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REVIEW

Immunotherapy of mold allergy: A review

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ABSTRACT

Mold allergies are common, mainly target the respiratory tract and present as allergic rhinitis and/or bronchial asthma. Molds include a large group of different allergens that induce all types of allergic reactions. Allergen specific immunotherapies (AITs) to molds are common; however, at the present time, they are limited to *Alternaria*. This review presents not only the benefits but also the problems with such types of AIT based on the literature and our experience.

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Introduction

Mold allergies are a significant problem all over the world.[1,2] Molds are an extensive source of allergens. Exposure and sensitization to fungal allergens can promote the development and worsening of allergic diseases.[1,3] Although numerous species of fungi have been associated with allergic diseases in the literature, the significance of fungi from the genera *Alternaria, Cladosporium, Penicillium*, and *Aspergillus* has been well documented.[4-7]

Among the various methods for the treatment of allergic diseases, allergen-specific immunotherapy (AIT) is of particular importance. For example, immunotherapy has been demonstrated to reduce the risk of developing asthma in children with allergic rhinitis.[8-10] The importance of immunotherapy, although increasingly well documented, still requires extended research, particularly through multigenerational observations.

AIT for mold is a relatively uncommon method of treatment as a result of the difficulty in acquiring standardized allergenic molds.[11-13]

Mold allergies

Allergic diseases are one of the major health problems of the 21st century. An increase in the incidence of allergic rhinitis and asthma cases has been observed, especially in developed countries. Despite many studies, the impact of the environment on the clinical manifestations of allergies remains an open topic.[14]

Under the proposed hygienic hypothesis, a reduction in the incidence of some viral or bacterial infections through the use of prophylaxis in the form of vaccination, as well as the use of antibiotics, promotes Th2 immune responses, which favors the development of allergic diseases. This hypothesis states that a reduced exposure to allergens in early life is solely implicated in the growing propensity for allergy sensitization. Important elements of the hypothesis include exposure to endotoxins, exposure to pets and growing up on a farm. However, the hygiene hypothesis alone does not provide an adequate explanation for the observed increase in allergic disease. There are still many questions about the patho-mechanism of the latter. An example of this is the fact that, in addition to well-known allergens, such as house dust mite or pollen, many allergens are still being researched and tested to determine their roles in inducing allergic diseases.[14] These include fungi and the clinical symptoms of allergies to them.[1,15,16]

Fungi are widespread in the environment, and their spores and mycelium fragments can be a source of allergens. Due to their differences from plants, they are in a separate kingdom, known as fungi. From the viewpoint of allergic diseases, the important types include *Ascomycetes, Zygomycetes, Deuteromycetes* and *Basidomycetes*.[1]

The clinical spectrum of hypersensitivity reactions elicited by molds is very broad. In addition to IgE-mediated type I allergies, there exist type II, III and IV reactions, which are defined according to the criteria proposed by Coombs and Gell.[17] Clinically, IgE-mediated sensitization to mold allergens can manifest as allergic rhinitis and rhinosinusitis, atopic dermatitis and allergic asthma.[17,18]

From the viewpoint of allergy, there are outdoor and indoor molds, but some species occur in both environments at the same time. *Alternaria, Cladosporium, Botrytis, Epicoccum and Fusarium* are fungi that are prevalent in the external environment. In addition to the presence of air, they can be found in soil, in plants and on food, especially vegetables and fruits. Fungi of the genus *Alternaria* and *Cladosporium* predominate in the external environment. Their peak exposures are from spring to summer or fall; specifically, from May to August for *Cladosporium* spores and from July to September for *Alternaria*. For example, in middle Europe during this period, in patients who are allergic, they can cause allergies following inhalation in the form of rhinitis and conjunctivitis and / or asthma.[1,17]

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Aspergillus and *Penicillium* are typical indoor molds. They favor the development of high humidity and a lack of access to light and ventilation. In the home environment, we meet a high content of other fungi allergens, such as *Aspergillus, Alternaria, Cladosporium, Mucor* and others, which are a source of allergies throughout the year.[4] Apart from asthma and allergic rhinitis, patients allergic to molds may suffer from allergic bronchial-pulmonary aspergillosis, allergic alveolitis, chronic allergic sinusitis, and even allergic dermatitis.[1,4,17] Some also induce systemic reactions, such as anaphylactic reactions, especially after ingestion of fungi allergens contained in some foods, such as selected types of cheese, wine, meats, juices and many others. Mold, due to its prevalence, may be responsible for occupational diseases, such as contact dermatitis, occupational asthma or the already mentioned respiratory allergic diseases, which may affect farmers, gardeners, foresters and many other professions. Additionally, some species of fungi of the genus *Candida* or *Trihophyton* can trigger infectious diseases in humans that require long-term treatment.[17,19]

Based on the literature, allergies to *Alternatia, Cladosporium* and *Aspergillus* are the most common. Allergic rhinitis and bronchial asthma are very common diseases among allergy patients. Moreover, there are data that indicate that patients allergic to mold have more severe asthma.[20]

Immunotherapy of mold allergy

AIT is a significant therapeutic tool for IgE-mediated allergic diseases.[21] It is known that AIT is an effective therapy for stopping allergic disease development. Current international and national consensuses indicate that AIT is a first line therapy for allergic rhinitis and some stable mild bronchial asthma types and venom allergies.[21-23] Other indications for AIT are ambiguous, and there is no evidence for their effectiveness (e.g., allergic sinusitis, atopic dermatitis and some food allergies).[21] Effective AIT results in desensitization to allergens, allergen-specific immune tolerance, and suppression of allergic inflammation. This is followed by allergen-specific regulatory T (Treg) and regulatory B (Breg) cell generation, as well as regulation of allergen-specific IgE and IgG establishment for immune tolerance.[24]

The current age limits are above 5 y of age, with no upper limit. AIT is an effective method of obtaining tolerance to certain specific allergens, such as house dust mites, pollens (e.g., grass, some trees and some weeds), cat dander and some molds.[21,22] However, over the years, the recommendations for desensitization to some allergens have changed. This is a consequence of new regulations for the accessibility to appropriate standardized allergen extracts. Additionally, AIT currently focuses on the administration of individual allergens and not mixtures, as they were previously.[21,24,25,26]

The prevalence of mold allergy is approximately 5 to 30% of patients with atopy. There are many patients with bronchial asthma or risk of asthma. Therefore, the needs for AIT in those patients could be large; however, it does not correspond with realty.[27,28]

The indications for AIT to molds include a relationship between clinical symptoms and the current exposure to the allergen, IgE mediated allergy confirmation, the exclusion of other factors that may cause symptoms and the availability of allergen extract.[18]

The main problem is the lack of sufficient prospective studies that support the effectiveness of AIT to mold allergies. The first such trial was performed by Dreborg et al. in 1986, which included 16 children with *Cladosporium* and respiratory allergies. This study confirmed the positive effect of AIT based on the Evidence Based Medicine (EBM) criteria.[28] Currently, there are very few studies that meet the double blind placebo control regimen criteria. In most, they only focused on *Alternaria*.

Immunotherapy to Alternaria *and* Cladosporium

Many authors highlight the effectiveness of AIT for *Alternaria* in patients with allergic rhinitis and / or bronchial asthma.[30-34] This applies to children and adults. This is the only mold allergen where medical documentation confirms a significant improvement after treatment in controlled studies. These studies are presented in Table 1.

The effectiveness of such AITs is dependent upon the quality of the vaccine. Development of methods for extraction and assessment of the main allergen, ALT a 1, occurred because standardization made it possible to extract *Alternaria alternata*. Studies that used a vaccine containing the standardized *Alternaria alternata* extract confirmed the effectiveness of such an AIT.[41] This treatment led to reduced clinical allergic rhinoconjunctivitis symptoms, bronchial asthma, reduced drug used, decreased serum specific IgE levels and increased serum specific IgG4 levels to *Alternaria*. It is also important to specify the cumulative Alt 1 antigen doses that patients received during AIT in these trials. This is one of the criteria for assessing the

Table 1. Selected controlled AIT trials with *Alternaria* extracts.

Author	Number of patients (verum/placebo) and type of AIT	AIT dose	Age, years	Duration, months	Efficacy
Horst et al.[35]	13/11 SIT	2,000 BU/ml	5–56	12	SC, MS, NCH, IgE, IgG
Cantani et al.[36]	39/40 SIT	3,000–5,000 PNU	5–14	36	SC, MS
Berbardis et al.[37]	12 SLIT 11 SIT	3.5–5 BU/ml	5–17 13–26	24	SC, MS, NCH
Tabar et al.[38]	14/14 SIT	1,670 UBE	12.85 ± 4.08/ 14.92 ± 6.41	12	SC, MS
Cortellini et al.[39]	15/12 SLIT	10 000 RU	14–42	10	SC, MS, IgE, IgG
Kuna et al.[40]	30/20 SCIT	5,000 TU/mL	5–18	36	SMS, CH

Legend: SIT- specific subcutaneous immunotherapy, SLIT – specific sublingual immunotherapy, SC – symptoms score, MS- medication score, SMS – symptoms medication score, NCH – nasal challenges, PNU- protein nitrogen units, BU – biological units, RU –radioallergosorbent test units, TU – therapeutic units, UBE – equivalent biological units.

effectiveness of AIT. These authors simultaneously observed very good tolerance of such vaccines. Adverse events were observed in less than 1% of all injections. There were mainly local reactions and only a few systemic reactions, which included dyspnea, cough and rhinitis.[42,43,44]

Earlier, an older vaccine (without proper allergen extract standardization) induced many adverse systemic reactions. This greatly limited the possibilities of such treatment.[45-47]

Despite the effectiveness of AIT *Alternaria*, there is a lack of long-term follow-ups with patients after such treatment. There is no feedback on how long the effect persists after desensitization to *Alternaria*. Does AIT really promote asthma modification in patients allergic to Alternaria? This question is open. Long-term observations of the effectiveness of AIT are difficult and expensive to implement. This problem also applies to other allergens.

We have much less evidence on the effectiveness of AIT to *Cladosporium*. Malling et al. described anaphylactic reactions with *Cladosporium* extract, which worsened asthma in some patients during AIT and caused many local reactions. At the same time, some investigators deny the effectiveness of such treatment.[48-50] Dreborg et al. emphasized the worsening of clinical symptoms in approximately 20% of studied patients, as mentioned above in his study.[29]

A meta-analysis of AIT injections by Helbing et al. revealed that the clinical efficacy of AIT to presented mold allergens was present in 79 actively treated subjects in 4 controlled trials (especially for *Alternaria*).[13]

The European Academy of Allergology and Clinical Immunology (EAACI) did not recommended AIT for mold extracts in children. This opinion was based on a lack of efficacy and safety.[21] On the other hand, The American Academy of Allergy, Asthma and Immunology (AAAAI) concluded that such AITs might be effective. An international consensus on immunotherapy indicated the possibility of AIT for molds, but only with standardized extracts.[51]

Currently, a major problem is the lack of access to a standardized extract for *Cladosporium*.[52] This problem and the lack of sufficient evidence for the effectiveness of AIT to the allergen led to no recommendation for this therapy by international consensuses.

At the present time, it is also possible to perform sublingual immunotherapy (SLIT) to *Alternaria*. In one study, very good tolerance and similar effectiveness of SLIT compared with conventional AIT in patients treated with *Alternaria alternata* extracts was shown.[53-55] However, there is a need for additional similar trials.

In patients with polyvalent allergies, (e.g., to mold and mites or molds and pollens), AIT is more complicated. A new international guideline allows for simultaneous AIT on different groups of allergens. However, these allergens must be included in 2 vaccines.[21] Fungal allergen extracts contain proteases that are able to degrade other allergens (e.g., mites, pollens) if they are together in one vaccine.[26,52]

The problem with the protease activity of mold allergens is more complicated. There are studies that revealed the deterioration of many mold extracts for testing or in vaccines due to the reaction between different molds with each other.[53]

AITs to other molds

As mentioned above, the main problem with AITs for other molds is a lack of standardized extract allergens. Moreover, there are no controlled studies that confirmed the effectiveness of such therapy. Single case reports or uncontrolled studies regarding AITs for *Candida albicans* or *Aspergillus fumigatus* are not sufficient for their recommendation.[39,54,55] Notably, not all allergic reactions induced by molds are IgE-mediated, which is the basis for AIT.

Immunotherapy for allergic fungal sinusitis could also be effective. There are some observations that AITs based on positive skin tests are useful, and no repeat surgeries were required in some patients after AIT. Further controlled studies are needed to confirm this. At the present time, there are no international recommendations to use such a therapy,.[18,56,57]

Conclusion

At the present time, AIT to *Alternaria alternata* is the only recommended AIT for mold allergy patients with allergic rhinitis and/or some types of bronchial asthma. This is because the only standardized extract that is available is for *Alternaria alternata*. Additionally, sufficient controlled trials confirmed the effectiveness and safety of this AIT, but this has only been done for this allergen.

Disclosure of potential conflicts of interest

No potential conflicts of interest were disclosed.

References

[1] D'Amato G, Spieksma FT. Aerobiologic and clinical aspects of mould allergy in Europe. Allergy 1995; 50(11):870-7; PMID:8748718; https://doi.org/10.1111/j.1398-9995.1995.tb02492.x

[2] Rick EM, Woolnough K, Pashley CH, Wardlaw AJ. Allergic Fungal Airway Disease. J Investig Allergol Clin Immunol 2016; 26(6):344-54; PMID:27996940; https://doi.org/10.18176/jiaci.0122

[3] Dziadzio L, Bush RK. Assessment and control of fungal allergens. Curr Allergy Asthma Rep 2001; 1(5):455-60; PMID:11892072; https://doi.org/10.1007/s11882-001-0033-3

[4] Chapman JA. Update on airborne mold and mold allergy. Allergy Asthma Proc 1999; 20(5):289-92; PMID:10566096; https://doi.org/10.2500/108854199778251889

[5] Mari A, Schneider P, Wally V, Breitenbach M, Simon-Nobbe B. Sensitization to fungi: epidemiology, comparative skin tests, and IgE reactivity of fungal extracts. Clin Exp Allergy 2003; 33(10):1429-38; PMID:14519151; https://doi.org/10.1046/j.1365-2222.2003.01783.x

[6] Simon-Nobbe B, Denk U, Pöll V, Rid R, Breitenbach M. The spectrum of fungal allergy. Int Arch Allergy Immunol 2008; 145(1):58-86; PMID:17709917; https://doi.org/10.1159/000107578

[7] Twaroch TE, Curin M, Valenta R, Swoboda I. Mold allergens in respiratory allergy: from structure to therapy. Allergy Asthma Immunol Res 2015; 7(3):205-20; https://doi.org/10.4168/aair.2015.7.3.205

[8] Cox L, Nelson H, Lockey R, Calabria C, Chacko T, Finegold I, Nelson M, Weber R, Bernstein DI, Blessing-Moore J, et al. Allergen immunotherapy: a practice parameter third update. J Allergy Clin Immunol 2011; 127(1 Suppl):S1-55; https://doi.org/10.1016/j.jaci.2010.09.034. Erratum in: J Allergy Clin Immunol. 2011;127(3):840

[9] Rodríguez Del Río P, Vidal C, Just J, Tabar AI, Sanchez-Machin I, Eberle P, Borja J, Bubel P, Pfaar O, Demoly P, Calderón MA. The European Survey on Adverse Systemic Reactions in Allergen Immunotherapy (EASSI): A paediatric assessment. Pediatr Allergy

Immunol 2017; 28(1):60-70; PMID:27637414; https://doi.org/10.1111/pai.12660

[10] Pfaar O, Bachert C, Bufe A, Buhl R, Ebner C, Eng P, Friedrichs F, Fuchs T, Hamelmann E, Hartwig-Bade D, et al. Guideline on allergen-specific immunotherapy in IgE-mediated allergic diseases: S2k Guideline of the German Society for Allergology and Clinical Immunology (DGAKI), the Society for Pediatric Allergy and Environmental Medicine (GPA), the Medical Association of German Allergologists (AeDA), the Austrian Society for Allergy and Immunology (ÖGAI), the Swiss Society for Allergy and Immunology (SGAI), the German Society of Dermatology (DDG), the German Society of Oto- Rhino-Laryngology, Head and Neck Surgery (DGHNO-KHC), the German Society of Pediatrics and Adolescent Medicine (DGKJ), the Society for Pediatric Pneumology (GPP), the German Respiratory Society (DGP), the German Association of ENT Surgeons (BV-HNO), the Professional Federation of Paediatricians and Youth Doctors (BVKJ), the Federal Association of Pulmonologists (BDP) and the German Dermatologists Association (BVDD). Allergo J Int 2014; 23(8):282-319; PMID:26120539; https://doi.org/10.1007/s40629-014-0032-2

[11] Malling HJ. Immunotherapy for mold allergy. Clin Rev Allergy 1992; 10(3):237-51; PMID:1477815

[12] Coop CA. Immunotherapy for mold allergy. Clin Rev Allergy Immunol 2014; 47(3):289-98; PMID:24057512; https://doi.org/10.1007/s12016-013-8389-4

[13] Helbling A, Reimers A. Immunotherapy in fungal allergy. Curr Allergy Asthma Rep 2003; 3(5):447-53; PMID:12906784; https://doi.org/10.1007/s11882-003-0082-x

[14] Pawankar R, Holgate ST, Canonica W, Lockey RF, Biass MS. WAO White Book on Allergy 2013 updated. [Accessed 2016 Oct 30]. http://www.worldallergy.org/UserFiles/file/WhiteBook2-2013-v8.pdf

[15] Kurup VP. Fungal allergens. Curr Allergy Asthma Rep 2003; 3 (5):416-23; PMID:12906780; https://doi.org/10.1007/s11882-003-0078-6

[16] Aukrust L. Mold allergy. Introduction. Clin Rev Allergy 1992; 10 (3):147-51

[17] Crameri R, Garbani M, Rhyner C, Huitema C. Fungi: the neglected allergenic sources. Allergy 2014; 176-85; PMID:24286281; https://doi.org/10.1111/all.12325

[18] Gawlik R. Swoista immunoterapia w alergii na grzyby pleśniowe w świetle EBM. Alergologia Współczesna 2008; 1(21):16-8

[19] Sharpe RA, Bearman N, Thornton CR, Husk K, Osborne NJ. Indoor fungal diversity and asthma: a meta-analysis and systematic review of risk factors. J Allergy Clin Immunol 2015; 135(1):110-22; https://doi.org/10.1016/j.jaci.2014.07.002

[20] Kołodziejczyk K, Bożek A, Jarząb J, Gawlik R. The clinical differences of asthma in patients with molds allergy. Pneumonol Alergol Pol 2016; 84(2):81-6; PMID:27238165; https://doi.org/10.5603/PiAP.2016.0005

[21] Jutel M, Agache I, Bonini S, Burks AW, Calderon M, Canonica W, Cox L, Demoly P, Frew AJ, O'Hehir R, et al. International consensus on allergy immunotherapy. J Allergy Clin Immunol 2015; 136 (3):556-68; https://doi.org/10.1016/j.jaci.2015.04.04

[22] Bousquet J, Lockey R, Malling HJ editors. World Health Organization Position Paper. Allergen immunotherapy; Therapeutic vaccines for allergic diseases. Allergy 1998; 53 (Suppl52):3-15

[23] Matricardi PM1, Kuna P, Panetta V, Wahn U, Narkus A. Subcutaneous immunotherapy and pharmacotherapy in seasonal allergic rhinitis: a comparison based on meta-analyses. J Allergy Clin Immunol 2011; 128(4):791-99; https://doi.org/10.1016/j.jaci.2011.03.049

[24] Jutel M, Agache I, Bonini S, Burks AW, Calderon M, Canonica W, Cox L, Demoly P, Frew AJ, O'Hehir R, et al. International Consensus on Allergen Immunotherapy II: Mechanisms, standardization, and pharmacoeconomics. J Allergy Clin Immunol 2016; 137(2):358-68; https://doi.org/10.1016/j.jaci.2015.12.1300

[25] Jutel M, Kosowska A, Smolinska S. Allergen Immunotherapy: Past, Present, and Future. Allergy Asthma Immunol Res 2016; 8(3):191-7; https://doi.org/10.4168/aair.2016.8.3.191

[26] Grier TJ, LeFevre DM, Duncan EA, Esch RE. Stability of standardized grass, dust mite, cat, and short ragweed allergens after mixing with mold or cockroach extracts. Ann Allergy Asthma Immunol 2007; 99(2):151-60; PMID:17718103; https://doi.org/10.1016/S1081-1206(10)60639-4

[27] Kaad PH, Ostergaard PA. The hazard of mould hyposensitization in children with asthma. Clin Allergy 1982; 12(3):317-20; PMID:7105396; https://doi.org/10.1111/j.1365-2222.1982.tb02534.x

[28] Ostergaard PA, Kaad PH, Kristensen T. A prospective study on the safety of immunotherapy in children with severe asthma. Allergy 1986; 41(8):588-93; PMID:3544937; https://doi.org/10.1111/j.1398-9995.1986.tb00351.x

[29] Dreborg S, Agrell B, Foucard T, Kjellman NI, Koivikko A, Nilsson S. A double-blind, multicenter immunotherapy trial in children, using a purified and standardized Cladosporium herbarum preparation. I. Clinical results. Allergy 1986; 41(2):131-40

[30] Gada S, Haymore B, McCoy L, Kosisky S, Nelson M. Frequency of mold and pollen mixing in allergen immunotherapy prescriptions within a large health care system, 1990-2010. J Allergy Clin Immunol 2012; 129(4):1151-53; https://doi.org/10.1016/j.jaci.2011.10.027

[31] Zapatero L, Martínez-Cañavate A, Lucas JM, Guallar I, Torres J, Guardia P, Torre Fde L, Pedemonte C. Clinical evolution of patients with respiratory allergic disease due to sensitisation to Alternaria alternata being treated with subcutaneous immunotherapy. Allergol Immunopathol (Madr) 2011; 39(2):79-84; https://doi.org/10.1016/j.aller.2010.03.011

[32] Martínez-Cañavate Burgos A, Valenzuela-Soria A, Rojo-Hernández A. Immunotherapy with Alternaria alternata: present and future. Allergol Immunopathol (Madr) 2007; 35(6):259-63; PMID:18047818; https://doi.org/10.1157/13112993

[33] Sanchez H, Bush RK. A review of Alternaria alternata sensitivity. Rev Iberoam Micol 2001; 18(2):56-9; PMID:15487907

[34] Kiliç M, Altintaş DU, Yilmaz M, Bingöl-Karakoç G, Burgut R, Güneşer-Kendirli S. Evaluation of efficacy of immunotherapy in children with asthma monosensitized to Alternaria. Turk J Pediatr 2011; 53(3):285-94; PMID:21980810

[35] Horst M, Hejjaoui A, Horst V. A souble blind, placebo –controlled rush immunotherapy with standardized Alternaria extract. J Allergy Clin Immunol 1990; 85:460-72; PMID:2406323; https://doi.org/10.1016/0091-6749(90)90156-X

[36] Cantani A, Businco E, Maglio A. Alternaria allergy: a three-year controlled study in children treated with immunotherapy. Allergol Immunopathol (Madrid) 1988; 16:1-4

[37] Bernardis P, Agnoletto M, Puccinelli P. Injective versus sublingual immunotherapy in Alternaria tenuis allergic patients. J Invest Allergol Clin Immunol 1996; 6:55-62

[38] Tabar AI, Lizaso MT, García BE, Gómez B, Echechipía S, Aldunate MT, Madariaga B, Martínez A. Double-blind, placebo-controlled study of Alternaria alternata immunotherapy: clinical efficacy and safety. Pediatr Allergy Immunol 2008; 19(1):67-75; PMID:17651380; https://doi.org/10.1111/j.1399-3038.2007.00589.x.

[39] Cortellini G1, Spadolini I, Patella V, Fabbri E, Santucci A, Severino M, Corvetta A, Canonica GW, Passalacqua G. Sublingual immunotherapy for Alternaria-induced allergic rhinitis: a randomized placebo-controlled trial. Ann Allergy Asthma Immunol 2010; 105 (5):382-6; https://doi.org/10.1016/j.anai.2010.08.007

[40] Kuna P, Kaczmarek J, Kupczyk M. Efficacy and safety of immunotherapy for allergies to Alternaria alternata in children. J Allergy Clin Immunol 2011; 127(2):502-8.e1-6; https://doi.org/10.1016/S0091-6749(11)00012-1

[41] Aden E, Weber B, Bossert J, Teppke M, Frank E, Wahl R, Fiebig H, Cromwell O. Standardization of Alternaria alternata: extraction and quantification of alt a 1 by using an mAb-based 2-site binding assay. J Allergy Clin Immunol 1999; 104(1):128-35; PMID:10400850; https://doi.org/10.1016/S0091-6749(99)70124-7

[42] Prieto L, Palacios R, Aldana D, Ferrer A, Perez-Frances C, Lopez V, Rojas R. Effect of allergen-specific immunotherapy with purified Alt a1 on AMP responsiveness, exhaled nitric oxide and exhaled breath condensate pH: a randomized double blind study. Allergy Asthma Clin Immunol 2010; 6(1):27; PMID:20846390; https://doi.org/10.1186/1710-1492-6-27

[43] Lizaso MT, Martínez A, Asturias JA, Algorta J, Madariaga B, Labarta N, Tabar AI. Biological standardization and maximum tolerated dose estimation of an Alternaria alternata allergenic extract. J Investig Allergol Clin Immunol 2006; 16(2):94-103; PMID:16689182

[44] Lizaso MT, Tabar AI, García BE, Gómez B, Algorta J, Asturias JA, Martínez A. Double-blind, placebo-controlled Alternaria alternata immunotherapy: in vivo and in vitro parameters. Pediatr Allergy Immunol 2008; 19(1):76-81; PMID:17662037; https://doi.org/10.1111/j.1399-3038.2007.00587.x

[45] Serna-Candel C, Moreno-Perez O, Soriano V, Martínez A. Churg-Strauss syndrome triggered by hyposensitization to Alternaria fungus. Clin Rheumatol 2007; 26(12):2195-6; PMID:17674119; https://doi.org/10.1007/s10067-007-0680-4

[46] Tabar AI, Lizaso MT, García BE, Gómez B, Echechipía S, Aldunate MT, Madariaga B, Martínez A. Double-blind, placebo-controlled study of Alternaria alternata immunotherapy: clinical efficacy and safety. Pediatr Allergy Immunol 2008; 19(1):67-75; PMID:17651380; https://doi.org/10.1111/j.1399-3038.2007.00589.x

[47] Martínez-Cañavate A, Eseverri JL, Ródenas R, Tabar AI, Gardee J, Torres J, Boné J, Pedemonte C. Evaluation of paediatric tolerance to an extract of Alternaria alternata under two treatment regimes. A multicentre study. Allergol Immunopathol (Madr) 2005; 33(3):138-41; https://doi.org/10.1157/13075696

[48] Malling HJ, Dreborg S, Weeke B. Diagnosis and immunotherapy of mould allergy. V. Clinical efficacy and side effects of immunotherapy with Cladosporium herbarum. Allergy 1986; 41(7):507-19

[49] Malling HJ, Dreborg S, Weeke B. Diagnosis and immunotherapy of mould allergy. VI. IgE-mediated parameters during a one-year placebo-controlled study of immunotherapy with Cladosporium. Allergy 1987; 42(4):305-14

[50] Malling HJ, Djurup R. Diagnosis and immunotherapy of mould allergy. VII. IgG subclass response and relation to the clinical efficacy of immunotherapy with Cladosporium. Allergy 1988; 43(1):60-70

[51] Calderon MA, Demoly P, Casale T, Akdis CA, Bachert C, Bewick M, Bilò BM, Bohle B, Bonini S, Bush A, et al. Allergy immunotherapy across the life cycle to promote active and healthy ageing: from research to policies: An AIRWAYS Integrated Care Pathways (ICPs) programme item (Action Plan B3 of the European Innovation Partnership on active and healthy ageing) and the Global Alliance against Chronic Respiratory Diseases (GARD), a World Health Organization GARD research demonstration project. Clin Transl Allergy. 2016; 6:41. eCollection 2016; https://doi.org/10.1186/s13601-016-0131-x

[52] Esch RE. Manufacturing and standardizing fungal allergen products. J Allergy Clin Immunol 2004; 113(2):210-5; https://doi.org/10.1016/j.jaci.2003.11.024

[53] Pozzan M, Milani M. Efficacy of sublingual specific immunotherapy in patients with respiratory allergy to Alternaria alternata: a randomised, assessor-blinded, patient-reported outcome, controlled 3-year trial. Curr Med Res Opin. 2010; 26(12):2801-06; PMID:21050060; https://doi.org/10.1185/03007995.2010.532201

[54] Benoliel P. Treatment of sino-nasal polyposis by Candida albicans immunotherapy: apropos of 4 cases. Allerg Immunol (Paris) 2001; 33(10):388-94

[55] Kniemeyer O, Ebel F3, Krüger T, Bacher P, Scheffold A, Luo T, Strassburger M, Brakhage AA. Immunoproteomics of Aspergillus for the development of biomarkers and immunotherapies. Proteomics Clin Appl 2016; 10(9–10):910-21; PMID:27312145; https://doi.org/10.1002/prca.201600053

[56] Hall AG, deShazo RD. Immunotherapy for allergic fungal sinusitis. Curr Opin Allergy Clin Immunol 2012; 12(6):629-34; https://doi.org/10.1097/ACI.0b013e328357a233

[57] Doellman MS, Dion GR, Weitzel EK, Reyes EG. Immunotherapy in allergic fungal sinusitis: The controversy continues. A recent review of literature. Allergy Rhinol (Providence) 2013; 4(1):e32-5; https://doi.org/10.2500/ar.2013.4.0045