

Update on the Medical Treatment of Allergic Rhinitis

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Abstract: Allergic rhinitis is a global health problem affecting at least 10 to 25 % of the population. So far, numerous classifications and treatment modalities have been described. In the treatment of allergic disorders Pharmacotherapy is the most used therapeutic modality, especially in allergic rhinitis. The first step to successful management is the accurate diagnosis of the type of AR (intermittent or persistent) and assessment of its severity (mild or moderate to severe). Although objective measurements of the nasal airway have great value to evaluate and follow up the cases, in most centers they are not done in routine clinical practice.

Allergen avoidance should be the initial step in the management of AR. Oral antihistamines are the first-line therapy for mild to moderate intermittent and mild persistent rhinitis. They are also recommended for moderate/severe persistent rhinitis cases which are uncontrolled on topical intranasal corticosteroids alone. Corticosteroids are well known for their anti-inflammatory and anti allergic effects. Topical usage provides topical efficacy while avoiding systemic side effects. Meta-analysis shows that intranasal corticosteroids are superior to antihistamines. They act by suppression of inflammation at multiple points in the inflammatory cascade and reduce all symptoms of rhinitis. A meta-analysis demonstrated that Montelukast was better than placebo, as effective as antihistamines, but less effective than nasal corticosteroids in improving symptoms and QOL in patients with SAR. Good results were reported with subcutaneous and sublingual immunotherapy. Further investigations are promising.

INTRODUCTION

Allergic rhinitis is a global health problem affecting at least 10 to 25 % of the population [1]. It is very well known that allergic rhinitis, the immunologic response, is directed by a variety of aeroallergen and food. The resulting spectrum of diseases is related to the inciting agent and the level of exposure [2, 3]. It has a tremendous impact on the quality of life and productivity of those it affects. Approximately 35 million Americans suffer from allergic rhinitis, roughly 10% to 30% of all adults. Annual direct medical cost of treating allergic rhinitis ranges from \$1.16 billion to \$4.5 billion. In Turkey, the cost is approximately \$400 000 a year.

Epidemiologic studies have demonstrated a strong link between allergic rhinitis and asthma through their incidence together, and the two disease processes are now beginning to be considered as results of the same underlying inflammatory process. In these studies, asthma has been demonstrated in up to 40% of adults with rhinitis [4, 5]. The prevalence of rhinitis in adults with asthma is variably reported as occurring in up to 80% of patients [5, 6].

In addition to asthma, there is evidence of a link between allergic rhinitis and rhinosinusitis. This evidence points to an increased prevalence of allergic sensitization, increased incidence of skin test positivity in response to aeroallergens, and increased levels of IgE in patients with sinusitis [7]. There is also strong evidence that treatment of allergic rhinitis reduces the severity of sinusitis, results in improved

outcomes following sinus surgery, and could result in improved outcomes from medical management of chronic rhinosinusitis [8]. Allergic rhinitis is also proposed to lead to the development of rhinosinusitis as a result of mechanical obstruction and mucous stasis [9].

For these reasons a huge amount of research and many clinical studies were performed in order to solve the allergy problem. Many classifications and treatment modalities have been described. Pharmacotherapy is the most used therapeutic modality in allergic rhinitis. The aim of this paper is to review previously described treatment modalities and future possibilities and discuss their advantages and disadvantages.

ARIA CLASSIFICATION & ALLERGIC RHINITIS

Classification of allergic rhinitis is based on whether the symptoms are intermittent or persistent, with categories of mild, and moderate to severe. This classification is now becoming fairly common in discussing the type of disorder and the severity of the disease, particularly in the context of those with asthma [3]. It is updated in 2007 [10] and then in 2008, which is announced as being more evidence-based [11]. While most recommendations result from existing systematic reviews, systematic reviews were not always available and the panel compiled the best available evidence in evidence profiles without conducting actual reviews. The panel conducted two meetings and used the GRADE criteria to assess the quality of evidence (four categories of high, moderate, low and very low) and the strength of recommendation (strong and weak) based on weighing up the desirable and undesirable effects of management strategies, considering values and preferences influencing recommendations, and resource implications [12].

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But the lack of seasonal concept is still a major problem as we all tend to group the cases as perennial and seasonal. Seasonal allergic rhinitis (SAR), or “hay fever,” is the most common form and easiest to diagnose. Nasal and associated ocular symptoms occur on a seasonal basis, primarily in the spring due to various seasonal pollens. Perennial allergic rhinitis (PAR) is a more chronic condition with symptoms that can fluctuate (e.g., mold, depending on humidity) but occur to some degree year round. Mites, molds, and cockroach feces are the most common causes. Occupational allergic rhinitis describes symptoms that are produced by continuous exposure to allergens in the work environment, and should be distinguished from symptoms caused by irritants in the same environment (e.g., chemical fumes, as with chemical/irritative rhinitis). It is not fair to group these cases as continuous and intermittent as described by ARIA guidelines.

Patients with intermittent AR have symptoms that are present for less than 4 days a week and/or for less than 4 weeks per year. Persistent AR refers to the disease when it is present for more than 4 days a week and/or more than 4 weeks per year. AR is further classified as either “mild” or “moderate to severe”. Patients with mild AR do not experience sleep disturbances, impairment of activities relating to sport or leisure, or impairment of school or work performance, and their symptoms are not “troublesome”. A patient with moderate-to-severe AR may experience any or all of these four signs (Bousquet *et al.*, 2000). A stepwise approach to the management of AR should be guided by symptom duration and severity and evaluation of treatment response [13, 14] (Table 1).

The diagnosis of allergic rhinitis requires a thorough history, paying special emphasis to previous occurrences of allergy, the presence of a family history of allergic disease, the main symptoms associated with an episode of allergy, and the time course over which symptoms developed [13, 14]. In-depth analysis of precipitating and mitigating factors not only helps to establish a diagnosis of allergy, but can also provide valuable information in how to best avoid allergic triggers. In describing these factors, the clinician should pay careful attention to work exposures, changes in the home environment, and pets. The time course during which symptoms developed is also very important, especially if the patient cannot directly identify the source of the allergy [14].

INVESTIGATIONS

Although objective measurements of the nasal airway have great value to evaluate and follow up the cases, they are not done in routine clinical practice in most of the centers. Peak nasal inspiratory flow, acoustic rhinometry, rhinomanometry, nasal endoscopy can be done to objectively measure the nasal airway. Investigations should include: full blood count and differential white cell count, C-reactive

protein, nasal smear/brushing for eosinophils, microbiological examination of sputum and sinus swabs, nasal secretions - CSF asialotransferrin for CSF rhinorrhoea [15-17].

Allergy testing can be performed to identify which allergens are responsible for the symptoms. There are two methods used to determine the presence of immunoglobulin (Ig)-E antibodies to specific allergens: skin testing, and radioallergen sorbent (RAST) testing.

Skin testing is typically performed with a set of allergens relative to the patient’s environment and clinical history [18]. Skin testing involves introduction of the allergen extract into the skin by “prick” or intradermally. The prick test is the most popular one all over the world. Histamine is used as a positive control, and saline is used as a negative control. The wheal and flare response to a specific allergen is then compared with the controls. To avoid false-negative tests, antihistamines should be withheld for 36 to 48 hours [14]. *In vitro* measurement of allergen-specific IgE also can be performed using the RAST test. Skin testing has greater sensitivity, is less expensive, and provides immediate results, whereas RAST is limited in the selection of allergens but has the advantage of not being affected by antihistamines. The demonstration of IgE-specific antibodies alone does not establish that the patient will have an adverse response on exposure to the allergen because sensitization can occur without reaction to inhalation. Thus, results must be interpreted along with the clinical picture before a diagnosis can be made.

TREATMENT

The first step to successful management is the accurate diagnosis of the type of AR (intermittent or persistent) and assessment of its severity (mild or moderate to severe) (Table 2). The results of the allergen avoidance studies for perennial allergic rhinitis indicate that, when compared with controls, significant reductions of allergen load can be achieved by physical and chemical means, but there is little evidence at present that these reductions translate into sustained improvements in clinical outcomes [19], whereas there are studies that dealt with the correlation of atmospheric pollens with common allergens determined by prick testing of a certain region [20]. It is known that symptoms of allergic rhinitis due to mites are related to the environmental mite level in places where the patients live. The relationship between mite levels and symptoms of allergic rhinitis diagnosed patients and the change of mite levels in the environment after appropriate education is shown in previous studies [21].

The epidemiology of allergic rhinitis varies depending on the geographic regions of the country. It also differs in urban and rural areas of the same region. After a screening questionnaire, ENT examination and prick testing, we found a

Table 1. Classification for AR (Aria Guidelines)

Persistent	Intermittent	Mild	Moderate-Severe
<ul style="list-style-type: none"> • Symptoms > 4 days per week • Symptoms > 4 weeks per year 	<ul style="list-style-type: none"> • Symptoms < 4 days per week • Symptoms < 4 weeks per year 	<ul style="list-style-type: none"> • Normal Sleep • No impairment of daily activities • Normal work/school performance 	<ul style="list-style-type: none"> • Abnormal sleep • Impairment of daily activities • Abnormal work/school performance

Table 2. Recommendations for Allergen Avoidance

Allergen	Avoidance Measures
Indoor	
Molds	<ul style="list-style-type: none"> • Use a bleaching agent on tile grout, sinks, shower walls, and garbage cans • Avoid humidifiers • Dehumidifiers in damp areas
Dust mites	<ul style="list-style-type: none"> • Bed linens should be washed in hot water (>130°F) once every other week • Pillow and mattress encasings • Removal of carpet from homes • Treat carpet with acaricides and the use of vacuum cleaners with (HEPA) filters and double-thickness bags
Animal dander	<ul style="list-style-type: none"> • Furry pets should be removed from the home • Carpets and furniture cleaned • Confine pet to a room with a HEPA or electrostatic air purifier
Cockroach	<ul style="list-style-type: none"> • Efforts should be made to prevent infestation
Outdoor	
Pollens	<ul style="list-style-type: none"> • Keep windows closed • Use air conditioning with external vents closed • Avoid window or attic fans • Wear mask and/or goggles while mowing grass

HEPA = High-efficiency particulate air.

higher incidence in urban areas compared with rural areas of the same region [22]. This data may be considered as the influence of environmental allergen conditions.

As minimal medical intervention is universally desirable, many pharmacological approaches were described (Table 3).

Table 3. Pharmacologic Treatment Approaches

Treatment	Mechanism/Reason for Use
Antihistamines	Blocks histamine (H1) receptor
Intranasal steroids (INS)	Exert anti-inflammatory effects
Cromolyn sodium	Stabilize mast cell membrane
Decongestants	Reduce nasal congestion
Leukotriene modifiers (LTRA)	Block leukotriene c4 receptor
Anticholinergics	Diminish parasympathetic tone
Immunotherapy	If other treatments fail

According to the ARIA guidelines, second-generation oral antihistamines are recommended for mild or intermittent AR. The concomitant use of LTRAs with an oral antihistamine may be considered for some patients; however, results to date are unconvincing. For more moderate-to-severe or persistent disease, particularly patients with severe nasal congestion, an INS should be considered first-line therapy. If symptoms are not adequately controlled, additional therapy can be considered, such as the addition of an oral antihistamine. In more severe or difficult to manage AR, patients should be referred to an allergy specialist for immunotherapy assessment [3, 11].

ORAL ANTIHISTAMINES

Oral antihistamines are the first-line therapy for mild to moderate intermittent and mild persistent rhinitis. They are also recommended for moderate/severe persistent rhinitis cases which are uncontrollable by topical intranasal corticosteroids alone [23-26]. Antihistamines relieve rhinitis, excess mucous production, as well as most ocular and non-nasal manifestations, but not nasal congestion with short-term therapy.

The older first-generation H₁-antihistamines, such as diphenhydramine and chlorpheniramine, are sedating antihistamines. These agents are effective in AR but cross the blood-brain barrier and are associated with sedation leading to impaired performance at home, work, and school [21]. With this high risk-to-benefit ratio, the first-generation H₁-antihistamines are not recommended.

For second-generation antihistamines, which are fairly specific to H-1 receptors, there is minimal to no sedation, longer duration of action, and mucosal drying is variably present (Table 4).

The newer second-generation H₁-oral antihistamines have improved H₁-receptor selectivity, absent or decreased sedation, and fewer adverse effects. They are recommended as first-line therapy for the treatment of mild-moderate AR [23]. H₁-antihistamines are effective in the treatment of nasal sneezing and pruritis. Clinical trials assessing QOL in patients with AR demonstrate that these drugs consistently improve QOL. Desloratadine, fexofenadine, cetirizine and levocetirizine have modest effects on nasal blockage [23]. Desloratadine is known as the most widely used antihistamine in our country. Regular therapy as daily routine usage

Table 4. Antihistamines

Type of Antihistamine	Specific Drugs	Properties of Mechanism
1st Generation	<ul style="list-style-type: none"> • Chlorpheniramine • Clemastine • Diphenhydramine • Hydroxyzine • Promethazine 	<ul style="list-style-type: none"> • Competitive H1 binding • Lipophilic • Cross blood-brain barrier • CNS effects • Anticholinergic activity • Urinary retention • Xerostomia
2nd Generation	<ul style="list-style-type: none"> • Acrivastine • Azelastine • Cetirizine • Levocetirizine • Fexofenadine • Loratadine • Desloratadine • Ebastine • Mizolastine • Rupatadine 	<ul style="list-style-type: none"> • Non-competitive H1 binding • Lipophobic • Less sedation • Less psychomotor depression • Improved performance • Little/No anticholinergic Activity

is more effective (and more commonly advised) than ‘as-needed’ use in persistent rhinitis.

Some second-generation antihistamines are approved for use in very young children, some are effective for other manifestations of atopy (such as urticaria) and some can cause very mild sedation (Table 5).

Table 5. Most Popular Second-Generation H₁-Antihistamines

	Usual Daily Adult Dose	Nonsedating
Oral		
Desloratadine	5 mg	Yes
Levocetirizine	5 mg	Yes
Fexofenadine	60 mg twice daily; 120 mg or 180 mg daily	Yes

Loratadine and mizolastine are less sedating in most patients, with fexofenadine the least sedating [21]. In addition, they do not cause significant QT prolongation at normal therapeutic doses have few major drug interactions, except for increased risk of ventricular arrhythmias, when mizolastine is co-administered with some antiarrhythmics, antibiotics and b-blockers. Most OTC antihistamines, except loratadine, cause drowsiness, dry mouth, blurry vision, constipation and urinary retention [23].

Rupatadine is a recently introduced dual inhibitor of histamine H(1)- and PAF-receptors, which has been shown to be an effective and generally well-tolerated treatment for allergic rhinitis [26]

TOPICAL ANTIHISTAMINES

The main idea of topical antihistamine application is to reach the target instead of whole body. Many investigations

we performed in order to prove that Azelastine improves symptoms in SAR and PAR, including ocular symptoms [23, 27, 28]. But adverse effects reported related with local irritation and taste disturbance. Nasal application of any drug is a decreasing factor of quality of life. We believe that if a patient should use a therapeutic agent through the nose, it should be a nasal corticosteroid which is proven to be much more effective than any nasal antihistamine. So, practically topical antihistamines are out of daily usage in allergic rhinitis treatment modalities.

DECONGESTANTS

Decongestants reduce nasal congestion by activating alpha-adrenergic receptors on the nasal vasculature leading to vasoconstriction (hence, edema & hyperemia) [26] but do not relieve rhinitis, pruritis, sneezing. They are most frequently prescribed as an adjunct to an antihistamine or topical steroid. A recent study showed that the combination of pseudoephedrine and an antihistamine was significantly more effective in reducing total nasal symptoms than either agent alone [27]. Caution must be taken when prescribing decongestants to patients with hypertension, diabetes, sleep disturbance, anxiety, glaucoma, prostatic hypertrophy, ASVD, hyperthyroidism, or patients taking monoamine oxidase inhibitors. Oral decongestants (pseudoephedrine) may also improve sinus ostial patency. But this group of drugs cannot be accepted as therapeutic for allergic rhinitis.

The Food and Drug Administration (FDA) is taking steps to remove phenylpropanolamine (PPA) from all drug products and has requested that all drug companies discontinue marketing products containing PPA due to its serious side effects. Topical decongestants, oxymetazoline and phenylephrine, are also available over-the-counter. These medications can be effective with nasal congestion associated with AR. Rebound nasal congestion, termed “rhinitis medicamentosa,” can occur if these medications are used for more than 5 to 7 days.

TOPICAL INTRANASAL CORTICOSTEROIDS

Corticosteroids are well known for their anti-inflammatory and anti-allergic effects. Topical usage provides topical efficacy while avoiding systemic side effects. Meta-analysis shows that intranasal corticosteroids (INS) are superior to antihistamines [25-31]. They act by suppression of inflammation at multiple points in the inflammatory cascade [32] and reduce all symptoms of rhinitis (congestion, sneezing, rhinorrhea, palatal pruritis) by about 17% greater than placebo, with a variable effect on associated allergic conjunctivitis. They are at first-line therapy for moderate to severe persistent symptoms and treatment failures with antihistamines alone [31]. Topical corticosteroids stabilize the membranes of mast cells and exert most of their effects *via* such and partial blocking of the Late Phase Reaction.

Times to onset and to maximum benefit are longer (6-8 h after the first dose) than with antihistamines, so are less suited to sporadic or PRN use. Maximal effect may not be apparent until after 2 weeks [31, 32]. Starting treatment 2 weeks before a known allergen season improves efficacy [33]. Systemic absorption negligible with mometasone and fluticasone, modest for the remainder and high for betamethasone and dexamethasone - these should be used short

term only [34]. Long-term growth studies in children using fluticasone, mometasone and budesonide have reassuring safety data, unlike beclomethasone [32-35].

Most intranasal corticosteroids are based on the molecule of dexamethasone, and have similar anti-inflammatory properties. They differ in bioavailability (some are approved for young children), preparation (micro-drop, micro-powder), odor, preservatives, and time of onset of action. They include : Fluticasone, Mometasone, Triamcinolone, and Ciclesonide.

Adverse events with INS are local nasal irritation, sore throat and epistaxis affect around 10% of users. Hypothalamic-pituitary axis suppression may occur when multiple sites are treated with topical corticosteroids in the same person (e.g. skin, nose and chest). Raised intra-ocular pressure has been described with INS [36], and patients with a history of glaucoma should be monitored more closely.

Adverse systemic side effects due to intranasal corticosteroids seem to be minimal in adults [34]. Epistaxis, secondary to irritation of the nasal mucosa, is the most common adverse effect but usually diminishes over time [37]. Therefore, patients should be instructed on the proper technique for administration. It also is important to routinely examine the nasal mucosa in patients using topical nasal steroids to look for signs of irritation and/or septal perforation.

Fluticasone furoate nasal spray is a new topical intranasal corticosteroid with enhanced affinity for the glucocorticoid receptor and low systemic exposure, which has recently been approved in the US for the treatment of seasonal or perennial allergic rhinitis in adults and in children aged ≥ 2 years. Fluticasone furoate nasal spray employs a novel delivery device with a unique side-actuated design, a short nozzle and a new trigger mechanism designed for ease of use. In well controlled clinical trials, intranasal fluticasone furoate 110microg once daily for 2 weeks in adults and adolescents with seasonal allergic rhinitis reduced nasal and ocular symptoms, and improved health-related quality of life to a significantly greater extent than placebo. Similarly, treatment with intranasal fluticasone furoate 110 microg once daily for 4-6 weeks in adults and adolescents with perennial allergic rhinitis was superior to placebo in reducing nasal symptoms and with respect to overall response to therapy. In children aged 6-11 years, fluticasone furoate nasal spray was shown to be effective in reducing the nasal symptoms of seasonal and perennial allergic rhinitis following treatment for 2 and 4 weeks, respectively [38]. Fluticasone furoate nasal spray consistently and significantly improves both the nasal and ocular symptoms of seasonal allergic rhinitis and it is the first intra nasal steroid to show consistent nasal and ocular efficacy across all seasonal allergic rhinitis trials [38].

CORTICOSTEROIDS

Systemic glucocorticosteroids should not be listed as first line treatment agents of allergic rhinitis. They are rarely indicated in the management of rhinitis, except for severe nasal obstruction or short-term rescue medication for uncontrolled symptoms on conventional pharmacotherapy. Corticosteroids down-regulate the immune system in general, but also have multiple other systemic effects, many of which are undesirable. Oral corticosteroids should be used briefly and always in combination with a topical nasal corticosteroid. A

suggested regime for adults is 0.5 mg/kg given orally in the morning with food for limited time period of 5-10 days [39].

LEUKOTRIENE MODIFIERS

Leukotrienes seem to be important mediators of nasal allergic reactions, and their application to the nose induces nasal obstruction [29]. They are involved in both the early and the late-phase allergic response. Leukotriene synthesis inhibitors or receptor antagonists commonly used for asthma for a long period of time. As the result of "one airway-one disease philosophy" some also have indications for AR [40]. Shirasaki reported that immunohistochemical studies show that in allergic rhinitis, the major target of CysLT [1] receptor antagonists are the vascular bed and infiltrated leukocytes such as mast cells, eosinophils and macrophages. CysLT [1] receptor antagonists provide a new opportunity for simultaneous management of allergic diseases of the upper and lower respiratory tract [41].

A meta-analysis demonstrated that Montelukast was better than placebo, as effective as antihistamines, but less effective than nasal corticosteroids in improving symptoms and QOL in patients with SAR [29, 40]. Montelukast has been generally accepted as an adjunct in the treatment of AR. Further studies should be performed about montelukast monotherapy. We believe that montelukast monotherapy will improve the QOL of the cases especially who do not benefit much from antihistamines.

MAST CELL STABILIZERS

Mast cell stabilizers (cromolyn or nedocromil) inhibit mast cell degranulation and thus inhibit the release of histamine and other mediators of the early phase of allergic inflammation. Cromolyn sodium, which is available over-the-counter, is generally not as effective as antihistamines or intranasal corticosteroids in reducing symptoms. Cromolyn is likely to be more effective when administered just before contact with an allergen [29]. The dosage interval of 4 times per day make this a less attractive option. Ophthalmic mast cell stabilizers, ocular antihistamines, mast cell-stabilizing/antihistamine agents, and the nonsteroidal anti-inflammatory drug Ketorolac have all been effective when used topically for the treatment of ocular symptoms associated with allergic conjunctivitis that often accompany AR [18].

ANTICHOLINERGICS

Topical anticholinergics (i.e. Ipratropium bromide) are not therapeutic agents for allergic rhinitis. They inhibit vagally mediated symptoms, do not reduce congestion, irritation or sneezing. The safety and effectiveness of the currently available preparations are not established beyond 3 weeks, and are used for such reasons as short-term issues (rhinitis associated with the common cold), or for a few days during particularly high levels of airborne pollen precipitate vasomotor rhinitis, or when gustatory rhinorrhea needs to be avoided for a short period of time [18, 30, 42]. They should be used with caution especially in patients with narrow-angle glaucoma, prostatic hypertrophy, or bladder neck obstruction

IMMUNOTHERAPY

Allergen immunotherapy can be accepted as the only treatment modality against the cause of AR. It is effective and should be considered with poor response to pharma-

cotherapy and avoidance [43]. Immunotherapy is warranted only if the preceding proves inadequate for symptom control and specific allergen sensitivities have been documented by *in vivo* (skin) or *in vitro* (serum) testing. Consideration of immunotherapy for a particular patient requires at least one positive *in vivo* or *in vitro* test confirming the presence of IgE specific antibody, and clinical symptoms that correspond to that allergen exposure.

Subcutaneous immunotherapy (SCIT) is indicated for the treatment of AR, and expert guidelines recommend its use for patients who continue to have moderate-severe symptoms despite therapy, have intolerable adverse effects with pharmacotherapy, patients who do not want to be on pharmacotherapy, and those have coexisting conditions such as asthma [44].

Subcutaneous immunotherapy involves the administration, in gradually increasing doses, of allergen to induce a degree of immune tolerance to the specific allergen. The maintenance dose is usually given at intervals ranging from 2 to 6 weeks. Drawbacks to SCIT include the frequent injection schedule and the requirement for the injections to be done in the office with a 20- to 30-minute SCIT observation period. The most common adverse effects associated with SCIT are local injection site swelling and erythema. However, systemic reactions, including anaphylaxis, have occurred but are less common [45]. Patients need to be aware of their commitment and of the very small but real risk for anaphylaxis following injection [44].

The indications for immunotherapy are avoidance and environmental measures fail/are impractical, when pharmacotherapy fails to adequately control symptoms, or produces bothersome side-effects or the occurrence of moderate to severe symptoms in 2 or more seasons. Contraindications include beta blocker therapy (affects response to epinephrine, should patient have anaphylactic reaction to immunotherapy), brittle asthma (immunotherapy reactions include bronchospasm), immunodeficiency disease (immune system must be relatively normal, and responsive, for immunotherapy to work), or unreliability (3-5 years of shots, initially weekly, are required to elicit an effective response). Immunotherapy is not started during a pregnancy, due to the small potential for anaphylaxis affecting the fetus, but can be continued during pregnancy in a patient who is already on a stable "maintenance" dose. Indeed, immunotherapy is probably the safest way to control inhalant allergies during pregnancy in such a patient [37, 46, 47].

Patients are treated individually, based on symptom relief and any adverse local or systemic reactions to the injections. The strength of the antigen solution in the treatment vials is slowly escalated until the patient is no longer having allergy symptoms (called "symptom relieving dose") or they reach the "maximum tolerated dose" (antigen concentration that provokes skin injection site or systemic side effects, with the antigen dose being thereafter decreased to the next lower dose that does not elicit such effects, and then called the "maintenance dose"). Side effects from immunotherapy are most common during the dose escalation phase, so during such patients should always be observed in the physician's office for 20 minutes after having an injection [23, 32, 42].

Causes for the implementation of immunotherapy include: a blunting of the post-seasonal rise in specific IgE antibody and pro-allergic cytokines, an increase in IgM and IgA which may increase the mucosal barrier to allergen penetration, an increase in allergen-specific suppressor T-lymphocytes, and a reduction in lymphocyte reactivity to antigens, a reduction in basophil and mast cell reactivity to antigens, an elevation of the threshold for histamine release, increases in the IFN-gamma to IL-4 and the IgG4 to IgG1 ratios, a shift of cytokine production by a patient's immune cells from a TH-2 to a TH-1 associated cytokine emphasis [48].

The response rate to therapy in carefully selected patients is good with trials reporting a two-thirds reduction in symptoms [49]. Other studies have shown persistent effects after the SCIT was stopped [45, 48]. SCIT is the only therapy that can alter the natural course of the disease.

There are several possible reasons for the failure of immunotherapy. The patient may fail to comply with the immunotherapy regimen, there may be incorrect antigen dosing or too infrequent shot intervals, existing food or chemical sensitivities, non-allergic rhinitis (vasomotor, occupational, atrophic, or medication-induced), or rhinosinusitis or similar anatomic airway obstruction [44].

Although traditional SCIT has proven to be effective but poor compliance can limit its wide use. Furthermore the possibility of important side effects lead allergists to investigate new routes. Two different routes of administration, such as sublingual-spit and sublingual-swallow methods have been defined. In the former, the allergenic extract is retained in the mouth for a certain period of time, with assumption that total absorption will take place at oral mucous membrane level and then the patients spits it out. The latter is the combination of oral and sublingual immunotherapy. The allergenic extract is retained in the mouth for a period of time and then swallowed. There are also successful reports obtained with this method as well as unsuccessful results. We had very good results in our study group who took sublingual-oral immunotherapy and followed for 2 years [50].

MANAGING PREGNANT PATIENTS

Managing AR in pregnancy and lactation can pose a challenge to the treating physician, mainly because of the medical-legal aspects. However, there are suitable pharmacologic agents available for use in these patients. Recent recommendations are summarized below [46, 47] (Table 6).

FUTURE THERAPIES

Pharmacotherapies currently under development involve antiinterleukins (particularly to IL-5, which regulates eosinophil recruitment and lifespan), anti-chemokines, and more effective or less toxic anti-leukotrienes [51].

The newest "frontier" in therapy for inhalant allergies refractory to traditional therapies are the IgE blockers/binders (currently available agents and those in Phase III clinical trials have various mechanisms of action). Such agents usually involve periodic injections, which are currently expensive, and where such will fit in a physician's anti-allergy armamentarium is as yet unclear, as the effects of the nasal symptoms of inhalant allergies have been less than those on asthma, for which this class of drugs was

originally designed, and none are as yet approved for use in allergic rhinitis. Such is a recombinant DNA-derived humanized IgG1 monoclonal antibody [24, 52].

Table 6. Managing Allergic Rhinitis During Pregnancy

- Avoid known allergens
- Ocular symptoms can be managed with topical cromolyn supplemented with loratadine or cetirizine (both pregnancy category B) as needed
- Mild intermittent rhinitis symptoms can be treated with loratadine or cetirizine
- Addition of intranasal budesonide (pregnancy category B) used intermittently for moderate-severe symptoms
- Intranasal cromolyn can be used for mild, persistent rhinitis symptoms supplemented with loratadine or cetirizine with the addition of intranasal budesonide used regularly for moderate-severe symptoms
- Immunotherapy is not recommended unless the patient was on this before pregnancy with good response. The dosage should not be escalated during pregnancy.

Omalizumab, decreases free IgE levels and reduces FcεRI receptor expression on mast cells and basophils. This results in decreased mast cell activation and sensitivity, leading to a reduction in eosinophil influx and activation. Anti-IgE treatment with omalizumab might also result in decreased mast cell survival. To date, clinical studies of the efficacy of this drug on moderate to severe asthma that is refractory to conventional pharmacotherapy (and such is the usual indication for using omalizumab) is much more impressive than is data on efficacy for allergic rhinitis. The reason for the aforementioned difference in clinical efficacy has not been fully explained, but it is real, and omalizumab is not currently indicated for the treatment of allergic rhinitis [53, 54]. The combination of anti-IgE with SIT is superior to each single treatment protocol in children and adolescents with allergic rhinitis and the combination of anti-IgE plus SIT may be beneficial for the treatment of allergic diseases, offering improved efficacy, limited adverse effects, and potential immune-modifying effects. This however has large costs and not licensed in our country yet [55].

Novel therapies usually interfere specifically with immunologic mechanisms underlying allergen-induced pathology. Anti-IgE, GATA-3 which is a transcription factor that is specifically expressed in T helper 2 (Th2) cells and plays a critical role in the differentiation of Th2 cells from uncommitted CD4+ lymphocytes seems to be new fields of research on allergic rhinitis treatment. On the other hand recent innovative strategies in SCIT and SLIT, such as cluster and rush schemes, pre-seasonal therapy, recombinant allergen extracts and additive therapy with adjuvants or IgE-specific antibodies, high-doses SLIT preparation or allergen tablets are very promising [52].

ABBREVIATIONS

- INCSs = Intranasal corticosteroids
 CSs = Corticosteroids
 AR = Allergic rhinitis
 IMS = Intercontinental Marketing Services/International Medical Statistics
 HPA = Hypothalamic-pituitary-adrenal
 BDP = Beclomethasone dipropionate

- F = Flunisolide
 BUD = Budesonide
 PAF = Platelet Activating ffactor
 FP = Fluticasone propionate
 TAA = Triamcinolone acetate
 QOL = Quality of life
 MF = Mometasone furoate

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