J. Biol. Macromol., **21** (1), 13-18 (2021)

Review

Recent Advances in the Pharmacotherapy of Allergic Diseases

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Corticosteroids are very effective drugs for the treatment of allergic diseases. For the treatment of bronchial asthma, inhaled corticosteroids are widely used for controlling airway inflammation, and short-acting β_2 adrenergic receptor agonists are used for the relief of asthma attack. In the treatment of atopic dermatitis, topical corticosteroids are predominant and tacrolimus ointment is also available. In the treatment of allergic rhinitis, second-generation antihistamines are widely used for nasal symptoms in mild to moderate cases, but nasal drops or spray of corticosteroids is also recommended. To overcome the allergic disease, it might be important to treat active allergic inflammation sufficiently by using effective drugs such as corticosteroids to lead to remission, and to keep the remission for a longer period by avoiding risk factors and maintaining basic care.

Received September 15, 2020; Accepted October 8, 2020

Key words: bronchial asthma; atopic dermatitis; allergic rhinitis; corticosteroid; adrenergic receptor agonist; antihistamine; leukotriene receptor antagonist; pharmacotherapy

Introduction

The number of patients suffering from allergic diseases has been increasing gradually and now the prevalence has reached around 50% in Japan. Development of allergic diseases seems to be dependent on both genetic factors and environmental factors, and it sometimes is difficult to cure completely, although childhood allergy reaches remission in many cases. Recently, guidelines for the diagnosis and treatment of allergic diseases have been established and frequently updated, and the updated treatment may be available anywhere in Japan.

Allergen-specific immunoglobulin E (IgE) antibodies seem to play important roles in the development of allergic symptoms, and high levels of IgE antibodies could be detected in the sera of most patients. However, the pathology of allergic diseases such as bronchial asthma and atopic dermatitis seems to be very complex, and there are some patients with normal serum IgE levels. In contrast, in allergic rhinitis patients, IgE-dependent symptoms seem to be predominant.

Corticosteroids are very effective drugs for the treatment of allergic diseases and widely used. For the treatment of bronchial asthma, inhaled corticosteroids are widely used for controlling airway inflammation, and short-acting β_2

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adrenergic receptor agonists are used for the relief of asthma attack. Although the number of patients has gradually increased, the incidence of asthma death has apparently decreased. In the treatment of atopic dermatitis, topical corticosteroids are used predominantly and tacrolimus ointment is also available. Recently, proactive therapy using milder drugs is recommended to prevent the recurrence of dermatitis. In the treatment of allergic rhinitis, second-generation antihistamines are widely used for sneezing and rhinorrhea in mild to moderate cases, and leukotriene receptor antagonists and thromboxane A_2 receptor antagonists are used for nasal blockage. Nasal drops or spray of corticosteroids is also recommended.

In the present review, pharmacotherapeutic strategy for adult bronchial asthma, atopic dermatitis and perennial allergic rhinitis are briefly summarized according to the guidelines reviewed in Allergology International in 2017 [1-3].

Pharmacotherapy for adult bronchial asthma

Bronchial asthma is characterized by chronic airway inflammation accompanied by airway narrowing and hyperresponsiveness. Although the airway narrowing caused by asthma attack is reversible, chronic inflammation will cause airway remodeling resulting in irreversible airflow limitation. The purpose of the pharmacotherapy for bronchial asthma is to control airway inflammation and prevent asthma attack. The goal is to recover the pulmonary function and lead to normal life without symptoms.

Pharmacotherapeutic strategy for adult bronchial asthma is summarized in table 1 [1]. Four treatment steps, 1 to 4, are set according to the severity of asthma symptoms, mild intermittent, mild persistent, moderate persistent and severe persistent. For each step, treatment drugs and their dosages are recommended. Treatment drugs are divided into 2 groups, one is drugs for the long-term management (controllers) and the other is for the relief of attack (relievers). Controllers are drugs possessing anti-inflammatory and/or long-term bronchodilatory effects, and improve disease condition. They are expected to alleviate asthma symptoms and to maintain respiratory functions under a continuous treatment. In contrast, relievers are drugs useful for relieving asthma attack, and exert bronchodilation promptly. They are used on demand.

In long-term management drugs, inhaled corticosteroids are recommended in all 4 steps as

Table 1 Treatment steps for asthma [1]

		Treatment step 1	Treatment step 2	Treatment step 3	Treatment step 4
Long-term manage-ment agents	Basic treatment	Inhaled corticosteroid (low dose)	Inhaled corticosteroid (low to medium doses)	Inhaled corticosteroid (medium to high doses)	Inhaled corticosteroid (high dose)
	Add-on treatment	If the above agent cannot be used, use one of the following agents. LTRA Theophylline sustained-release preparation (unnecessary for rare symptoms)	If the above agent is ineffective, concomitantly use one of the following agents. LABA (compounding agent can be used) LTRA Theophylline sustained-release preparation	Concomitant use one or more of the agents below. LABA (compounding agent can be used) LTRA Theophylline sustained-release preparation LAMA	Concomitantly use multiple agents below. LABA (compounding agent can be used) LTRA Theophylline sustained-release preparation LAMA Anti-IgE antibody Oral corticosteroid
	Additional treatment	Anti-allergics other than LTRA	Anti-allergics other than LTRA	Anti-allergics other than LTRA	Anti-allergics other than LTRA
Exacerbation treatment		Inhaled SABA	Inhaled SABA	Inhaled SABA	Inhaled SABA

LABA: long-acting β_2-adrenergic receptor agonist, LAMA: long-acting muscarinic receptor antagonist, LTRA: leukotriene receptor antagonist, SABA: short-acting β_2-adrenergic receptor agonist

basic treatment drugs. Inhaled corticosteroids possessing an ante-drug property exhibit potent anti-inflammatory effects locally in the airway, but after absorption from the airway tissue into the blood vessels, they are easily metabolized to inactive forms. Therefore, systemic effects of locally applied inhaled corticosteroids are apparently reduced when compared to the systemic treatment with oral corticosteroids. As add-on drugs, long-acting β_2 adrenergic receptor agonists, leukotriene receptor antagonists, sustained-release theophylline preparations and long-acting muscarinic receptor antagonists are recommended. Compounding preparations of inhaled corticosteroids and long-acting β_2 adrenergic receptor agonists are also used widely. For the treatment of the most severe and persistent asthma patients, anti-IgE antibody and oral corticosteroids are considered. Antibodies against interkeukin-5, interleukin-5 receptor α and interleukin-4 receptor α are also available at present. As an additional treatment, anti-allergic drugs except for leukotriene receptor antagonists, and herbal medicines are used occasionally.

For the exacerbation treatment, inhaled short-acting β_2 adrenergic receptor agonists are used to prevent or attenuate asthma attack as a reliever. These drugs are inhaled on demand, and bronchodilatory effects could be obtained promptly. However, frequent usage of these drugs is not recommended, as over use may have a relation to asthma death. Increased need for the usage of the reliever indicates insufficiency of controller treatment, and the treatment step should be stepped up.

Although the number of patients has gradually increased, the frequency of emergency transport and the incidence of asthma death have apparently decreased recently. Introduction of inhaled corticosteroids and spread of updated pharmacotherapy seem to contribute to the achievement.

Pharmacotherapy for atopic dermatitis

Atopic dermatitis is a chronic skin disease with repeated exacerbation and remission, and characterized by eczema with severe itching. Most patients possess atopic diathesis, defined by (i) personal or family history of bronchial asthma, allergic rhinitis, and/or atopic dermatitis and/or (ii) easiness for IgE antibody production. Although high levels of serum IgE antibodies could be detected in most patients, serum IgE antibody levels are normal in about 20% patients. Severe itching is the most important problem of atopic dermatitis and impairs patients' quality of life too much. Repeated scratching caused by itching brakes skin barrier and worsens the dermatitis and itching. Scratching is the most important cause to worsen the dermatitis and itch-scratch circle is formed. So, itching is one of the most important targets in the treatment of this disease. The goal of the treatment is to control the dermatitis as well as itching and recover satisfactory quality of life.

Pharmacotherapeutic strategy for atopic dermatitis is summarized in table 2 [2]. Disease severity is divided into 4 grades, mild, moderate, severe and most severe, and treatment drugs, their potencies and dosages are recommended for each grade. Topical corticosteroids are the main stay for the treatment of atopic dermatitis. Preparations of topical corticosteroid are graded into 5 groups according to their anti-inflammatory potencies as weak, medium, strong, very strong and strongest. According to the disease severity and patient age, an appropriate preparation is selected. Topical corticosteroids are provided as 5 g tubes and the amount of ointment used for the treatment is shown as units (1 unit denotes 1 tube, 5 g). Furthermore, finger-tip unit (FTU) is also introduced as an easier and practical index to use. One finger-tip unit

Table 2 Administration method of topical steroid against atopic dermatitis [2]

<table>
<tr><td></td><td>Mild</td><td>Moderate</td><td>Severe</td><td>Most severe</td></tr>
<tr><td></td><td>Only mild rashes are observed irrespective of the area</td><td>Rashes with severe inflammation: less than 10% of the body surface area</td><td>Rashes with severe inflammation: 10% or more to less than 30% of the body surface area</td><td>Rashes with severe inflammation: 30% or more of the body surface area
Temporary hospitalization is recommended, in principle</td></tr>
<tr><td></td><td colspan="4">Moisturizer / protectant (applicable to mild to most severe cases)</td></tr>
<tr><td>Younger than 2 years old</td><td rowspan="4">All age groups

Topical steroid as needed (mild or lower)</td><td>Topical steroid (mild or lower)</td><td>Topical steroid (strong or lower)</td><td>Topical steroid (strong or lower)</td></tr>
<tr><td rowspan="2">2 to 12 years old</td><td colspan="3">Tacrolimus (0.03%) (2 to 12 years old, to sites where the use of steroid is not appropriate)</td></tr>
<tr><td>Topical steroid (strong or lower)</td><td>Topical steroid (very strong or lower)</td><td>Topical steroid (very strong or lower)</td></tr>
<tr><td rowspan="2">13 years old or older</td><td colspan="3">Tacrolimus (0.03%) (13 to 15 years old, to sites where the use of steroid is not appropriate)
Tacrolimus (0.1%) (16 years old or older, to sites where the use of steroid is not appropriate)</td></tr>
<tr><td>Topical steroid (very strong or lower)</td><td>Topical steroid (very strong or lower)</td><td>Topical steroid (very strong or lower)</td></tr>
<tr><td>Index of doses of ointment (5g tube)</td><td>Very small amount</td><td>0.5 units or less (2.5g)
5 FTU</td><td>0.5 to 1.5 units (7.5g)
15 FTU</td><td>1.5 to 5 units (25g)
50 FTU</td></tr>
<tr><td rowspan="3">Oral medicine</td><td colspan="4">Antihistaminics, antiallergics, herbal medicine (as needed)</td></tr>
<tr><td colspan="3"></td><td>Oral corticosteroid (temporary as needed)</td></tr>
<tr><td colspan="3"></td><td>Cyclosporine</td></tr>
</table>

FTU: finger-tip unit

corresponds to about 0.5 g ointment, and for an area of adult 2 palms.

About 20 years ago, tacrolimus ointment was introduced for the treatment of atopic dermatitis. There are 2 preparations, 0.03% preparation for 2 to 15 years old patients and 0.1% preparation for 16 years old or older patients. The potency of tacrolimus ointment corresponds to topical corticosteroids of medium to strong classes. Tacrolimus ointment is very useful for treating the sites where the use of topical corticosteroids is not appropriate. Although corticosteroids do not seem to possess direct anti-itch property, they may attenuate itching secondarily through inhibiting inflammation. In contrast, tacrolimus may inhibit itching more directly.

Anti-allergic drugs including antihistamines, and herbal medicines are used supplementally. Especially, antihistamines are frequently prescribed to attenuate itching, but they may not be so effective for severe itching associated with atopic dermatitis. For the treatment of most severe patients, oral corticosteroids and cyclosporine are also used. Recently, anti-interleukin 4 receptor α antibody has become available. This antibody preparation inhibits not only interleukin-4 response but also interleukin 13 response and may be effective for itching. In all patients, skin care with moisturizers and/or protectants is essential at any treatment stage.

For the treatment of atopic dermatitis, a sufficient amount of appropriate class of topical corticosteroid preparation should be used to lead to the remission, and potency and dosage of topical

corticosteroid are gradually reduced according to the attenuation of dermatitis. If the efficacy of drug treatment is insufficient, disease severity grade should be stepped up.

Previously, application of topical corticosteroid has been terminated after reaching the remission (reactive therapy). Recently, however, topical corticosteroid of milder preparation or tacrolimus ointment is recommended to used intermittently after reaching the remission (proactive therapy). Proactive therapy seems to be useful for preventing recurrence and maintaining remission. Avoidance of risk factors and skin care are always important for all patients.

Pharmacotherapy for allergic rhinitis

Allergic rhinitis is an allergic disease of nasal mucosa characterized by sneezing, rhinorrhea and nasal blockage associated predominantly with type I allergic reaction. Allergic rhinitis is classified into perennial and seasonal. Perennial allergic rhinitis is induced by allergens present throughout the year such as dust mites, whereas seasonal allergic rhinitis is caused by seasonal allergens such as Japanese cedar pollen (Japanese cedar pollinosis). The number of patients with allergic rhinitis has markedly increased, especially those with Japanese cedar pollinosis.

Pharmacotherapeutic strategy for perennial allergic rhinitis is summarized in table 3 [3]. Severity of perennial allergic rhinitis is divided into 3 grades, mild, moderate and severe, and in the case of moderate and severe, they are subdivided into sneezing and rhinorrhea type, and nasal blockage type or combined type with nasal blockage as a chief complaint. For each grade, treatment drugs and treatment methods are recommended. As type I allergic reaction mainly contributes to the development of nasal symptoms, anti-allergic drugs including second-generation antihistamines are used for mild and moderate cases. However, nasal corticosteroids are also recommended even in these cases. In the severe

Table 3 Treatment of perennial allergic rhinitis [3]

Severity	Mild	Moderate		Severe	
Disease type		Sneezing and rhinorrhea type	Nasal blockage type or combined type with nasal blockage as a chief complaint	Sneezing and rhinorrhea type	Nasal blockage type or combined type with nasal blockage as a chief complaint
Treatment	a. Second-generation antihistamine b. (Mast cell) stabilizer c. Th2 cytokine inhibitor d. Nasal steroid	a. Second-generation antihistamine b. (Mast cell) stabilizer c. Nasal steroid	a. Anti-LTs agent b. Anti-PGD_2/TXA_2 agent c. Th2 cytokine inhibitor d. Second-generation antihistamine and vasoconstrictor combination e. Nasal steroid	Nasal steroid + second-generation antihistamine	Nasal steroid + anti-LTs agent or anti-PGD_2/TXA_2 agent or second-generation antihistamine and vasoconstrictor combination
	Choose one of (a), (b), (c) and (d)	Choose one of (a), (b) and (c) Combine (a) or (b) with (c), as needed	Choose one of (a), (b), (c), (d) and (e) Combine (a), (b) or (c) with (e), as needed		Use vasoconstrictor nasal spray for only 1-2 weeks at the start of treatment as needed
				Perform surgery for cases with nasal deformities of a nasal blockage type	
	Allergen-specific immunotherapy				
	Elimination and avoidance of antigen				

LT: leukotriene, PGD_2: prostaglandin D_2, TXA_2: thromboxane A_2

cases, nasal corticosteroids are used with second-generation antihistamines. Nasal blockage, one of the important symptoms in allergic rhinitis, is not attenuated by antihistamines, because leukotrienes and thromboxane A_2 predominantly contribute to the symptom. Therefore, in nasal blockage type or combined type with strong nasal blockage, leukotriene receptor antagonists and thromboxane A_2 receptor antagonists are useful for the symptom. Furthermore, vasoconstrictors are also very effective for nasal blockage.

Allergen-specific immunotherapy seems to be effective for the treatment of allergic rhinitis. Recently, allergen preparations (dust mite and Japanese cedar pollen) for sublingual immunotherapy have become available. Although the recommended treatment period is 3 to 5 years, reactivity against the allergen could be expected to be reduced by the immunotherapy. Elimination and avoidance of allergens are also important.

Conclusion

Allergic diseases are chronic inflammatory diseases with repeated exacerbation. Both genetic factors and environmental factors are involved in the development of the diseases. Although recent increase in the number of patients could depend mainly on the environmental factors, participating genetic factors may hinder the complete cure of the diseases. Corticosteroids are very effective for the treatment of allergic diseases and widely used. However, all treatment drugs for the diseases including corticosteroids are symptomatic. Therefore, it seems to be important to prevent the recurrence. To overcome the allergic disease, it should be considered to treat active allergic inflammation sufficiently by using effective drugs such as corticosteroids to lead to remission, and to keep the remission for a longer period by avoiding risk factors and maintaining basic care.

It is well known that corticosteroids exhibit variety of adverse effects under a prolonged usage. However, sufficient doses of corticosteroids should be used for controlling active allergic inflammation, and then the dose is reduced gradually and carefully. Repeated insufficient treatment with corticosteroids may increase the severity of the disease finally. Patients should consult with a specialist for allergic diseases.

In 2019, Japanese Guideline for the Diagnosis and Treatment of Allergic Diseases 2019 [4], a book covering updated guidelines for a variety of allergic diseases, was published. An updated pharmacotherapy could be expected to be available anywhere in Japan

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Communicated by Kiyoshi Yasukawa