluorocarbon (CFC)-fluticasone 330µg/day in addition to their current asthma therapy.25 Those that were treated with the small particle size inhaled steroid showed significant improvement in forced expiratory flow (FEF)5–15% as well as in the closing volume/total capacity ratio and residual volume. These results not only suggest a role for HFA propellants with small particle sizes, but also indicate that small airways present an important therapeutic target for ICS.

Summary
Small-airways diseases such as asthma and COPD are currently a major respiratory health problem in the US. Current guidelines in asthma suggest starting treatment with rescue therapy such as SABAs. In persistent cases of asthma, long-acting medications are recommended, the most common of which are ICS and, when needed for more severe cases, a LABA. All current guidelines for asthma recommend the use of ICS as a first-line treatment in persistent asthma, although ICS are recommended only for severe COPD. LABAs are not recommended for monotherapy in asthma owing to an association with asthma-related deaths. In COPD the long-acting anti-cholinergic ipratropium is added early, and ICS and LABAs can be considered as adjunctive agents. Combination treatment with ICS and LABAs in both COPD and asthma has been shown to be more beneficial compared with monotherapy; however, in some cases this is linked to an increase in side effects. Future long-term studies are required to discover the true impact of combination therapy for small-airways diseases. Lastly, many existing therapeutic interventions do not address small airway pathology, in spite of the growing database of evidence pointing towards the importance of therapeutics that can reach the distal airways.