

Recent Advances in the treatment of Allergic Rhinitis

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ABSTRACT

Allergic Rhinitis is a very common disease and many people suffer from it, but it has never had any full-scaled treatment method up until the last few years. In light of this, this Review will cover several different treatment methods of AR and how they have varied over time along with the latest developments in this area (1). There are many pharmacological methods used to treat the disease such as antihistamines, which are usually the first line of treatment. Other sources of treatment include Anti-IgE therapies, Intranasal steroids, Leukotriene Receptor Antagonists, Immunotherapy and Biologics. This paper reviews evidence from the past and more recent articles to make a literature review that helps distinguish between different treatment methods and explains how each method helps treat AR.

Introduction

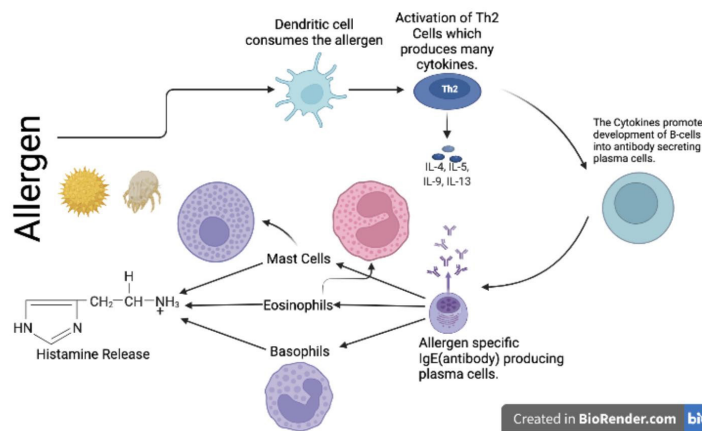
Allergic Rhinitis (AR) is defined as an immunoglobulin E(IgE)–mediated inflammatory response of the nasal mucous membranes after exposure to inhaled allergens, characterized by rhinorrhea (anterior or postnasal drip), nasal congestion, nasal itching, and sneezing (2). AR is the most common atopic disease in the world that affects 400 million people globally. It is increasing in prevalence and it affects both adults and children, however it is more prevalent in children. It is more common in boys than girls and a person is diagnosed with the disease 80% of the time before the age of 20 (3).

Some risk factors for the disease are a family background history of asthma and genetics. Environmental factors such as exposure to pollutants and climate change can also increase the likelihood of having allergic rhinitis. Outdoor allergens such as dust mites, cockroaches, pets, weeds and smoke are usually associated with AR.

The actual Pathophysiology of Allergic Rhinitis is as such: Firstly an allergen is taken up by a dendritic cell which leads to the activation of the Th2 cell. The Th2 cell produces many inflammatory cytokines such as IL-4, IL-5, and IL-13 and is very important in fighting extracellular pathogens. These promote the development of B-cells into plasma cells that produce IgE antibodies. These antibodies bind to mast cells, basophils, and eosinophils which then produce another inflammatory signaling molecule called histamine. Histamines have a role in removing allergens from the body and they do this in many ways. These ways represent the AR symptoms experienced by patients such as sneezing and itching (1).

This review paper aims to show how different treatment methods approach this disease with different mechanisms and treat AR. In order to accomplish this aim. The following treatment methods are reviewed: Allergen avoidance and pharmacotherapy. Pharmacotherapy is clinical where-as allergen avoidance is non-clinical so pharmacotherapy is explored in more detail. Also, pharmacotherapy comprises more recent treatment than allergen avoidance as avoidance is just an old precautionary measure to prevent AR from happening.

Figure 1



This figure simply explains the step-by-step process that starts from the allergen and leads to a histamine release

Allergen Avoidance

Allergen avoidance is a precautionary measure and it helps to remove allergens and thus the associated symptoms. However, complete avoidance of the most common allergens, such as dust mites and fungi, is not always possible and can result in breakthrough symptoms. This is why there is a great need for pharmacotherapies that can help reduce inflammation associated with AR and treat the disease (4).

Pharmacotherapy

Pharmacotherapy is a more modern treatment method for AR. It consists of a broad range of different treatment methods like antihistamine drugs and intranasal steroids. Newer immunotherapy and biologics are also now approved for the treatment of AR.

Antihistamines

These are commonly used as the first line of treatment as they provide rapid relief from histamine-induced symptoms such as sneezing, itching, and having a runny nose. "There are two generations of antihistamines (first and second generation)". Overall, they are more effective if used repeatedly rather than intermittently. Antihistamines are drugs that block and work against histamines. First - Generation Antihistamines, however, cross the blood-brain barrier while working on the brain's histamine receptor which leads to drowsiness (5). Only second-generation antihistamines should be used for symptom relief as they penetrate less into the brain therefore the patient is less in danger of its side

effects and it also has negligible anticholinergic effects. One famous example of a non-drowsy antihistamine is fexofenadine. Some common side effects of all types of antihistamines are headache, tiredness, nausea, dizziness, and drowsiness (6).

Intranasal Steroids

Intranasal Steroids (INS) are sprays that are used for improving nasal obstruction and conjunctival symptoms. They are very effective in reducing nasal inflammation. They are the primary treatment for nasal blocking and they do this by reducing cytokine production by cells in the nasal passages and thereby reducing eosinophil recruitment (Eosinophil cells are multi-functional cells that are linked with allergic reactions) (7). Pre-treatment with INS shows significant inhibition of basophils, eosinophils, and neutrophils to nasal secretions thereby reducing the effect of AR. There are very few side effects, mainly drying and bleeding of the nose. Some commonly used types of nasal sprays are mometasone and fluticasone (7,8).

Leukotriene Receptor Antagonists

“Leukotrienes are made by mast cells following allergen challenges and are then released into the nose to produce allergic inflammation” (9). The role of the Leukotriene receptor antagonists is to inhibit the production of leukotrienes thereby reducing allergic inflammation. The Leukotriene receptor antagonists like Montelukast/Zafirlukast reduce symptoms of AR (10). It is not recommended for first-line and is mostly used as second-line treatment because it is mostly used for moderate-severe cases only (11). Leukotriene Receptor Agonists also decrease the recruitment of eosinophils and thereby reduce allergic inflammation (10).

Immunotherapy

“Allergen immunotherapy is a form of therapy that has been modified over time based on new developments.” Immunotherapy is a method that helps your body learn to tolerate allergens by receiving repeated sets of doses of a small amount of the allergen. Over time the immune system will stop giving a reaction to the allergen (12). It decreases the recruitment of mast cells, basophils, and eosinophils in the skin, nose, eyes, and bronchial mucosa which helps block both the basic and severe allergic responses. A basic allergic response would be sneezing, headache, nausea, or itching whereas a more severe allergic response would be anaphylaxis (13).

One way that immunotherapies can help relieve symptoms is to help a patient achieve immune tolerance to allergens. Immunotherapies that inject small doses of a particular allergen in increasing amounts over time may help achieve immunologic tolerance to the specific allergen.

There are two phases of immunotherapy, namely the build-up phase and the maintenance phase. In the build-up phase, the patient receives the injections over the course of three-six months in increasing doses. In the maintenance phase, once the effective dose has been reached (based on the patient’s allergic sensitivity and response to the build-up phase), this dose is administered over longer periods of time determined by the immunologist (14). This has been effective for AR specific to pollens and dust mites for example however is not as effective for indoor/outdoor molds and animal dander (13).

SCIT and SLIT

Subcutaneous immunotherapy (SCIT) is currently the most commonly used method of administering immunotherapy. Sublingual Immunotherapy (SLIT) is similar to SCIT but is administered sublingually, therefore no injection is required

(15). SLIT is not FDA approved (in the United States) and is slowly increasing in popularity (15). However, as of right now the only forms approved by the FDA are for ragweed, northern pasture grasses like timothy, and dust mites.

SLIT therapies are placed under the tongue for 1-2 minutes and then swallowed once dissolved. This can be repeated anywhere from three days a week to daily as advised by the immunologist (14).

Over time immunologic tolerance will develop. The treatment is typically continued for 2-3 years in order to be fully effective. Although SCIT is considered to be a safe and causal form of treatment for IgE mediated diseases it still has side-effects. The most common of these is redness at the site of the injection whereas both SLIT and SCIT also have others such as: sneezing, watery eyes, nasal congestion, hives and rashes. However there are rare cases where, mostly within the first 30 minutes of the injection being administered, a patient may have a serious reaction to the allergy shots such as anaphylaxis. As a precautionary measure, a patient is not permitted to leave the premises for 30 minutes after receiving treatment (14,16).

Biologics

Biologics includes newer drugs that are being used for patients with severe uncontrollable or long-lasting AR. These patients are usually known to have long-term issues with inflammation within the nose and sinuses.

The three biologics that are most commonly used for AR are omalizumab (targets the IgE receptor), dupilumab (targets the IL-4 receptor), and mepolizumab (which is one of three biologics that target the IL-5 receptor) (17). Overall, Omalizumab, Mepolizumab and Dupilumab are thought to be safe forms of treatment. However in a few cases, patients experience significant side effects, the most common being burning, hives, pain, swelling, redness at the site of the injection and also headache. Some people also experience fever and joint pains due to reaction of the body to the protein content in these medicines (18).

Omalizumab

Omalizumab (Xolair) is a monoclonal antibody directed against the high-affinity receptor binding domain of IgE (19). “Omalizumab forms complexes with free IgE, blocking its interaction with mast cells and basophils and lowering free IgE levels in the circulation” (20).

Omalizumab was originally developed for the treatment of allergic asthma and was FDA approved for this. However, it has been investigated in trials for managing AR and recently received FDA approval in moderate to severe cases of AR. A study found that it had several beneficial effects in patients with AR, including a reduction in daily complaints and rescue medication usage, as well as a reduction in nasal allergen challenge responses. It also improved quality of life and reduced missed school or work days (19).

Dupilumab

Dupilumab, delivered as a subcutaneous injection, is a human monoclonal antibody of the IgG4 subclass that targets the IL-4R α subunit and disrupts IL-4 and IL-13 signaling of which both are major effectors of type-2 diseases such as AR (17,21). The implementation of Dupilumab helps block both cytokines and thereby helps reduce inflammation of AR. Dupilumab has been recently FDA approved for CRSwNP (chronic rhinosinusitis with nasal polyps) based on its efficacy as compared to intranasal steroids. However, in the case of AR, dupilumab is only used for perennial AR (17,21).

Mepolizumab

Mepolizumab is delivered subcutaneously or intravenously, and is a human monoclonal (IgG1) antibody targeting interleukin 5 (IL-5) or the IL-5 receptor α subunit on the surface of eosinophil white blood cells (17,21). IL-5 increases eosinophil counts within the body, therefore inhibiting IL-5 helps reduce this count which helps to manage AR. Mepolizumab is also FDA approved for CRSwNP.

Conclusion

AR is a disease that millions of people suffer from and places a great burden on medical institutions around the world. This review summarizes the impact that each of the major forms of treatments have on AR and how modern treatments have adapted to treat AR in ways that are more efficient and productive. Overall the goal of this review was to identify all the different treatment methods and explain how they treat AR.

There are some forms of treatment that have been used over the years to manage and reduce the severity of symptoms in patients. Avoidance is the oldest non-clinical approach to minimize the effects of AR. Pharmacotherapies are the major form of management. Within this the first-line of treatment are antihistamines (second-generation) and intranasal steroids which are effective for minor cases of AR. The second-line are the Leukotriene Receptor Antagonists which help reduce symptoms of AR. Lastly, the most recent forms of treatment found to be most effective for the treatment of this disease are immunotherapy and biologics. Immunotherapy can be administered via either SCIT or SLIT which help decrease the recruitment of mast cells, basophils and eosinophils in the skin, nose, and eyes and bronchial mucosa. Biologics on the other hand are injections that inhibit certain inflammatory mediators such as IgE, IL-5 and IL-4. Each biologic therapy has benefits; however they are very costly and are limited by the fact that there is very little FDA approval as of now, which means that Biologics are still relatively new and need time to be used in full force. Biologics and Immunotherapy are commonly used in combination with 1st and 2nd line treatments such as antihistamines and leukotriene-receptor antagonists by immunologists while treating patients as this takes care of the short-term symptoms and also provides a long-term solution to the disease. Overall, AR is one of the most common atopic diseases and is a big burden on both a patient and the government which is why the recent advances in treatment for this disease are so important.

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