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Allergic Rhinitis

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Abstract

Allergic rhinitis (AR) has a negative impact on the quality of life and its incidence and prevalence is increasing worldwide. Depending on the sensitization pattern, patients may develop seasonal- or perennial symptoms: seasonal rhinitis is caused by aeroallergens such as pollens while the perennial form is mostly induced by mites, mold, and dander. In many cases allergen avoidance may contribute significantly to reduce the use of medications. The most common agents to treat AR include antihistamines, decongestants, steroids, mast cell stabilizers, anticholinergic agents, antileukotrienes and mucolytics: topical corticosteroids are the preferred method of treatment for both seasonal and perennial allergic rhinitis. Specific allergen immunotherapy should be considered when there is a poor response to pharmacotherapy, particularly as it is effective and modifies the course of the disease. A clear advantage of SIT over pharmacotherapy, the benefits of which last as long as it is continued, is a long-lasting relief of allergic symptoms after treatment discontinuation. Novel forms of SIT are currently under investigation including peptide vaccine using T cell epitopes, recombinant hypoallergenic allergens, and conjugated DNA vaccines.

Definition

Allergic rhinitis is a global health problem that affects patients of all ages and ethnic groups [1]. According to the ARIA document, allergic rhinitis is defined as a symptomatic disorder of the nose, induced after allergen exposure due to an immunoglobulin (Ig) E-mediated inflammation of the membranes lining the nose [2]. This document was made following the regulations of the World Health Organization on Evidence-Based-Medicine, and it was last updated in 2008 [3]. However, this disorder was first defined in 1929: "The three cardinal symptoms in nasal reactions occurring in allergy are sneezing, nasal obstruction, and mucous discharge" [4]. Because allergic rhinitis is commonly associated with sinus inflammation, it is also termed "allergic rhinosinusitis"

The ARIA document (Allergic Rhinitis and Its Impact on Asthma). The concept of "unified airway" proposed by Krouse, affirms that the inflammatory process coexists and affects the lower and upper airways [5]; so what is conventionally considered as distinct clinical disorders; allergic rhinitis and rhinosinusitis, are increasingly being regarded as interrelated and part of a spectrum of upper airway inflammatory disease. Both conditions are characterized by an inflammatory response leading to an altered milieu within the nose and paranasal sinuses, thus rendering normal host defenses weakened and susceptible to further inflammatory damage [6]. For this reason, we include the definition for rhinosinusitis too, as an inflammatory response involving the mucosa of the nasal cavity and paranasal sinuses, fluid within the cavities, and/or involvement of underlying bone [7].

Epidemiology

Rhinitis is the most frequent respiratory disease in the world and the most frequent manifestation of allergic disease in humans. It is often linked to other atopic diseases such as food allergy, atopic dermatitis or asthma [8]. Nearly a quarter of the global population suffers this disorder which represents a world health problem, because it affects the quality of life, the sleep, the work and the learning. Data principally obtained by questionnaires [9], however, shows that there are problems with them, secondary to the subjectivity: Many patients poorly perceive nasal symptoms of allergic rhinitis: some exaggerate symptoms, whereas many others tend to dismiss the disease [10].

It is estimated that 400 million people suffer from allergic rhinitis across the world [11], which affect approximately 20% of the adult population in the United States, and up to 40% of children [12]. Similar data have been reported in The United Kingdom [13]. The incidence reported in a cohort study in Germany showed that 15% of children developed seasonal allergies in their 7 first years of life, defined as a combination of exposure-related symptoms and evidence of sensitization [14]. In the Tucson Children´s Respiratory Study, the incidence reported was 42% in 6-year-old children, only by doctor-diagnosed rhinitis [15]. The ISAAC study (Third phase) reported a prevalence of 37.2% of allergic rhinitis in Latin-American adolescents [16].

Although allergic rhinitis is not a life-threatening condition, it has important impact on the quality of life and it has become an economic burden in both, direct (office visits, medication) and indirect costs (work and school days lost). The economic loss caused by AR is greater than those caused by diseases such as diabetes, hypertension, depression and coronary heart disease. The total average productivity (absenteeism) losses for AR were $593/employee per year in United States [17]. Allergic rhinitis results in an estimated 3.5 million workdays lost and 2 million schooldays lost [18]. Children with allergic rhinitis were almost twice as likely to be limited in their activities compared with children without the disease. Compromised health interfered with school performance in 4 of 10 children with the condition compared with only 1 in 10 children without rhinitis [19].

Nasal obstruction is the main component which predisposes both children and adults with allergic rhinitis to develop sleep disorders. This reduces a patient's daytime concentration leading to daytime sleepiness [20]. Indeed, children with nasal allergy have been found to describe sleep problems, (difficulty in falling asleep, waking during the night, and lack of a good night's sleep) as compared with non-allergic children [19]. 43.7% of patients with allergic rhinitis report feeling fatigue on awakening despite a normal night's sleep. Headache on awakening, anx-

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iety, depression and daytime somnolence are also frequently reported by patients with allergic rhinitis [21].

Several studies have assessed the social impact of allergic rhinitis and reported negative impact on their daily activities in both children and adults, especially feelings of embarrassment or frustration which limits the interaction in public places and school [22,23].

Allergic rhinitis is also associated with the subsequent development of asthma or lower airway disease [24]. The first manifestation of allergic rhinitis occurs in preschool children, and in this age group, allergic rhinitis is a risk factor for subsequent wheezing onset [25]. Children with allergic rhinitis and asthma had an increased prevalence of bronchial hyperresponsiveness and elevated FeNO in comparison with children with nonallergic rhinitis and asthma, which suggests different endotypes of asthma in children with allergic and nonallergic rhinitis [26].

Physiopathology

The nasal mucosa is in direct contact with the external environment; and it is exposed constantly to air pollutants, pathogenic viruses, bacteria, fungal spores, and allergens derived from pollens, house dust mites, and animal dander [27]. Thus, the nose protects the lower airways from the harmful effects of the inspired air in addition to warming and filtering the inspired air.

Allergic rhinitis is characterized by a two phase allergic reaction: an initial sensitization phase where allergen exposure results in IgE formation as well as induction of the humoral response, and subsequent clinical disease after repeated antigen exposure (Figure 1). The clinical allergic reaction can also be further subdivided into early- and late-phase responses: the early or immediate response-phase occurs within minutes after allergen exposure [28,29] while the late phase-response starts 4-8 h after allergen exposure [30].

Sensitization phase

During the sensitization process, Presenting-Antigen Cells (Macrophages and Dendritic Cells) capture and process the allergen to present it to the Cells T (T $CD4^+$ type 2 [Th2]) through the Mayor Histocompatibility Complex type II (MHC II). Th2 cells then release IL-3, IL-4, IL-5, and IL13 which allow B cell differentiation into plasma cells (PC). These cells are responsible for the IgE production.

Early-phase response

This phase is mediated by mast cells and basophils. Cross-linking of IgE with an allergen results in rapid (5 mins) release of a variety of mediators from these two cells types, including histamine, prostaglandins, kininogens and proteases (tryptase, chymase) and TNF-α (Figure 1). This occurs 5 mins after allergen exposure. These mediators are responsible for some of the general symptoms associated with allergic rhinitis such as rhinorrhea. Within 15 minutes, the mast cells secrete a new set of inflammatory mediators which are products of the metabolism of arachidonic acid, including prostaglandin D2 and the cystenil leukotrienes C4, D4 and E4; platelet-activating factor is also produced: cystenil leukotrienes, and bradykinin, cause blood vessels to dilate and leak being responsible for mucosal edema and watery rhinorrhea. Along with the mucoglycoconjugates produced by mucosal glands, these mediators also cause sensory neural stimulation and plasma exudation from blood vessels, leading to sinusoidal filling and subsequent nasal congestion. Sensory nerves stimulation leads to the release of neurotransmitter which in turn produces itching, nasal congestion, and sneezing. The neurotransmitters released include the sensory neuropeptides, substance P, neurokinin A, and calcitonin gene-related peptide (CGRP) [28,30-33].

Late-phase response

The late phase response that may occur 4 - 6 hours after allergen exposure is characterized by the recruitment of inflammatory cells, (eosinophils, basophils, macrophages and T cells), as a result of endothelial cell activation in postcapillary venules by the inflammatory mediators released during the early phase which in turn promote the expression of vascular cell adhesion molecule-1 and E-selectin facilitating the adhesion of circulating leukocytes to the endothelial cells. Chemoattractants such as the chemokines and IL-5 promote further cell migration [7,8] which then become activated and release additional inflammatory mediators resulting in increased symptoms usually associated with nasal congestion [34]. Indeed, accumulation of mast cells, Th2 cells, basophils and eosinophils has been found in the airway epithelium [35]. For instance, the chemokines RANTES (CCL5), eotaxin-1, 2, and 3 (CCL11, CCL24 and CCL26) and MCP-3 and -4 (CCL7 and CCL13) play a prominent role in attracting eosinophil [36], whereas IL-5 primary role is priming these cells to migrate in response to the chemokines [37]. In the bone marrow, IL-5, IL-3 and Granulocyte-Macrophage-Colony Stimulating Factor (GMC-SF), stimulate the production of eosinophils neutrophils and macrophages [38]. The eosinophil products, major basic protein, eosinophilic cationic protein, and leukotrienes cause epithelial damage; (Figure 2).

Clinical

The symptoms of allergic rhinitis after aeroallergen exposure include rhinorrhea (hyaline type), sneezing, nasal itching as well as unilateral or bilateral nasal obstruction and there may even be symptoms in other organs such as the eyes with tearing, hyperemia and eye pruritus, pharyngeal or otic itching. These symptoms improve by preventing contact with the allergen [39,40]. The early response is characterized by sneezing and runny nose while in the late phase; nasal congestion is the predominant symptom.

It is important to determine if any subsequent purulent discharge, facial pain and anosmia sinus are involved, since many patients with sinusitis suffer from rhinitis at the same time [6,7]. In these cases the possibility of allergic rhinitis should be evaluated. The correct diagnos-

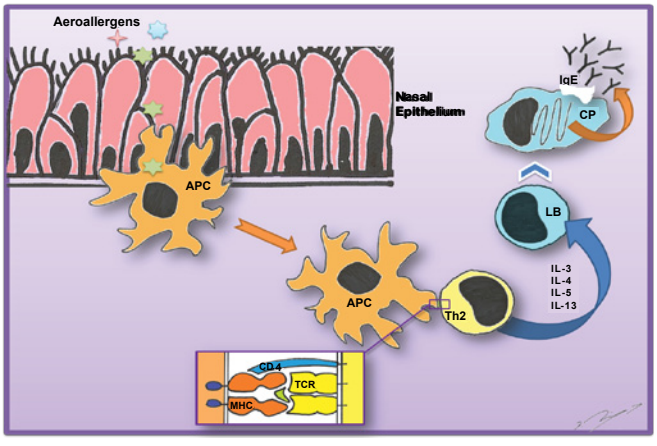

Figure 1: Sensitization to aeroallergen.

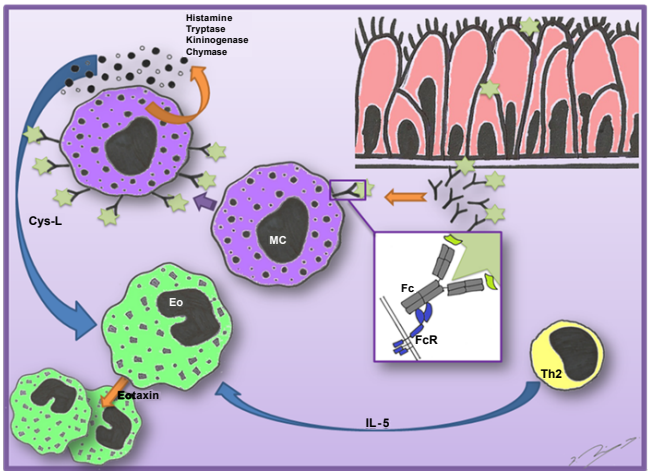

Figure 2: Early-and-Late-Phase Response on Physiopatology of Allergic Rhinitis

Symptoms suggestive of allergic rhinitis	Symptoms not associated with allergic rhinitis
Anterior rhinorrhea	Nasal obstruction without other symptoms associated
Especially sneezing paroxysms	Posterior rhinorrhea
Nasal obstruction	Facial pain
Nasal itching	Recurrent epistaxis
Conjunctivitis unilateral symptoms	Anosmia

Table1: Symptoms in allergic and nonallergic rhinitis

tic is based on signs and symptoms suggestive of rhinitis as noted in the table below (Table 1).

Classification

Allergic rhinitis is classified as seasonal or perennial classically; the first one is caused by a hypersensitivity reaction mediated by IgE to aeroallergens like pollens. Perennial allergic rhinitis is also a hypersensitivity type I response to environmental aeroallergens; but in this case allergens such as mites, mold, and dander can be the cause of the disease [41,42]. The ARIA initiative classifies allergic rhinitis in either intermittent or persistent and mild or moderate/severe, based on the frequency of the symptoms and their impact on the quality of life [3,43].

Intermittent symptoms occur less than four days per week for less than four weeks while in persistent allergic rhinitis symptoms are present more than four days per week and for more than four weeks. For mild cases, this condition should not present any of the next symptoms: sleep disturbance, impairment of school or work performance, impairment of daily activities, leisure and/or sport activities, and troublesome symptoms; but moderate-severe level should present one or more of the conditions listed [11].

Diagnosis

The diagnosis of allergic rhinitis (AR) is inferred from the interrogation and nasal symptoms (bilateral rhinorrhea, sneezing, nasal itching and constipation) as well as its severity and findings that are sustainable in the exploration of the nasal mucosa, and it is confirmed with skin test or serum specific IgE determination against allergens [44]. The ARIA document classifies the AR according to the frequency (intermittent or persistent) and intensity of symptoms (mild or moderate) as depicted above (Chart 2). Nasal examination should be performed by flexible rhinoscopy: the simple inspection may reveal external and internal nasal deformity of the septum. Posterior rhinoscopy performed with a mirror placed below the soft palate will show a bluish or pale, swollen turbinates, rhinorrhea, postnasal discharge hyaline and polyposis in case of active allergic rhinitis [45,46] the facial features include "allergic shiners" dark semicircles, infraorbital venous congestion caused by subcapilar, mouth breathing due to nasal congestion, nasal transverse crease secondary to rubbing upturned nose, dental malocclusion and overlapping toothed. It is also necessary to evaluate tearing and conjunctival injection [12,47].

Both skin prick test (SPT) and the allergen-specific immunoglobulin E (IgE) antibody test are the most common diagnostic tests for allergic rhinitis. Less common diagnostic tools include nasal provocation testing and nasal cytology [48].

The SPT is the most appropriate diagnostic approach to identify IgE sensitization to aeroallergens, foods, hymenoptera venom and some pharmacological compounds. This method is especially useful in patients with a diagnosis based on history of nasal allergic symptoms and its comorbidity with asthma. It has two objectives: avoid the exposure to the responsible antigen and give specific immunotherapy [49]. In the event negative skin tests, the diagnosis can be supported through the quantification of specific Inmunoglubolin E, the radioallergosorbent test (RAST) and multiple allergen simultaneous test (MAST) [50]. The first test consists of a solid phase that is manufactured in which allergens react with serum drawn from a patient. Antigen-specific Ig E binds to the solid phase antigens. This solid phase antigen-antibody complex is then incubated with radiolabeled rabbit antibodies to human Ig E. The amount of antibody present is calculated by measurement of the radioactive marker. Although MAST uses a photo reagent instead of a radioactive isotope, it does not require expensive equipment and can detect multiple allergens simultaneously, which makes it widely used. Bought tests are not affected by drugs such as antihistamines, are less invasive, and can be adopted in patients with dermographism [50,51].

Chart 1: Allergic rhinitis Bousquet J et al. (2001) [11].

In case patients with symptoms of AR do not have any positive skin tests or serum specific Ig E, the nasal provocation test (NPT) with specific allergens could help in the establishment of reliable diagnosis of AR [52]. An allergen extract or other provocative agents is instilled into the nostril, and the intensity of nasal symptoms (itching, sneezing, rhinorrhea and nasal obstruction) should be recorded with clinical scales. The most important outcome parameter is nasal obstruction which can be assessed by various methods such as peak nasal inspiratory flow (PNIF), rhinomanometry (RMM) or acoustic rhinometry (ARM) [53]. Nasal peak expiratory flow (PEFn) and PIFn are techniques for measuring nasal resistance to air flow. Airflow is measured using a specially adapted peak flow meter. The technique is easy to perform and inexpensive, but less exact than rhinomanometry in evaluating NPT results [54].

Rhinomanometry is the measurement of nasal pressure flow relationships during normal breathing, and it is generally accepted as the standard technique of measuring NAR and assessing the patency of the nose flow, providing a sensitive and functional measure of nasal patency. Total nasal resistance gives an overall measurement of nasal function, but it is a very crude measurement because it provides no information about the separate nasal passages. The nasal cavity where the pressure is measured is sealed and a cannula connected to a pressure gauge is introduced. Air flow through a mask fitted to the face is measured in the contralateral nasal cavity. The readings are represented on mirror-image coordinate axes in which flow is shown on the y-axis and pressure on the x-axis. Air flow is measured at a specific pressure (generally 150 Pa) and resistance is calculated with the equation $r = \Delta p/v$. The technique is sensitive and highly specific, but it cannot be used in cases of perforated septum, intense rhinorrhea, or nasal obstruction [55]. Blood eosinophil count and total serum IgE level tend to be elevated in AR, although clinically, these tests on their own are not very useful, as the diagnostic sensitivity and specificity for both are suboptimal [56].

It is important to assess whether nasal cytology of nasal symptoms are allergic and come from a background. The essence of the assessment is to demonstrate the presence of eosinophils; (> 10%) indicates active inflammatory disease. A decline in the percentage is considered as good evolution if the patient is with nasal steroid therapy.

The nasal lavage consist in introduction of fluid into the nasal cavity and its recovery after a predetermined dwell time. It has been used to investigate nasal, mucosal, and intralumenal events in allergic rhinitis. This technique is relatively noninvasive, easy to perform, and repeatable over relatively short periods. It has also been widely used as a research tool to gain a greater understanding of rhinitis. Through this technique, the mechanisms underlying the early and delayed nasal responses to intranasal allergen challenge have been understood. Similarly, nasal lavage has been undertaken before and after nasal challenge with a range of stimuli, (histamine, bradykinin, capsaicin, methacholine and substance P) and gain insight into their effects on the nasal vasculature, glandular secretion, and cell recruitment and activation [57].

Not all diagnostic tools referred to are performed in medical practice, although their importance lies on the fact that they have contributed to understanding and support the pathophysiology of allergic rhinitis.

Treatment

Treatment of allergic rhinitis (AR) should be based on three basic steps: 1) Control of the environment, 2) Drug therapy and 3) Immunomodulating therapy [3]. Efforts to avoid exposure to allergens are intended to prevent the development of symptoms in sensitive patient. It is particularly effective in reactions mediated by food, medicine, dander and mites. Protective measures such as use allergy covers, wash clothes with water at the temperature of 56°C, replace carpets and rugs at home have also been used. In the case of pollen allergies air specific measures are controversial [3,58].

Nasal glucocorticoids (NGC) remain the cornerstone in the treatment of AR [3] (beclomethasone, flunisolide, budesonide, fluticasone propionate, mometasone furoate, fluticasone and ciclesonide). Glucocorticoids inhibits the functions of infiltrating inflammatory cells and their recruitment into the nasal mucosa. GC inhibits the maturation, cytokine production, FceRI expression and mediator release of mast cell; inhibits histamine release from basophils; induces apoptosis of eosinophils and reduces the recruitment of antigen-presenting cells such as Langerhans cells; decreases the numbers of GATA-3+ Th2 cells and the production of Th2 cytokines, such as IL-4, IL-5, IL-6 and IL-13, while having little effect on T-bet+ Th1 cells and the production of Th1 cytokines such as IL-2, IL-12 and interferon IFN-Y [59]. The effects of the glucocorticoids depend on its pharmacokinetic properties like lipophilicity and systemic availability being mometasone and ciclesonide the nasal steroids with the best characteristics [60]. NGC are the most effective medications for controlling all rhinitis symptoms. Their onset of action is from 3 to 12 hours. Their use on an as needed basis is not as effective as continual use but may not be required continu¬ally in all patients [61]. The use of nasal glucocorticods are safe not suppressing the hypothalamic-pituitary-adrenal axis with prolonged use; effect that is supported since 2002 where when the growth of children with AR who had used fluticasone propionate 200µg for a year was evaluated by comparing the speed decrease against a control group with similar characteristics to placebo, finding that there is no alteration in the growth rate [62]. Ciclesonide is a nasal steroid which has showed efficiency in solving nasal symptoms, the use of 200 µg once a day for 2-4 weeks is more effective than placebo in terms of improving nasal symptoms during the first two weeks of therapy in adolescents and adults with moderate and severe allergic rhinitis through quality of life measures. Its usefulness is showed in perennial allergic rhinitis after six weeks of therapy [63].

Antihistamines are considered as second-line therapeutic agents in the control of RA. First-generation antihistamines (diphenhydramine, chlorpheniramine, hydroxyzine, and brompheniramine), tend to reduce itching, sneezing and rhinorrhea, with less impact on nasal congestion [64]. They cause significant sedation, as they are lipophilic because they cross the blood-brain barrier, so they are contraindicated in the treatment if the patient performs operator-dependent activities [65], in addition to having cholinergic effects that become more evident in the elderly population.

The use of second-generation antihistamines (loratadine, cetirizine, azelastine, and olopatadine) whose characteristic is to be lipophobic and were developed to avoid the sedative effects on the central nervous system of the antihistamines of the first generation, the new antihistaminic (desloratadine, fexofenadine, and levocetirizine) are effective in relieving the nasal congestion associated with AR , the effect begin as early as day 2 and is consistent and progressive throughout treatment [66,67]. The use of antihistamines is approved by international consensus, although the effect is lower than nasal steroids, but greater than antileukotrienes and cromones [68]. Azelastine and nasal antihistamines olopatadine are better for nasal congestion, and time of action is faster

compared with oral antihistamines. The advantages of such therapy include attaining higher concentrations of active drug directly to the target tissue with the added benefit of reduced systemic side effects [69].

The use of combinations of antihistamines and oral decongestants (pesudofedrine) are most useful, but its prescription should be monitored because they can produce side effects such as headache and hypertension and are contraindicated in patients with angle-closure glaucoma and cardiovascular or cerebrovascular disease. A major limitation of the topical decongestants is rebound hyperemia and worsening of the symptoms that occur with chronic use (rhinitis medicamentosa). Therefore, topical decongestants are generally used on a short-term basis for less than 5 days [70].

Membrane stabilizers such as cromolyn sodium and nedocromil inhibit the release of mediators such as histamine libelous by inhibition of chloride channels in the membrane of mast cells. Cromolyn sodium is effective in the treatment of seasonal allergic rhinitis when evaluated against placebo, however, most studies show that it is less effective than INGCs or second-generation antihistamines. Its usefulness is limited by the need for frequent dosing and the lower relative efficacy of other agents [71,72].

Receptor antagonists of leukotrienes as montelukast inhibits the development of nasal symptoms by preventing the binding of LTC4 and LTD4 receptor CysLT1 in its improvement through questionnaires assessed value as the rhinitis severity score has shown its impact in alleviating nasal congestion and the clinical improvement experienced by patients is comparable with the use of antihistaminics without clutch. These effects are outweighed by the intranasal glucocorticoids. Prescription medication should be cautious in patients with psychiatric illnesses [73].

In case rhinorrhea is the predominant symptom of allergic picture, ipratropium bromide may be administered by the nose 0.03%, this effect is done by decreasing the levels of substance P, and it should not be considered as a drug of choice [74].

Nasal decongestants (phenylephrine, oxymetazoline, xylometazoline and naphazoline) are not recommended in the treatment of chronic allergic rhinitis. Their administration may be useful in specific cases in patients with severe nasal obstruction. There is the disadvantage of reactivation of nasal symptoms because the development of rhinitis medicamentosa.

Short courses of systemic corticosteroids may be indicated for severe symptoms of allergic rhinitis that do not respond to other drugs or for those who are intolerant to intranasal drugs that prevent the patient from performing daily activities. Injections of long acting corticosteroids are not recommendeddue to unpredictable absorption and inability to adjust the dose if side effects occur [75].

Anti-IgE monoclonal antibody (omalizumab)

Omalizumab is a "humanized" monoclonal antibody which binds the IgE molecule at its IgE receptor-binding portion, preventing IgE's interaction with the high-affinity IgE receptor present on mast cells, basophils, and dendritic cells. A number of randomized, double-blind, placebo-controlled studies have shown to be effective in seasonal and perennial AR [76,77]. However, it is quite costly compared with the other therapies. Omalizumab was primarily used to treat allergic asthma difficult to control.

Immunotherapy

Specific allergen immunotherapy (SIT) is a unique therapy for allergic rhinitis because it provides symptomatic relief while modifying the allergic disease process by targeting the underlying immunologic mechanisms. Sublingual (SLIT) and subcutaneous (SCIT) immunotherapy are the two most commonly prescribed routes for administering SIT [75]. The mechanisms of action of allergen-specific immunotherapy include the very early desensitization effects, modulation of T-and B-cell responses and related antibody isotypes, and migration of eosinophil, basophils, and mast cells to tissues, as well as release of their mediators. Regulatory T (Treg) cells have been identified as key regulators of immunologic processes in peripheral tolerance to allergens: skewing of allergen-specific effector T cells to a regulatory phenotype appears as a key event in the development of healthy immune response to allergens and successful outcome in patients undergoing allergen-specific immunotherapy.

Naturally occurring forkhead box protein 3-positive CD41CD251 T reg cells and inducible TR1 cells contribute to the control of allergen-specific immune responses in several major ways, which can be summarized as suppression of dendritic cells that support the generation of effector T cells; suppression of effector TH1, TH2, and TH17 cells; suppression of allergen-specific IgE and induction of IgG4; suppression of mast cells, basophils, and eosinophils; and suppression of effectorT-cell migration to tissues [78].

Jacobsen demonstrated a 3-year course of SIT with standardized allergen extracts has shown long-term clinical effects and the potential of preventing development of asthma in children with allergic rhinoconjunctivitis up to 7 years after [79].

Independent studies show that both forms of immunotherapy are effective in allergic rhinitis and asthma if optimally used. Side-effects of SLIT and SCIT differ. No fatal and only a few severe adverse events have been reported with SLIT. Moreover, SCIT induces more frequently systemic adverse events, while SLIT appears to have a higher rate of local side-effects that are frequently short-lasting. It must be noticed that the occurrence of adverse events with SCIT largely depends on the allergen type and preparation. Higher frequency is seen with native allergens compared to allergoids and animal dander compared to pollen and mite [80].

Novel strategies for SIT have been developed including peptide vaccine containing T cell epitopes, DNA vaccines and recombinant hyollergenic SIT [81-83]. In a double-blind, placebo-controlled study, adults treated with CpG conjugated vaccine before ragweed season had better peak-season rhinitis scores than the placebo group [82]. It has been shown that allergens conjugated with CpG reduce allergenesis of the allergens by diminishing the binding activity of specific IgE for native allergens [83]. Similarly, subcutaneous immunotherapy with the hypoallergenic recombinant Bet v 1 derivatives inhibited allergic patients' IgE binding to Bet v 1 [84]. Currently, the hypoallergenic Bet v 1 derivatives have been tested several clinical trials up to phase III.

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