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Recent research and developmental strategy of anti-asthma drugs

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ABSTRACT

Extensive research over the past decade has provided information about the pharmacotherapy of bronchial asthma (BA). Anti-asthma drugs are classified into two categories: relievers (for the relief of asthma attack symptoms) and controllers (for the prevention of asthma symptoms). This paper aims to review the recent advancements of anti-asthma drugs that are controller medicines. The controllers mainly act on immune and inflammatory responses in BA development.

1) Immunomodulators. Drugs that act on the immune response are classified into two categories: immunosuppressors and immunomodulators, including immunopotentiators. The immunomodulation of the Th1 and Th2 imbalance is the first strategy of the controller because allergic BA is thought to be caused by Th2-polarized immunity. Suplatast is a novel immunomodulator that can adjust the imbalance in the Th1/Th2 immune response and shows clear clinical efficacy against BA. The immunomodulator approach has shifted from a more theoretical and conceptual model to one supported by evidence of clinical efficacy.
2) Anti-inflammatory agents. Corticosteroids, mast cell stabilizers and autacoid inhibitors are anti-inflammatory agents for BA. The clinical superiority of the combined therapy of inhaled corticosteroids and long-acting beta2 agonists is evident. This combined therapy shows a potent synergic anti-inflammatory effect compared to the effect by corticosteroids alone. Currently, the anti-inflammatory agents for BA under development are drugs affecting lipid mediators. The prostaglandin (PG) D2 antagonist, PGE2, EP3 agonist and PGI2 agonist are being considered in addition to well-established leukotriene and thromboxane A2 inhibitors. New development strategies and therapeutics for controllers are described in this review.

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1. Introduction

Bronchial asthma (BA) is a common disease affecting almost 300 million people in the world, and the prevalence of the disease is steadily increasing (Milian & Diaz, 2004; Clark et al., 2010; Pan et al., 2010; Spergel, 2010; and Duramad & Holland, 2011). BA is thought to be caused by sub-chronic eosinophilic epithelial desquamative inflammation of the airway. Pathomechanistic studies have indicated that allergic inflammation contributes to the onset of acute and/or chronic symptoms of the disease (Galli et al., 2007; Akhabir & Sandford, 2011; Eiwegger & Akdis, 2011; Gordon, 2011 and Knosp et al., 2011). Despite our understanding of the underlying mechanism, there are some therapeutic problems due to disease heterogeneity and variability. This heterogeneity is influenced by multiple factors, including age, sex, race, ethnicity, genetics and environmental conditions. To unify current research and create a consensus on drug management, groups such as the National Institutes of Health (USA), the Global Initiative for Asthma (GINA) and the Japanese Society of Allergology (JSA) have each published several asthma prevention and management guidelines (Moore & Pascual, 2010; O'Byrne, 2010; Dahlén et al., 2011; Hoeksema

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et al., 2011 and Ohta et al., 2011). The implementation of guideline-based therapy seems to be effective in the prevention and treatment of child and adult asthma throughout the world. However, the complete remission of the disease by pharmacotherapy is still difficult. Therefore, there has been an international effort to conduct research toward the discovery of new drugs for BA.

In most guidelines, the drugs for BA are classified into two categories: relievers (which provide the symptomatic relief of air flow limitation by asthma attack) and controllers (which suppress airway inflammation) (Table 1). The basic strategy of therapy is mainly to combine the use of the two different kinds of drugs mentioned above (Enarson et al., 2005; Sears & Radner, 2009 and Anselmo, 2011). This strategy seems to provide effective relief of some BA symptoms. The relievers, bronchodilators and expectorants are effective enough to relieve the airflow limitation in clinical situations, but controllers are not yet very effective.

As indicated in Fig. 1, the immunological and inflammatory process is the underlying cause of asthma attacks that are predominately related to tissue reactions. The immunological and inflammatory stages are the target steps for the controller. The immune response is initiated by the activation of the adoptive immune response, which is affected by the innate immune response, including natural killer T (NKT) cells, myeloid dendritic cells (DCs) and the toll-like receptor (TLR). The allergic immune response results from the allergen's impact on the mucosal surface. Whole allergen is taken up by antigen-presenting cells, and peptides are presented to naïve helper T (Th0) cells, resulting in T cell activation and the elaboration of cytokines. When the Th2 cells are activated and Th2 cytokines, including interleukin-4 (IL-4) and IL-13, are produced, the Th2 immune response leads to allergic inflammation. In most cases of BA, immunoglobulin E (IgE) production is the result of the Th2 immune response, which causes mast cell activation. Mast cell activation is an important factor in the inflammatory response. During this stage, many chemical mediators are released from mast cells, and eosinophils accumulate in the lesion. This process introduces asthmatic symptoms in the tissues. Airflow limitation from smooth muscle contraction, edema and hypersecretion is a major symptom caused by airway tissue reactions. In these tissue reactions, certain proinflammatory lipid mediators including leukotrienes (LTs), thromboxanes (Txs) and prostaglandins (PGs) play an important role. Understanding the pathophysiological process of BA may help to reveal a strategy to discover new anti-asthma drugs. In this review, the research and development strategy of anti-asthma drugs, especially the controller medicines acting on immunological and inflammatory stages during BA development, will be discussed.

2. Immunomodulators

Recent advancements in immunology research have revealed the contribution of several types of immune responses that regulate the onset and development of some diseases, such as allergies or autoimmune diseases. BA is a typical allergic disease, and the precise mechanisms involved are being widely researched. Consequently, many researchers have concluded that Th2-polarized immunity is the main cause of the disease (Fang et al., 2008; Broide, 2009; Ohnmacht et al., 2010; Libetta et al., 2011; Wang et al., 2011 and Yamanaka & Mizutani, 2011). The concept of immunotherapy for BA is summarized in Table 2. Appropriate allergens or specific molecules acting on IgE antibody production are applied for immune suppression. In addition, advances in the understanding of the Th2-polarized immune response have opened up the possibility of specific immunomodulation to control allergic BA. Although much effort has been made to find a drug that can adjust the imbalance of the Th1/Th2 immune response, to date, no data have been obtained that might suggest any clinical success of such drugs. Our initial study conducted 30 years ago in collaboration with a pharmaceutical company was focused on this question. From our prior data, the compounds that act as methyl group donors generally showed immunomodulating activity. Then, the pharmacological activities of more than 100 compounds were tested. After extensive research, methylmethionine sulfonium chloride (vitamin U) was nominated as the final and the most effective compound. When the pharmacological action of vitamin U derivatives was examined, one derivative, Suplatast, showed potent immunomodulating and anti-inflammatory activity in the Th2-polarized immune processes. Fig. 2 indicates the chemical structure and possible mechanism of Suplatast (IPD). In basic research (Matsuura et al., 1992a,b; Yanagihara et al., 1993a,b; Iijima et al., 1999; Oda et al., 1999; Shim et al., 2000; Zhao et al., 2000; Capron et al., 2001; Myou et al., 2001; Nagai, 2001; Suwaki et al., 2001; Oda et al., 2002; Agrawal et al., 2007 and Hst et al., 2007), it adjusts the imbalance of the Th1/Th2 immune response, which results in the suppression of IgE antibody production. In addition, it inhibits eosinophilic inflammation by interfering with Th2 cytokine production and inhibiting chloride ion channel activation on eosinophils. A summary of the basic research on the pharmacological activity of Suplatast is listed in Table 3.

Based on the positive results from prior research, careful clinical studies on the efficacy of Suplatast were carried out in Japan. Consequently, Suplatast showed adequate efficacy for the treatment of BA, allergic rhinitis and atopic dermatitis (Tamaoki et al., 2000, 2003; Horiguchi et al., 2001, 2005; Shioya et al., 2002; Sano et al., 2003a,b; Ishiura et al., 2004; Wada et al., 2009; Yoshihara et al., 2009 and Kondo et al., 2010). A summary of the clinical results on BA is shown in Table 4. Suplatast is now available for the management of BA as a controller of the Th2-dependent allergic inflammation. This agent is the first successful Th2 immunomodulator to be used as a remedy for allergic diseases such as BA.

The other examined immunomodulators are CpG-oligonucleotides (ODNs), which are activators of toll-like receptor 9. Many researchers have reported on the efficacy of CpG-ODNs in both the prevention of antigen-induced asthma and the treatment of previously established experimental asthma and atopic dermatitis (Kim et al.,

Table 1
The classification of anti-asthma drugs.

Classification	Medical drugs (typical example)
Controllers	
a) Taken daily on a long-term basis,	1 Immunomodulator (Suplatast)
b) Prophylactic and preventive medication	2 Anti-inflammatory agent
	(1) Inhaled corticosteroid (beclomethasone, budesonide)
	(2) Leukotriene inhibitor (pranlukast, montelukast)
	(3) Thromboxane A2 inhibitor (ramatroban, ozagrel)
	(4) Mast cell stabilizer (tranilast, cromoglycate)
Relievers	
a) Taken on demand	1 Short acting β2 agonist (procaterol, salbutamol)
b) Quick relief for the severe symptoms	2 Systematic corticosteroid (prednisolone, hydrocortisone)
	3 Anti-cholinergic (ipratropium)
	4 Methylxanthine (theophylline)