

Simpósio SPAIC-SEAIC

Imunoterapia com Aeroalergénios

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Nos últimos anos a Sociedade Portuguesa de Alergologia e Imunologia Clínica (SPAIC) e a Sociedad Española de Alergologia e Inmunología Clínica (SEAIC) têm-se unido no sentido de desenvolver várias atividades em comum, nomeadamente com a organização de dois simpósios anuais, que decorrem em Portugal e em Espanha, respetivamente. No passado dia 10 de outubro de 2015, durante a reunião anual da SPAIC, realizou-se mais um Simpósio SPAIC-SEAIC inti-

titulado Imunoterapia com Aeroalergénios, moderada pelos Professores Doutores Joaquim Sastre e Luís Delgado. Este simpósio decorreu sob a forma de mesa-redonda, onde participaram os Professores Manuel Branco Ferreira e Ignacio Dávila e Carmen Vital com os temas: Imunoterapia para quem e como?, Mechanisms of action e Immunotherapy With Mites, News Issues, respectivamente. De seguida apresenta-se o resumo da autoria de cada um destes três preletores.

IMUNOTERAPIA COM ALERGÉNIOS – PARA QUEM E COMO?

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Na prescrição consciente de um tratamento com imunoterapia com alergénios (ITA) a um doente devem estar previamente respondidas uma série de questões relevantes e que a seguir se tentam expor de uma forma detalhada e sistemática.

Há evidência de doença IgE-mediada a aeroalergénios?

Para responder a esta questão o percurso inicia-se numa anamnese detalhada, acompanhada de testes cutâ-

neos, tentando-se correlacionar temporalmente as queixas do doente com os períodos de exposição alérgica aos alergénios identificados. A avaliação laboratorial com a pesquisa de IgE específica é muitas vezes utilizada para complementar os dados dos testes cutâneos, mas quer num caso quer noutro o que estamos a usar são extratos complexos contendo vários alergénios. Assim, a utilização de tecnologias que empreguem alergénios moleculares tem-se vindo a afirmar como uma ajuda importante na identificação de sensibilizações relevantes e, consequentemente, importante para uma mais correta seleção dos alergénios a incluir na imunoterapia¹. Por outro lado, atualmente há também um melhor conhecimento de patologias alérgicas locais, em que apesar de uma história típica não se encontra evidência sistémica de IgE específicas, as quais só são encontradas no órgão-alvo e que só podem ser demonstrados através da positividade de provas de provocação específicas com o alergénio implicado².

Qual o alergénio implicado?

Para ácaros e vários pólenes (gramíneas, oliveira, parietária, bétula, ambrósia, entre outros) há uma ampla demonstração de eficácia da imunoterapia. No entanto, no caso de vários alergénios fúngicos ou de alergénios provenientes de epitélios de animais a evidência é muito mais escassa e esse facto pode e deve pesar na decisão sobre a imunoterapia.

Qual a doença respiratória que se quer tratar?

A ITA tem uma evidência de eficácia muito mais consensual na rinite e rinoconjuntivite do que na asma brônquica. No entanto, e apesar de nos *guidelines* GINA se afirmar que a eficácia da ITA é limitada na asma e que comparando com as opções de farmacoterapia e de evicção alergénica os potenciais benefícios da ITA devem ser pesados contra o risco de efeitos adversos, a inconveniência e o custo, a realidade é que existem várias meta-análises que demonstram a eficácia da ITA em adultos e crianças com asma³ e vários trabalhos têm demonstrado redução de *scores* de gravidade e de consumo de fármacos em doentes asmáticos submetidos a ITA, incluindo alguns estudos recentes efetuados no nosso hospital^{4,5}. Para além da doença respiratória, também o eczema atópico com alergia relevante a ácaros do pó doméstico tem sido foco de atenção em relação à imunoterapia com ácaros, com publicação de algumas meta-análises demonstrando a eficácia clínica da ITA nestes doentes⁶.

Há alguma contra-indicação para a imunoterapia com alergénios?

Neste capítulo a atenção vai essencialmente para a presença de asma não controlada ou instável, bem como para a presença concomitante de doenças que contraindiquem o uso de adrenalina em caso de reação sistémica à imunoterapia. Também a presença de doença grave, autoimune por imunodeficiência ou por neoplasia, desaconselha a instituição de ITA. A medicação concomitante com betabloqueantes ou IECA não é uma contra-indicação absoluta mas deverá representar um

cuidado adicional se se decidir avançar com a prescrição de ITA. Prévias reações sistémicas à ITA, bem como uma má *compliance*, são igualmente fatores que desaconselham a ITA. No caso específico da imunoterapia sublingual a presença de doenças agudas inflamatórias da cavidade oral também contraindica a administração de ITA.

Do ponto de vista do doente, a ITA justifica-se?

Aqui há que ponderar, do ponto de vista do doente, se a intensidade e duração dos sintomas justifica a ITA, se o controlo farmacológico é ou não suficiente e se tem ou não secundarismos relevantes para o doente, se para o doente é suficientemente importante tentar evitar o uso a longo prazo de fármacos, bem como a eventual prevenção do desenvolvimento de asma em doentes com rinite e, por último, mas desempenhando um papel fulcral nos dias de hoje, se o doente tem a disponibilidade económica e de tempo para uma correta adesão.

No caso de todas estas questões atrás indicadas estarem respondidas de forma favorável para a ITA, haverá ainda que decidir com o doente qual a via de administração que melhor se adapta àquele doente individual. Atualmente temos essencialmente duas vias: a injetável subcutânea e a não injetável sublingual, sendo que depois também se podem colocar uma série de questões adicionais quanto aos esquemas posológicos mais indicados em cada uma delas. No entanto, é possível que num futuro próximo possamos dispor de uma outra via injetável (intralinfática) e de outra via não injetável (epicutânea), sendo que estas duas vias se caracterizam, em princípio, por necessitarem de muito menor número de administrações e poderem, por isso, ser mais convenientes e mais económicas, podendo vir a permitir uma muito maior generalização desta forma terapêutica e, dessa forma, podermos conseguir combater mais eficazmente a epidemia das doenças alérgicas.

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REFERÊNCIAS

1. Luengo O, Cardona V. Component resolved diagnosis: when should it be used. *Clin Transl Allergy* 2014;4:28
2. Rondón C, Campo P, Tógias A, *et al.* Local allergic rhinitis: concept, pathophysiology and management. *J Allergy Clin Immunol* 2012;129:1460-7
3. Cappella A, Durham SR. Allergen immunotherapy for respiratory diseases. *Hum Vaccin Immunother* 2012;8:1499-512.
4. Branco Ferreira M, Rodrigues Alves R, Pereira Barbosa M. Imunoterapia específica: uma mais valia no tratamento da asma e rinite alérgicas. *Rev Port Imunoalergol* 2009;17:13-35
5. Spinola Santos A, Branco Ferreira M, Pereira Barbosa M. Imunoterapia específica e controlo da asma. *Rev Port Imunoalergol* 2012;20:109-20
6. Lee J, Park CO, Lee KH. Specific immunotherapy in atopic dermatitis. *Allergy Asthma Immunol Res* 2015;7:221-9.

AEROALLERGEN IMMUNOTHERAPY: MECHANISMS OF ACTION

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Allergic diseases are among the most frequent diseases worldwide, with increasing rates of prevalence and allergen sensitization¹. Main therapies include antihistamines, corticosteroids, leukotriene antagonists, beta-adrenergic agents and omalizumab. None of these treatments has a disease modifying effect. Allergen specific immunotherapy (AIT) has proved to be the only treatment capable to induce a modification in the evolution of allergic diseases, leading to a cure in selected patients and improvement in most². In addition it can also have a sustained effect.

AIT is an immune therapy aiming to restore tolerance to specific allergens. In the last decades a significant increase in the knowledge of mechanisms tolerance to allergens has occurred. In parallel, a significant increase in the understanding of the mechanisms of action of AIT has developed. The allergic reaction involves all the immune system. Concisely, in allergic diseases there is a first sensitization phase during which the allergen is presented to naïve T cells by antigen presenting cells with

a subsequent Th2 deviation and allergen T-cell clonal expansion occurs³. In this process, the innate immune system has an important role; exemplified by the production of Th2 cytokines by type 2 innate lymphoid cells at the very beginning of the allergy process. Then, class switching to IgE synthesis occurs upon cognate interaction between Th2 and B cells, leading to the development of allergen-specific IgE producing B-cells as well as the appearance of memory B cells. Upon reexposure to the same allergen, the crosslinking of specific IgE bound to IgE receptors in the surface of mast cells and basophils leads to their degranulation and the release of inflammatory mediators, chemotactic factors and cytokines. The infiltration of effector cells such eosinophils and Th2 cells aggravates the condition and increases the allergic tissue inflammation leading to the late-phase reaction. The generation and maintenance of allergen-specific T regulatory cells (Treg) is an essential event in the development of healthy responses to allergens. In this process, IL-10 and TGF-b are two important cytokines. IgG4 is also important.

Allergic diseases are considered the result of a loss of peripheral immune tolerance to allergens. The administration of AIT results in the development of a series of mechanisms aimed to restore the tolerance to the allergen. These mechanisms are produced from the very

Table 1. Immunology and clinical changes occurring during the administration of immunotherapy

<p>Effects on cytokines and antibodies</p>	<p>Transient increase in serum specific IgE followed by a late decrease Increase in allergen specific IgG1 and IgG4 Increase in specific IgA Reduction of Th2 cytokines Increase of IL-10 and TGF-β Increase of IL-12 Increase in histamine receptor 2 levels in basophils</p>
<p>Effects on immune cells</p>	<p>Reduction in mediator releasability and tissue infiltration by mast cells and basophils Decrease in IgE-facilitated antigen presentation by antigen presenting cells Induction of Treg and Breg cells Decrease allergen-specific lymphocyte proliferation Reduction in Th2 cells Reduction in Th1 cells</p>
<p>Clinical effects</p>	<p>Decrease of symptoms (conjunctival, nasal and bronchial) Decrease of medication use Decrease of late phase reactions Reduction of bronchial responsiveness Increase in the threshold of specific challenge tests Prevention of disease progression Prevention of new sensitization Increase in quality of life</p>

beginning of the treatment. Clinical and immunological changes are specified in Table 1.

One the most rapid effects of AIT is the desensitization of mast cells and basophils, i.e., the unresponsiveness of these cells to allergens, even in the presence of high levels of specific IgE. This effect occurs very early after the administration of AIT, starting from the first dose. Its underlying molecular mechanisms are unknown, although this effect could be related to the similar one observed during drug desensitization procedures. Recent studies have suggested that the antihistamine receptor 2 could be involved⁴.

This is followed but one of the key mechanisms of AIT, i.e., the development of regulatory cells. During the administration of AIT an expansion of Treg and B regulatory cells (Breg) occurs (reviewed in 5). These cells produce IL-10, which is a cytokine with suppressor capacities. High IL-10 producing Treg and Breg cells are denominated T_R1 and B_R1 cells, respectively. In healthy individuals these cells are predominant. Dendritic cells and oral Langerhans cells are able to stimulate the develop-

ment of Treg cells and can themselves secrete IL-10 and TGF-b thus inducing tolerance⁶.

AIT also induces an initial increase in serum specific IgE levels that is followed by a gradual decrease over months to years of sustained treatment⁷. These changes have not been correlated with the clinical efficacy of AIT.

During AIT an increase in specific IgG1 and IgG4 has been observed. It has been suggested that IgG4 is able to capture the allergen, thus preventing an IgE-mediated activation of mast cells and basophils. Some studies have shown that IgG4 can prevent IgE-facilitated antigen presentation by APCs⁸. Furthermore, the production of IL-10 and TGF-b stimulates B cells to undergo class switching to produce IgG4 and IgA, respectively. It has been recently published that production of IgG4 could be confined to Breg1 cells⁹.

In the long run, Treg cells can suppress mainly Th2 but also Th1 responses¹⁰, in consequence decreasing all the allergic response, with a reduction in the mediator release from mast cells, basophils and eosinophils and a reduction in the number of inflammatory cells in tissues.

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REFERENCES

1. Ariano R, Canonica GW, Passalacqua G. Possible role of climate changes in variations in pollen seasons and allergic sensitizations during 27 years. *Ann Allergy Asthma Immunol* 2010;104:215-22.
2. Jutel M, Agache I, Bonini S, et al. International consensus on allergy immunotherapy. *J Allergy Clin Immunol*. 2015;136(3):556-68.
3. Palomares O, Cramer R, Rhyner C. The contribution of biotechnology toward progress in diagnosis, management, and treatment of allergic diseases. *Allergy* 2014;69(12):1588-601.
4. Novak N, Mete N, Bussmann C, Maintz L, Bieber T, Akdis M, et al. Early suppression of basophil activation during allergen-specific immunotherapy by histamine receptor 2. *J Allergy Clin Immunol* 2012;130:1153-8.
5. Akdis M, Akdis CA. Mechanisms of allergen-specific immunotherapy: multiple suppressor factors at work in immune tolerance to allergens. *J Allergy Clin Immunol* 2014;133(3):621-31.
6. Allam JP, Würtzen PA, Reinartz M, et al. Phl p 5 resorption in human oral mucosa leads to dose-dependent and time-dependent allergen binding by oral mucosal Langerhans cells, attenuates their maturation, and enhances their migratory and TGF-beta1 and IL-10-producing properties. *J Allergy Clin Immunol* 2010;126(3):638-645.
7. Van Ree R, Van Leeuwen WA, Dieges PH, et al. Measurement of IgE antibodies against purified grass pollen allergens (Lol p 1, 2, 3 and 5) during immunotherapy. *Clin Exp Allergy* 1997;27:68-74.
8. Scadding GW, Shamji MH, Jacobson MR, et al. Sublingual grass pollen immunotherapy is associated with increases in sublingual Foxp3-expressing cells and elevated allergen-specific immunoglobulin G4, immunoglobulin A and serum inhibitory activity for immunoglobulin E-facilitated allergen binding to B cells. *Clin Exp Allergy* 2010;40(4):598-606.
9. van de Veen W, Stanic B, Yaman G, Wawrzyniak M, Sollner S, Akdis DG, et al. IgG4 production is confined to human IL-10-producing regulatory B cells that suppress antigen-specific immune responses. *J Allergy Clin Immunol* 2013;131:1204-12.
10. Oda N, Yamashita N, Minoguchi K, et al. Long-term analysis of allergen-specific T cell clones from patients with asthma treated with allergen rush immunotherapy. *Cell Immunol* 1998 25;190(1):43-50.

AEROLLERGEN IMMUNOTHERAPY: IMMUNOTHERAPY WITH MITES, NEW ISSUES

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House dust mite allergy is a worldwide health problem. More than 49% of patients with allergic rhinitis have house dust mite (HDM) allergy and 50 to 89% of patients with allergic asthma are allergic to HDM.

The most relevant and best-known HDM from the allergological point of view are *Dermatophagoides* species. Allergen immunotherapy seems to be an efficacy treatment for HDM allergic individuals but, in order to achieve the best results, a profound knowledge of HDM biology and a precise diagnosis are needed.

HDM allergens belong to at least 4 main families: proteases, proteins displaying affinities for lipids, non proteo-

lytic enzymes and non enzymatic components. But, HDM are not only allergens but also carrier of microbial PAMPs able to trigger innate immunity: LPS, β -glucans, chitinases and flagellin. So, in the end, a mutual interaction between innate and adaptive immune happens when allergic patients are exposed to HDM.

Regarding diagnosis of HDM allergy and taken into account the development of molecular diagnosis in this field of allergic diseases and the possible influence of the pattern of sensitization in the selection of the vaccine or the recognition of the most relevant allergen, one could ask about the value of this diagnostic tool in HDM allergy. And, for instance, recent studies have shown a certain relationship between sIgE against Der p 2 and asthma. Thus, the risk of being asthmatic was more than 2-fold and 5-fold higher in children with IgE to Der p 2 and Der p 5 respectively in a study performed in European children.

Finally, new products will be available soon to treat HDM allergic patients. Positive results have been reported with HDM tablets in both rhinitis and asthma. Well-

-designed clinical trials have been carried out in Europe, USA and Japan in more than 5000 patients and some results of them will be presented during the meeting.

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REFERENCES

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2. Herman J, Thelen N, Smargiasso N, Mailleux AC, Luxen A, Cloes M, De Pauw E, Chevigné A, Galleni M, Dumez ME. Der p 1 is the primary activator of Der p 3, Der p 6 and Der p 9 the proteolytic allergens produced by the house dust mite *Dermatophagoides pteronyssinus*. *Biochim Biophys Acta* 2014;1840:1117-24.
3. Golebski K, Röschmann KI, Toppila-Salmi S, Hammad H, Lambrecht BN, Renkonen R, Fokkens WJ, van Drunen CM. The multi-faceted role of allergen exposure to the local airway mucosa. *Allergy* 2013;68:152-60.
4. Calderón MA, Linneberg A, Kleine-Tebbe J, De Blay F, Hernandez Fernandez de Rojas D, Virchow JC, Demoly P. Respiratory allergy caused by house dust mites: What do we really know? *J Allergy Clin Immunol* 2015;136:38-48.