LITERATURE REVIEW

The concept of control in allergic rhinitis: a new perspective

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ABSTRACT

The concept of disease control has recently been discussed for allergic rhinitis. The disease severity and control are distinct, yet related concepts. Allergic rhinitis control may be defined in several ways. A simple visual analog scale and the Rhino-Conjunctivitis Allergy-Control-Score are currently discussed. The treatment algorithm for allergic rhinitis in relation to control may be adapted from the state-of-the-art ARIA guidelines. Allergic rhinitis management driven by the level of control demands a close partnership relation between the physician and the patient. Several unmet needs must also be taken into account regarding the control of allergic rhinitis. The concept of control in this allergic inflammatory disease offers a new perspective for its assessment and therapeutic approach.

KEYWORDS: allergic rhinitis, severity, control

INTRODUCTION

The purpose of **Allergic Rhinitis and its Impact on Asthma (ARIA)**, the world health initiative on allergic rhinitis, is to educate and implement evidence-based management of allergic rhinitis in conjunction with asthma. ARIA is a non-governmental organization working in collaboration with the World Health Organization.

According to ARIA documents, **allergic rhinitis** is **defined** as an immune-mediated inflammatory disease of the nasal mucosa, induced after allergen exposure by an IgE-mediated hypersensitivity reaction in the nose, clinically characterized by suggestive symptoms of sneezing, nasal itching, rhinorrhea and nasal obstruction. Rhinitis symptoms occur during two or more consecutive days for more than one hour on most days[1].

Allergic rhinitis requires the demonstration of IgE-mediated hypersensitivity. The role of the **allergy specialist**, in the multidisciplinary approach together with ENT specialists, resides especially in[2]:

- performing and interpreting allergic history,
- *in vivo* and *in vitro* allergy testing (avoiding unevaluated risks for the patient or wrong evaluations),
- assessment of allergen cross-reactivities and allergic inflammation,
- complex environmental modification strategies to reduce allergen exposure,
- allergen-specific immunotherapy and/or anti-inflammatory pharmacologic therapies for patients with respiratory allergies,
- evaluating the ***control*** of the respiratory allergies.

Misinterpretation of the results for diagnostic tests or in assessing the control level by non-specialists can lead to inappropriate diagnosis and/or management. Conversely, the under-appreciation of the severity of respiratory allergy can lead to life-endangering under-treatment or the lack of potentially specific immunotherapy[2].

Allergic rhinitis **classification** consisted previously into *seasonal*, *perennial* and *occupational* forms, but this subdivision is nowadays considered *not satisfactory* because[1,3]:

- in certain regions, pollens and molds are perennial allergens,
- weather/climatic changes modify the timing, distribution, quantity and quality of pollens as aeroallergens,
- traveling creates different exposure conditions to aeroallergens in different times of the year,
- symptoms to perennial aeroallergens may not always be present all year round,
- lifestyle, building and inhabited conditions influence indoor aeroallergen exposure,

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- many patients are sensitized to several different allergens,
- nonspecific irritants, such as air pollution, may aggravate symptoms.

State-of-the-art ARIA guidelines recently classified allergic rhinitis[1]:

- according to **evolution of symptoms**:
  - ***intermittent allergic rhinitis***
    - less than 4 days per week *or*
    - for less than 4 consecutive weeks;
  - ***persistent allergic rhinitis***
    - more than 4 days per week *and*
    - lasting more than 4 consecutive weeks;
- according to the **severity of symptoms**:
  - ***mild allergic rhinitis***
    - normal sleep,
    - no impairment of school or work activities,
    - no impairment of daily activities, leisure, sport,
    - symptoms present, but not troublesome;
  - ***moderate-severe allergic rhinitis***
    - sleep disturbance,
    - impairment of school or work activities,
    - impairment of daily activities, leisure, sport,
    - troublesome symptoms.

A **modified ARIA criterion** (m-ARIA) for the allergic rhinitis severity classification is a validated useful clinical tool to discriminate moderate from severe forms, in both treated and untreated patients. The m-ARIA classification categorizes allergic rhinitis severity into:

- *mild allergic rhinitis* (no affected items),
- *moderate allergic rhinitis* (1-3 affected items),
- *severe allergic rhinitis* (all four affected items)[4].

The classical clinical **phenotypes** of seasonal and perennial rhinitis cannot be used interchangeably with those from ARIA classification, "*intermittent*" and "*persistent*" being not synonymous with "*seasonal*" and "*perennial*".

Severe chronic upper airway disease is defined by patients whose symptoms are inadequately controlled despite pharmacologic treatment based on guidelines[5,6].

Endotypes are subtypes of allergic rhinitis, considered an inflammatory disorder, which are defined by distinct pathobiological mechanisms. Using the level of concordance between allergic symptoms induced on exposure to pollen in a pollen challenge chamber, some allergic rhinitis endotypes reflect concordantly low versus high total symptom scores in both the natural season and the pollen challenge chamber, respectively, while another endotype presents greater total symptom scores in the natural season than in the pollen challenge chamber[7]. Moreover, by assessing nasal inflammation, using cellular (GATA-3 T lymphocyte, eosinophil, mast cell numbers) and allergic inflammation soluble markers (IL-5, eosinophil cationic protein), persistent allergic rhinitis is characterized by a significantly greater eosinophilic and predominantly Th_2 cell-mediated nasal inflammatory profile compared with intermittent allergic rhinitis[8].

PHARMACOTHERAPEUTIC APPROACH

Pharmacotherapeutic approach of inflammation in allergic rhinitis includes nowadays several classes of intranasal and oral drugs, generally considered effective and safe.

Intranasal glucocorticosteroids are recommended for the treatment of allergic rhinitis because they have potent anti-inflammatory effects by activating the glucocorticoid receptor, to directly or indirectly regulate the transcription of the target genes. Glucocorticosteroids available for intranasal administration in allergic rhinitis are (in alphabetical order): beclomethasone dipropionate, budesonide, ciclesonide, flunisolide, fluticasone propionate, fluticasone furoate, mometasone furoate, triamcinolone acetonide[1]. Although new-generation, oral nonsedating H_1-antihistamines and antileukotrienes possess anti-inflammatory effects, intranasal glucocorticosteroids are the ***most effective anti-inflammatory medication*** for controlling symptoms of allergic rhinitis[1,9].

New generation intranasal halogenated glucocorticosteroids, *fluticasone furoate* and *mometasone furoate*, have high affinity for the glucocorticoid receptor compared with other corticosteroid molecules[10]. Such new second-generation agents, currently in use, have favorable pharmacokinetic characteristics that minimize systemic bioavailability compared with older representatives[11]. Yearlong therapy with either fluticasone furoate or mometasone furoate nasal sprays reveals no mucosal atrophy as well as reduction in inflammation[12].

Fluticasone furoate represents a molecular evolution of fluticasone propionate and there is scientific evidence of therapeutic advantages over fluticasone propionate. A literature review, achieved through PubMed and Medline research methods, supports the clinical efficacy of fluticasone furoate *versus* placebo in reducing nasal and ocular symptoms related to allergic rhinitis, with a good safety profile[13].

Because intranasal glucocorticosteroids are considered *first-line treatment* for moderate-to-severe allergic rhinitis, to guide clinical decision-making, it was evaluated a therapeutic index (TIX) for such drugs reflecting efficacy and safety, using a Medline search (1966 to June 2009), identifying all placebo-controlled randomized trials and reports for safety issues. Three parameters each for efficacy: patient rated total nasal symptom score (TNSS), patient rated total ocular symptom score (TOSS), patient or physicians global assessment (PGA), and safety: epistaxis, long term side effects on growth or cortisol levels (observation period at least 6 month), systemic ocular side effects such as glaucoma or an increased ocular pressure were defined. The highest value of therapeutic index score obtained for *mometasone furoate* indicates its high efficacy and low potential of adverse events[14].

Systemic glucocorticosteroids should not be considered usually for the treatment of allergic rhinitis, due to their adverse effects. They can be used only for few

days (short course of oral corticosteroids) as a last resort of treatment when combinations of other medications are ineffective. These drugs should be avoided in children, pregnant women and patients with known contraindications[15]. Moreover, a systemic oral corticosteroid in seasonal allergic rhinitis has no significant therapeutic advantage, as a recent direct comparison between mometasone furoate nasal spray and betamethasone valerate oral tablets revealed[16].

Cysteinyl leukotriene 1 ($CysLT_1$) receptor blockers are the orally active ***antileukotrienes*** suggested for the allergic rhinitis treatment in adults and children with seasonal forms, in preschool children with persistent allergic rhinitis and in patients with concomitant asthma, due to their anti-inflammatory effects. Cysteinyl leukotrienes are inflammatory lipid mediators (LTC_4, LTD_4 and LTE_4) synthesized from arachidonic acid by a variety of cells, including mast cells, eosinophils, basophils and macrophages, and involved as multifunctional mediators not only in asthma, but also in allergic rhinitis. Evidences that support the recommendation for the treatment of allergic rhinitis are available only for *montelukast*[1,15].

Intranasal chromones, described as mast cell stabilizers with weak non-steroidal anti-inflammatory effects, disodium cromoglycate and nedocromil sodium, have excellent safety profile, but a relatively low therapeutic value, due to limited efficacy and poor patient adherence, as a consequence of the need for administration four times daily[15].

Second-generation, non-sedating ***oral H_1-antihistamines***, with no cardiotoxicity or anticholinergic effects and which do not interact with cytochrome P450, are recommended in patients with allergic rhinitis.

Such second generation H_1-antihistamines are (in alphabetical order): bilastine, cetirizine, desloratadine, ebastine, fexofenadine, levocetirizine, loratadine, mizolastine, rupatadine[1,17].

Several *in vivo* studies support anti-inflammatory activity for treatment with non-sedating H_1-antihistamines, especially for long-term periods.

Loratadine decreases serum vascular cell adhesion molecule 1 (VCAM-1, CD106) levels in patients with house dust mite-induced allergic rhinitis[18].

Desloratadine, active metabolite of loratadine, reduces, in patients allergic to weed pollen, the peripheral expression of chemokines CCL3 (macrophage inflammatory protein MIP-1*alpha*), CCL4 (macrophage inflammatory protein MIP-1*beta*) and CCL5 (regulated and normal T cell expressed and secreted, RANTES), suggesting that it may act as down-modulator of allergic inflammation, possibly through a negative regulation of the chemokines involved in activation and attraction of eosinophils[19]. In patients with seasonal allergic rhinitis, desloratadine significantly reduces IL-4 levels in fluids recovered from nasal lavage[20].

Cetirizine treatment induces a significant decrease of local nasal IL-4 and IL-8 levels in children with persistent allergic rhinitis[21].

Levocetirizine, the active enantiomer of cetirizine, reduces nasal inflammation present in children with mite-induced persistent allergic rhinitis, indicated by nasal exhaled nitric oxide changes after allergen specific nasal challenge and confirmed by the reduction in nasal eosinophil cationic protein. This anti-inflammatory effect is likely to be not due to the effect on H_1 receptors, but rather to a direct influence on eosinophils[22]. Levocetirizine also significantly reduces IL-4 and IL-8 in nasal lavage fluids in patients with seasonal allergic rhinitis[23].

In adults with symptoms not controlled with new generation oral H_1-antihistamine alone and who are less averse to side effects of oral decongestants, administration of a combined treatment as a rescue medication may be beneficial[15]. For example, the *desloratadine / pseudoephedrine combination* may be considered for patients with seasonal allergic rhinitis and moderate-to-severe nasal congestion who do not receive adequate relief of congestion symptoms from H_1-antihistamine monotherapy[24].

Intranasal H_1-antihistamines, azelastine and levocabastine, are effective and safe in the treatment of moderate-to-severe persistent allergic rhinitis[25]. *Azelastine*, with many pharmacologic effects on mediators of allergic inflammation[26], was recently proved to be an useful therapeutic approach when administered together with fluticasone propionate in a novel intranasal formulation[27].

For all clinical forms of allergic rhinitis, ***allergen and irritant avoidance*** may be appropriate[1].

Allergen-specific immunotherapy is effective in reducing the symptoms of allergic rhinitis and the use of symptom relieving medications. This type of therapy is currently the only treatment with long-lasting clinical effects and potential to modify the natural course of the disease, to prevent the development of new allergen sensitizations and to reduce the risk for development of asthma, especially in children[28-30].

Allergen-specific sublingual immunotherapy (SLIT) is a valid non-invasive form of immunotherapy, considered a safe and efficacious treatment for allergic rhinitis. There is an evidence-based practice for sublingual immunotherapy in allergic rhinitis[31].

The **compliance to treatment** indicates how much doses of the prescribed medication for allergic rhinitis are taken, whereas **adherence** implies also an agreement between patient and physician about the therapeutic plan. Adherence is a main problem in all long-term treatments for allergic rhinitis. There are few data on the adherence in real life for pharmacological treatments (intranasal glucocorticosteroids or H_1-antihistamines), whereas more data are available for specific immunotherapy[32].

ALLERGIC RHINITIS CONTROL

The concept of **disease control** has recently been discussed for allergic rhinitis. Diagnosis should be re-evaluated in case of uncontrolled disease, also for exclusion of concomitant anatomic nasal deformities, global airway dysfunction and systemic diseases[33].

Allergic rhinitis control may be defined in several ways. For someone who is not an expert in the field of respiratory allergy control may indicate disease prevention, or even cure, but in clinical practice it refers to the achievement of a generally acceptable clinical state for which the manifestations are minimized by therapeutic interventions. The goal of the treatment for a chronic inflammatory disease, for which there is currently no cure, is to achieve and maintain clinical control for prolonged periods with due regard to the safety profiles and the costs of the treatments in order to achieve this goal.

Allergic rhinitis control may be clinically defined as a disease state in which patients do not have symptoms or the remaining symptoms are not considered bothersome, do not affect sleep, school or work activities and daily activities, leisure or sport.

Allergic rhinitis severity and allergic rhinitis control are distinct, yet related concepts. Severity describes the underlying disease in the absence of therapy and is ideally defined without concurrent treatment confounding its assessment. Control describes the clinical status of disease in the face of intervention.

There are limitations to classifying allergic rhinitis severity in patients already being treated. Management based on allergic rhinitis control encompasses the principles of chronic disease management, goal orientation and individualization of therapy. Allergic rhinitis control can be expected to change over time. Therefore, control level should be assessed at every clinical visit, and management decisions should consider the level of control. Individual parameters by which allergic rhinitis severity and control can be defined overlap in some ways.

The overall control of allergic rhinitis should encompass reduction of symptoms, as well as improvements in health-related quality of life, limitations of daily activity, cognition status and comorbid conditions. None of the currently available instruments for measuring the control of allergic rhinitis are capable of assessing all these aspects, therefore there is a need to develop appropriate new more detailed tools[34].

A simple **visual analog scale** (VAS) score as a clinical tool for evaluation of allergic rhinitis control was recently proposed[5], with a VAS score for total nasal symptoms (TNS) ≥ 5 as the cut-off point for uncontrolled allergic rhinitis. One-fifth of the patients with allergic rhinitis are uncontrolled despite medical treatment[5].

Treatment of allergic rhinitis according to the ARIA guidelines is associated with a lower incidence of uncontrolled rhinitis (10%) than the free-of-choice anti-allergic treatment (18%). The use of a VAS score for total nasal symptoms is a convenient tool for evaluation of control in allergic rhinitis as it embedded information on a validated quality of life questionnaire for rhinitis and the reflective total nasal symptoms scores (RT4SS)[5,33].

The **treatment algorithm** for allergic rhinitis **in relation to control** was recently adapted from the ARIA guidelines[33]. If VAS score is ≥ 5 for TNS or there is a need of treatment, than a *first-line treatment* is applied for 2-4 weeks and recommendations to avoid irritants and allergens if possible.

1. if allergic rhinitis is controlled (VAS value < 5):
   continue treatment as needed and consider allergen-specific immunotherapy.
2. if allergic rhinitis is uncontrolled (VAS ≥ 5):
   - than *second-line treatment* is applied for 2-4 weeks, recommendations to avoid irritants and allergens if possible and consider allergen-specific immunotherapy:
     - if allergic rhinitis is controlled (VAS value < 5): continue treatment as needed and consider allergen-specific immunotherapy.
     - but if allergic rhinitis is uncontrolled (VAS ≥ 5) after this step:
       reconsider diagnosis, exclude concomitant pathology, consider immunotherapy or surgery33.

Such an allergic rhinitis management driven by level of control demands a close **partnership relation** between physician and patient.

Recently, it was reported the validation of an **Allergy-Control-SCORE** (ACS), including three categories of symptoms, for lung, nose and eyes[35]. Moreover, it was also reported the validation of the score for eyes and nose symptoms only, using symptomatic allergy medication to a *combined symptom-medication score* (SMS), the **Rhino-Conjunctivitis Allergy-Control-Score** (RC-ACS) and, in addition, the validation of the Eye-Allergy-Control-Score (E-ACS) and the Nose-Allergy-Control-Score (N-ACS)[36].

The *symptom score* evaluate the severity of allergy symptoms on a scale[36] ranging from 0 to 3:

0 = absent (no sign/symptom evident);
1 = mild (sign/symptom clearly present, but minimal awareness; easily tolerated);
2 = moderate (definite awareness of sign/symptom that is bothersome, but tolerable);
3 = severe (sign/symptoms hard to tolerate; causes interference with daily activities and/or sleeping).

For each day, the sum of the values of the seven *allergy symptoms* is calculated, including:

- nasal (sneezing, itching, running, blockage) and
- ocular (itching, tearing, redness) symptoms[36].

The allergy medication needed is also documented.

Categories of medication considered include:

- nasal and ocular H_1-antihistamines and glucocorticosteroids,
- nasal decongestants, nasal cromones,
- oral antileukotrienes,
- systemic H_1-antihistamines, glucocorticosteroids and their combinations[36].

The total number of score points (SP) for symptoms for one day is 21 (each of the 7 symptoms scored with a maximum of 3). The maximum SP that can be achieved by used medication is also set to 21 SP, subdivided into the two sub-scores for the nose (max. 12 SP) and the eyes (max. 9 SP). Each drug is scored considering pharmacological action (corresponding ATC code), expected impact on symptoms, route of administration, the dose and effect duration. Each *medication score* is balanced for the respective weight on symptoms and within the maximum score of each organ system[36].

The RC-ACS is obtained by adding the daily medication score to the daily symptom score leading to a range of 0 to 42 SP. The daily E-ACS and N-ACS range from 0 to 18 SP and 0 to 24 SP, respectively[36].

Several **unmet needs** must also be taken into account regarding the control of allergic rhinitis: validation of VAS scoring system as a clinical tool for evaluation of control (involving short-term and long-term evaluation of symptom control), defining success of pharmacotherapy and allergen-specific immunotherapy in terms of control in allergic rhinitis[33].

In **conclusion**, the concept of control in allergic rhinitis offers a new perspective for its assessment and therapeutic approach.

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