

NEWS AND COMMENTARIES

Allergen immunotherapy: a new semantic framework from the European Academy of Allergy and Clinical Immunology/American Academy of Allergy, Asthma and Immunology/PRACTALL Consensus Report

DOI:10.1111/all.12180

Immunotherapy for allergic diseases has entered a new age, marked by the development of a small number of new therapeutic classes of standardized allergen formulations registered as pharmaceutical specialties after large, robust, pivotal Phase III clinical trials (1). Furthermore, concepts in general medicine and our understanding of the immune system's functions have changed substantially. These developments in pathophysiology, pharmacology, and clinical practice suggest that there is a need to change and align our current semantic frameworks about the terminology used for immunotherapy.

With the aim of promoting the broad uptake of a single nomenclature, we reviewed current terminologies and sought a consensus from the European Academy of Allergy and Clinical Immunology (EAACI) and the American Academy of Allergy Asthma and Immunology (AAAAI) via the PRACTALL initiative (2). We propose the term 'allergen immunotherapy' for the treatment of an allergic disease with an allergen-containing therapeutic. The rationale for this choice is described below.

Going back as far as 1911, Leonard Noon and John Freeman used the terms 'prophylactic inoculation against hay fever' and 'treatment of hay fever by hypodermic inoculation of pollen vaccine' (3, 4). After more than 100 years of use, many different terms are employed in different languages by the leading allergy societies, working groups and regulatory authorities ((5–16), summarized in Table 1). Statements by the World Allergy Organization, the WHO, the Allergic Rhinitis and its Impact on Asthma initiative and the Global Allergy and Asthma European Network (5–10) have acknowledged the confusion caused by the use of different terms (sometimes even within the same document).

We found that the most widely used term at present is 'specific immunotherapy' (abbreviated as 'SIT'). But does this term adequately describe today's practice? And what does each of the term's two words mean in today's context?

Let us first consider 'immunotherapy'. As we gain a better understanding of the immune system's composition and function (notably thanks to the use of molecular analysis techniques), it is now clear that the term 'immunotherapy' encompasses many disease pathways and treatment approaches. Immunotherapy can variously be defined as (i) the treatment for disease by inducing, enhancing, or suppressing immune response, (ii) a therapy designed to produce immunity to a microorganism or a transplanted organ or to enhance resistance or tolerance by the immune system, (iii) any approach aimed at

mobilizing or manipulating a patient's immune system to treat or cure disease, and (iv) a general term encompassing active and passive immunization. Immunotherapy can be prophylactic or therapeutic. It may involve the administration of antibodies, antibody fragments, peptides of antigens, polypeptide allergens, immunosuppressants, immunomodulators, nucleic acids, small molecules, and even immune system cells and can be used to treat cancer, heart failure, organ transplantation, autoimmune disease, and, of course, a number of allergic conditions.

Assuming that the term 'immunotherapy' is relevant but overly general, does qualifying it with 'specific' provide us with a better understanding? The term 'specific immunotherapy' is also used outside the field of allergy – notably as a short form of 'antigen-specific immunotherapy' in oncology (17). In fact, the word 'specific' is no longer specific enough. Indeed, the word may variously refer to a specific medical condition (whether allergic or not), a specific allergen, a specific medicinal product, a specific patient, or even several of these entities at the same time. Of course, it makes more sense to use the term 'specific' than the term 'non-specific'. However, the main problem with 'specific immunotherapy' is that the term is concept based. Concepts are changing, so it is time to shift our semantic paradigm and adopt a clear, intuitive, product-based nomenclature.

We need to specify what an immunotherapy product contains – that is, one or more allergens. Indeed, this is crucial in view of the significant differences between Europe and the USA regarding the number of allergens that are typically used in a named-patient preparation; in Europe, most administered formulations are single-allergen extracts, while those in the USA contain an average of eight different allergic components (18). Our working group found that the term 'allergen immunotherapy' (abbreviated as 'AIT') is preferable for an allergen-containing therapeutic, and 'non-allergen immunotherapy' is used to describe a therapeutic that does not contain allergen but that is used to treat an allergic disease (such as anti-IgE, antitumor necrosis factor, anti-interleukin-13, and antithymic stromal lymphopoietin approaches). Furthermore, 'allergen immunotherapy' has none of the disadvantages associated with the term 'specific', because it is immediately clear that the treatment's specificity is related to the allergen. Although combining the two terms as 'allergen-specific immunotherapy' has been suggested (19, 20), this ambiguously implies that 'non-allergen-specific immunotherapy' or 'allergen-non-specific immunotherapy' also exist.

Table 1. Terminology used in the field of immunotherapy for allergic diseases

Allergy society/ organization/ regulatory agency	WAO (5)	WHO (6)	GA2LEN (7–9)	ARIA (7, 10)	EAACI (11, 12)	AAAAI (13)	EMA (14)	FDA (15, 16)	EAACI, AAAAI PRACTALL Consensus
General terms used	allergen-specific immunotherapy allergen immunotherapy allergen vaccination allergen vaccines	allergen immunotherapy allergen-specific immunotherapy specific immunotherapy allergen vaccines	specific immunotherapy allergen-specific immunotherapy	specific immunotherapy allergen-specific immunotherapy	specific immunotherapy allergen immunotherapy allergen-specific immunotherapy	allergy immunotherapy, also known as allergy shots or desensitization	specific immunotherapy specific immunotherapy for the treatment of allergic diseases <i>none used</i> <i>none used</i>	allergen vaccine immunotherapy allergy immunotherapy	'allergy immunotherapy', which should include (i) 'allergen immunotherapy' and (ii) 'non-allergen immunotherapy' sublingual allergen immunotherapy
Term used for sublingual administration	sublingual vaccines sublingual immunotherapy vaccines sublingual immunotherapy subcutaneous immunotherapy subcutaneous immunotherapy vaccines subcutaneous injection allergen-specific immunotherapy	sublingual (swallow) immunotherapy sublingual (spit) immunotherapy sublingual immunotherapy subcutaneous immunotherapy subcutaneous immunotherapy vaccines subcutaneous injection allergen-specific immunotherapy	sublingual immunotherapy sublingual allergen-specific immunotherapy	sublingual immunotherapy sublingual allergen-specific immunotherapy	sublingual immunotherapy sublingual immunotherapy	sublingual immunotherapy sublingual immunotherapy	<i>none used</i> <i>none used</i>	<i>none used</i> <i>none used</i>	
Term used for subcutaneous administration	subcutaneous immunotherapy subcutaneous immunotherapy vaccines subcutaneous injection allergen-specific immunotherapy	subcutaneous immunotherapy subcutaneous immunotherapy vaccines subcutaneous injection allergen-specific immunotherapy	subcutaneous immunotherapy	subcutaneous immunotherapy subcutaneous specific immunotherapy subcutaneous allergen-specific immunotherapy	subcutaneous allergen immunotherapy				
Acronyms used	SIT SLIT SCIT	<i>none used</i>	SIT SCIT SLIT	SIT SCIT SLIT	SIT ASIT SLIT SCIT	SIT, SLIT SCIT	<i>none used</i>	<i>none used</i>	AIT SLIT SCIT

WAO, World Allergy Organization; WHO, World Health Organization; GA2LEN, Global Allergy and Asthma European Network; ARIA, Allergic Rhinitis and its Impact on Asthma; EAACI, European Academy of Allergy and Clinical Immunology; AAAAI, American Academy of Allergy, Asthma and Immunology; EMA, European Medicines Agency; FDA, US Food and Drug Administration.

A number of other terms used in the medical and scientific literature contain the word 'allergen' (such as 'allergen shots' and 'allergen vaccination') but are less descriptive. Although the historical term 'desensitization' and the more measured 'hyposensitization' (12, 20) have some degree of mechanistic meaning, they are too strongly associated with allergen sensitization (rather than allergic symptoms). 'Shots' is a particularly American expression and is restricted to a subcutaneous administration route. We also consider that the terms 'vaccination' and 'inoculation' are too strongly associated with the prophylaxis of infections caused by pathogenic microorganisms.

'Subcutaneous immunotherapy' and its often-used acronym 'SCIT' and 'sublingual immunotherapy' and its acronym 'SLIT' are so well accepted that they will continue to be used in clinical practice and research (although 'SCAIT' and 'SLAIT' could be considered). In the future, it may be that patients and physicians will recognize a particular allergen immunotherapy product and its implicit administration pathway through its brand name, as has long been the case in other fields of medicine. Similarly, other administration routes and their related acronyms should be acknowledged; these include nasal, bronchial, oral, epicutaneous, and intralymphatic allergen immunotherapy (NIT, BIT, OIT, EPIT, and ILIT, respectively; Table 1). Moreover, SLIT products are available both as SLIT drops and as SLIT tablets.

Much effort has been devoted to defining nomenclatures for allergic diseases and allergens themselves (21). It is crucial to now harmonize the nomenclature we use for the allergen-based treatment for allergic diseases. Although moving from 'specific immunotherapy (SIT)' to 'allergen immunotherapy (AIT)' might appear to be a small step, we are pleased that the EAACI and AAAAI have formed a consensus on this topic – a consensus that we hope will spread to other allergy societies worldwide – and we are confident that adoption of a single terminology will stimulate further progress in this field over the next one hundred years.

Author contributions

Moisés A. Calderón, Thomas Casale, Linda Cox, Cezmi A. Akdis, A. Wesley Burks, Harold S. Nelson, Marek Jutel and Pascal Demoly all made substantial contributions to drafting the article or revising it critically for important intellectual content and have given their final approval of the version submitted for consideration for publication.

Conflict of interest

M. Calderón declares that he has no relevant conflicts of interest. T. Casale has received grants from Novartis, Stallergenes, Genentech, and Merck; has consultant arrangements with Novartis, Stallergenes, Genentech, and ALK-Abello; and is the executive vice president of the AAAAI. L. Cox has consultant arrangements with Stallergenes and the US Food and Drug Administration Allergenic Products Advisory Committee; has received travel support from the AAAAI; has received fees for participating in review activities from Circassa and Novartis; has received payment for writing or reviewing the manuscript from the Blue Cross Blue Shield Technology Evaluation Center; is a

board member for the American Board of Allergy and Immunology; has provided expert testimony in cases related to chronic ciguatera; and has received payment for lectures from the Southeastern Allergy Asthma Immunology Association and the Virginia Allergy Asthma and Immunology Society. C. A. Akdis has received grants from Novartis, the European Commission, the Swiss National Science Foundation, the Global Allergy and Asthma European Network, and the Christine Kuhne-Center for Allergy Research and Education; has consulted for Actellion, Aventis, Stallergenes, and Allergopharma; is president of the European Academy of Allergy and Clinical Immunology; is a fellow and interest group member of the AAAAI; is a former committee member of GA2LEN, and is director of the Christine Kuhne-Center for Allergy Research and Education. A. W. Burks is a board member of the American Academy of Allergy, Asthma & Immunology (AAAAI); the Hypersensitivity, Autoimmunity, and Immune-mediated Diseases Study Section for the National Institutes of Health (NIH); the Food and Drug Administration Food Advisory Committee; the Food Allergy & Anaphylaxis Network Research Advisory Board; and the Merck US Allergy Immunotherapy Allergist Advisory Board; has had consultant arrangements with ActoGenix, Curalogic, Dow Agrosciences, McNeill Nutritionals, Merck, Novartis Pharma AG, Sanofi-Aventis US, Schering-Plough, and Unilever; is employed by the University of North Carolina Children's Hospital; was previously employed by Duke University; has received research support from the NIH and the Wallace Research Foundation; has received payment for lectures from Abbott Laboratories and Mylan Specialty; has patents related to peanut allergy planned or pending; has received payment for the development of educational presentations from Current Views 2012; and is a minority stockholder in Allertein Therapeutics LLC. H. Nelson has consultant arrangements with Merck and Circassia and has received grants from Circassia. M. Jutel has consultant arrangements with Anergis and Allergopharma and has received payment for lectures from Allergopharma, Stallergenes, and GlaxoSmithKline. P. Demoly has received consulting fees or honoraria from ALK-Abello, Stallergenes, Circassia, and Allergopharma and has consultant arrangements with Merck, AstraZeneca, Menarini, Chiesi, and GlaxoSmithKline.

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