Chapter 7

Allergic Sensitization in Rhinitis and Asthma

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Additional information is available at the end of the chapter

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Abstract

Allergic rhinitis (AR) is usually defined as an inflammatory disease of the nasal mucosa induced by an interaction of environmental allergens and IgE in sensitized patients. Its symptoms are sneezing, nasal itching, rhinorrhoea and nasal obstruction. Allergic rhinitis affects approximately 20- 30% of the population worldwide and its prevalence is increasing. Isolated AR is rare and it actually has to be considered as a systemic allergic disease, associated to comorbidities, such as conjunctivitis, chronic middle ear effusions, irregular sleep, sinusitis, lymphoid hypertrophy with obstructive sleep apnoea. The most relevant comorbidity is asthma, a heterogeneous disease, usually characterized by chronic airway inflammation in which many cells and cellular elements play an important role. Bronchial asthma is characterized by bronchial hyper-reactivity and symptoms may be triggered or worsened by factors such as viral infections, allergens, tobacco smoke, exercise and stress. A state of "minimal persistent inflammation" is permanently maintained in the lower respiratory tract of asthmatic individuals. The diagnosis of asthma is based on evidence of variable airflow limitation tested with spirometry and a positive bronchodilation reversibility test. Skin prick tests (SPTs) are widely used to demonstrate an immediate IgE-mediated allergic reaction. They represent a major diagnostic tool in the field of allergy. Skin prick tests have a high specificity and sensitivity for the diagnosis of inhalant allergens. Immunotherapy (AIT) for allergic diseases has entered in a new age characterized by the development of a few innovative therapeutic classes of standardized allergen formulations registered. Clinical randomized trials have demonstrated the efficacy of AIT in allergic rhinitis in children and in adults, expressed in terms of reduction of symptom score and use of rescue medication. The efficacy is confirmed both for subcutaneous (SCIT) and sublingual (SLIT) immunotherapy in adults and in pediatric patients. The long lasting effect of AIT after its discontinuation is an important added value of this therapy. Controlled studies are available, where the carry-over effect of AIT is demonstrated for two years after discontinuance. The capacity to prevent new sensitizations, and to modify the evolution of the disease from the rhinitis to asthma are two important features of AIT. Allergen immunotherapy showed preventive capacity and also a carryover effect once treatment is discontinued.

Keywords: Rhinitis, asthma, allergy diagnostic, specific immunotherapy

1. Introduction

Allergic rhinitis (AR) is an inflammatory disease of the nasal mucosa induced by allergens in sensitized patients with specific immunoglobulin E (IgE).

Its symptoms include sneezing, nasal itching, rhinorrhoea and nasal obstruction. Epidemiologically, AR represents a health problem for both children and adults on a global basis: approximately 20–30% of the population worldwide suffer its affects and its prevalence is increasing.

Genetic and socio-environmental factors may influence the development of AR: the urbanization processes, high levels of motor engine pollution and western lifestyles are significantly linked to high incidences of respiratory allergy diseases. Allergic rhinitis is not considered to be a serious disease but it significantly limits daily life activities, such as school and work performance – this leads to increased direct social costs (i. e., medical costs, mainly related to symptomatic medications) and indirect costs due to decreased work performance (AR is in fact one of the most significant causes of absenteeism from work).

The guidelines ARIA introduced for the first time represented a classification of severity of two degrees, according to the presence or absence of the effects of rhinitis on general well-being and quality of life (HRQL) and a classification regarding the duration of symptoms: "intermittent" and "persistent".

One component part of the symptoms of AR is nasal obstruction –the most disabling symptom as it seriously affects quality of life by interfering with normal sleep structures and over time facilitates the onset of complications such as allergic conjunctivitis, rhino-sinusitis and nasal polyposis, otitis media, adenoid hypertrophy and orthodontic problems.

The most relevant comorbidity is asthma. Past observations about the link between upper and lower airway disease has generated a united airway disease (UAD) notion. Around 38% of all AR patients present asthma symptoms or show a higher frequency of bronchial hyper-reactivity. In addition, 78% of asthma patients present rhinitis symptoms.

Allergic rhinitis can be considered a risk factor for asthma exacerbation. In asthmatic patients, AR symptoms induce worsened asthma control, more frequent asthma attacks and admission to emergency rooms; in addition the use of drugs for asthma significantly increases with the severity of AR. Diagnosis of asthma is based on evidence of a variable airflow limitation which is tested via spirometry and a positive bronchodilation reversibility test. Another test used to diagnose asthma is airways responsiveness: it is necessary in this test to measure how airways react when they are challenged with a trigger. Airway inflammation may also be tested via measurement of exhaled nitric oxide concentration. Nitric oxide is physiologically produced by lungs, but higher than normal levels indicate airways are inflamed, a condition which is associated with asthma.

The concordance of a typical history of allergic symptoms and the results of proper diagnostic tests forms the basis for AR diagnosis.

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Skin prick tests (SPTs) are usually considered the standard diagnostic procedure to support an allergic basis for the patient's symptoms, to confirm suspected causes of the patient's symptoms and/or to identify sensitizing allergens.

The SPT represents the first line approach, to be preferred to *in vitro* IgE determination due to its high sensitivity, rapidity of performance, simplicity, ease of use and low cost.

International (EAACI, WAO) and national guidelines (SIAAIC) considered *in vitro* tests for allergic diseases as second-level tests, to be used after a SPT, for confirmation or in cases when an SPT cannot be carried out. Specific IgE for inhalant allergens (dust mites, dermatophagoides pteronyssinus, dermatophagoides farinae , pollens, latex, molds) and for some food allergens that can induce respiratory symptoms, are measured to understand trigger agents of allergic diseases such as conjunctivitis, rhinitis, asthma or professional allergic respiratory diseases.

This assay allows identification, in a quantitative way, of the sensitization towards a complete allergen and/or a specific allergy molecule. The possibility of performing a deeper analysis with molecular diagnostics gives important information which is more specific than from an SPT.

The identification of specific IgE against cross reacting molecules such as Profilins, Bet v1-PR10, lipid transfer protein and calcium-binding protein, or against "genuine molecules", represents an added value and allows distinction between true and false polysensitizations. Component resolved diagnosis has an important impact on the management of the patient in terms of the accuracy of the diagnosis, or the decision on therapies like specific immunotherapy prescription.

Immunotherapy for allergic diseases (AIT) has entered a new age, characterized by the development of a few innovative therapeutic classes of standardized, registered allergen formulations. AIT is considered a safe and efficacious treatment for patients with type-1 respiratory allergies. The ability of sublingual immunotherapy (SLIT) to elicit antigen specific tolerance is linked to the peculiar biology of oral antigen-presenting cells. In the absence of danger signals, Langerhans cells, myeloid dendritic cells and the macrophages located in oral tissues or the tonsils are biased towards the induction of Th1 and IL 10 producing CD4+ regulatory T cells.

Clinical randomized trials have demonstrated the efficacy of AIT in AR in children and adults, expressed in terms of are duction in symptom scores and the use of rescue medication.

2. Allergic rhinitis and its comorbidities

Allergic rhinitis (AR) is usually defined as an inflammatory disease of the nasal mucosa induced by an interaction of environmental allergens and immunoglobulin E (IgE) in sensitized patients [1].

Allergic rhinitis is the most widespread type of non-infectious rhinitis. Its symptoms include sneezing, nasal itching, rhinorrhoea and nasal obstruction. Ocular signs, such as itching of the eyes, redness and tearing, occur in a large percentage of patients suffering from AR.

Epidemiologically, AR represents a health problem for both children and adults on a global basis. Allergic rhinitis affects approximately 20–30% of the population worldwide and its prevalence is increasing. In Italy it is estimated that 24% of the population suffers of AR (data 2007–2010 GEIRD-LIBRA) [2]. Nevertheless, around one-third of allergic patients have never visited a physician, an observation which suggests that the actual prevalence of AR may be underestimated with the condition perhaps being mistreated [3].

Allergic rhinitis is usually categorized as a multi-factorial disease and many hypothesis hypotheses have been suggested to explain its increasing occurrence.

As in case of asthma, genetic factors may influence the development of AR; these diseases reveal strong familial and intra-individual clustering, implying an overlapping disease aetiology.

A socio-environmental hypothesis is based on several studies, demonstrating that the urbanization process, high levels of motor engine pollution and western lifestyles are significantly linked to the high incidence of respiratory allergy diseases, found to prevail among inhabitants of metropolitan areas over rural areas [4].

Allergic rhinitis is not considered a serious disease and although it is certainly not life threatening it does significantly limit daily activities such as an individual's performance at school or work, which leads to increased direct social costs (i. e., medical costs, mainly related to symptomatic medications) and indirect costs due to a decrease in workforce performance (AR is in fact one of the most significant causes of absenteeism).

The guidelines ARIA introduced had for the first time a classification of severity of two degrees, according to the presence or absence of the effects of rhinitis on general well-being and on the quality of life (health-related quality of life, HRQL).

By means of a validated questionnaire, it has been possible to demonstrate that AR has a real and measurable impact on HRQL, considered more important than more serious, chronic diseases, such as diabetes mellitus. For a patient with AR, important limitations coexist, due directly to rhinitis symptoms and indirectly to chronic use of drugs –both can impact social life: e. g., sleep disorders leading to daytime sleepiness and increased accidents, difficulty in concentrating, headaches, mood changes, depression, irritability and fatigue. When considered altogether, these conditions can heavily weigh on a person's social and professional life [5].

As part of the symptoms of AR, nasal obstruction is the most disabling as it seriously affects quality of life by interfering with normal sleep patterns. It also facilitates the onset of complications such as rhino-sinusitis and nasal polyposis.

Allergic Rhinitis classification is based on both duration and chronicity as well as on the grading of severity (mild or moderate–severe) of symptoms. It also takes into account the impact of the disease on daily activities, such as work/school performance and impaired sleep.

Regarding duration of symptoms, AR is defined "intermittent" when it occurs less than 4 days per week or less than 4 consecutive weeks per year. Vice versa, "persistent" AR occurs when symptoms are present more than 4 days per week and more than 4 consecutive weeks per year.

Isolated AR is rare and it actually has to be considered as a systemic allergic disease, associated to comorbidities, such as conjunctivitis, chronic middle ear effusions, irregular sleep, sinusitis, lymphoid hypertrophy with obstructive sleep apnoea. However, the most relevant comorbidity is asthma. Past observations about the link between upper and lower airways disease has generated the notion of united airway disease (UAD) [6].

The relationship between the two compartments is clinical, epidemiological, functional and immunological. Subsequently, the official standpoint is that rhinitis is both allergic and non-allergic, and is acknowledged as a risk factor for asthma.

Recent surveys show that around 38% of all AR patients present asthma symptoms too. On the other hand, 78% of asthma patients present rhinitis symptoms.

This finding is based not only on epidemiological data but also on physiological evidence. In fact, patients with AR (even without asthma) show a higher frequency of bronchial hyperreactivity. This could be linked to the duration of AR and the number of sensitizations of patients.

Furthermore, AR can be considered as risk factor for asthma exacerbation. In asthmatic patients, AR symptoms induce worsened asthma control, more frequent asthma attacks and admission to emergency rooms. In addition, the use of drugs for asthma significantly increase with the severity of AR.

Other comorbid disorders and links to AR, are:

a. **Allergic conjunctivitis,** resulting in conjunctival injection chemosis, itchy eyes and tearing. These symptoms have been observed in more than 75% of patients with AR caused by pollen. Moreover, patients sensitized to pollen report ocular symptoms more frequently than patients sensitized to house dust mites [7].

b. AR patients compared with non-allergic subjects are more frequently affected by **rhinosinusitis**. Infections of the ear and of the nasal and paranasal sinuses are conditions secondary to the obstruction of the Eustachian tube as a consequence of local inflammatory infiltrate [8]. Patients with AR, particularly those sensitized to house dust mites, rarely develop **nasal polyps** [9]. Some studies show that around 21% of AR patients are affected by **otitis media**. In the case of AR in children, the incidence of otitis media is twice as large when compared to non-allergic children [10].

c. It has been reported that among children with AR, particularly if sensitized to dust mites, **adenoid hypertrophy** (AH) occurs significantly more frequently than in children with other allergic diseases (asthma/atopic dermatitis) or without allergies. **Sleep and quality of life**: nasal obstruction resulting from rhinitis causes sleep disorders, fatigue and tiredness during the day, as well asloss of smell and taste [11]. Chronic nasal obstruction in children can cause excessive breathing through the mouth which leads to **orthodontic problems** such as an excessive stretching of the face and malocclusion.

The concordance of a typical history of allergic symptoms and the results of properdiagnostic tests formsthe basis of AR diagnosis.

Skin prick tests (SPTs) are usually considered the standard diagnostic procedure to support an allergic basis for the patient's symptoms, to confirm suspected causes of the patient's symptoms and/or to identify sensitizing allergens.

The reasons for preference of the SPT as a first line approach, over *in vitro* IgE determination are the following: high sensitivity, rapidity of performance, simplicity, ease of use and low cost.

Nonetheless, particular situations (extensive skin disease, skin test suppressive therapy, such as antihistamines that cannot be discontinued, or uncooperative patients) are indications for using serum specific IgE determination by immunoassays.

In some cases of rhinitis further study is useful via fibre optic nasal endoscopy, such as for a typical symptoms or physical findings, complications, other suspected conditions or when symptoms apparently do not respond to therapy. For suspected complications or comorbidities such as nasal polyposis with sinusitis, a computed tomography (CT) scan may be useful.

Before prescribing immunotherapy it is useful to study nasal cellularity via nasal cytology [12]. Cytological findings can in fact support the allergic pathogenesis of rinithis (neutrophil infiltration for mite allergy, eosinophilic infiltrate in the case of hay fever) or might indicate non-allergic rhinitis [13].

3. Asthma

Asthma is a heterogeneous disease, usually characterized by chronic airway inflammation in which many cells and cellular elements play an important role.

Chronic inflammation causes an associated increase in airway hyper-responsiveness leading to recurrent episodes of wheezing, breathlessness, chest tightness and coughing, particularly at night or in the early hours of the morning. Generally, these episodes are accompanied by widespread but variable airflow obstruction that is often reversible, either spontaneously or following therapy.

The pathogenesis of these alterations involves many mechanisms, in particular inflammatory cell infiltration, mediator release and airway remodelling.

As reported in the definition, bronchial asthma is characterized by bronchial hyper-reactivity, and its symptoms may be triggered, or worsened, by factors such as viral infections, allergens, tobacco smoke, exercise and stress. A state of "minimal persistent inflammation" is permanently maintained in the lower respiratory tract of asthmatic individuals. The intensity of clinical symptoms varies in relation to the actual size of the bronchial obstruction and to the degree of its subjective perception by the patient [14].

The probability that respiratory disease is really asthma becomes lower if the patient has:

- An isolated cough with no other respiratory symptoms. Chronic production of sputum. Shortness of breath associated with dizziness, light-headedness or peripheral tingling. Chest pain. Exercise-induced dyspnoea with noisy inspiration (stridor).

The diagnosis must be done preferably before starting treatment because it is often more difficult to confirm the diagnosis afterwards.

It is increasingly clear that bronchial asthma is not a single disease but a complex set of overlapping syndromes; for classification purposes it is necessary to take into account the phenotype of the disease resulting from a given set of genetic and environmental interactions.

In a recent review a classification has been proposed based on phenotypes of asthma which takes into account both clinical and physiological triggers as well as the cell types involved in inflammation.

From the clinical and physiological point of view it is necessary to classify asthma according to its severity; in order to define severity several parameters are considered: for instance, the frequency of exacerbations and age of onset correlate with a more favorable prognosis and improved lung function in the case of early-onset, typically allergic asthma; in contrast, resistance to drug treatment(especially neutrophilic asthma) and its possible association with chronic restriction is mainly observed in non-allergic patients.

As far as triggering factors are concerned, bronchial asthma should be further divided into allergic asthma, often associated with rhinitis and conjunctivitis but with a favorable prognosis; exercise-induced asthma; occupational asthma (about15% of asthma in adults); aspirin sensitive asthma (with eosinophilic inflammation and frequent association with nasal polyposis and sinusitis) and premenstrual asthma [15].

Finally, asthma should be characterized according to the specific cellularity responsible for inflammation in eosinophilic or neutrophilic. It is increasingly clear that the correct identification of phenotype of asthma is essential to set a targeted therapy and to obtain good control of symptoms and improve the quality of life of patients [16]. The classification of severity of asthma is assessed retrospectively from the level of treatment required to control symptoms and exacerbations:

- Mild asthma: well controlled with as needed relief medication alone or with a low dose of inhaled corticosteroids (ICS), leukotriene receptor antagonist or cromones.
- Moderate asthma: well controlled with a low dose of ICS/long-acting beta agonist (LABA).
- Severe asthma: controlled with high dose ICS/LABA or asthma that remains uncontrolled despite this treatment. In the diagnosis of severe asthma it is important to exclude common causes of uncontrolled asthma such as poor inhaler technique, poor medication adherence, incorrect diagnosis of asthma, comorbidities (rhinosinusitis, gastroesophageal reflux, obesity, obstructive sleep apnoea).

Asthma can be effectively treated and when asthma is well-controlled, patients can avoid troublesome symptoms during the day and night, need little or no relief medication, have productive, physically active lives, normal lung function and avoid serious exacerbations.

The diagnosis of asthma is based on evidence of variable airflow limitation tested with spirometry and a positive bronchodilation reversibility test [17].

The spirometry allows to two main measurements: the volume of air that the patient can exhale in the first second of exhalation (the forced expiratory volume in one second, or FEV_1] and the total amount of air that the patient blows out (the forced vital capacity or FVC). These readings are compared against the average measurements for people of the same age, sex and height, and immediately indicate if airways are obstructed or not. The most important spirometric value is the FVC. To measure FVC, the patient inhales maximally, and then exhales as rapidly and as completely as possible. Normal lungs generally can empty more than 80%of their volume in 6 seconds or less. The forced expiratory volume in one second (FEV_1] is the volume of air exhaled in the first second of the FVC maneuver. The FEV_1/FVC ratio is expressed as a percentage and is known as the Tiffeneau Index. A reduced value of FEV_1 and of absolute FEV_1/FVC ratio indicates an obstructive ventilatory pattern. In this case, a bronchodilator challenge test is recommended to detect patients with reversible airway obstruction. This is known as "reversibility testing", and it can be useful in distinguishing asthma from other lung pathological conditions, such as chronic obstructive pulmonary disease (COPD).

Another test used to diagnose asthma is airway responsiveness. When the diagnosis is not possible from the above described test it is necessary to measure how airways react when they are challenged with a trigger. The test involves inhaling progressively increasing amounts of a medication (e. g., metacholine, histamine) at regular intervals, and taking FEV_1 measurements to see if they fall below a certain threshold (typically 80% of baseline values). In some cases, exercise may be used as a trigger.

Testing airway inflammation may also be useful. This can be done by measuring the exhaled nitric oxide concentration. Nitric oxide is physiologically produced by the lungs, but higher than normal levels indicate airways are inflamed, a condition which is associated with asthma [18].

4. Allergy diagnostics *in vivo*: when, what, who?

The SPT is widely used to demonstrate an immediate IgE-mediated allergic reaction. These tests represent a major diagnostic tool in the field of allergy. Skin prick tests have a high specificity and sensitivity for the diagnosis of inhalant allergens.

Their simplicity, rapidity of performance, low cost, and high sensitivity explain their key position in the diagnosis of allergies. If properly performed, they yield useful evidence for the diagnosis of a specific allergy. In respiratory allergies skin tests represent the first diagnostic method used in patients with a suggestive clinical history of allergic rhinitis, conjunctivitis and/or asthma. They can be used from infancy to old age [19].

Usually, skin tests are performed on one or both forearms, depending on the age and size of the patient. SPTs can be performed and interpreted in infants; usually the size of the lower arm limits the number of allergens that can be tested. Prick testing involves introducing a needle

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into the upper layers of the skin and releasing a drop of allergen extract after gently lifting the epidermis. The release of preformed histamine from mast cells causes increased vascular permeability via smooth muscle contraction and development of a wheal; inflammatory mediators initiate a neural reflex causing vasodilatation, leading to erythema (the flare). The distance between two prick tests should be 2 cm to avoid cross-contamination [20]. It is important to avoid bleeding of the skin. Negative (saline) and positive (e. g., 9% histamine hydrochloride solution) controls are required in SPTs to make any interpretation possible. The positive control should optimally show a wheal diameter of ‡3 mm [21].

Skin tests are regarded positive if the mean wheal diameter is ≥3 mm. Very large reactions are not necessarily associated with a more severe disease. Skin test results may be negative even if patients are allergic. If a skin test is positive, one will have to distinguish reactions which are clinically relevant from those which are not. History and/or challenge tests help to clarify the relevance of a sensitization. Usually, a clinically irrelevant sensitization does not lead to practical consequences.

Drugs can suppress skin tests, therefore, it is always necessary to ask patients about the medication they have taken in the preceding days. This is particularly the case for oral H1-antihistamines [22], but I also the case for anxiolytics –not however for antidepressants [23]. Topical skin corticosteroids may also alter skin reactivity. The inhibitory effect of H1-antihistamines lasts about 2–7 days while the inhibitory effect of topical steroids lasts up to 7 days.

False-positive skin tests may result from dermographism, 'irritant' reactions or a non-specific enhancement from a nearby strong reaction. Contamination of the needle by another allergen extract may also induce false-positive results. To overcome this problem, it is recommended that needles or puncture devices be changed between each test.

False-negative skin tests can be caused by poor potency of extracts [24], drugs modulating the allergic reaction, diseases attenuating the skin's response, weak punctures or a limited local production of allergen-specific IgE– only in the nose [25] or eyes [26].

Inhalant allergens to be tested should be chosen after considering various factors: the spread environment, the homologies between the various pollen and lifestyle habits. The Global Allergy and Asthma European Network suggested a panel of allergens to be tested in all patients in Europe: Pollen (Birch, Cypress, Grass, Mugwort, Olive, Parietaria officinalis, Ragweed), house dust mites, animals (dog and cat) and moulds (Alternaria, Cladosporium).

The SPT is usually considered to be a safe procedure, but recently there have been occasional reports of generalized allergic reactions or vasovagal reactions [27]. Based on the literature, the occurrence of systemic reactions with inhalant allergens has diminished over the last 30years. In general, the risk of systemic reactions is lower with SPTs than with intradermal testing. Some patients (those with histories of previous anaphylactic reactions, small children, pregnant women, uncontrolled asthmatic sand those with a high degree of reactivity) should be considered at higher risk of systemic/anaphylactic reactions. Based on the literature, the risk of fatality due to an SPT is extremely remote, and severe/anaphylactic reactions are rare. Nevertheless, this risk cannot be completely excluded, especially in highly susceptible subjects. Physicians who perform SPTs should be aware of this and apply simple precautionary rules [28].

5. Allergy diagnostics *in vitro*: few appropriate allergens

Specific IgE can be detected either *in vivo* by SPTs or *in vitro* by specific IgE assay: both methods usually employ whole extracts from allergenic sources which contain a mixture of allergenic and non-allergenic proteins [29] –the IgE response is specifically directed towards some molecules [30]. Specific IgE for inhalant allergens (dust mites, dermatophagoides pteronyssinus, dermatophagoides farinae, pollens, latex, molds) and for some food allergens that can induce respiratory symptoms (serum albumin, wheat flour, casein, fish parvalbumin, vegetables as Lipid Transfer Protein, lysozyme, etc.) are measured to understand the trigger agents of allergic diseases such as conjunctivitis, rhinitis, asthma or professional allergic respiratory diseases.

International (EAACI European Allergy Asthma Clinical immunology, WAO World Allergy Organization) and National Guidelines (SIAAIC Società italiana Asma Allergia Immunologia Clinica) considered *in vitro* tests for allergic diseases as a second-level test, to be used after the SPT, for confirmation or in the case where the SPT cannot be carried out because the patient takes antihistamine drug so r shows atopic dermatitis, etc.

Measurement of *in vitro* specific IgE (sIgE) is an important tool.

It allows the identification, in a quantitative way, of the sensitization towards a complete allergen and/or a specific allergy molecule. The possibility to perform a deeper analysis with molecular diagnostics gives important information, more specific than that gained from the SPT. Specific IgE is usually measured for common allergens: dermatophagoides, grass, trees, cypress, pellitory, ragweed, plantagolanceolata, olive pollen, alternaria, dog and cat dander and cladosporium herbarum with particular concern to botanicals.

Extractive preparations used for SPTs usually contain cross-reactive components which are highly conserved across widely different allergen sources [31]. This may complicate the interpretation of the diagnostic results, especially in polysensitized subjects. The introduction of highly purified natural and recombinant single allergenic molecules represents an important improvement in the diagnosis of IgE sensitizations and cross reactivities.

6. Component resolve diagnostics

The identification of a specific IgE against cross-reacting molecules such as Profilins, Bet v1-PR10, lipid transfer protein, calcium-binding protein or against “genuine molecules”, represents an added value and allows the distinction between true and false polysensitizations. A true polysensitization occurs when specific IgE is present against genuine components of different allergenic sources. The genuine molecules for grass sensitization are: Phl p1, usually the first allergen of grass induces IgE and Phl p 5; Bet v 1, is the genuine molecule of birch, Par j2 of Pellitory, Pla l 1 of Plantago l, Amb a 1 of ragweed, Fe d1 of cat, Der p 1 and Der p 2 of Dermathophagoides are the genuine molecules of dust mites. False polysensitizations are due to the presence of panallergens like profilin or calcium-binding proteins causing SPT positive results [32].

Component resolved diagnosis (CRD) has an important impact on the management of the patient in terms of the accuracy of the diagnosis, or decision on therapy (like specific immunotherapy prescription). Recent studies [33] demonstrated that CRD use in the diagnostic pathway implies a change in the decision regarding treatment in more than 50% of patients compared to diagnosis based only on clinical history and skin test results [34].

An *in vitro* test is useful in these cases:

- *Positive SPT is in agreement with clinical history –in this case in vitro tests add information* [35] and allows: Detect of patients with sensitization to genuine molecules that cause allergic diseases [2]. Distinction among patients with positive prick tests for more than one allergen, about70% of allergic patients have a polysensitization due to sensitization to pan-allergens [36, 37]. Evaluate in childhood of the "spreading" of sensitization towards each grass molecule and has prognostic information about the evolution of the disease: a correlation between phenotypes of sensitization and illness severity [38, 39, 40]. Choice of better therapies: if only clinical history and prick tests are used, without the support of CRD results, the choice of the therapy is incorrect in more than 50% of the cases, with an important cost increase [41, 42, 43]. Identification of the ideal patient for immunotherapy, represented by the patients with sensitization towards genuine molecules [44, 45] with high possibilities of improving symptoms and increasing safety during administration. Improvement to quality of life of allergic patients via the correct diagnosis [32]. Detection of patients with sensitization to pan-allergens such as *profilin* or *calcium-binding protein*. This can induce cross-reactivity with foods and pollens. Additionally, symptoms are shown for a long period of time if pollen grains are not detected in the air: the profilin, a molecule from grass, trees, ragweed pollen is able to induce nasal and bronchial inflammation for a long time period [34]. Management of the risk of anaphylaxis for allergic latex patients: it is important to detect IgE for latex molecules inducing anaphylaxis like Hev b 1, Hev b 3, Hev b 5, Hevb 6, to predict the risk of anaphylaxis; patients with only IgE for Hev b8 are not able to develop anaphylaxis because Hev b8 is not present in the surgery devices.
- *Negative prick tests and clinical history suitable for allergies: when there is not agreement between prick test results and clinical history*. Sometimes prick tests are less sensitivity than *in vitro* tests because the extract used for prick tests could miss some important allergenic molecules. *In vitro* tests can identify IgE towards particular molecules that induce allergic professional reactions: serum albumin, lipid transfer protein, lysozyme intake like preserves in some drugs, molecular allergens of Aspergillus like Asp f 4, Asp f6, Asp f 3 markers of Bronchopolmonar Aspergillosy or molecular allergens of Alternaria like the Alt a 1 marker of asthma [46, 47].

6.1. Allergen-specific immunotherapy can modify the natural history of allergies: The eligible patient

Immunotherapy for allergic diseases has entered a new age characterized by the development of a few innovative therapeutic classes of standardized, registered allergen formulations, which have been assigned marketing authorization codes (in Italy: AIC, Autorizzazioneall'Im-

missione in Commercio) as *bona fide* pharmaceutical specialties, having been supported by large and robust, randomized controlled clinical trials (RCT) [48].

The European Academy of Allergy Clinical Immunology EAACI and the American Academy of Allergic Asthma and Immunology (AAAI) has recently proposed the term "allergen immunotherapy" (AIT) to indicate the treatment of an allergic disease by a drug containing a given allergen.

To date, AIT products available on the market can be administered as sublingual immunotherapy (SLIT), but in principle subcutaneous immunotherapy (SCIT) products could be registered as well. AIT is considered a safe and efficacious treatment for patients with type-1 respiratory allergies [49, 1]. The ability of SLIT to elicit antigen-specific tolerance is linked to the peculiar biology of oral antigen-presenting cells. In the absence of danger signals, Langerhans cells, myeloid dendritic cells, macrophages located in oral tissues or tonsils are biased towards the inductions of Th 1 and IL 10 producing CD4+ regulatory T cells. This supports the induction of tolerance rather than an effector immune response generating inflammation. Sublingual administration does not lead to any detectable systemic exposure of intact allergens nor to the induction of new IgE sensitizations. Furthermore, due to the limited numbers of mast cells located in submucosal areas, SLIT has a very favorable safety profile, being adverse in its reaction locally and, only rarely systemically. The induction of CD4+ regulatory T cells and blocking anti-inflammatory IgGs or IgAs is considered important for tolerance induction after SLIT [50]. The clinical efficacy of AIT is supported by numerous clinical trials and meta-analyses [51].

6.1.1. Eligible patient for AIT

To identify the right patient to benefit from AIT the following criteria should be considered.

A) Proper diagnosis (IgE-mediated respiratory diseases).

B) Symptoms

- Rhinocongiuntivitis (rhinitis should be mild–severe persistent according to ARIA).
- Persistent symptoms for subjects responding poorly to medication. Interference with quality of life.
- Worsening of quality of life (sleep, social, working and school activities).
- Poor compliance to pharmacological therapy.
- Lack of comorbilities.

6.1.2. Clinical efficacy and disease-modifying effect

Clinical randomized trials have demonstrated the efficacy of AIT in AR in children and adults, expressed in terms of are duction of symptom score and use of rescue medication. The efficacy is confirmed both for subcutaneous (SCIT) and sublingual (SLIT) immunotherapy in adults and pediatric patients. AIT efficacy has been demonstrated with these allergenes: alternaria, grass, birch, pellitory, ragweed and Dermatophagoides.

In childhood SLIT is preferred to SCIT for patient compliance and safety.

The choice of SLIT or SCIT depends on several factors, including clinical conditions and risk–benefit evaluation. The long-lasting effect of AIT after its discontinuation is an important added value of this therapy as compared to pharmacological therapy. Controlled studies are available, where the carry-over effect of AIT is demonstrated, including the capacity to decrease symptom scores and rescue medication for two years after discontinuance. Previously, SLIT with non-registered products had been reported to maintain a favorable effect on patient respiratory allergies up to 12 years after discontinuation.

The capacity to prevent new sensitizations and to modify the evolution of the disease from rhinitis to asthma are two important features of AIT [52]. A trial which will formally evaluate the prevention of asthma with grass-based AIT is ongoing [53].

As part of acorrect allergic evaluation at baseline, the "asthma control test" (ACT), the "visual analog scale" (VAS) of symptoms, the results of spirometry and records of drug consumption should be completed before beginning AIT.

AIT is usually continued for 3–5 years. Patients undergoing this treatment should be controlled at least yearly and at the end of the treatment re-evaluated via ACT, VAS, spirometry and drug consumption.

Recent multicenter randomized double-blind studies with AIT in tablet form (registered drugs with AIC) demonstrated changes in the natural history of the disease.

The primary endpoint of this randomized controlled clinical study was to evaluate the efficacy of 75. 000 SQ grass tablets in patients with rhinoconjunctivitis to grass-based pollen. Major end-points were the score of rhinoconjunctivitis symptoms and symptomatic drug usage. The observation was extended not only to the 3 years of treatment but also to the 2 years of follow -up without therapy, in order to document the "disease modifying effect", according to the EMA's European Medicines Agency definition.

A total of 634 patients were randomized (1:1) to receive the tablet or placebo once a day.

The subjects had to receive the drug 4–8 months before the start of the grass pollen season.

The subjects in the active arm of this study had a symptoms score and drug usage of 31% and 21% lower than placebo, respectively.

If we also consider the weighted average of the combined score of symptoms and drug efficacy in the long term it is even more evident. The effect of the weighted mean score of symptoms and medications was 33%, and in each study year statistically significant results were observed. Some studies also included patients with mild and/or moderate asthma. In this case the combined weighted score for the symptoms of asthma was reduced by 39% compared to the placebo over the entire pollen season and 44% when taking into account only the peak of the pollen season. Importantly, a carry-over effect was observed both in the first and second year after the discontinuation of a 3-year treatment.

The treatment at the end of the fifth year (3 years of treatment and 2 years of follow-up without treatment) resulted in a statistically significant and clinically relevant 25% reduction (p = 0.

004) in the score of rhinoconjunctivitis symptoms, associated with a reduced usage of symptomatic drugs. In addition, the combined score of symptoms and medication showed a statistically significant reduction (-33%) on average for the 5 pollen seasons.

The efficacy of treatment was similar in monosensitized and polisensitized patients.

When considered together, these data confirm that AIT is capable of modifying the natural history of allergic with a carry-over effect which, being persistent for at least 2years after AIT discontinuation, can be considered "disease modifying" according to an EMA classification document [54].

6.1.3. Polisensitized patients

Epidemiological studies and clinical trials have shown that the percentage of polisensitization ranges from 20% to 90% with great variability depending on populations.

Polisensitization may also be associated with different clinical pictures with respect to monosensitized patients, especially those with a more impaired quality of life and more severe symptoms. In addition allergic children seem to display a higher frequency of sensitizations than their parents, especially in families with polisensitization. In addition, a small proportion of patients remain monosensitized during their whole lives. A functional defect of T-regulatory cells may explain the tendency to develop polisensitization. Children with persistent monosensitization produce higher amounts of Interleukin 10 and interferon gamma than children who develop polisensitization. This observation might envisage different immunologic phenotypes for monosensitizedand polisensitized patients [55]. While in North America AIT is composed of a mix of allergens, in Europe clinicians prefer to identify the most important allergen causing symptoms to choose AIT.

A series of real life multicentre observational studies named POLISMAIL (Polysensitization Impact on Immunotherapy) were conducted to elucidate the clinical relevance of polisensitization and were conducted in 11 allergy centers in Italy.

The POLISMAIL studies are based around several issues: polisensitization usually starts from childhood – polisensitization progresses with age for up to 80% of allergic adults – polisensitizationmay depend on a T-regulatory cell defect – polisensitization may significantly affect quality of life – polisensitizationmay be associated with more severe symptoms– polisensitization may discourage immunotherapy prescription.

The POLISMAIL studies indicated that polisensitization should not constitute an obstacle to AIT prescription. Only the clinically relevant allergens, such as the sensitizing allergen which is capable of inducing symptoms when inhaled, were chosen for AIT 56Some cases demonstrate true polisensitizations, other cases are sensitizations for pan allergens like profilin or calcium-binding proteins. Component resolve diagnosis (with either recombinant or purified allergens for prick tests or IgE in serum dosage) is a tool to improve the accurate identification of the sensitization allergens [57, 58]. A positive skin test could be a sensitization to a major allergen or simply be a result of a cross-reacting response to a panallergen like profilin Bet v 2 or Phl p 12, present with small conformational changes in both species of pollen. The

demonstration of sensitization for genuine allergenic components and/or pan allergenic components can modify vaccine strategies [59].

6.1.4. AIT and quality of life

The aim of this position paper (the GA [2] LEN taskforce on patient reported outcomes (PROs) and health-related quality of life (HRQL)) is to define PROs and their meaning in asthma and rhinitis treatment, explore the available tools to provide criteria for a proper choice, identify patient-related factors which could influence PRO assessment, define specific recommendations for assessment, analysis and results spreading and underline unexplored areas and unmet needs. PROs assessment is gaining increasing importance, and it must be performed with a rigorous methodological procedure using validated tools. This approach enables a better understanding of patient-related factors influencing clinical trials and real-life management outcomes, identify patients subgroups that can benefit from specific treatment and management plans and tailor treatment to address PROs (not only physician-defined targets) to improve allergic asthma and rhinitis management and therapy. Allergic diseases can deeply interfere with patients' HRQL with detrimental effects to life being physical, psychological and social. Allergic rhinitis and asthma cause substantial social and economic burdens. School and work performance, including school and work absences, daily activity and quality of life are significantly impaired in both children and adults with respiratory allergies.

In order to measure if allergy disease modifies quality of life [60] many validated questionnaires are available. Most of them are specifically developed for AR, asthma and the evaluation of patients in AIT. HRQL has become an increasingly important aspect of outcome evaluation in healthcare research, providing a more comprehensive approach to patients, proving that nowadays we cannot renounce this tool [61].

International guidelines consider quality of life and other PROs an important primary outcome of clinical trials in order to evaluate the efficacy of AIT in allergic respiratory diseases ("Guideline on the clinical development of products for specific immunotherapy for the treatment of allergic diseases" 20 November 2008). Some variables could interfere with the results of PROs: age, stress, depression, coping, alessitimia. Clinical randomized trials show that AIT (SCIT and SLIT) improves quality of life and HRQL significantly [62, 63]).

6.1.5. Safety and tolerability

Clinical trials demonstrated that SLIT is generally safe and well tolerated in a real world setting. Usually adverse events are mild with rare and few severe reactions. Adverse reactions occur frequently during the first month of initiation or at the first administration: this confirms the importance of the first uptake being in the physician's office. Most of the patients show mild to moderate adverse reactions at the beginning of the treatment, however, the side effects tend to disappear after a few minutes. No fatal or near-fatal adverse reactions have been noticed [64]

6.1.6. AIT cost- effectiveness

The social costs of AR are very relevant and are estimated to be 4–6 billion dollars/year in the United States with average annual costs of 1089 euros per child and 1549 euros per adult in

Europe. The cost is higher if allergic asthma is included. Allergen immunotherapy showed a preventive capacity and also a carry-over effect once the treatment is discontinued.

International literature on the cost-effectiveness of immunotherapy for respiratory allergies included studies conducted based on an economic evaluation of AIT or allergic rhinoconjunctivitis, AR, asthma and rhinitis in combination with asthma. The evidence appears to support the cost-effectiveness of immunotherapy compared with pharmacotherapy for allergic rhinoconjunctivitis, and subcutaneous immunotherapy compared with pharmacotherapy for AR and asthma [65, 66].

The cost-effectiveness of immunotherapy depends on the duration of the clinical benefit of AIT following treatment discontinuance and on the break-even point of cumulative costs between immunotherapy and pharmacotherapy. This retrospective, and partly cross-sectional, study shows that high-dose sublingual immunotherapy may be effective in reducing the burden of disease as measured by the number of exacerbations need for medical visits and school–nursery time losses, with a considerable reduction of annual management costs. Also when considering only direct medical costs, the reduction is clear and appreciable when considering the whole population, as well as in the allergen type sub-samples and in the case-control sub-analysis of allergic asthmatic patients [67]. Patients with newly diagnosed AR initiating AIT incurred significantly in a lower healthcare costs than matched control subjects beginning 3 months after AIT initiation and continuing throughout the 18 month follow-up period. The significant cost benefits achieved by children with AR diagnoses who initiated AIT were also observed for adults with AR [68].

A prospective study demonstrated that SCIT was cost effectiveness after 6years of follow-up, in particular 3years after the drop of AIT [69]. The comparison of the cost of AIT and drug treatment must be discussed regarding the few available studies conducted in Germany and in the United states in the 1990s. Buchner reported in a retrospective, 10-year study that the direct and indirect costs in patients with AR and asthma were reduced by 54% in subjects treated with AIT compared with those treated with symptomatic drugs. Fisher estimated that the use of AIT could save respectively DM500 (610 dollars) and DM 1000 (1220 dollars) per year in subjects with AR and asthma. A recently retrospective study examined the economic effect of 3 years of AIT and a follow-up of 10 years: and found that the advantage ofdrug therapy started after 6 years.

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