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ALLERGIC RHINITIS: CURRENT AND FUTURE TREATMENT OPTIONS

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ABSTRACT

Allergic rhinitis is an inflammation of nasal mucosa occurring in previously sensitized people after exposure to an offending allergen due to specific IgE antibody production. The main symptoms involve nasal obstruction, rhinorrhea, sneezing and itching. Moreover, allergic rhinitis has a significant impact on a person's quality of life, affecting physical, emotional and social well-being. The pathophysiology of allergic rhinitis is complicated and involves numerous changes within the immune system, including activation and differentiation of various immune cells, degranulation of basophils and mast cells, production of IgE antibodies, cytokines and chemokines, immune cell migration into the site of allergic inflammation. Various treatment options, such as topical glucocorticoids, oral or topical antihistamines, oral leukotriene receptor antagonists, mast cell membrane stabilizers, decongestants, as well as allergen specific immunotherapy and monoclonal anti-IgE antibody are currently available and even more methods are under investigation.

The purpose of this article is to review epidemiology, clinical significance, pathophysiology and current and future treatment options for the allergic rhinitis.

Keywords: Allergic rhinitis, immunologic desensitization, treatment

INTRODUCTION

Allergic rhinitis (AR) is an inflammation of nasal mucosa occurring in previously sensitized people after exposure to an offending allergen due to specific IgE antibody production. The main symptoms involve nasal obstruction, rhinorrhea, sneezing and itching. In addition, the disease has an important impact on patients' daily lives. The prevalence of AR varies throughout the world, although the considerable increase was observed in last decades (1).

Different treatment methods for AR are currently available including environmental control measures and allergen avoidance, pharmacotherapy, immunotherapy, and new treatment options are actively being investigated. In this article, epidemiology clinical significance, pathophysiology and current and future treatment options for allergic rhinitis will be reviewed.

EPIDEMIOLOGY

The prevalence of allergic rhinitis (AR) varies throughout the world, although the considerable increase was observed in last decades. It is estimated that approximately 60 million people are suffering from AR in the US and the prevalence varies between 10-30% in adults and nearly 40% in children (1, 2). There are few large-scale standardised studies on the prevalence of AR in Europe. The European Community Respiratory Health Survey (ECRHS) conducted between 1990 and 2000 showed that the overall prevalence of AR in an adult population was 21% (3, 4). In 2001 a two-step, cross-sectional, population-based survey was performed in Belgium, France, Germany, Italy, Spain and the UK to estimate the overall prevalence of AR. The results revealed that 22% of population, corresponding to 53 million people, suffer from AR (4).

CLINICAL SIGNIFICANCE

Approximately 62% of patients with AR reveal that the disease has a significant impact on their daily life

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(2). It is partly due to chronic nasal obstruction that affects patient's physical, emotional, and social well-being eliciting daytime sleepiness, fatigue, headaches, mood changes, depression, anxiety and poorer work and school performance and partly due to direct effects of inflammatory mediators like histamine that regulates sleep-wake cycle by prolonging wakefulness and preventing sleep (2, 5).

Olfactory dysfunction is another problem caused by AR that affects patients' quality of life due to diminishing sense of taste and smell, problems related to social competence, and especially due to increased risk of food poisoning. Both mechanical blockage and inflammatory component are likely causes of the dysfunction (6). The presence of olfactory dysfunction seems to correlate with the severity of the AR; furthermore, its frequency increases with the duration of the disorder (7).

Due to similar epidemiological, immunological, clinical, pathophysiological data and common therapeutic approach, AR is firmly associated with asthma (8). The "united airway disease hypothesis" postulates that upper and lower airway diseases are linked together as a manifestation of a single inflammatory process. Several mechanisms, including protective role of nasal mucosa on entire respiratory tract, neural interaction between upper and lower airways and irritating/inflammatory effects of nasal and paranasal secretions on lower airways, as well as expansion of local nasal inflammation into lower airways have been proposed to explain the association (9).

PATHOPHYSIOLOGY

Allergic Rhinitis manifests itself after exposure to allergic stimuli. Although being constantly subjected to environmental allergens, AR occurs only in those people who have a genetic predisposition to develop allergies. In these individuals, repeated contact with aeroallergens induces B cell activation and maturation into plasma cells with a subsequent production of specific IgE antibodies (2).

During the sensitization process, an aeroallergen is engulfed and partially degraded into peptides by macrophages and other antigen-presenting cells (APCs) that reside in the nasal mucosa. These peptides are afterwards expressed on the surfaces of APCs and are presented to naive CD4+ T lymphocytes (Th0) (1). Upon receiving the adequate stimulus these cells differentiate into the T-helper type 2 (Th2) cells that are crucial for the development of allergic reactions. Ensuing interaction between Th2 cells and B-lymphocytes leads to the differentiation of B-lymphocytes into IgE producing plasma cells. This process requires presence of Th2 secreting cytokines IL-4 and IL-13, as well as costimulatory molecules (1, 8). The newly secreted antigen-specific IgE molecules bind to specific IgE receptors: high-affinity FcεRI receptors found on basophils and mast cells, thus sensitizing the nasal mucosa. Upon subsequent exposure to the offending allergen, these IgE antibodies serve as receptors for the antigen molecules (8).

Within minutes after exposure of a sensitized patient to the allergen, a symptomatic response called an immediate reaction occurs (1). It is induced by rapid release of mediators that have been previously formed and stored within a cell, such as histamine and tryptase, and swift synthesis and secretion of cysteinyl leukotrienes (CysLTs) (leukotrienes C4, D4, and E4) and prostaglandin D2 (PGD2). These mediators lead to dilatation and increase blood vessel permeability, with consequent oedema, blood accumulation in the cavernous sinusoids and occlusion of the nasal passages. Nasal congestion mainly induced by leukotrienes and PGD2 is enhanced due to increased mucus secretion from glandular and goblet cells, whereas rhinorrhea, itching and sneezing are principally caused by histamine (1, 10).

The late-phase reaction takes up to 8–12 hours to establish. It is caused by the release of newly synthesized mediators, such as leukotrienes, chemokines and cytokines from the activated mast cells (1, 10). Mediators and cytokines released during the early response promote the expression of various adhesion molecules to improve adherence of circulating eosinophils to postcapillary endothelial cells. These molecules include vascular cell adhesion molecule 1 (VCAM-1), intercellular adhesion molecule 1 and E-selectin, whereas factors with chemoattractant properties promote the infiltration of the nasal mucosa with basophils and eosinophils, as well as neutrophils, and finally Th2 cells and macrophages (10). Mediators released during the late-phase reaction muster further mobilization of eosinophils and Th2 cells into the site of inflammation with subsequent activation of these cells (1, 10). Once activated these cells secrete more mediators capable to activate anew many immediate response reactions (10).

TREATMENT

The treatment is directed to diminish and prevent chronic allergic inflammation in the nasal mucosa, as well as improve patients' quality of life (8). The management consists of 3 main methods: environmental control measures and allergen avoidance, pharmacotherapy, immunotherapy (1).

Environmental control measures and allergen avoidance:

Due to the fact that AR does not occur in the absence of the inducing allergen, it is logical to assume that the first-line treatment of AR involves the avoidance of relevant allergens and irritants. Thus the identification of the responsible allergen is of great importance. However, no clinical trials have shown conclusive evidence of clinical benefit from avoidance measures. Nonetheless, most doctors still suggest allergen avoidance as the first treatment option (2, 11). When allergen avoidance is suggested, the combination of multiple preventive methods is the most effective option (1, 11).

Pharmacotherapy:

Since intranasal glucocorticosteroids (GCs) are the most effective therapeutic agents for AR, they are recommended as the first-line treatment option alone or in combination with other drugs (11). When used regularly and correctly, they effectively reduce inflammation of the nasal mucosa resulting in reduction of sneezing, nasal itching, rhinorrhea and especially nasal congestion (8). When moderate to severe nasal and/or ocular symptoms that are not controlled with other treatments are present, short courses of oral GCs might be considered, however systemic GCs do not appertain to the first-line treatment (11).

Since H1-antihistamines possess antiallergic and anti-inflammatory properties that clinically result in the reduction of nasal itch and rhinorrhea, they are used as the first-line therapeutic agents along with GCs. Antihistamines based on their function and adverse effects are classified into first and second generation (1, 8). However, efficient, cost-effective and broadly available, the first generation antihistamines are discouraged in favour of the second generation oral H1-antihistamines due to their ability to penetrate blood-brain barrier and subsequently induce sedation (8). H1-antihistamines are available in intranasal form as well, but since there are no clinical trials comparing effectiveness between intranasal and oral H1-antihistamines, the use of new generation oral H1-antihistamines is advised over intranasal form (11).

A lot of attention has been recently paid to effectiveness of leukotriene receptor antagonists (LTRAs) in AR. Previous clinical trials showed that LTRAs are better than placebo, but not as effective as intranasal GCs in relieving symptoms and improving quality of life in patients with AR (12). Moreover, it has been confirmed that compared to H1-antihistamine and GCs, LTRAs cause the most significant reduction of ocular, nose, throat and palate itching (13). A recently published systematic review preliminary concluded that the combined therapy of nasal GCs and LTRA is more effective than nasal GCs alone in the management of AR, however further clinical trials to assess the clinical benefit of the polytherapy are still required (14).

Intranasal cromolyn sodium, a mast cell membrane stabilizer, might be used to prevent occurrence of AR symptoms due to its inhibitory effect on mast cell degranulation, poor systemic absorption and good tolerability (11). Due to short half-life, the drug must be administered up to 4 times a day before the onset of symptoms, since no clinical improvement happens once they appear (2).

Intranasal decongestants can be used as add-on rescue medications for the relief of nasal congestion for up to five days, due to the fact that prolonged use is associated with rhinitis medicamentosa (11).

Immunotherapy:

A long-term symptom relief can be achieved with allergen specific immunotherapy (ASIT) that involves repeated administration of the relevant allergen extracts to induce immunologic tolerance. The main indication is the persistence of symptoms despite allergen avoidance and adequate management. Additionally it might be offered to those who are unable to tolerate pharmacotherapy (15). The action of ASIT is based on its ability to change the phenotype of Th2 cells that are responsible for the production of IL-4, IL-5, IL-13, IL-17 and IL-32 cytokines in case of allergy, into Th1 type response with an increased IFN-γ and IL-2 production. This change is achieved by the production of allergen-specific T regulatory (T-reg) cells that generate cytokines with immunosuppressant and/or immunoregulatory activity (IL-

10 and TGF-β). Moreover, ASIT influences dendritic cells located in the oral mucosa, which are important in the induction of antigen tolerance. The aim of the ASIT is to switch antibody synthesis from antigen specific IgE to IgG, especially to IgG4 and suppress activity of inflammatory cells. A systemic review of subcutaneous immunotherapy (SCIT) and recently updated review of sublingual immunotherapy (SLIT) for AR shows significant reduction in symptoms and medication requirements compared with placebo treatment in adults and in children (16, 17). Although numerous studies are conducted, it is not yet clear whether SCIT and SLIT are of equivalent efficacy (15). An indirect and a direct comparison of clinical efficacy of SCIT and SLIT have been performed. In case of the indirect comparison, the reduction in symptoms or medication use with SCIT or SLIT was compared with that of placebo. Both reviews show greater clinical benefit for SCIT, however, in the studies used for the comparison SLIT was often administered in low doses and the regimen was irregular, whereas it is known that daily SLIT is more effective. Therefore, the clinical efficacy of SCIT and SLIT remains to be defined (18, 19).

A new treatment option for AR is omalizumab – a monoclonal anti-IgE antibody that targets the Cε3 domain of IgE at the site of its binding to basophils and mast cells, thus preventing degranulation of these cells and the consequent onset of AR symptoms (8). In the trials conducted to evaluate the efficacy of omalizumab, it was concluded that omalizumab significantly reduces nasal symptoms, decreases IgE levels and the use of rescue medication (1, 8). Coadministration of omalizumab with ASIT resulted in reduction of symptoms only during the treatment period, however, it was noted that those patients who were formerly treated with the combination therapy had a modest increase in lung function (FEV1), showing a necessity for further evaluation of long-term effects of omalizumab (20). Despite clinical benefits in those using omalizumab, the high cost and potential to cause anaphylaxis precludes its wide use for the treatment of AR (8).

Future treatment options:

The recent discovery of the histamine H4 receptor on mast cells, basophils and eosinophils and its role in expression of adhesion molecules and augmentation of chemotaxis of eosinophils and mast cells into the site of allergic inflammation provides a new possibility for the therapy of AR (8). Studies on the efficacy of selective H4 receptor antagonist on animals show that due to the decreased airway inflammation, it significantly reduces nasal symptoms; supresses cough and inhibits airway reactivity to histamine (21, 22). Moreover, the reduction of the total IgE level in serum and levels of IL-4 testifies to its importance in the pathogenesis of AR (22, 23). Since PGD2, released after allergen stimulation mainly by mast cells, as well as lymphocytes and dendritic cells, has the ability to initiate acute allergic reaction, the inhibition of PGD2 binding to DP1 and CRTH2/DP2 receptors is being assessed for the treatment of AR. During allergen sensitization process, the activation of DP1 inhibits IL-12 production by dendritic cells, thus inducing the differentiation of Th0 cells to Th2 (8). Moreover, DP1 mediates vasodilatation with a subsequent nasal congestion (24). Meanwhile, CRTH2 expressed on eosinophils, basophils, Th2 cells and monocytes stimulates intracellular Ca2+ mobilization, chemotaxis of these cells during the late-phase reaction and production of TH2 cytokines and IgE (8).

Highly selective phosphodiesterase 4 (PDE4) inhibitors mainly investigated for the treatment of chronic obstructive pulmonary disease have been evaluated in cases of allergic conditions as well. Roflumilast showed efficacy in controlling AR symptoms in comparison with placebo, thus providing a future treatment option for AR (25). PDE4 is the main cyclic adenosine monophosphate (cAMP) degrading enzyme in many inflammatory cells (8). Elevation of cAMP due to PDE4 inhibitors results with suppression of chemotaxis due to reduced production of cytokines and chemokines by inflammatory cells and reduced expression of adhesion molecules (26).

Bradykinin is a bioactive peptide involved in pathophysiology of allergic conditions by activating endothelial B1 and B2 receptors that subsequently induce vasodilatation, increase vascular permeability, resulting in oedema and promote tissue infiltration with leukocytes. Additionally, bradykinin possesses potent bronchoconstrictory action and stimulates production of other mediators maintaining allergic inflammation. Since the B2 receptors are constitutively expressed on cells and activation of these receptors results in rapid response, it is believed that acute reactions are induced by them, thus development of a B2 receptor antagonist seems to be an option for AR treatment (27). A study by Turner et al (28) showed that pre-treatment with B2 receptor antagonist did not reduce nasal obstruction; however, it decreased nasal hyperresponsiveness to allergen and nasal eosinophilia.

p38 protein kinase, a member of one of the four mitogen-activated protein (MAP) kinase subgroups, plays an essential role in the development and maintenance of inflammation due to its ability to enhance synthesis of proinflammatory cytokines and chemokines (IL-1, TNF-α and IL-6) and expression of adhesion molecules such as VCAM-1, induce synthesis of intracellular enzymes such as iNOS, a modulator of oxidation process and at least partially regulate expression of cyclooxygenase-2, an enzyme responsible for the connective tissue remodelling. In addition, p38 protein kinase is able to regulate proliferation and differentiation of immune cells (8). Due to the aforementioned, p38 protein kinase inhibitors are being investigated as potential drugs for inflammatory disorders.

Production and actions of pro-inflammatory cytokines are vital in inflammatory processes, therefore inhibition of cytokines such as TNF-α, IL-1, IL-4, IL-5, IL-8, IL-9, IL-13 seems to be a plausible approach to treat AR (8, 29).

A proteolytic enzyme from the chymotrypsin-like family of serine proteases, human neutrophil elastase (HNE) is released from primary granules of neutrophils and binds to a specific receptor on neutrophils and macrophages. It contributes to neutrophil infiltration, aggregation, adhesion and migration into the site of inflammation, regulates the production of cytokine at the membrane of epithelial and endothelial cells, promotes generation of IL-6, IL-8, TGF-β and GM-CSF, whilst inducing degradation of IL-1, IL-2 and TNF-α (8, 30). The inhibition of this enzyme has shown a potent anti-inflammatory effect in preclinical models of lung, bowel and skin inflammation (31).

Very late antigen-4 (VLA-4) is an integrin found on the surface of eosinophils, lymphocytes, and monocytes, and during the migration of these cells into the site of inflammation functions as VCAM-1 receptor (8). In vivo studies have shown that administration of a VLA-4 antagonist inhibits eosinophil infiltration, late phase allergic reactions and airway hyperresponsiveness demonstrating its potential in the treatment of AR (32-34).

Tryptase-β is a trypsin-like serine protease mainly expressed in mast cells and to a lesser extent in basophils and serves as a marker of mast cell activation. During degranulation, it is released from the mast cell granules and contributes to the pathogenesis of inflammation. Therefore the inhibition of tryptase-β is of interest for the treatment of AR (8). A study by Rice et al. (35) showed that inhibitors of tryptase abolish bronchoconstriction that is seen in the late phase allergic reaction and hyperresponsiveness of the airway in a dose-dependent manner. Another study evaluating efficacy of a reversible tryptase-β and trypsin inhibitor on male patients demonstrated similar results (36).

Aldose reductase is a broadly expressed enzyme involved in the metabolization of aldehydes and is associated with the development of secondary diabetic complications (37). Moreover, recent studies demonstrate that aldose reductase also plays an important role in inflammatory processes. Aldose reductase in response to multiple stimuli causes activation of transcription factor NF-κB that induces production of various inflammatory cytokines, growth factors and chemokines (38). Numerous studies demonstrate that administration of aldose reductase reduces airway hyperresponsiveness, IgE levels, eosinophil infiltration, and release of TH2 type cytokines in the airway, as well as prevents airway remodelling (39-42).

Functions of many cells, including mast cells, depend on the transmembrane potential that is regulated by ion channels (8). Degranulation of mast cells and subsequent release of preformed and newly produced mediators require the influx of extracellular Ca2+. Besides Ca2+ channels, mast cells have K+, Cl- and transient receptor potential channels. All these channels participate in the regulation of cell membrane potential, modulating mast cell activity. Due to their role on the function of mast cells, ion channels have become an attractive approach for the treatment of AR (43).

Toll-like receptors (TLRs) belong to a family of pattern recognition receptors which recognize common patterns expressed by the invading pathogens and coordinate subsequent immune responses. TLRs function as the first line of defence against invading pathogens as well as aeroallergens and have two opposed roles in allergic conditions. Some of TLRs induce sensitization to a specific allergen and, thus break the tolerance, whereas activation of other TLRs, especially in childhood and early adolescence, by the contrary, enhance tolerance to aeroallergens. Moreover, TLRs are essential in the development of effective and healthy adaptive immunity with mature T-reg cells and predominance of Th1 over Th2 cells, therefore TLRs have become interesting targets to modulate pathophysiology of allergy. Numerous studies have been performed to evaluate the role of TLR modulators in allergic diseases. These studies revealed efficacy in the relief of AR symptoms, suppression of airway inflammation, eosinophilia and airway hyperresponsiveness in animal models (44). Up to this date,

two TLR agonist-containing vaccines have been evaluated in clinical trials. The results show that preseasonal injection is safe and results in reduction of nasal symptoms in patients with AR. More TLRs agonists are in the development process (45).

Intralymphatic immunotherapy (ILIT) is a newer form of ASIT that is being actively evaluated. Although effective, SCIT and SLIT require numerous allergen administrations during period of 3 to 5 years to achieve clinical improvement, whereas ILIT with lower allergen doses and markedly reduced numbers of injections may provide faster amelioration of symptoms, thus making it an attractive form of ASIT (46, 47). Various studies have been performed to evaluate the efficacy and safety of ILIT. These studies concluded that intralymphatic administration is practically painless and effective in reduction of AR symptoms, although in one trial where grass pollen extract was administered, only immunological changes were detected without clinical benefit (47-49). Notably, no severe adverse effect was observed (47-50). Several of these studies showed efficacy after 3 injections, significantly reducing duration of therapy and improving patient compliance compared with SCIT and SLIT (47, 48, 50). As so far clinical trials have assessed the efficacy of ILIT in cases of allergy to grass pollen and bee venom, further investigations are necessary to evaluate clinical benefit of ILIT for other frequent aeroallergens (47).

T cell epitope peptide based immunotherapy (PIT) consists of peptides that contain T cell epitope from an allergen (8). These peptides possess all the immunogenic and antigenic properties as whole antigens, but the appeal of PIT lies in the fact that it causes less adverse events compared to ASIT. This is explained by the fact that these peptides have reduced ability to bind to IgE on mast cells and basophils, thus activation and degranulation of these cells is prevented (8, 51). Studies suggest that PIT reduces specific and serum total IgE level, increases TH1 response, while significantly reduces TH2-associated antibody and cytokine responses, induces T-reg cell response, and reduces IL-5, IL-13 level and eosinophilia in the bronchoalveolar lavage (52-54).

CONCLUSION

Allergic Rhinitis is widely encountered throughout the world. It significantly affects person's health, quality of life and work performance. Due to complicated pathophysiological mechanisms, until this day no drug has been proved to be consistently curative. Immunotherapy can provide a long-term symptom control by the induction of tolerance in T-cells, however, numerous allergen administrations are needed to achieve clinical effect. Due to the aforementioned, new therapeutic options for the treatment of AR are actively being sought.

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