
A REVIEW ARTICLE ON NOVEL IMMUNOPHARMACOLOGICAL DRUGS FOR THE TREATMENT OF ALLERGIC DISEASES

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ABSTRACT

Allergic diseases result from IgE-mediated immune responses to foreign protein (allergens). The majority of such reactions are IgE-mediated (type I) reactions. Individuals who develop such reactions are allergic. Those predisposed on a genetic basis to synthesize IgE to environmental allergens are atopic. Most allergic reactions are precipitated when a specific allergen aggregates several IgE molecules attached to IgE receptors on the surfaces of mast cells and basophils. Chemical mediators are released which lead to the immediate signs and symptoms associated with allergic diseases including hives, asthma, and anaphylaxis. More prolonged reactions follow if significant numbers of other cells including eosinophils, macrophages, and lymphocytes are drawn into sites of mast cell activation. Therefore, allergic diseases result from a complex interplay of immune cells, foreign proteins, and tissue inflammation. Allergy diseases, including asthma, allergic rhinitis, atopic dermatitis, and food allergies, impact millions worldwide and are often resistant to conventional treatments, leading to a pressing need for novel therapeutic strategies. Advances in immunopharmacology have led to the development of new drug classes that specifically target immune pathways involved in allergic responses.

Key Words- Allergic rhinitis, dermatitis, allergic conjunctivitis, cromolyn sodium, Corticosteroids, leukotriene inhibitors.

1. INTRODUCTION

The most common manifestations of allergic diseases are IgE-mediated hypersensitivity reactions which in the last decades have become a major health problem as already more than one quarter of the population in industrialized countries is affected and prevalence is further rising. Allergen sources include a wide variety of environmental substances such as pollen, house dust mites, animal dander, foods, drugs or insect venoms and the disease can manifest itself e.g. as rhinitis, conjunctivitis, chronic asthma, urticaria or even life-threatening anaphylaxis. Long before the availability of anti-allergic drugs, Leonard Noon demonstrated in 1911 that prophylactic inoculation with grass pollen extract was efficient in suppressing symptoms of hay fever. Since that time, allergen-specific immunotherapy (AIT) remains the only available curative treatment for allergic patients.

Nevertheless, in recent times, several novel approaches aiming at enhancing therapeutic efficacy and diagnostic accuracy have been developed. Moreover, the ongoing elucidation of immunological mechanisms of allergic sensitization, disease progression and tolerance induction to allergens will facilitate the development of new preventive and therapeutic strategies against allergy. Although AIT is a well-established disease-modulating treatment for IgE-mediated allergic diseases, the induction of immune tolerance is involving an area that is still not sufficiently understood. Allergen tolerance depends on multiple mechanisms across different immune cell and tissue compartments. Hence, it is likely that only combinations or ratios of gene expression levels are promising to achieve predictive value and definition of helpful biomarkers. Outstanding effective tolerance induction can be achieved by AIT of Hymenoptera venom-allergic patients. Describe how the classification of venom-allergic patients into different disease endotypes and phenotypes applying available biomarkers and diagnostic tools can provide therapeutic guidance and strengthen personalized treatment strategies and precision medicines.

Allergy and hypersensitivity are chronic non-communicable diseases related to environmental exposure and lifestyle. Based on 2019 global burden of disease data, the prevalence of asthma and atopic dermatitis (AD) is more than 260 and 170 million cases, respectively. The World Health Organization's International Classification of Diseases 11 dedicated pioneer sections to allergic and hypersensitivity disorders in the immune system chapter. Allergy and hypersensitivity comprise numerous disorders, including urticaria (hives), asthma, allergic rhinitis (AR; hay fever), (rhino)conjunctivitis, chronic rhino sinusitis with nasal polyps (CRN), AD (eczema), drug and food allergy, and anaphylaxis, which is an acute, life-threatening medical emergency. These disorders are an abnormal duration and/or intensity of type 2 (T₂) immune responses to a stimulus normally tolerated by non-affected individuals. Unresolved chronic high allergic inflammation (ALLINF) creates detrimental changes to the structure and function of the affected organs. ALLINF develops in response to non-infectious, often innocuous, environmental insults and involves a diverse

array of cells . Allergen crosslinking of adjacent immunoglobulin (Ig)E molecules bound to their high-affinity receptors on sensitized mast cells (MCs) and Basophils generates downstream activation signals . After MC activation, three distinct con-Seductive phases are typically observed. The early phase occurs within seconds to minutes and is characterized by the release of predominantly preformed mediators and newly synthesized arachidonic acid metabolites. The late phase takes place after a few hours and involves the migration and infiltration of eosinophils (Eos), macrophages, lymphocytes, and other immune cells to the site of MC activation.

2. DIFFERENT TYPES OF ALLERGIC DISEASES

- 2.1. allergic rhinitis
- 2.2. Food allergy
- 2.3. Hives
- 2.4. eczema
- 2.5. allergic conjunctivitis
- 2.6. insect sting allergy
- 2.7. allergic asthma
- 2.8. drug allergy
- 2.9. contact dermatitis

3. CAUSES OF ALLERGIC DISEASES

3.1. Genetic Predisposition: A family history of allergies or atopic conditions (e.g., asthma, eczema) increases the risk of developing allergic diseases. Variations in genes involved in immune regulation, such as those encoding cytokines, immunoglobulin E (IgE), and receptors, may contribute to susceptibility.

3.2. Immune Dysregulation: allergies are characterized by a skewed immune response, often involving an imbalance between Th1 and Th2 Helper T cells. Excessive activation of Th2 cells leads to the production of cytokines such as IL-4, IL-5, and IL-13, which promote IgE production and eosinophilic inflammation.

3.3. Allergens: Common environmental allergens include pollen, dust mites, animal dander, mold spores, and certain foods (like peanuts, shellfish, and milk).

4. TREATMENT FOR THE ALLERGIC DISEASES

4.1. Leukotrienes antagonist

Leukotriene antagonists are medications used to manage asthma and allergic rhinitis by blocking the action of leukotrienes, which are inflammatory chemicals in the body. Here are some common brand names

4.1.1. Montelukast : Brand Names: Singulair, Montair, Montek LC (in combination) Montelukast generally has a low potential for drug interactions, but there are a few notable interactions that healthcare providers consider:

Interactions

- Phenobarbital and Rifampin Interaction : These drugs are enzyme inducers and can reduce blood levels of montelukast, potentially lowering its effectiveness.
- Carbamazepine and Phenytoin Interaction: These anticonvulsants may increase the breakdown of montelukast, also potentially reducing its effectiveness.

4.1.2. Zafirlukast : Brand Name: Accolate

Dose: Adults and Adolescents (12 years and older): 20 mg taken orally twice daily.

Children (5 to 11 years old): 10 mg taken orally twice daily.

Interactions

- Warfarin Interaction: Zafirlukast can increase blood levels of warfarin, an anticoagulant, potentially raising the risk of bleeding. Close monitoring of the INR (International Normalized Ratio) is recommended when these drugs are used together.
- Aspirin Interaction: Aspirin can increase the blood levels of zafirlukast, potentially leading to a higher risk of side effects.

4.1.3. Pranlukast : Brand Name: Onon, Ultair

Interactions

- Theophylline Interaction: Pranlukast may interact with theophylline, a bronchodilator. Although this interaction is not typically severe, dose adjustments may be necessary if both drugs are used together for asthma management.

- Cyclosporine Interaction: Pranlukast may increase blood levels of cyclosporine, an immunosuppressant, possibly leading to toxicity. Cyclosporine levels should be closely monitored if used concurrently.

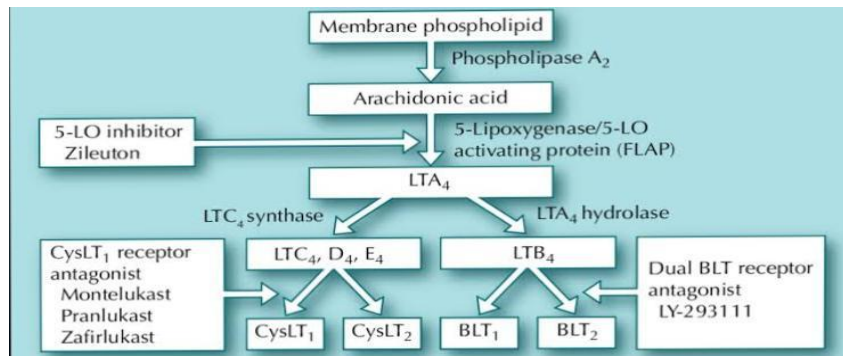


Fig 1 . Inhibition of leukotrienes synthesis

4.2. Antihistamines

Antihistamines (H1 blockers) These are the first-line treatments for hives, which help reduce itching and swelling:

Cetirizine (Zyrtec)

Loratadine (Claritin)

Fexofenadine (Allegra)

Diphenhydramine (Benadryl)

Chlorpheniramine (Chlor-Trimeton)

Hydroxyzine (Vistaril, Atarax)

Antihistamines are often used to relieve mild allergic symptoms. They block the action of histamine, a substance in the body that causes allergic symptoms. Common Antihistamines: Diphenhydramine (Benadryl): Effective for short-term relief of symptoms like hives, itching, and nasal congestion. Cetirizine (Zyrtec): Less sedating, used for allergic rhinitis and urticaria. Loratadine (Claritin): Non-sedating, suitable for long-term management of allergy symptoms.

4.3. Receptor-Mediated Mast Cell Activation

Most of the knowledge regarding mast cell Activation derives from studies on immuno-Globulin (Ig)E receptor-mediated anaphylaxis. These reactions are induced by IgE crosslinking Of the allergen because the high-affinity receptor for IgE (FcεRI) induces aggregation of the FcεRI receptors, which is followed by activation of the syk and lyn intracellular signaling Pathways, resulting in a potent mast cell activation The FcεRI is a molecular complex comprised of four subunits as well as an α-chain that Binds IgE, a β-chain, and a dimer of γ-chains (6) Intracellular signaling is mediated by β- and γ-Chains. FcεRI intracytoplasmic portion comprises Tyrosine and leucine residues representing an Immune recognition receptor tyrosine-based Activation motif (ITAM), which associates with Protein tyrosine kinases of the Src family, such As p53/p56lyn. These enzymes also allow the Phosphorylation of the ITAM motif of phospholipase γ1 through the recruitment of p72syk, Another protein tyrosine kinase. Activation of Phospholipase-γ induces the production of Secondary messengers like inositol 4, 5-triphos-Phate and diacylglycerol, which are responsible For the intracellular mobilization of Ca⁺⁺ and for Activation of phosphokinase C, respectively (7. All the hypotheses on mast cell activation In urticaria rely on these observations and Postulate that interaction of any ligand with Its receptor on the surface of a mast cell leads To patterns of cell activations.

4.4. Cromolyn sodium

Cromolyn sodium can help relieve hay fever symptoms by preventing the release of histamine. This medicine is most effective if you start using it before you have symptoms. Cromolyn is available as a nonprescription nasal spray to be used several times a day. It also is available in eye drop form with a prescription. Cromolyn doesn't have serious side effects. Cromolyn sodium is usually taken orally four times a day, or 15 to 20 minutes before meals if it's being used to prevent food allergies or treat inflammatory bowel disease. The dosage depends on your medical condition and how you respond to the treatment.

4.5. Leukotriene modifier

Montelukast (Singulair) is a prescription tablet taken to block the action of leukotrienes. Leukotrienes are immune system chemicals that cause allergy symptoms, such as irritation in the nose and making too much mucus. It's especially effective in treating allergy-induced asthma. It's often used when nasal sprays can't be tolerated or for mild asthma. Montelukast can cause headaches. In rare cases, it has been linked to psychological reactions such as insomnia, anxiety, depression and suicidal thinking. Get medical advice right away for any unusual psychological reaction.

4.6. Immunotherapy

Immunotherapy aims to desensitize the immune system to specific allergens. Types: Allergen Immunotherapy (Allergy Shots): Gradual exposure to increasing doses of allergens. Sublingual Immunotherapy: Dissolvable tablets placed under the tongue, used for certain allergies.

4.7. Epinephrine

Epinephrine is the first-line treatment for anaphylaxis, a severe and potentially life-threatening allergic reaction. Forms: Epinephrine Auto-Injectors (EpiPen, Auvi-Q): Pre-measured doses for self-administration during anaphylaxis.

4.8. Glucocorticosteroids

Topical Glucocorticosteroids are the first alternative for the Treatment of inflammatory skin in AD. In case of moderate AD, topical applications of corticosteroids two or three times In a week following the usage of emollients aids ineffective Treatment. The corticosteroids were categorized into a category I (mild) to group IV (super potent) by Niedner based on their potency. Super potent corticosteroids are not recommended to babies and children. The adrenal Gland functions are usually suppressed by group III (Potent) and group IV (super potent) than group I and group II corticosteroids, but their systemic effects will reduce rapidly due to immediate repair of the skin barrier [48]. Group I and II Corticosteroids would be used for the treatment of face Lesions, particularly the eyelid area. According to the US American classification, the corticosteroids are classified from Group VII (mild) to the group I (super potent). The long term Use of Glucocorticosteroids produces numerous adverse Effects include skin atrophy, spontaneous scars, ecchymosis, Stretch marks, dirty neck, hypertrichosis and perioral dermatitis.

4.9. Decongestants

Decongestants reduce nasal stuffiness and pressure from swelling. Because they do not relieve other symptoms of hay fever, they're sometimes combined with other medicines such as antihistamines. Decongestants are available as liquids, tablets and nasal sprays. They also are available with and without a prescription. Oral decongestants include pseudoephedrine (Sudafed). Nasal decongestant sprays include phenylephrine hydrochloride (Neo-Synephrine) and oxymetazoline (Afrin). Oral decongestants can cause a few side effects, including increased blood pressure, insomnia, irritability and headache. Decongestants may cause problems urinating if you have an enlarged prostate. Check with a healthcare professional before taking decongestants if you have high blood pressure or heart disease or if you're pregnant. Don't use a decongestant nasal spray for more than 2 to 3 days at a time because it can worsen symptoms when used continuously. This is known as rebound congestion.

4.10. Venom therapy

Venom therapy, or venom immunotherapy, is generally used for people who are allergic to insect stings (like bees, wasps, or hornets) to build immunity and reduce the risk of severe allergic reactions. However, for most insect stings without an allergy component, venom therapy isn't typically needed. For general insect stings, here are some practical steps to manage pain, swelling, and discomfort: Clean the Area: Gently wash with soap and water to prevent infection. Ice: Apply an ice pack for 10-15 minutes at a time to reduce swelling and pain. Pain Relief: Over-the-counter pain relievers, like ibuprofen, can help manage pain and inflammation.

5. CONCLUSION

Allergic diseases, including asthma, allergic rhinitis, atopic dermatitis, and food allergies, remain pervasive and challenging health concerns globally. Traditional approaches to managing these conditions, primarily through antihistamines, corticosteroids, and symptomatic relief methods, have proven beneficial but fall short of offering sustained relief or cure, especially for patients with severe or treatment-resistant forms. This limitation, combined with a growing understanding of immunology, has driven research into novel immunopharmacological therapies targeting the immune pathways that underpin these allergic responses. Recent advances have focused on precise molecular targets to inhibit the pathways responsible for allergic inflammation and hypersensitivity. These include monoclonal antibodies targeting IgE, interleukins (IL-4, IL-5, IL-13, IL-31), and tumor necrosis factors (TNFs) among others. Omalizumab, for example, was one of the earliest biologics to gain prominence by blocking IgE, and it remains a cornerstone for treating moderate to severe asthma. Other monoclonal antibodies, such as dupilumab, have made significant impacts on diseases like atopic dermatitis and asthma by targeting IL-4 and IL-13 pathways. These biologics represent a new generation of targeted therapies that provide more effective, sustained, and safer options than traditional drugs.

The Introduction of biologics, however, comes with its own set of challenges. One notable limitation is the high cost associated with these therapies, which restricts access for many patients. Additionally, biologics can lead to side effects, such as injection site reactions and the risk of infection, due to immune suppression. Moreover, while biologics offer promising results, they are not curative; they suppress the immune response but do not address the root cause of allergic

disease, which often includes genetic and environmental factors. In parallel, research has explored small molecules and peptides that can modulate immune signaling with increased specificity and fewer side effects. Janus kinase (JAK) inhibitors, for instance, are showing potential for treating inflammatory and allergic conditions by interfering with signal transduction pathways central to cytokine activity.

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