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Safety of Immunotherapy

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Synonyms

Allergen immunotherapy; Allergen-specific desensitization; Allergy immunotherapy; Allergy injections; Allergy shots; Hyposensitization; Immunotherapy

Background

Although the benefits of immunotherapy have been well demonstrated for the treatment of many allergic conditions such as allergic rhinitis, allergic asthma, and stinging insect allergy (Casale and Stokes 2011), the risks of adverse reactions must be considered when immunotherapy is used.

Local Reactions

Localized reactions at the site of immunotherapy injections are fairly common, with frequencies ranging from 26 % to 82 % patients and 0.7 % to 4 % of injections (Cox et al. 2011). These local reactions may involve local erythema, swelling, and itching. In one survey of 249 patients

undergoing immunotherapy and who experienced local reactions, 84.7 % reported reactions smaller than the palm of the hand, and 81.9 % classified local reactions as not bothersome at all or only slightly bothersome. Ninety-six percent of these individuals who had local reactions stated they would not stop immunotherapy because of the local reactions (Coop and Tankersley 2008). In one retrospective study, local reactions were found to not be predictive of local reactions at the next injection (Calabria et al. 2009). Individual local reactions also do not appear to be predictive of subsequent systemic reactions. However, some individuals who have a large frequency of large local reactions may have an increased risk for future systemic reactions (Cox et al. 2011).

Systemic Reactions

Systemic reactions to immunotherapy involve organ-specific systems distant from the injection site and can be very serious with symptoms potentially including generalized rash/urticaria, rhinorrhea, dyspnea, wheezing, hypotension, and anaphylactic shock (Windom and Lockey 2008). Although the risk of severe systemic reactions is very low, life-threatening and fatal reactions do occur. The prevalence of severe systemic reactions after immunotherapy ranges from less than 1 % of patients receiving conventional immunotherapy to about 34 % of patients who undergo rush immunotherapy (Cox et al. 2011).

A review of systemic reaction rates reported in studies published within the past 15 years found the rate of systemic reactions per injection with conventional immunotherapy to be approximately 0.2 % (Cox et al. 2010). Through survey data, it is estimated that the fatality rate in the United States from immunotherapy injections is about one per 2.5 million injections (Nelson 2009).

Specific Important Considerations and Precautions

Asthma: Immunotherapy for asthma should not be initiated unless an individual's asthma is stable and under control. Patients with severe or uncontrolled asthma have an increased risk for systemic reactions when receiving immunotherapy injections. Moreover, fatal and near-fatal reactions from immunotherapy injections were found to be more common in those with severe asthma. An assessment of a patient's asthma control should be performed prior to each immunotherapy injection (Cox et al. 2011).

Timing of Anaphylactic Reactions: Most serious systemic reactions from immunotherapy injections occur within 30 min after an injection. Therefore, patients should remain in the physician's office/medical facility for at least 30 min after an immunotherapy injection for continued observation (Cox et al. 2011).

Beta-Adrenergic Blocker Medication: Use of beta-adrenergic blocking agents is a risk factor for more serious and treatment-resistant anaphylaxis. Concomitant use of beta-blocker medications and immunotherapy should be carefully considered from an individual patient's risk/benefit standpoint (Cox et al. 2011).

Angiotensin-Converting Enzyme (ACE) Inhibitor Medication: A greater risk of more severe reactions from venom immunotherapy has been associated with the use of ACE inhibitors. Discontinuation of ACE inhibitors should be considered for patients receiving venom immunotherapy. If ACE inhibitor therapy is required and no alternative therapy is available, then immunotherapy

should be carefully considered from an individual patient's risk/benefit standpoint (Cox et al. 2011).

Pregnancy: Immunotherapy can be continued but is typically not initiated in a pregnant individual. If an individual becomes pregnant during the buildup phase of immunotherapy, and the current dose of immunotherapy is subtherapeutic, then discontinuation of immunotherapy should be considered (Cox et al. 2011).

Cross-References

- ▶ Allergen Immunotherapy, Overview
- ▶ Immunotherapy for Allergic Rhinitis
- ▶ Immunotherapy for Asthma
- ▶ Immunotherapy for Hymenoptera Allergy
- ▶ Immunotherapy, Mechanisms
- ▶ Immunotherapy with Recombinant and DNA-Conjugated Allergens
- ▶ Sublingual Immunotherapy

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Sensitization and Allergy to Natural Rubber Latex

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Synonyms

Caoutchouc; Latex allergy

Definition

While additives which are required for the manufacturing process and for stabilization of rubber (like the sulfur-containing vulcanizers (mercaptobenzothiazoles, carbamates, thiurams), antioxidants (amines), and rubber pigments) may induce an allergic late-phase (type IV) sensitization and allergic contact dermatitis (Shah and Chowdhury 2011), rubber products made from natural latex contain a small amount of proteins, which can induce immediate-type (type I) sensitization and allergic immediate-type symptoms. This entry will focus on sensitization and allergy to natural rubber latex produced from the rubber tree *Hevea brasiliensis*.

Historical Background

Latex is a sap-like extract which is derived from various plants. It is usually exuded upon tissue injury and has important functions involved in wound healing and antimicrobial defense. Latex contains a complex mixture of various biochemical compounds, e.g., proteins, resins, and gums. Some components of latex (poly-cis-isoprene) qualify for raw material for rubber products. Several plants serve as latex sources, e.g., the rubber tree (*Hevea brasiliensis*), guayule (*Parthenium argenteum*), gutta-percha tree

(*Palaquium*), or *Manilkara chicle*. The most important source is the rubber tree *Hevea brasiliensis*.

Initially, *Hevea brasiliensis* grew only in the Amazon rainforest in Brazil. The discovery of the vulcanization procedure in 1839 by Charles Goodyear and the local monopoly on the plants caused a regional economic boom in that region. Although exporting seeds or living trees was prohibited, in 1875, British citizens finally succeeded to smuggle seeds to Kew Garden in London. After the seeds had germinated, seedlings were sent to the British colonies Ceylon and Singapore. Today, the most important producers of natural rubber latex (in the following named latex) are located in the Far East (Thailand, Indonesia, Malaysia, India, and China). In addition *Hevea brasiliensis* is also cultured in Africa (Ivory Coast, Nigeria, and Liberia) (http://en.wikipedia.org/wiki/Latex_allergy).

The first allergic, immediate-type symptoms elicited by rubber contact were observed upon exposure to dental materials and rubber-coated cables. Later, also household gloves, condoms, balloons, pacifiers, and other products containing latex were found to induce immediate-type symptoms. With increasing use of medical gloves, allergic reactions became an important medical problem mainly for health-care workers and for certain patient groups with a history of repeated surgical procedures, e.g., because of congenital malformations (spina bifida). The increasing use of medical gloves and a simultaneous change in the production process both increased the risk of immediate-type allergies. The mass production of low-priced medical gloves was associated with a shortening of washing processes and with a decreased denaturation of latex allergens by reduced ammonia. As a result, medical gloves were rich of intact latex proteins. Another important aspect contributing to the epidemic of latex allergy was the powdering of medical gloves with cornstarch instead of talcum. Latex allergens excellently bind to cornstarch powder, thereby contaminating large areas by airborne powder particles loaded with latex allergen.

Allergens

Ultracentrifugation of the fresh rubber sap results in nine fractions of which three can most easily be discerned: rubber particle proteins, the C-serum, and the bottom fraction (B-serum). Rubber particles are water insoluble, whereas most of the C- and B-serum proteins are water soluble (Steinman and Ruden 2008). Proteins are classified into rubber particle proteins, C-serum proteins which present in the cytosol fraction, and B-serum proteins which are extra-cytosolic proteins.

More than 200 proteins have been identified in latex from *Hevea brasiliensis*, and about one quarter of them may bind to human IgE, a process which is a necessary prerequisite for the induction of immediate-type allergy. Thus far, 14 allergens of *Hevea brasiliensis* (Hev b) have been identified (<http://www.allergome.org>, Table 1). Some of them contain different allergenic fragments like prohevein, which yields Hev b 6.02 and 6.03. Others exist in various isoforms. Latex allergens either belong to plant defense proteins or are involved in the biosyntheses of polyisoprene and in the coagulation of rubber elongation factor. Some latex allergens have structural- or pathogenesis-related functions.

Different patient groups, i.e., patients with congenital malformations and health-care workers, exhibit a different sensitization pattern. Moreover, the sensitization pattern may vary between different regions. These observations may be explained by the finding that latex allergens are not homogeneously distributed in the glove, i.e., outside or inside parts of medical gloves may present different allergens. Furthermore, the manufacturing process may change the composition of latex allergens in rubber products, thereby causing different sensitization patterns.

Some latex allergens show sequence homology to allergens from other sources (fruits, vegetables, indoor plants, or molds), thereby explaining the cross-reactivity between latex and foods. On the other hand, sensitization to latex may be primarily acquired by the exposure to non-latex allergens, suggesting that latex sensitization or allergy is a secondary phenomenon (Rihs et al. 2006).

Symptoms

Latex allergy may involve all symptoms of an IgE-mediated disease, ranging from urticaria, rhinoconjunctivitis, or asthma to anaphylactic shock. Symptoms are classified according to the severity grade in mild (only skin manifestation), moderate (mild internal symptoms), severe (anaphylactic shock), and fatal or near-fatal reactions (Ring and Meßmer 1979). Another form is the “contact urticaria syndrome” (Gimenez-Arnau et al. 2010), which, however, is not universally accepted. The first latex-associated fatal or near-fatal anaphylactic reactions were observed during surgical procedures or invasive diagnostics (e.g., barium enema examination). Today, unrecognized latex allergy is responsible for about 20 % of perioperative anaphylaxis (Mota and Turrini 2012).

Nearly all patients suffering from latex allergy complain about contact urticaria, itching, and/or erythema at the site of direct exposure (mostly to latex gloves or other latex rubber material). Some patients also develop more widespread urticaria, and systemic reactions of the respiratory tract, cardiovascular system, or visceral organs may occur upon either skin contact or allergen uptake through the surgical sites. In addition, respiratory symptoms may be elicited when powdered latex gloves are used. Other manifestations are delayed eczematous reactions due to a late-phase immediate-type reaction at the site of latex exposure (protein contact dermatitis). Finally, it has been discussed that latex allergy might result in disturbed wound healing.

Frequently, cross-reactivity between latex and certain, mainly tropical, foods (e.g., banana, chestnut, kiwi, avocado) induce anaphylactic reactions to food (Blanco et al. 1994). Another cross sensitization may be caused by the common indoor plant weeping fig (*Ficus benjamina*).

Epidemiology

The major risk factors for becoming sensitized to latex are intense exposure to latex allergens, preexisting hand eczema, and atopy (defined as

Sensitization and Allergy to Natural Rubber Latex, Table 1 Allergens of *Hevea brasiliensis* (Hev b) (<http://www.allergome.org>; Yeang 2004; Steinman and Ruden 2008)

Name	Common name	Significance as allergen for	Cross-reactivity
Hev b 1	Rubber elongation factor	RPP +++ → P ^a	
Hev b 2	Glucanase	B ++ → HCW ^b	Allergen possibly responsible for cross-reactivity with food allergens → “Latex-fruit syndrome”
Hev b 3	Small rubber particle protein	RPP +++ → P ^a	
Hev b 4	Component of microhelix complex, lecithinase homologue	B ?	
Hev b 5	Hev b 5-like	C +++ → HCW ^b +++ → P ^a	Re
Hev b 6.01	Prohevein	B +++ → HCW ^b and P ^a	High for Hev b 6.01 and 6.02 (banana, kiwi, avocado)
Hev b 6.02	N-terminal hevein	B +++ → HCW ^b and P ^a	
Hev b 6.03	C-terminal hevein	+++ → HCW ^b and P ^a	
Hev b 7.01	Patatin (esterase)	B ?	Structural homology to proteins from potato and tomato
Hev b 7.02		C ++ → P ^a	
Hev b 8	Profilin	C +	Partial sequence homology with profilin from other sources
Hev b 9	Enolase (glycolytic enzyme)	C +	Medium cross-reactivity with molds
Hev b 10	Mn superoxide dismutases	B +	Medium cross-reactivity with molds
Hev b 11	Chitinase, hevein-like protein	B +	Allergen possibly responsible for cross-reactivity with food allergens → “Latex-fruit syndrome”
Hev b 12	Lipid transfer proteins (LTP)	B +	Cross-reactivity with LTP from fruits, vegetables, nuts, pollen
Hev b 13	ENSP (esterase)	B +++ → HCW ^b	
Hev b 14	Chitinase, hevamine		

RPP, rubber particle protein; B, B-serum proteins (extra-cytosolic); C, C-serum proteins (cytosol fraction of latex); +, mild; ++, moderate; +++, strong

^aP, patients with congenital malformations

^bHCW, health-care workers

history of hay fever, allergic asthma, or atopic eczema and/or immediate-type sensitization to common aeroallergens such as cat dander, house dust mite, or grass pollen). Since gloves and other devices made of latex are widely used in medicine, health-care workers and patients with congenital malformations (e.g., spina bifida, urogenital abnormalities), who need frequent or

continuous medical care, have been found to be particularly affected.

When the latex allergy epidemic had reached its peak, up to 17 % of health-care workers (Agarwal and Gawkrödger 2002) and 20–72 % of patients with spina bifida (Taylor and Erkek 2004) were found to be allergic to latex. An increased frequency was also evident in rubber

industry workers. Among unselected adults undergoing surgical procedures in Germany, more than 1 % were found to suffer from latex allergy (Ruëff et al. 2001). A similar incidence of latex allergy was found in the general population of France (Bousquet et al. 2006).

Throughout the following years, the costs, which the statutory accident insurances had to bear for compensation of affected workers, significantly increased in many countries forcing specific countermeasures. Due to measures of primary prevention, the frequency of immediate-type allergy to latex fell significantly. Today, latex allergy is still present in subjects who got sensitized before the implementation of countermeasures. New cases of latex allergy occur mainly in atopic subjects being intensely exposed to the allergen.

Diagnostics

History, skin testing, determination of specific IgE antibodies in the serum, and challenge tests are the standard tools to diagnose an immediate-type allergy. For skin testing, the use of standardized skin test extracts is recommended. The raw latex milk may be also used but can evoke false-negative (ammoniated) reactions or systemic anaphylactic symptoms. Use of recombinant molecular latex allergens may improve measurement of latex-specific IgE antibodies in the serum.

Challenge tests can be performed using suspected material, which releases latex allergens. Alternatively, conjunctival or nasal challenge tests are possible using incremental concentrations of diluted skin test extracts.

Treatment/Management

Primary Prevention: In order to prevent de novo sensitization to latex, individuals presenting with a significant atopic disease (or with hand dermatoses) should avoid exposure to latex allergens.

A general ban of medical gloves made of latex is not recommended, as they tend to be stronger, more flexible, and are better accepted by health-care workers (Palosuo et al. 2011). Banning of powdered latex gloves and reducing the amount of allergens in latex products are the cornerstones for preventing latex sensitization and allergy (Wrangsjö et al. 2012).

Management of Patients Suffering from Latex Allergy: Allergen avoidance is the mainstay of treatment (Taylor and Erkek 2004). Patients or workers with latex allergy have to avoid any latex exposure. Non-latex alternatives should be practiced for all skin contacts involving latex allergic individuals. Use of non-powdered latex gloves in the environment of latex allergic subjects (working place or medical environment) will significantly reduce the allergenicity of the gloves and will prevent airborne symptoms. Within a few years after these preventive measures had been started, the intensity of latex sensitization in latex allergic health-care workers significantly decreased (Ruëff et al. 2004).

An emergency kit should be provided to patients with a history of anaphylaxis upon exposure to low amounts of latex allergens and/or with a reaction to hidden allergens (e.g., food contaminated by handling with latex gloves). The emergency kit contains antihistamines and corticosteroids for oral treatment and an epinephrine injector.

Specific immunotherapy with latex was effective in small cohort studies (Tabar et al. 2002; Lasa Luaces et al. 2012). However, this type of therapy is not yet available and probably never will be. Because of the excellent results of primary and secondary prevention, the development of licensed products will presumably not be pursued.

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Single-Plex Immunoassays and Autoanalyzers

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Synonyms

ELISA; FEIA; HytTECH-288; IEMA; Immulite; ImmunoCAP; MAST; RAST; RIST

Definition

Single-plex immunoassays are procedures used in laboratories to detect and quantify individual analytes (antigens or antibodies), one specificity at a time. They involve the manual or computer-automated mixing of individual antigen and antibody reagents together at different steps throughout the assay to permit immune-complex formation and ultimately generation of a final isotopic, colorimetric, fluorescent, or chemiluminescent response signal. The measured response is either proportional (noncompetitive binding) or inversely proportional (competitive binding) to the analyte's concentration following interpolation from a reference curve. This section will use IgE as the model analyte for illustration.

Introduction

The first immunoassay was reported in 1968 for the measurement of human insulin (Berson and Yalow, 2006). They described a competitive-binding reaction in a series of test tubes containing radiolabeled and unlabeled insulin for limited insulin-specific IgG antibody binding sites. The more (unlabeled) insulin in a specimen, the less

radioactive insulin would bind to antibody. Thus, the final radioactivity response measured was inversely proportional to the concentration of the insulin in the standard or unknown serum. From this origin, many modifications of this basic immunoassay format have been developed over the years. One widely used modification has been the noncompetitive assay format in which a solid-phase anti-insulin binds insulin from serum. Then, following a buffer wash, bound insulin is detected with a second radiolabeled antibody to insulin that binds to a different determinant or epitope on the insulin molecule. This noncompetitive-binding immunoassay that uses an unlabeled immobilized capture antibody and a labeled detection antibody is called a two-site immunoradiometric assay to distinguish it from the single antibody-dependent competitive-binding radioimmunoassay. In later years, the isotopic labels have been replaced by non-isotopic labels that involve the coupling of enzymes or fluorescent molecules to the detection antibody. The use of non-isotopic labels has increased the shelf life of the reagents and reduced the hazard associated with radioisotope use and disposal.

Radioimmunosorbent Test and Radioallergosorbent Assay

By 1967 when IgE was discovered, two noncompetitive solid-phase radioimmunoassays called the radioimmunosorbent test (*RIST*) for total serum IgE and the radioallergosorbent test or *RAST* for allergen-specific IgE had been developed as a modification to the Berson and Yalow immunoassay format (Wide et al. 1967). In its original form, the *RIST* used an antihuman IgE coupled to a paper disk solid phase to bind IgE, and following a buffer wash, a second radioiodinated antihuman IgE was used to detect bound IgE on the disk. The *RIST* was cross-calibrated against the WHO IgE Reference preparation, and this assay became the primary method for measuring total serum IgE for many years. As a modification of the *RIST*, the *RAST* employed a paper disk solid phase to which allergenic molecules typically prepared as crude

extracts of biological materials were covalently attached to make an allergosorbent. Once serum was added, allergen-specific antibodies of any isotype (primarily IgE, IgG, IgA) would bind to the immobilized allergen. Following a second buffer wash to remove unbound serum proteins, bound IgE was detected with ^{125}I -labeled polyclonal antihuman IgE. *RAST* results were reported in log-related classes or in arbitrary units following interpolation from an IgE anti-birch pollen reference curve. Since IgE antibodies to hundreds of different allergen specificities were interpolated from the IgE anti-birch reference curve, this process was called heterologous interpolation (Matsson et al. 2008). The term reflects the fact that the reference curve was constructed with dilutions of IgE antibody to a different specificity (birch pollen) than those being detected in the test sera. The original assay assigned increasing levels of IgE antibody detected to arbitrary classes. The isotopic form of the *RIST* and *RAST* and the use of classes to report IgE antibody levels are now considered antiquated and they should no longer be used.

MAST, ELISA, IEMA, FEIA

Over the years, modifications of the paper disk-based *RAST* assay have been commercialized. The multi-thread allergosorbent test or *MAST* replaced the paper disk with individual cellulose threads. The *MAST* was configured in a pipette in which serum was drawn up, left to react with different allergens on individual threads, and then unbound serum proteins were washed out with buffer. An isotopic or non-isotopically labeled anti-IgE detection antibody was then drawn into the pipette to detect bound IgE antibody. Following a final buffer wash, remaining radioactivity and enzyme-generated chemiluminescence were detected on film and the density was shown to be proportional to IgE antibody concentration the original serum.

Other groups replaced the plastic pipette with a plastic microtiter plate and configured the assay into an enzyme-linked immunosorbent assay (*ELISA*) or a fluorescence enzyme immunoassay (*FEIA*)

for allergen-specific IgE or a two-site immunoassay or *IEMA* for total serum IgE. The ELISA used allergen that had been adsorbed onto plastic wells in the microtiter plate. Following serum addition, antibodies would bind and allergen-specific IgE would finally be detected after a buffer wash with enzyme-labeled anti-human IgE. This assay works poorly with crude allergen extracts since the plastic plate has minimum protein-binding capacity and the percentage of the total protein that contains allergens is sometimes very low. The IEMA uses a microtiter plate adsorbed capture anti-IgE and an enzyme-labeled detection antibody to detect total serum IgE in a chemistry similar to the RIST.

Autoanalyzers

ImmunoCAP, *IMMULITE*, and *HYTEC 288* are 3 present-day autoanalyzers that are designed to quantify IgE antibody to over 200 allergen specificities. Their chemistries are patterned after the early RAST assay. The ImmunoCAP by Thermo Fisher Scientific [UniCAP100, ImmunoCAP 250] uses a cellulose sponge matrix in the form of a small cap as an allergosorbent on which allergen is covalently coupled. The IMMULITE System from Siemens uses a biotinylated allergen that is bound to an avidin-solid phase. The HYTEC 288 System from HYCOR/Agilent Technologies uses a cellulose wafer on which allergen is covalently coupled. All three systems are performed on computer-driven autoanalyzers to maximize precision and minimize assay turnaround time. All three of these autoanalyzers are calibrated using a heterologous total serum IgE calibration curve that is referenced to the WHO total IgE serum standard (Matsson et al. 2008). While the analytical sensitivity (0.1 kUa/L), precision, and reproducibility of these three autoanalyzers are all comparable, they measure different populations of allergen-specific IgE antibody which makes their reported quantitative allergen-specific IgE results noninterchangeable (Hamilton 2010).

Each of the autoanalyzers offers a multi-allergen screen version which is a single qualitative

IgE antibody assay that detects IgE antibody that is specific for 10–15 indoor and outdoor aeroallergens that induce the majority of aeroallergen-related allergic disease. A pediatric version of the multi-allergen screen is designed to also detect IgE antibody to a number of important food allergen specificities (e.g., milk, egg, peanut, wheat, soybean). Manufacturers intentionally have chosen not to disclose which allergen specificities are on their multi-allergen sorbent so that the clinician cannot use the information directly to treat the patient without further clinical assessment and IgE antibody testing. A negative multi-allergen screen result reduces the probability that IgE-mediated allergic disease is involved in the patient's clinical problem (Wickman et al. 2003).

Summary

Single-plex immunoassays that measure a single analyte, one at a time, have evolved from early radioimmunoassays into computer-controlled non-isotypic autoanalyzers that maximize performance (analytical sensitivity and specificity, precision and reproducibility, linearity/parallelism) and minimize turnaround time for obtaining results. While the three current IgE antibody autoanalyzers display comparable analytical sensitivities (0.1 kUa/L or 0.24 ng/mL) and excellent precision and reproducibility, they measure different populations of IgE antibody, and thus while their reported results are qualitatively comparable, they are not quantitatively equivalent. The use of multi-allergen solid phases in a single-plex assay format to screen sera for IgE antibody to principal aero- and food allergens that induce the majority of the aeroallergen- and food-allergen-induced allergic disease allows effective assessment of populations for atopic status.

Cross-References

- ▶ [Analytes and Biomarkers: IgE](#)
- ▶ [Assay Performance Parameters](#)
- ▶ [Cow's Milk Allergy](#)
- ▶ [Diagnostic Assay Components](#)

- ▶ Egg Allergy
- ▶ Food Allergies, Diagnostic Testing
- ▶ Food Allergy, Overview
- ▶ IgE Testing
- ▶ Imported Fire Ant Allergy
- ▶ Peanut Allergy

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Specific IgE

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Definition

Immunoglobulins of the IgE heavy chain isotype that are specific for a given antigen/allergen.

Specific IgE

Allergen-specific IgE is the end product of allergen-specific naïve B cells that underwent class switch recombination (CSR) and plasma cell differentiation. At the plasmablast stage, B cells start secreting immunoglobulins, which

reach the circulation. Some of these plasmablasts can become long-lived plasma cells, which reside in tissues (primarily the bone marrow) for many years from where they secrete immunoglobulins. This long-term production of immunoglobulins does not require persistent exposure to antigens (Radbruch et al. 2006). The presence of such long-lived plasma cells is a complicating factor for the treatment of allergies since there is no therapy available that targets these bone marrow resident plasma cells. Therefore, once allergen-specific IgE-producing long-lived plasma cells are generated, there is constant production of allergen-specific IgE that is independent of allergen exposure.

Serum concentrations of IgE are typically very low and represent less than 0.05 % of the total immunoglobulin pool. Free IgE has a relatively short half-life of around 2 days. Despite its low abundance, allergen-specific IgE is a key mediator of the type I hypersensitivity reaction. Circulating allergen-specific IgE antibodies bind to high affinity IgE receptors (FcεRI) on the surface of circulating basophils and tissue-resident mast cells as well as antigen-presenting cells. These cell surface-bound IgE molecules have a long half-life (up to several months). Upon subsequent encounter with a polyvalent allergen to which the specific IgE was generated, FcεRI on mast cells and basophils are cross-linked, leading to the release of several preformed inflammatory mediators including histamine, lipid mediators, leukotrienes, chemokines, and cytokines which cause the symptoms of the type I hypersensitivity reaction (Larche et al. 2006). Allergen-specific IgE bound to FcεRI on the surface of antigen-presenting cells greatly facilitates the capacity to bind and internalize allergens, leading to enhanced antigen-presenting capacity of these cells.

Methods to Determine the Presence of Specific IgE

There are several different methods to assess the sensitization status of an individual. In vitro tests for detection of specific IgE are frequently

used for this purpose. Specific IgE in circulation is typically measured for diagnostic purposes using immunoassays. Recently microarray-based methods have been developed which allow simultaneous assessment of IgE specific for multiple allergens. This approach has the advantage that it requires only a small amount of serum to measure IgE antibodies of different specificities in a single test (Hiller et al. 2002). The presence of allergen-specific IgE in circulation does not necessarily imply that a patient will show clinical symptoms when exposed to this allergen since this depends on the capacity of an allergen to cross-link FCεRI-bound IgE molecules. One method to assess this capacity is the basophil activation test (BAT) in which a blood sample from a patient is incubated with allergen and basophil activation is measured by flow cytometry. Despite its high sensitivity, BAT is currently not routinely performed for diagnostic purposes. This is mainly because the method has not been sufficiently standardized to guarantee reliable and reproducible results in different institutions.

Besides *in vitro* methods for measuring the allergen-specific IgE in serum, *in vivo* skin tests are frequently used to assess the sensitization status of an individual. *In vivo* skin testing is generally more sensitive than *in vitro* assays to measure serum IgE. Skin testing is typically done by injecting antigen into the epidermis (prick-puncture test) or into the dermis (intradermal test). When an individual is sensitized to a given allergen, the typical reaction to a skin test consists of an immediate reaction followed by a late-phase reaction (LPR). The immediate reaction, which starts within minutes after application of the allergen, is the result of degranulation of skin-resident mast cells. This leads to a wheal and flare reaction that can be observed macroscopically. The LPR starts 4–8 h after allergen exposure and is characterized by swelling of the skin. The LPR is initiated by cytokines and chemokines that were released by mast cells during the immediate reaction. These factors facilitate the recruitment of activated T cells, eosinophils, and neutrophils to the site of the reaction. Tissue-infiltrating CD4+ T cells play an important role in the LPR through production of cytokines.

Skin Prick Test (SPT) are generally regarded as the method of choice to diagnose clinically relevant sensitization to a given allergen. There are some considerations that need to be taken into account when deciding to perform SPT. Under some circumstances, SPT may give false-negative results. SPT may, for example, be affected by the use of drugs like antihistamines, which suppress the histamine response. In contrast, circulating IgE levels are normally not affected by such treatments. Furthermore, there are several risks associated with SPT. There is a chance for systemic reactions in response to SPT, especially with certain anaphylactogenic allergens. On the other hand, since allergens are presented to the immune system, SPT can lead to *de novo* sensitization to allergens to which the patient was not sensitized before the therapy.

Cross-Reactivity

IgE that specifically binds to a given antigen (antigen A) can be the product of a plasma cell originating from a B cell that was activated in response to antigen A. It is however also possible that this IgE is the product of a plasma cell originating from a B cell that was activated in response to a different antigen (antigen B) that shares some degree of homology with antigen A. This phenomenon is referred to as IgE cross-reactivity. IgE immunoglobulins that were raised against a certain allergen can sometimes be cross-reactive to other antigens. Homologous allergens from phylogenetically related organisms are often cross-reactive. Such allergens have a high degree of sequence homology, resulting in similar three-dimensional protein structures that can have identical conformational epitopes. On the other hand, several allergens that are only distantly related show strong cross-reactivity (Aalberse et al. 2001). It can be of importance for therapeutic purposes to know the allergen that initiated the production of specific IgE antibodies. This initiating allergen will have the broadest range of IgE epitopes and therefore have the broadest therapeutic effect when used in allergen-specific immunotherapy.

Cross-References

- ▶ [Activating and Inhibitory Receptors on Mast Cells](#)
- ▶ [Analytes and Biomarkers: IgE](#)
- ▶ [Basophils](#)
- ▶ [Diagnostic Components: Allergen for In Vivo \(Skin Testing, Immunotherapy\) and In Vitro \(Serology\) IgE Antibody Testing](#)

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Sublingual Immunotherapy

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Synonyms

Allergen immunotherapy; Allergen-specific desensitization; Allergy drops; Allergy immunotherapy; Hyposensitization; Immunotherapy

Definition

Sublingual immunotherapy involves the administration of specific allergens by placement of allergen extract in a liquid or tablet formulation under the tongue for 1–2 min followed by swallowing (Canonica et al. 2009) and is conducted for the purpose of lessening or preventing the allergic symptoms due to exposure to those specific allergens (Cox et al. 2011).

Background

Conventional subcutaneous immunotherapy is an effective treatment option for many allergic diseases such as allergic rhinitis, allergic asthma, and Hymenoptera allergy. Despite the benefits of subcutaneous immunotherapy, not all individuals improve, significant time and expense may be involved, and the risk of adverse reactions, such as anaphylaxis, remains (Casale and Stokes 2011). Thus, other forms of immunotherapy have been explored, and sublingual immunotherapy is being increasingly used worldwide. Sublingual immunotherapy is currently commercialized and used in most European and South American countries as well as in Australia and Asia. However, sublingual immunotherapy is not approved for use by the Food and Drug Administration of the United States (US) and is not currently recommended for clinical practice in the United States. Several aspects of sublingual immunotherapy are under investigation, including optimal dosing, duration of treatment, mechanisms of action, preventive effects, and efficacy. Numerous clinical trials are ongoing to further define the parameters and guidelines for the use of sublingual immunotherapy (Canonica et al. 2009).

Clinical Indications

In general, immunotherapy should be considered for individuals who demonstrate evidence of allergic sensitization to applicable environmental allergens and have symptoms of allergic rhinitis or asthma after allergen exposure (Cox et al. 2011).

As noted previously, specific guidelines for the use of sublingual immunotherapy are not yet firmly established.

Efficacy

A meta-analysis of 60 randomized, blinded, placebo-controlled studies of sublingual immunotherapy for allergic rhinitis was conducted which pooled 2,333 patients receiving sublingual immunotherapy and 2,256 patients receiving placebo. Overall, participants receiving sublingual immunotherapy had a significant reduction in symptoms (SMD -0.49 ; 95 % confidence interval (CI) -0.64 to -0.34), $P < 0.00001$ and in medication requirements (SMD -0.32 ; 95 % CI -0.43 to -0.21), $P < 0.00001$ compared to placebo. None of the trials in this analysis reported severe systemic reactions or anaphylaxis (Radulovic et al. 2010).

Another meta-analysis reviewed the clinical efficacy of sublingual immunotherapy for the treatment of asthma. Twenty-five randomized controlled trials were included in this review involving 1,706 patients. Sublingual immunotherapy was seen to significantly reduce asthma severity in terms of categorical outcomes. For this, all outcomes were analyzed together including asthma symptoms, medication use, and respiratory function test results. However, when asthma symptoms were analyzed using continuous outcomes by standardized mean differences, there was a trend toward improved asthma outcomes favored by sublingual immunotherapy, but without statistical significance (Calamita et al. 2006).

Nieto et al. studied the results of five published meta-analyses reviewing the efficacy of sublingual immunotherapy for the treatment of allergic asthma and allergic rhinoconjunctivitis. The five meta-analyses included 43 studies, 17 of which were used in more than one meta-analysis. Numerous discrepancies were found in the data used for the meta-analyses. The results used differed from the original study to those used in the meta-analysis or across meta-analyses many times. There were also inconsistencies among

the meta-analyses in the reported benefits when considering factors such as age, disease, allergen, symptoms, and medication use. Due to these discrepancies and inconsistencies, there was a lack of robustness among the meta-analyses, and this review concluded that there was not enough evidence to support sublingual immunotherapy as a routine treatment option for patients with allergic asthma and allergic rhinoconjunctivitis (Nieto et al. 2009).

Conclusion

Sublingual immunotherapy is becoming increasingly prescribed around the world and in several European countries is the standard of care for patients with allergic diseases who are treated with immunotherapy. A substantial number of clinical studies have demonstrated the efficacy of sublingual immunotherapy, but a great deal of heterogeneity exists in the designs of these studies, making it difficult to assess the value of sublingual immunotherapy accurately (Casale et al. 2009). More studies are needed to further evaluate the parameters and benefits of the use of sublingual immunotherapy, especially when compared to subcutaneous immunotherapy.

Cross-References

- ▶ Allergen Immunotherapy, Overview
- ▶ Immunotherapy for Allergic Rhinitis
- ▶ Immunotherapy for Asthma
- ▶ Immunotherapy for Hymenoptera Allergy
- ▶ Immunotherapy with Recombinant and DNA-Conjugated Allergens
- ▶ Immunotherapy, Mechanisms
- ▶ Safety of Immunotherapy

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