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Review Article

New Trends in Asthma Treatment

David El-Qutob*

Unit of Allergy, Hospital Universitary of La Plana in Vila-Real, Spain

Abstract

Despite adequate adherence and completion of anti-asthmatic treatment, many patients remain poorly controlled or uncontrolled. Asthma management is based on the use of medication to reverse the bronchial obstruction and eliminate the airway inflammation. New drug development is expected in the future as a consequence of discoveries in the pathophysiology and mechanisms of asthma. Currently, a good and effective set of treatments is available for these diseases. However, the search for new treatment modalities to improve the currently available is especially important for those patients unresponsive to current therapy. In this review we summarize new anti-cytokines therapies, anti-immunoglobulin molecules, immunomodulatory agents and corticosteroids plus broncodilators.

***Corresponding author**

El-Qutob D, Unit of Allergy of Hospital Universitary La Plana, Vila-Real Carretera Vila-Real-Burriana Km. 0.5 Vila-Real (Castellón) 12540, Spain, Tel: 964-75- 3600 ext 54310; Fax: 00-34-964-35-7601; Email: elqutob@comv.es

Submitted: 19 July 2014

Accepted: 07 October 2014

Published: 10 October 2014

ISSN: 2333-6625

Keywords

- Asthma
- Recent
- New
- CRTH2
- Treatment
- Antileukotrienes
- Immunomodulation
- AntilgE
- Corticosteroids
- Bronchodilator

ABBREVIATIONS

CRTH2: Chemoattractant Receptor-Homologous Molecule Expressed On Th2 Cells; COPD: Chronic Obstructive Pulmonary Disease; WHO: World Health Organization; SIT: Allergen-Specific Immunotherapy; ICS: Inhaled Corticosteroids; LABA: Long-Acting-B-Agonist; SABA: Short-Acting-B-Agonist; MDI: Metered Dose Inhaler; 5-LO: 5-Lipoxygenase; FLAP: 5-Lipoxygenase-Activating Protein; 5-Oxo-ETE: 5-Oxo-6,8,11,14-Eicosatetraenoic Acid; FEV1: Forced Expiratory Volume In 1 Second; PGD_2: Prostaglandin D2; LAR: Late Asthmatic Response; AHR: Airway Hyperresponsiveness; DREAM: Dose Ranging Efficacy And Safety With Mepolizumab In Severe Asthma; CCR4: C-C Chemokine Receptor 4; AD: Atopic Dermatitis; CCR3: C-C Chemokine Receptor Type 3; TLSP: Thymic Stromal Lymphopoietin

INTRODUCTION

Asthma is a chronic inflammatory disorder of the airways with participation of various types of cells. It leads to recurrent episodes of wheezing, breathlessness, chest tightness and cough, usually accompanied by variable airflow obstruction, usually reversible with medication, as well spontaneously, and bronchial hyperresponsiveness against different stimuli [1]. Allergic and infective causes are most common and have a substantial socioeconomic impact. Asthma significantly impairs quality of life and affect both school and work performance. Respiratory diseases, including allergies, asthma and chronic obstructive pulmonary disease (COPD), are a major public health with great impact worldwide. The latest WHO statistics (2007) estimate that 300 million people worldwide have asthma, and millions of people are affected by allergies. Each year, 250,000 people die of asthma. The prevalence of these diseases is increasing, and there is a continued need for new and improved therapies[2].

Despite adequate adherence and completion of anti-asthmatic treatment, many patients remain poorly controlled or uncontrolled. A proper diagnostic of asthma is basic for the implementation of an appropriate treatment plan. Treatment of asthma has four cornerstones: education of the patient, triggers avoidance measures, symptomatic treatment and allergen immunotherapy. Pharmacotherapy is effective in controlling the symptoms of allergic diseases, but withdrawal of medication leads to reappearance of symptoms in a short span of time. Allergen-specific immunotherapy (SIT) is the only etiologic treatment of allergic disorders like asthma that can alter the natural course of the disease [3,4] but SIT is only effective in extrinsic asthma.

Asthma management is based on the use of medication to reverse the bronchial obstruction and eliminate the airway inflammation. Uncontrolled inflammation can lead to structural changes in the airway walls - a process known as remodeling [5]. This can lead to fixed airflow obstruction and worse clinical outcomes. The patient's active collaboration is needed [6]. The goal of asthma treatment is the long-term control of the disease, including nocturnal symptoms and exercise-induced asthma, preventing exacerbations and achieving the best possible lung function with none, or minimal, side effects. At this time, multiple drugs are available and they are divided into preventive medication, chronically used for control the disease, and rescue medication, used for the treatment of acute clinical symptoms (See table 1[7]).

From a pathogenic point of view, asthma could be treated through several targets. The approaches that have usually been taken are to improve existing treatments, such as ICSs and LABAs, or to find drugs against novel targets identified through better understanding of the disease process, such as cytokine blockers[8]. The aim of this article is to review new trends in asthma treatment in the last times.

Table 1: Medication for asthma.

PREVENTIVE MEDICATION	RESCUE MEDICATION
1.Inhaled corticosteroids (ICS)	1.Short-acting-β-agonist (SABA)
2.Long-acting-β-agonist (LABA)	2.Anticholinergics
3.Leukotriene modifiers	3.Parenteral corticosteroids
4.Cromones	4.Inhaled corticosteroids (ICS)+
5.Theophyllines	Long-acting-β-agonist (LABA)
6.Oral corticosteroids	
7.Others: omalizumab, cyclosporine, ketotifen	

Abbreviations: ICS: Inhaled Corticosteroids. LABA: Long-Acting- β -Agonist. SABA: Short-Acting- β -Agonist.

RECENT TRENDS FOR ASTHMA TREATMENT

Corticosteroids and bronchodilators

Corticosteroids are anti-inflammatories that reduce the number of inflammatory cells in the airways and prevent blood vessels from leaking fluid into the airway tissues. By reducing inflammation, they reduce the spontaneous spasm of the airway muscle. Corticosteroids are used as a preventive measure to minimize the risk of acute asthma attacks. The corticosteroids are given in two ways, inhaled via a metered dose inhaler (MDI) or orally via pill/tablet or liquid form.

Bronchodilators work by increasing the diameter of the air ways and easing the flow of gases to and from the lungs. They have two forms, short-acting (SABA) and long-acting (LABA). These drugs are inhaled and are used to relieve symptoms during acute asthma attacks. LABA are also used as preventive treatment.

In a recent study, once-daily repeated dosing of FF/VI, 100/25 µg, using the ELLIPTA dry powder inhaler was as well tolerated as FF, 100 µg in a selected population of 5- to 11-year-old children [9]. Moreover, the efficacy of once-daily FF/VI was compared with bid FP/SAL in improving lung function in patients with persistent asthma and both drugs have similar results [10]. Recently, has been discovered AZD3199, an inhaled ultralong acting β_2 receptor agonist with rapid onset of action [11]. A single-dose crossover study was conducted to investigate and compare with formoterol the bronchodilatory and systemic effects, tolerability and safety of AZD3199. AZD3199 was associated with a lower level of systemic side effects than formoterol, and was also well tolerated [12].

Targeting cysteinyl-leukotrienes

The only mediator antagonists currently used in asthma therapy are antileukotrienes, which block cysteinyl-leukotriene $CysLT_1$-receptors. Three drugs, zafirlukast, montelukast and zileuton), are part of a class of anti-inflammatories called leukotriene modifiers. Taken orally, these drugs work by inhibiting leukotrienes (fatty acids that mediate inflammation) from binding to smooth muscle cells lining the airways. They also reduce the recruitment of inflammatory cells to the airways. These drugs both prevent and reduce symptoms, and are intended for long-term use. 5-Lipoxygenase (5-LO) catalyzes the first two steps in the biosynthesis of leukotrienes, a group of pro-inflammatory lipid mediators derived from arachidonic acid. 5-Lipoxygenase-activating protein (FLAP) is an 18-kDa integral membrane protein which is essential for cellular leukotriene synthesis, and is the target of LT biosynthesis inhibitors [13]. Several novel 5-LO and FLAP inhibitors are currently in clinical development. GSK2190915, a potent 5-LO-activating protein inhibitor, prevents the synthesis of leukotrienes and 5-oxo-6,8,11,14-eicosatetraenoic acid (5-oxo-ETE) and shows potential as a treatment for patients with asthma[14]. Another study demonstrated efficacy for GSK2190915 30 mg compared with placebo in day-time symptom scores and day-time SABA use, but not with greater dosis than 30 mg[15].

Leukotriene B4 (LTB_4) is a chemotactic mediator implicated in the pathogenesis of asthma. JNJ-40929837 is an oral inhibitor of LTA_4 hydrolase, which catalyzes LTB_4 production. In a double-blind, 3-period crossover study, 22 patients with mild, atopic asthma, no significant impact in response to allergen inhalation and FEV_1 were observed with JNJ-40929837 versus placebo[16].

Cytokines modulators

CRTH2 (Chemoattractant Receptor-homologous molecule expressed on Th2 cells) is a G-protein coupled receptor expressed by Th2 lymphocytes, eosinophils, and basophils. The receptor mediates the activation and chemotaxis of these cell types in response to prostaglandin D2 (PGD_2), the major prostanoid produced by mast cells[17]. QAW039 is an oral antagonist of CRTH2/DP2 receptor developed by Novartis. There are several clinical trials studying its application in asthma and atopic dermatitis[18-20]. Some are recruiting patients yet and others have finished but without results posted.

AZD1981 is a potent fully reversible, functionally non-competitive antagonist of human CRTH2/DP2, developed by Astra-Zeneca. AZD1981 blocks functional responses in eosinophils, Th2 cells and basophils [21]. It has been conducted several clinical trials (asthma, COPD and chronic urticaria) [22,23] but without results posted. There was no beneficial clinical effect of AZD1981, at a dose of 1000 mg twice daily for 4 weeks, in patients with moderate to severe COPD [24].

Setipiprant (ACT-129968) is orally active CRTH2 antagonist. In a 3-center, double-blind, placebo-controlled, cross-over study was well tolerated and reduced both the allergen-induced late asthmatic response (LAR) and the associated airway hyperresponsiveness (AHR) to methacholine in 18 allergic asthmatics[25]. Mogamulizumab (KW-0761; AMG-761), under development by Kyowa Hakko Kirin and Amgen, is a defucosylated humanized IgG1 mAb against C-C chemokine receptor 4 (CCR4) for the potential intravenous treatment of asthma[26]. In *CC chemokines*, these two cysteines are adjacent. By licensee Amgen for asthma, this company is conducting a phase II clinical trial in patients with asthma [27, 28]. C-C chemokine receptor type 3 (CCR3) has also recently been designated CD193. It is highly expressed in eosinophils and basophils, and is also detected in Th1 and Th2 cells, as well as in airway epithelial cells. This receptor may contribute to the accumulation and activation of eosinophils and other inflammatory cells in the allergic airway [29]. The role of CCR3 agonists in asthma was investigated by observing the effect of an oral antagonist of the CCR3 receptor (GW766994) on sputum eosinophil counts in patients with eosinophilic asthma. There was no improvement in FEV1; however, there was a modest but statistically significant improvement in PC20 methacholine (0.66 doubling dose) and ACQ scores, (0.43)[30].

Thymic stromal lymphopoietin (TSLP) is a fibroblast, epithelial cells and different types of stromal or stromal-like cells derived cytokine that plays an important role in initiating allergic inflammation through activation of antigen presenting cells. AMG157 is a human anti-TSLP monoclonal immunoglobulin G2λ that binds human TSLP and prevents receptor interaction. Gauvreau *et al* have studied the effects of an anti-TSLP antibody on allergen-induced asthmatic responses. Treatment with AMG 157 reduced allergen-induced bronchoconstriction and indexes of airway inflammation before and after allergen challenge [31]. More clinical studies are needed.

Anti-allergic therapy

Omalizumab is an anti-IgE monoclonal antibody indicated as an add-on therapy for patients with uncontrolled severe allergic (IgE-mediated) asthma. This drug can significantly reduce the risk of exacerbations in patients with severe allergic asthma[32]. Mepolizumab is a humanized monoclonal antibody that recognizes interleukin-5 (IL-5). The larger Dose Ranging Efficacy and Safety with Mepolizumab in Severe Asthma (DREAM) trial provided evidence of efficacy of mepolizumab in the reduction of asthma exacerbation in patients with severe eosinophilic asthma with an acceptable safety profile [33]. Several clinical trials with mepolizumab reported that treatment of patients with mild to severe asthma resulted in a substantial reduction in blood and sputum eosinophil numbers. However, clinical outcomes were disappointing as there were no significant effects on airway hyper-reactivity or the late asthmatic reaction to inhaled allergen challenge [34].

QGE031 is a humanized anti-Immunoglobulin E monoclonal antibody in development for the treatment of IgE-mediated allergies such as severe uncontrolled asthma, atopic dermatitis (AD) and food allergies. A clinical trial (NCT01703312) has evaluated the efficacy of QGE031 compared to omalizumab in patients with allergic asthma. Each treatment's effect in changing the concentration of inhaled allergen that is required to elicit a 15% fall in the forced expiratory volume in one second (FEV1) at 12 weeks compared to baseline was evaluated. No results have been posted [35]. Novartis is studying the possibility of using this treatment in atopic dermatitis, peanut allergy and bullous pemphigoid[36-38]. Lebrikizumab blocks interleukin 13 (IL-13). IL-13 induces the expression of periostin, by epithelial cells of the bronchi. Periostin participates in bronchial hyperresponsiveness, inflammation, and activation and proliferation of airway fibroblasts, which are involved in airway remodeling [39]. To evaluate efficacy and safety of lebrikizumab in subjects with mild asthma, a clinica trial was conducted. Lebrikizumab-treated subjects with elevated baseline levels of peripheral blood eosinophils, serum IgE, or periostin exhibited a greater reduction in LAR compared with subjects with lower baseline levels of these biomarkers[40]. Dupilumab blocks IL-4Rα and then modulates signaling of both the IL-4 and IL-13 pathway[41]. Actually, there are several clinical trials studying long safety and effectiveness in patients with moderate to severe uncontrolled asthma[42, 43]. Another clinical is determining the safety and effectiveness of dupilumab for treatment of atopic dermatitis (AD) [44]. All three are recruiting patients. Brodalumab binds to the interleukin-17 receptor and blocks its action. A randomized, double-blind, placebo-controlled study in moderate to severe asthma showed no effect in asthma [45]. It is being tested also for the treatment of moderate to severe psoriasis with better results than in asthma [46].

CONCLUSION

Targeting novel immunomodulatory/anti-inflammatory approaches to the appropriate asthmatic patient presents considerable challenges to ensure that any adverse effects or risk of these new drugs outweigh the therapeutic benefits. The more systemic effect of a drug, more side effect it has. Another problem is that actual therapies are highly effective, relatively inexpensive, and safe. Therefore, new treatments, usually more expensive, are intended for severe asthma.

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Cite this article

El-Qutob D (2014) New Trends in Asthma Treatment. Clin Res Pulmonol 2(2): 1017.