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Promising future therapies for asthma

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ABSTRACT

Asthma affects 300 million people worldwide and that number has been increasing especially in developed countries. The current standard of care for asthma treatment is based on 2 key pathological features of asthma, airway inflammation and airway obstruction. Improving bronchodilation can be accomplished with ultra-long acting beta2 agonists or long-acting muscarinic agonists used in combination with inhaled corticosteroids. These combinations have already been used effectively for the treatment of COPD. An inhaled phosphodiesterase inhibitor has been shown to improve bronchodilation and decrease airway inflammation. Directly altering the airway smooth muscle with bronchial thermoplasty in select patients has demonstrated long-term benefits but must be measured with immediate post procedure complications. The development of monoclonal antibodies to directly target specific cytokines has had mixed results. In eosinophilic asthma blocking IL-4, IL-5 and IL-13 have improved asthma outcomes. The promise of more directed therapy for asthma appears closer than ever with increased options available for the clinician in the near future.

1. Introduction

Asthma affects 300 million people worldwide and its prevalence increases by 50% every decade [1]. In North America about 10% of the population has asthma while in other developed countries this is greater than 15% [1]. Asthma is a heterogenetic disorder characterized by chronic inflammation with variable airflow obstruction and airway hyperresponsiveness. The asthma inflammatory milieu consists of eosinophils, lymphocytes, mast cells, and epithelial cells. [2]. Neutrophils may play a key role in sudden onset-fatal asthma, occupational asthma and asthmatic smokers. Later in the disease airway remodeling occurs with the development of sub-basement fibrosis, goblet cell hyperplasia, smooth muscle hypertrophy and angiogenesis. Atopy, the genetic predisposition for the development of IgE mediated allergy, is the strongest predictor for the development of asthma. Typically allergic inflammation is geared towards a T helper lymphocyte (TH_2) profile with the generation of cytokines IL-4, IL-5, and IL-13 leading to increased airway eosinophilia, mast cell activation and IgE production.

Current treatment goals consist of reducing inflammation with inhaled corticosteroids or leukotriene modifying agents, and decreasing airway obstruction via bronchodilation with beta$_2$-agonists or anticholinergics. Patients with moderate and severe persistent perennial allergic asthma are candidates for monoclonal antibody therapy with omalizumab or anti-IgE antibodies. Future therapies will build on our expanding understanding of the pathogenesis of asthma and effective treatment strategies already in place.

2. Bronchodilators

2.1. Long-acting beta$_2$-agonist (LABA)

The use of an inhaled corticosteroid (ICS) combined with a long-acting beta$_2$-agonist (LABA) is the standard of care for treating moderate–severe asthma [2]. In 2013, a newer ICS/LABA combination consisting of fluticasone furoate (FF) and vilanterol (VI) was approved by the Food and Drug Administration (FDA) of the United States for the treatment of COPD. This combination has an ultra long acting beta$_2$-agonist, vilanterol, with 24 h bronchodilator activity, allowing for once a day dosing. Early studies in asthma patients demonstrated a good safety profile with superiority to inhaled corticosteroid monotherapy in reducing asthma symptoms [3,4].

A recent randomized, double-blind, double-dummy, parallel group study by Woodcock et al evaluated 806 patients treated with once daily inhaled FF/VI 100/25 μg compared to twice daily dosing of, fluticasone propionate (FP)/salmeterol (SAL) 250/50 μg for 24 weeks [5]. Prior to treatment patients in the study were not optimally controlled on medium dose ICS alone. Both ICS/LABA therapies equally improved lung function, asthma control, exacerbation rates and quality of life measures. Both treatments were well tolerated with no difference in urinary cortisol levels between the two groups. The advantage of daily dosing makes this a useful alternative to the current twice daily ICS/LABA therapies.

2.2. Long-acting muscarinic agonist (LAMA)

The use of long-acting muscarinic agonist (LAMA) medications as bronchodilators, such as tiotropium, is standard therapy for COPD. The

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addition of these types of medications for the treatment of patients with asthma has been evaluated in several different patient populations. The types of patients evaluated fall into 2 categories, moderate patients not well controlled on ICS alone and patients symptomatic despite high dose ICS/LABA therapy.

In patients not well controlled on low dose ICS alone current interventions include increasing the ICS or adding a LABA. Peters et al designed a three-way, double-blind, triple-dummy crossover trial involving 210 patients with asthma, evaluating the addition of tiotropium bromide to an ICS, as compared with doubling the dose of the inhaled glucocorticoid, or the addition of the LABA, salmeterol [6]. Compared to doubling the ICS, the addition of tiotropium improved lung function (peak flows and FEV_1) and symptoms (ACT scores, asthma control days, and daily symptoms). Similar improvement was noted with the addition of salmeterol to ICS compared to higher dose ICS. When the tiotropium arm was compared to the salmeterol arm the only significant difference was a greater improvement in FEV_1 with tiotropium. In a double-blind, double-dummy, placebo-controlled trial 388 asthmatic patients who had a single nucleotide polymorphism at amino acid 16 (B16-Arg/Arg) of the β2-adrenergic receptor gene (ADRB2B16-Arg/Arg) were randomized to 16 weeks of treatment with daily tiotropium, salmeterol administered twice daily through a metered-dose inhaler, or placebo in addition to their regular ICS doses [7]. Tiotropium and salmeterol were superior to placebo in maintaining lung function, while tiotropium was evaluated noninferior to salmeterol with similar improvements noted.

An early concept study evaluated the addition of tiotropium to standard ICS/LABA therapy [8]. In this double blind, randomized, placebo-controlled, crossover study evaluating the effects of halving ICS dosage and adding either salmeterol alone, or salmeterol and tiotropium in 18 non-smoking severe asthmatics, both the ICS/LABA and ICS/LABA/LAMA treatments were more effective than twice the dose of ICS in improving PEF and airway resistance. The addition of tiotropium additionally improved FEV_1 and FVC while exhaled NO was reduced compared to double the dose of ICS. In another study comparing 2 different doses of tiotropium (5 and 10 μg daily) added to patients uncontrolled on high dose ICS/LABA, both doses of tiotropium improved lung function, while the higher dose was associated with more side effects such as dry mouth [9]. Based on those results a subsequent 48 week randomized, double-blind, placebo-controlled, parallel-group study, was undertaken evaluating the addition of tiotropium (5 μg daily) for asthmatics not well controlled on ICS/LABA [10]. The addition of tiotropium increased the time to first exacerbation by 56 days compared to placebo, reducing both exacerbation risks by 21%, and the total number of severe exacerbations. The median time to the first episode of asthma worsening was 315 days with tiotropium compared to 181 with placebo treatment. Again this study demonstrated improvement in lung functions, FEV_1, FVC and peak flow measurements similar to previous studies.

One potential future therapy could be the use of one inhaler with a corticosteroid, ultra-long acting beta agonist, and tiotropium as a once a day medication for treating moderate to severe asthma.

3. Phosphodiesterase inhibitors

Phosphodiesterases (PDEs) are enzymes associated with airway smooth muscle activity and airway inflammation. Inhibitors of PDE_3 act as bronchodilators while inhibition of PDE_4 is anti-inflammatory. Roflumilast, an oral PDE_4 inhibitor was shown to increase the FEV_1 in patients already taking salmeterol or tiotropium with COPD. The main drawback was associated GI side-effects leading to increased study withdrawals [11]. A novel inhaled $PDE_{3/4}$ inhibitor RPL554 has been evaluated in 4 proofs of concept studies involving healthy volunteers and patients with COPD or mild asthma [12]. Treatment was well tolerated in all study groups with similar adverse reactions with study drug compared to placebo. In patients with asthma or COPD bronchodilation was rapid, and was maintained after 6 days of daily dosing in patients with asthma. RPL554 significantly reduced total number of neutrophils and cells in sputum of healthy volunteers after lipopolysaccharide challenge. Overall RPL55 was well tolerated, not demonstrating the same GI effects as the oral PDE_4 inhibitor.

4. Bronchial thermoplasty

Bronchial thermoplasty (BT) is a novel invasive treatment for severe asthma. Bronchial thermoplasty reduces airway smooth muscle mass by delivering radiofrequency energy by bronchoscope directly to larger lobar and segmental bronchi (3–10 mm in diameter). Airway smooth muscle is active in producing and responding to inflammatory cytokines such as IL-4 and leukotriene B_4. In addition to decreasing the smooth muscle thickness and leading to fixed airway size other potential mechanisms include reduction of goblet cell hyperplasia and alteration of bronchomotor tone [13].

An initial study on 16 patients with mild to moderate asthma tolerated the standard bronchial thermoplasty of 3 treatments 3 weeks apart [14]. The most common side effects were airway irritation presenting as increased cough, dyspnea, wheeze and bronchospasm typically within the first day or two post procedure resolving within 5 days. Twelve weeks post treatment patients had significant improvement in peak flow readings and symptom-free days and 2 years post procedure airway hyperresponsiveness had improved from a mean PC_{20} of 0.92 mg/ml to 3.40 mg/ml.

A larger prospective, randomized, controlled study involving 112 moderate–severe asthmatics were treated with 3 BT procedures 3 weeks apart and evaluated a year after last treatment [15]. One year post therapy the BT group compared to control group had greater improvements in morning peak flow readings and symptom scores. In addition thermoplasty patients had a reduction in the number of mild exacerbations estimated at 10 fewer mild exacerbations per subject per year with 86 additional symptom-free days per subject per year. After 5 years no evidence of adverse events due to BT were noted while spirometry was stable during this period of time [16].

A more severe subset of refractory asthmatics (32 patients) requiring high dose ICS/LABA with and without oral corticosteroids were randomized to BT (15) or standard therapy (17) [17]. During the bronchoscopy treatment period, the first 6 weeks of the study having 3 treatments 3 weeks apart, 4 BT patients were hospitalized a total of 7 times while the control group had no hospitalizations. In the post treatment period 5 hospitalizations occurred in 3 BT patients while 4 hospitalizations occurred in one control patient. Bronchial thermoplasty patients had improvements in rescue medication use and quality of life 52 weeks after treatment compared to the control group.

Castro and colleagues evaluated 288 severe asthmatics symptomatic despite high dose ICS/LABA who were randomized to thermoplasty or sham control bronchoscopies [18]. A year after treatment completed 79% patients treated with BT had improvement in quality of life compared to 64% of sham treated patients. In the post treatment period (after the initial 6 weeks of procedures) the BT group had reductions in severe exacerbations by 32%, ER visits due to respiratory symptoms by 84%, time lost from work/school by 66%, and hospitalizations for respiratory symptoms by 73% compared to the sham treated group. During the treatment period, the first 6 weeks, 85% of the BT subjects experienced adverse events compared to 76% of sham bronchoscopy patients. During this period 8.4% of BT patients (16/190) required 19 hospitalizations compared to 2% of sham patients (2/98). One of the thermoplasty patients required bronchial artery embolization for treatment of his post procedure hemoptysis. Of the 190 BT treated patients 162 (85%) were evaluated 5 years after treatment [19]. These patients had an average reduction over 5 years in severe exacerbations and ER visits by 48% and 78% respectively compared to the 12 months prior to BT treatment. Prebronchodilator FEV_1 remained unchanged during the 5 years even with a decrease in ICS dose by 18%.