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Review

Personalized medicine for bronchial asthma and allergies

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ABSTRACT

The pathogeneses and clinical features of allergies vary greatly from patient to patient. Therefore, the establishment of individualized therapy in the form of personalized medicine is essential. We have published a guideline on personalized medicine for asthma, based on a patient's clinical symptoms, laboratory findings, and the pharmacogenetics of anti-asthmatic drugs. Here, we describe personalized treatments for bronchial asthma and food allergies that we are currently putting into practice.

1. Introduction

The recent increase in the incidences of allergic diseases such as bronchial asthma, atopic dermatitis, and food allergies has become a serious social problem. Therefore, there is an urgent need to establish effective measures against such diseases. Standardized treatment management guidelines for diseases such as bronchial asthma are useful in medical practice; however, the pathogeneses and clinical features of allergies in different patients vary greatly. Furthermore, allergic diseases are caused by both environmental and genetic factors. Therefore, in addition to using standardized treatment management guidelines, there is an urgent need to implement individualized therapies in medical practice to improve patients' quality of life and cure asthma and allergies. In other words, the establishment of personalized medicine (i.e., treatments tailored to individual patients) is essential.

In this article, we report our current strategies for using personalized medicine to treat bronchial asthma and food allergies.

2. Genetic predisposition to development of asthma and atopy

Evidence largely indicates that asthma is hereditary. A number of studies have shown an increased prevalence of asthma and the phenotype associated with asthma among the offspring of subjects with asthma compared to that in the offspring of subjects without asthma. Many studies have shown that there is a genetic contribution to the development of asthma and allergic disorders [1–9]. The development of asthma and allergic disorders is correlated with some genes. We suspect that multiple causative genes are involved because there are multiple pathologies observed in asthma and allergic reactions.

3. Pharmacogenetics of asthma

The response of an individual patient to a given drug depends on several factors such as the pathogenesis of the disease, the patient's medication compliance, disease severity, and the patient's genetic background [10]. The great hope in pharmacogenetics for personalized medicine is that it will help to predict either treatment response (efficacy) or the risk of adverse drug reactions in the patient population, and that it will prove cost-effective to genotype individuals before treatment [10].

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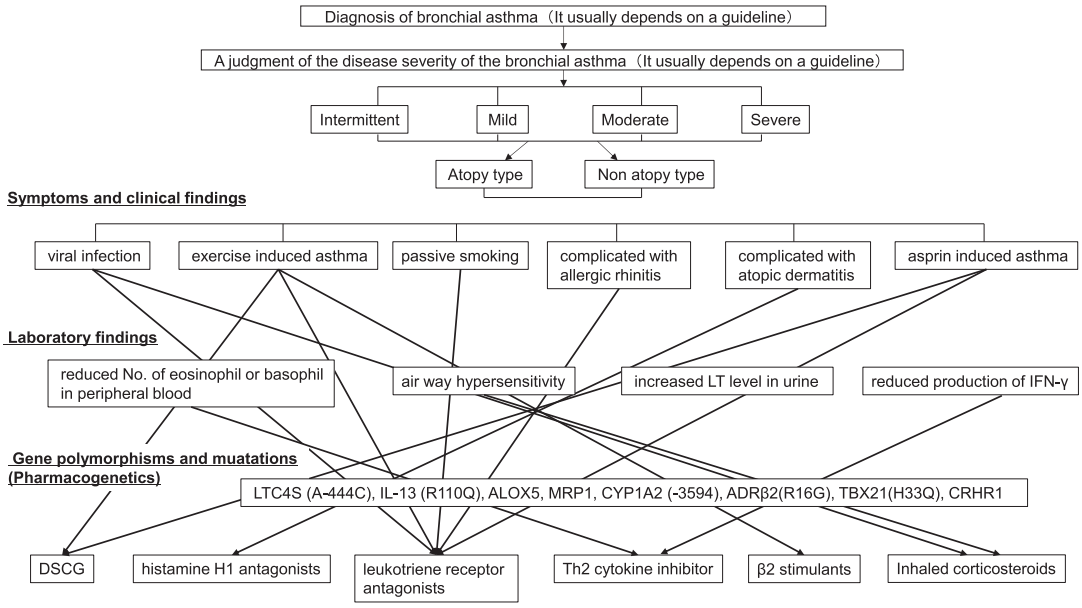
a



b

	DSCG	H1–antagonists	LTRA	Th2 cytokine inhibitor	long–acting theophylline	β 2 agonists		ICS
	effective	effective	effective	effective	(side effect)	effective	(non–effective)	effective
1 Symptoms and clinical findings								
viral infection			○					○
exrecise induced asthma	○		○			○		
asprin induced asthma	○		○					
complicated with allergic rhinitis			○					
complicated with atopic dermatitis		○						
2 Laboratory findings								
reduced No. of eosinophil or basophil in peripheral blood				○				
reduced production of IFN–γ				○				
increased LT level in urine			○					
reduced expression of CysLT1R in eosinophil (less than 60%)			○					
3 Gene polymorphisms and muatations (Pharmacogenetics)								
LTC4S A–444C (AA)				○				
LTC4S A–444C (AC or CC)			○					
IL–13 R110Q (R)				○				
ALOX5 (rs2115819 GG)			○					
MRP1 (rs119774 CT)			○					
CYP1A2 –3594(GT)					○			
ADRβ2 R16G (R)							(○)	
TBX21 (T–bet) H33Q (H/Q)								○
CRHR1 (rs1876828)								○

○:positive markers
(○): possible markers.
DSCG: disodium cromoglycate
H1–antagonists: histamine H1–receptor antagonists
LTRA: leukotriene receptor antagonists
ICS: inhaled corticosteroids

LT:leukotriene
LTC4S:leukotriene C4 synthase
ALOX5:5–lipoxygenase
MRP1:Multidrug resistance–associated protein 1
ADRβ2:β 2–aderenergic receptor
CRHR1:corticotropin–receptor 1 releasing hormone

R:Arginine
G:Glycine
H:Histidine
Q:Glutamine

Fig. 1. a. Flow from a guideline to personalized (tailor-made) medicine (drug). b. Personalized (tailor-made) medicine (drug) based on [1] symptoms and clinical findings [2], laboratory findings, and [3] pharmacogenetics.

Leukotrienes are very important mediators of asthma in children and adults. They are released by eosinophils, mast cells, and alveolar macrophages. Several enzymes, including 5-lipoxygenase and leukotriene C4 synthase (LTC4S), are important in the production of leukotrienes. LTC4S is a membrane-bound glutathione transferase that synthesizes cysteinyl-leukotrienes, converting LTA4 to LTC4.

When being treated with zafirlukast, a leukotriene receptor antagonist, patients who are homozygous for LTC4S A-444 show a lower forced expiratory volume (FEV)1 response than those with the A/C or C/C genotype [11]. Moreover, treatment with leukotriene receptor antagonists (montelukast or pranlukast) was more effective in adult or pediatric patients with the A/C or C/C genotype at position −444 (LTC4SA-444C) than in those with the A/A genotype [12,13].

Suplatast tosilate is a Th2 cytokine inhibitor. In our recent study [14], treatment with suplatast tosilate was more effective in children without the A-444C polymorphism of the *LTC4S* gene and in