

Asthma Pharmacotherapy

a report by

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Asthma is a common respiratory disease that affects millions of people of all ages across the globe. It is a chronic disease with episodes of flares or acute exacerbations. Although the pathogenesis of asthma is still not completely understood, there are effective treatments to control the disease. In the therapy of patients with asthma, it is important to separate the concept of asthma severity from asthma control. The former refers to the intensity of the underlying disease process while the latter relates how well the manifestations of the disease are minimized by therapy. The goal of achieving asthma control, i.e. minimizing symptoms of breathlessness, cough, chest tightness and nocturnal awakenings, is therefore the same regardless of the underlying disease severity.

Pharmacotherapy of asthma is unique in several ways. First, asthma is characterized by airway inflammation, bronchial hyperresponsiveness and reversible bronchospasm. Standard asthma therapy therefore consists of an anti-inflammatory medication to suppress airway inflammation and a fast-acting bronchodilator to relieve bronchospasm as needed. The use of two different classes of medication to treat different aspects of the same disease is not an easy concept for patients to grasp. Since relief with bronchodilators is immediate and perceptible, there is often an over-usage of bronchodilators by patients, with a corresponding neglect of anti-inflammatory medications. Over-reliance on bronchodilators leading to uncontrolled airway inflammation is a cause of majority of asthma morbidity and mortality.

Second, most of the first-line agents are administered via inhalation. The choice of which medication to use is often framed within the context of the delivery device, dose frequency, lung deposition, systemic bioavailability, educational requirement for proper medication and inhaler usage, patient adherence and motor coordination. These unique features of asthma therapy add several layers of complexity to the pharmacotherapy of asthma. These issues have to be factored in for each and every patient and are critical in determining the ultimate success of asthma therapy.

Third, unlike adjusting medication and diet to achieve a low glycosylated hemoglobin level, there is no equivalent

biomarker for asthma. In the past, therapeutic endpoints have included spirometry, peak flow rates, clinical symptoms, and bronchial hyperresponsiveness. The ability to quantitate airway inflammation with exhaled nitric oxide and sputum eosinophil may change how management of inhaled corticosteroids is handled in the future. The use of validated simple asthma control questionnaires to adjust medications and improve asthma control may also redefine treatment outcomes in asthma.

Inhaled Corticosteroids in Asthma

Inhaled corticosteroids (ICS) remain the most efficacious therapy for chronic persistent asthma for all age groups and for different levels of disease severity. As the main anti-inflammatory therapy in asthma, it is effective in controlling the clinical manifestations of asthma and in reducing airway inflammation. The efficacy of inhaled corticosteroids is now confirmed in new onset asthma, and in mild persistent asthma for improving asthma control, preventing exacerbations and reducing hospitalizations. It is superior to mast cell stabilizers and leukotriene antagonists as monotherapy. Regular use of inhaled corticosteroids was superior to intermittent-use inhaled corticosteroids or daily leukotriene antagonist therapy in improving lung function, reducing asthma symptoms, and reducing bronchial hyperresponsiveness. The regular use of inhaled corticosteroid was a major reason for significant reductions in asthma morbidity and mortality.

In choosing which inhaled corticosteroid to use, the delivery device, i.e. dry powder inhaler or metered dosed inhaler, and the best achievable technique by the patient are probably the most pragmatic criteria for the individual patient. Serial measurement of sputum eosinophil and exhaled nitric oxide has been shown to be useful in titrating inhaled corticosteroids in asthma in adults and children.

Long-acting Bronchodilators in Asthma

The current recommendation by several asthma guidelines for persistently symptomatic asthma in spite of low-to-moderate dose of inhaled corticosteroid is to add a

long-acting bronchodilator. Combination therapy with low-to-moderate dose-inhaled corticosteroid and a long-acting bronchodilator is more effective than high-dose corticosteroid monotherapy in reducing exacerbation and controlling asthma symptoms. Current concern regarding long-acting β_2 -agonists have centered on their safety and their over-usage. When the *post hoc* analysis of the Strategies for Management of Anti-Retroviral Therapy (SMART) study showed that African-Americans had a number-needed-to-harm (NNH) of 159 compared with 943 for the total group, the study was terminated. The US Food and Drug Administration (FDA) has added a black box warning label to prescribers and patients regarding the safety of salmeterol and formoterol. The SMART was not designed to test the safety of salmeterol as an adjunct to inhaled corticosteroid. Based on numerous published studies on combinational therapy, there is no direct evidence that the use of long-acting bronchodilators as

considered for treatment of mild persistent asthma and are useful adjunctive therapy in asthma. Leukotriene receptor antagonists are less efficacious than inhaled corticosteroids in persistent asthma as monotherapy and are less potent in preventing exacerbation as add-on therapy. Leukotriene receptor antagonists are efficacious as adjunctive therapy in allergic rhinitis, nasal polyposis, and aspirin-induced asthma.

Biological Agents in Asthma

Although expensive, the advent of biological agents in asthma is a real advancement. Anti-IgE therapy, omalizumab, is effective in reducing exacerbation rates and in improving quality of life in patients with difficult-to-control, moderate-to-severe persistent allergic asthma. Clinical studies suggest that Etanercept has recently been shown effective to

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adjunctive therapy with inhaled corticosteroids is associated with an increase in asthma mortality or morbidity. The release of fixed-dose budesonide/formoterol combination therapy in the US as both maintenance and acute reliever medication may further simplify asthma therapy.

Short-acting Bronchodilators in Asthma

Short-acting β_2 adrenergic agonists are quick-acting bronchodilators. They continue to be first-line treatment for mild intermittent asthma and for relief of bronchospasm in chronic persistent asthma. It is recommended that short-acting β_2 adrenergic agonists should only be used as intermittent or 'as needed' therapy for symptom control rather than as regularly scheduled medications. They are effective as premedication for exercise-induced broncho-constriction. There is no clear advantage to using the single enantiomer form of albuterol. No anticholinergic agent has been approved for use in asthma in the US. There is scant evidence to support the practice of adding ipratropium bromide to albuterol when the initial response to albuterol is poor.

Anti-Leukotrienes in Asthma

Leukotriene receptor antagonist and five lipoxygenase inhibitors are weak bronchodilators that can be

improve bronchial hyperresponsiveness, lung function and asthma symptoms in severe patients. Allergen immunotherapy is effective for selected patients with allergic asthma.

The future of asthma pharmacotherapy is very promising. The use of combination quick-onset long-acting bronchodilator and corticosteroid may simplify therapy further. The better inhalation delivery devices will soon be available to improve drug delivery to the lungs. The non-pharmacologic treatment of bronchial hyperresponsiveness with bronchial thermoplasty is also a promising development in the treatment of asthma. There is still the potential of pharmacogenetics in guiding asthma management especially refractory asthma in the future. The elucidation of novel genes and cellular pathways involved in asthma may offer newer targets for therapy such as ADAM-33. The pharmacotherapy of asthma will continue to evolve with more patient-friendly medications and devices. This should be a pleasant prospect for patients currently suffering from severe asthma as well as for their care providers. ■

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