



Novel treatments for asthma: Corticosteroids and other anti-inflammatory agents.

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ABSTRACT

Asthma management is a challenge due to the prevalence of disease in the world. Based on the immunological and inflammatory mechanisms of asthma, corticosteroids and anti-inflammatory participate greatly in the treatment plan. Due to different reasons, there is still an unmet need to develop new agents in this field. A lot of compounds with anti-inflammatory effect are investigated in both pre-clinical and clinical studies.

Keywords: Asthma, Corticosteroids, Anti-inflammatory.

Introduction

Most asthma cases are responsive to inhaled corticosteroids (ICS) and long-acting beta agonists (LABA). Theophylline and leukotriene antagonists are also used in the management of this widely spreaded disease. However, about 40% of asthmatic patients stay suffering from symptoms in spite of receiving the prescribed therapy. Severe cases can be controlled by increasing the dose of ics and laba or the usage of omalizumab, an anti-immunoglobulin-E (anti-igE) therapy, which decreases the exacerbation rates and improve quality of life[1]. There are some problems facing the usage of traditional drugs for asthma. The side effects and non preference of inhalation

administration by patients are among the obstacles of ICS treatment. Severe asthmatic patients can not be well treated by the current medications. Moreover, there is no cure to asthma disease. All the previous problems need to be solved through developing new drugs[2]. There are many compounds related to different categories being developed in the pre-clinical and clinical studies. Corticosteroids, anti-inflammatory drugs, anti-allergy agents and cytokine antagonists are examples of therapeutic agents with promising effect in the management of asthma. In this article, corticosteroids and other anti-inflammatory will be discussed.

Corticosteroids

Corticosteroids used successfully to treat allergic and idiosyncratic asthma. Current guidelines recommend the administration of ics and laba as first option in managing asthma exacerbations due to their proven effectiveness compare with other drugs. The mechanism of action of corticosteroid is not well understood but it can be

explained through different theories. First, corticosteroids could increase the beta-adrenergic response providing relaxation of bronchial muscle. Second, corticosteroids produce the vasoconstriction effect leading to lowering edema. Third, steroids decrease the mucus secretion. Finally, corticosteroids interfere with chemotaxis and therefore inhibit the inflammatory response of bronchial injury. Consequently, many physician

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consider ics the gold standard for asthma treatment [3][4].

The side effects of corticosteroids are minimal in case of short-term usage. On the other hand, mood changes, adrenal suppression and high blood sugar level are the prominent features for the long-term administration[5].

Beclomethasone dipropionate, budesonide, fluticasone propionate, and mometasone furoate are examples of ics therapies used nowadays. They are all similar in terms of efficacy. Furthermore, beclomethasone is preferred as it is the least expensive one[4]. Ciclesonide is a prodrug converted to the active form (Desisobutyryl ciclesonide) by the esterase enzyme in the lung, so it has lower systemic absorption and in turn less systemic side effects compared with currently available ics. In a long duration randomized clinical trial, ciclesonide at lower concentration (320 micrograms daily) was more effective than budesonide (400 micrograms daily) but with unknown systemic side effect. Ciclesonide development was an effective process to produce anti-asthmatic agent deprived from serious side effect of corticosteroids [6].

Another tactic used to develop ics free from side effects is the synthesis of dissociated steroids which are intended to separate the anti-inflammatory mechanisms and the side effects mechanisms. Mechanisms of either action is different. Firstly, the molecular mechanisms of corticosteroids such as osteoporosis and metabolic effects may be due to gene activation. Transactivation occurred through binding of corticosteroid to its receptor, then the complex binds to glucocorticoid response elements (GRES) in the promoter of genes, and activates transcription process. Secondly, transrepression is thought to be responsible for the anti-inflammatory activity of the drug. Some agents show a promising effects but only in vitro[7][8].

Non-steroidal steroidal receptor modulators are expected to have fewer side effects than glucocorticoids. AI-438 is less potent than prednisolone, but it produces less hyperglycemic and bone formation inhibition effect [9]. Selective glucocorticoid receptor modulators (SGRMs) are believed to be able to dissociate transactivation

activity from transrepression activity, and the drug discovery and development industry has focused fundamentally on identifying SGRMs to reach this purpose [10].

Although ics are among the most prescribed drugs for asthma treatment, both acquired and intrinsic resistance asthma cases to glucocorticoids were reported. This is called glucocorticoid-resistant asthma which defined as a lack of improvement in airway obstruction following a 2-week course of oral glucocorticoid therapy [11].

Anti-inflammatory agents

Targeting type 4 phosphodiesterase (PDE4) enzyme has become hopeful process for the management of asthma and chronic obstructive pulmonary disease (COPD). PDE4 is responsible for the metabolism of intracellular second messenger cyclic adenosine monophosphate (AMP). PDE4 inhibitors (eg, Cilomilast, and roflumilast) stimulate the relaxation of airway smooth muscles leading to increase airflow, inhibit bronchiolar–alveolar–vasculature remodeling, and fibrosis, reduce pro-inflammatory mediator release, improve patients' exercise capacity, and prevent the progressive loss of pulmonary function [12].

Roflumilast is a selective PDE4 inhibitor which reduces inflammation and ameliorate lung function in asthma and copd. It shows mild clinical benefits with some gastrointestinal side effects. This drug provides an additional option in the treatment of asthma depending on its ease of administration [13]. Cilomilast might be effective in the treatment of asthma but with low incidence of side effects. It is a well-tolerated agent without safety concerns reported in the clinical trials [14].

Future concepts

Although there are a lot of anti-asthmatic drugs in the market and in the clinical development phases, none of those therapeutic agents achieve a satisfied efficacy toward the disease. Vaccine design is considered novel concepts in the prevention of allergic asthma disease through reversing the normal immunological regulation process of asthma disease [2].

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