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Review Article

Novel treatments of asthma and allergic diseases

L. Chini, E. Monteferrario, S. Graziani, V. Moschese *

Department of Pediatrics, Policlinico Tor Vergata, University of Rome Tor Vergata, Rome, Italy

EDUCATIONAL AIMS

- To revise recent advances on the old therapy of asthma
- To summarize the advent of new therapeutic approaches
- To introduce the role of new players in the pathogenesis of asthma and their potential implications for future therapies

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SUMMARY

The prevalence of allergic diseases has considerably increased, mostly in industrialized countries (> 20%), and asthma affects approximately 300 million individuals worldwide. Current therapies are able to control symptoms although they do not modulate immunological dysregulation that characterizes allergic diseases. Over the last 30 years, only a few new drugs have been introduced on the market and they all act on Th2-type response which has a critical role in the pathogenesis of allergic diseases. Recently, a new scenario has been opened on Th17-cells, Th1-type cytokines and innate immune system components involved in the inflammatory pathogenesis of asthma and other allergic diseases. These findings suggest a promising therapeutic role of new agents that block the action of specific cytokines. Furthermore, the concept of an intrinsic structural defect in the bronchial epithelium paves the way to innovative therapeutic strategies. In this review we present an update on therapies for allergic diseases with special focus on asthma.

INTRODUCTION

In recent years, the prevalence of allergic diseases has globally increased but, despite wide research, more efforts are needed to understand better the mechanism of allergy development [1].

Among allergic diseases, asthma is very common. Asthma is a chronic inflammatory disease with high incidence, about 300 million people worldwide. Its prevalence is expected to rise particularly in pediatric population [2]. In Europe asthma affects around 30 million people and the total cost of this disease is estimated to be 17.7 billion euro/year with a productivity loss of 9.8 billion euro/year (http://www.efanet.org/asthma/#_ftn7). Particularly, European Lung Foundation (ELF) reports that in UK 3.4 million of people (1:7 in the 2-15 years age group and 1:25 in adults) needs asthma therapy as well as in Germany (http://www.it.european-lung-foundation.org/431-impatto-in-europa.htm). Epidemiological studies performed in the U.S. population [3] revealed that asthma caused 48% of emergency admissions and approximately 500.000 hospitalizations/year (35% in < 18 years patients). The Center for Disease Control and Prevention (CDC) estimates that children aged 5–17 years with at least one asthma attack missed 10.5 million school days in the past year. In the same age group asthma is responsible for a loss of 10 million school days and 726 million dollars for missed parental work days [3]. Similar data are reported for other industrialized countries [4].

Several studies have demonstrated that genetic, environmental, epigenetic and other factors contribute to asthma heterogeneity [5]. One of these factors is atopy which is not synonymous with asthma. In fact, while 50% of asthmatic population is atopic, only a small proportion of atopic subjects develops asthma supporting the notion that this disease results from a complex and unpredictable combination of factors [6].

Classification of different asthma pheontypes has been based on various types of inflammatory cells with a potential critical role in the pathogenesis of this disease by secreting cytokines and pro-inflammatory molecules. Indeed, Th2 cells

* Corresponding author. Department of Pediatrics, Policlinico Tor Vergata, University of Rome Tor Vergata, Viale Oxford, 81- 00133 - Roma.
Tel.: +39 0620900525; fax: +39 0620900530.
E-mail address: moschese@med.uniroma2.it (V. Moschese).

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and their cytokines predominate in mild to moderate asthma, whereas steroid-resistant asthma has a mixed Th2/Th1 phenotype with a Th17 component [7,8]. Furthermore, cells of innate immunity (neutrophils, macrophages, natural killer cells, dendritic cells, smooth muscle cells) have recently been involved in the pathogenesis of asthma because of the secretion of several cytokines that contribute to the different features of asthma [9].

Recently, bronchial epithelium has been identified not only as an important player in asthma but also as a regulator of immune function [10].

In contrast to the significant health and economic impact of asthma, only two novel classes of controller medications have been introduced on the market in the last decades. One class is the anti-leukotrienes with zafirlukast, montelukast and zileuton. The second group is represented by anti-IgE monoclonal antibody, omalizumab. Other new drugs have been introduced in the marketplace but they are advanced versions of historical drugs (inhaled steroids, beta2 agonists, anticholinergic and their various combination) [6].

These "old" classes of anti-asthmatic drugs have been updated to ensure greater specificity and efficacy as well as greater convenience of use in order to increase and improve patient compliance. However, there is still concern about the use of inhaled corticosteroids (ICS) and long-acting bronchodilators because of the fear of long-term side effects, worst acceptance of inhaled medications than those with oral administration and exacerbation of symptoms when the treatment is discontinued. Also, in 5–10% of patients we usually observe a control failure despite adequate compliance to the therapy [11]. Thus, the requirement of new therapies, that act on the immunological mechanisms of allergic diseases, including suppression of disease associated cytokines, is critical.

In this review we will discuss recent advances on the "old" drugs and on new potential immunomodulators to combat asthma and allergic diseases. Furthermore, the crucial function of the airway epithelium in asthma and related implications will be presented.

ASTHMA PATHOGENESIS: THE TRADITIONAL CONCEPT AND THE REVOLUTIONARY SCENARY

Asthma is considered a typical Th2 cell-mediated disorder. IL-4, IL-13, IL-9 and IL-5 have been identified as main cytokines involved in airway inflammation. Recently, Th1, Th17, regulatory T (Treg) cells, cytotoxic CD8+ T cells, natural killer T cells and γδ T cells have been involved in the asthma process [6]. All these mechanisms contribute to differentiate asthma phenotypes. Particularly, mild to moderate allergic asthma is prevalently characterized by Th2 cells, eosinophil infiltrates, mucus secreting cells hyperplasia and metaplasia, remodeling airway wall and airway hyperresponsiveness [9]; conversely, severe asthma is characterized by a prevalent involvement of both Th2 and Th1 cells, with a Th17 cells cooperation. In severe asthma neutrophilic inflammation and infiltration, induced by the production of particular cytokines, such as TNFα, INFγ, IL-17 and IL-27 [12], might account for the development of corticosteroid resistance. Molecular mechanisms implicated in this resistance might be activation of p38 MAPK activity, increased expression of a mutated glucocorticoid receptor GRβ, increased concentration of macrophage migratory inhibitory factor (MIF) and reduced expression of histone deacetylase-2 [13]. Thus, all of them might represent a potential therapeutic target to overcome corticosteroid resistance and treat severe asthma phenotypes.

Until few years ago asthma has been considered only a Th2 cell mediated disease and many studies concentrated on adaptive immunity and its mediators. Nowadays, the new concept of asthma as an epithelial disease with structural and functional damages [14] could revise the pathophysiological knowledge of this disease. Indeed, recent genetic studies disclosed many epithelial genes and innate immune pathways involved in asthma process [15]. Particularly, an intrinsic structural defect in the bronchial epithelium, due to impaired formation of tight junctions and aberrant barrier function, might contribute to the pathogenetic basis of asthma, leading to the airway remodeling [14]. In allergic diseases the pathogenetic role of epithelium damage has been described in atopic dermatitis with a potential link to subsequent development of asthma as in "atopic march" [16].

Moreover, recent studies have also highlighted an impaired innate immune response, as expressed by a deficiency of Toll-like receptor 3 response to rhinovirus infections in epithelial cells and a reduced airway interferon response, with an altered airway microbiome in asthmatic patients [17,18]. These exciting findings pave the way for strategies acting on epithelium reconstruction widening the therapeutic armamentarium.

THE (G)OLD THERAPY OF ASTHMA

Corticosteroids

Inhaled Corticosteroids (ICS) represent the milestone of asthma controller therapy. Several ICS, with similar clinical efficacy but different pharmacodynamic properties and systemic exposure, are now available for clinical use. Since patients with severe asthma may require high doses of ICS, research is focusing on the development of new molecules with low risk of side effects, like ciclesonide, a newly licensed steroid (for children $>$ 12 years and adults). Its little activation in the oropharynx [19] explains few systemic side effects since the prodrug is converted in the lungs into the active principle des-ciclesonide by esterases. Since side effects mainly derive from transactivation and binding of the glucocorticoid receptors to DNA, whereas pharmacological effects are mediated through transrepression of transcription factors through a non-genomic effect [20], current attempt is "to dissociate" side-effect mechanisms of steroids from their pharmacological effect. Indeed, "Dissociated" steroids are designed to act predominantly on modulation of transactivation than on transrepression with an excellent cost-benefit ratio [21]. Further improvement is now obtained with the use of pressurized inhalers containing hydrofluoroalkane 134a rather than chlorofluorocarbons as propellant with smaller particle sizes deposited in peripheral airways [22].

Bronchodilators

Bronchodilators are effective in reducing symptoms in patients with asthma because they relieve and prevent obstruction. Safety of long acting bronchodilators (LABA) is matter of debate and current guidelines recommend their combined use with ICS, as controller medications, to limit severe exacerbations and mortality [23]. Alternative classes of bronchodilators, such as vasoactive intestinal peptide analogs and potassium-channel openers are under investigation. They seem to have more potent vasodilator than bronchodilator effects. In murine models agonists of bitter taste receptors (TAS2Rs), such as quinine, chloroquine and saccharin, appear to be more effective than β-agonists, although further studies are needed to test their efficacy in humans [24]. New other molecules with a bronchodilator effect, such as selective agonists of prostaglandin, are being evaluated. Particularly, EP4-selective agonists might be useful both in bronchodilatation and in the control of coughing induced by PGE2 through EP3 receptors on sensory nerve endings [25].