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Single, pauci, and multi-allergen immunotherapy

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Abstract. *Single, pauci, and multi-allergen immunotherapy. Objectives:* This paper's aim is to review single, pauci, and multi-allergen immunotherapy.
Methods: Search is made through PubMed, Google, Google Scholar and Proquest Central database of the Kırıkkale University Library.
Results: Allergen immunotherapy (AIT) modifies the immune response to a specific allergen. AIT has been used to treat allergic rhinitis, allergic conjunctivitis, allergic asthma and also insect venom allergy. Immunotherapy can be administered subcutaneously (SCIT) or sublingually (SLIT). Patients may be mono-, pauci-, or polysensitized to allergens. Polysensitization is more common and usually increases with age. AIT is maximally effective when one or two allergens are used. There is a similar effect in both mono and polysensitized patients. However, in polysensitized patients, immunotherapy with multiple allergens is less effective compared with desensitization treatment in monosensitized patients using one allergen. This may relate to dose, or to the fact that polysensitization might merely reflect cross-reactivity to one or two major causative allergens.
Conclusion: We suggest that in polyallergy, where symptoms of rhinitis or asthma, are related to the exposure of multiple allergens; would be a better subject for multiple allergen desensitizations than polysensitization. This need is to explore in well-designed experiments.

1. Introduction

Allergen immunotherapy (AIT) changes how the immune system responds to an allergen[1] or an allergenic determinant, which is usually a protein (e.g., mites, grass, trees, moulds).[2] AIT alters the immune response, modifies the disease course of allergic rhinitis (AR), allergic asthma and conjunctivitis. Subcutaneous immunotherapy (SCIT) can be used to treat allergic rhinitis with or without allergic asthma. Sublingual immunotherapy (SLIT) has been a focus of research because of increased safety and patients' comfort.

In the USA, the debate remains about the use of multiple allergens for AIT in polysensitized patients. An historical practice involves the use of many allergens to which the patient is sensitized.[3] This contrasts practice in the UK and Europe, where one or two major allergens which appear from history to drive diseases. A recent understanding of molecular Allergology suggests that the shared allergenic epitopes may be responsible for multiple positive skin prick tests, whereas in fact, only one major allergen is responsible for symptoms. To understand the approach in polysensitized patients the following definitions can be used.[4]

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Allergen: a protein or glycoprotein that binds specific IgE. **Monosensitization**: sensitization (confirmed by skin testing or specific sIgE test) to one allergen. **Polysensitization**: sensitization to two or more allergens. **Paucisensitization**: sensitization to two or four allergens. **Cross- action/ cross-reactivity**: IgE sensitization to one molecule which is present in other allergen(s). **Polyallergy**: Clinically confirmed sensitization (positive skin/ sIgE +symptoms on exposure) to two or more allergens.

Polysensitization can be confirmed in at least 10% of the population (and more than 50% of the patients sensitized to respiratory allergens).[4] Polysensitization is more common (50-80%) than monosensitization, in those with high moderate respiratory allergies. Compelling single-allergen arrangements have doubtlessly been tried for polysensitized patients. Using grass pollen sub-lingual tablets, polysensitized patients benefited from AIT, as did monosensitized patients.[5]

2. Materials and methods

To perform this review, the search is made through PubMed, Google, Google Scholar and Proquest Central database of Kırıkkale University Library. The used keywords were "allergen immunotherapy", "allergens", "sensitization", "subcutaneous immunotherapy", "sublingual immunotherapy", "allergic rhinitis", "allergic conjunctivitis", "allergic asthma", "monosensitization", "paucisensitization", "cross-sensitization", "polyallergy" and "polysensitization".

3. Results

3.1. Sensitization

Data from the main European Respiratory Wellbeing Study that included 11,355 participants with a mean age of 34 years who had 4-9 skin-prick tests and/or 4 or 5 serum allergen-specific IgE tests revealed that 57.0-67.8% of this European population were not sensitized to any of the test allergens, 16.2-19.6% were monosensitized, and 12.8-25.3% were polysensitized[6]. The second and third National Wellbeing and Sustenance Examination Reviews confirmed that in skin testing to basic aeroallergens among American participants aged 6-59 years, 45.7% were not sensitized to any of the test allergens, 15.5% were monosensitized, and 38.8% were polysensitized.[5,7]

Most participants in AIT clinical trials are polysensitized[5,8]. Demoly et al.[9] demonstrated that AIT was safe and effective in polysensitized patients. Desensitization should be used for one or more clinically relevant allergens. Nyembue, et al.[10] used skin prick testing (SPT) to assess sensitization to major aeroallergens and evaluated the frequency of polysensitization. They found that 31.6% of the patients had positive SPT results, mainly to house dust mites and grass pollen. Among sensitized patients, 54.2% were polysensitized.

3.2. Mechanisms of SCIT and SLIT

3.3.1. Subcutaneous immunotherapy (SCIT)

Allergen specific IgE rises initially during SCIT, then later falls. There is also a reduction in the usual seasonal rise in specific IgE and an increase in allergen-specific IgG antibodies, especially IgG4[11]. T cells reduce allergen-specific Th2 response via cytokines, including TGF b and IL-10, which is known to cause a switch from IgE to IgG4 generation.[12]

3.3.2. Sublingual immunotherapy (SLIT)

Increase in IgG4 during SLIT is similar to SCIT, and is associated with a transient increase in IgE, and reduced eosinophil enrollment and activation.[13]

4. Discussion

4. 1. Single-allergen immunotherapy

SCIT and SIT with one allergen (grass or house dust mite) has shown to be safe and effective in studies that included polysensitized participants.[14] Malling et al.[8] demonstrated that grass and house dust mite sublingual tablets in their study involving 628 patients from 42 sites (10 in Europe) showed improvement in symptoms and demonstrated safety. Passalacqua et al.[15] reported that sublingual immunotherapy was safe and effective in patients sensitized to house dust mites. Sublingual immunotherapy was administered in the form of tablets of monomeric carbamylated allergoid (Table 1).

Demoly et al.[9] reported that AIT with one allergen was appropriate in polyallergic patients in whom

Table 1
Clinical trials for single-allergen sublingual immunotherapy

Authors	Trial	Subjects	Treatment	Main outcomes
Malling et al.,[8] Denmark, 2009	Multi-national, randomized, double-blind, placebo-controlled	628 adults 18-45 years	300 IR 5-grass pollen SLIT tablets	The risk-benefit ratio supports the use of 300 IR tablets in clinical practice in these patient subgroups, paying little regard to severity profile, sensitization status, and severity of asthma
Passalacqua et al.,[15] Italy, 2006	Randomized, double-blind, placebo-controlled	56 patients with mite allergy	Soluble tablets of monomeric carbamylated allergoid	Sublingual immunotherapy was clinically successful and safe in mite-instigated mild infection
Ciprandi, et al[16] Italy,2009	The kind and the number of prescribed allergen extracts, type of diagnosis, severity of symptoms, use of drugs, and adverse events were evaluated at baseline and after 1 year.	244 patients with allergic rhinitis and/or mild to moderate asthma (109 males, 135 females) Mean age 28.7 years	A total of 230 patients were treated with SLIT for one year: 165 with a single extract, and 65 with two different extracts (mix).	- SLIT treatment significantly improved disease staging, and reduced symptom severity and drug use. No systemic reaction was reported. - SIT is effective and safe in polysensitized patients after 1 year of treatment also using single extracts, and thus does not represent an obstacle for prescribing SIT.

that allergen clearly causes symptoms. Parallel two-allergen immunotherapy and mixed two-allergen immunotherapy have been shown to be effective in polyallergic patients who had clinical symptoms that significantly influenced their QoL.

Ciprandi et al.[16] reported the results of use single-allergen SLIT in polysensitized patients (adults and children). These 165 polysensitized adult patients with confirmed AR and/or asthma (Global Initiative for Asthma criteria) received one year of SLIT with one allergen, and 65 received a mix of two allergens. The mean number of positive skin prick tests per patient was 3.65, with sensitization to grasses (81.6%), Parietaria species (48.4%), and Dermatophagoides species (46.7%). Based on the significant reduction in symptoms and medication scores after one year of treatment and absence of systemic side effects in both groups, the investigators concluded that single-allergen SLIT (in 71% of patients) were safe and effective in polysensitized patients (Table 1).

4.2.Pauci-allergen immunotherapy

Jong, et al.[17] proposed the term 'paucisensitization' to describe sensitization to 2-4 allergens, in contrast with 'polysensitization'defined as sensitization to five or more allergens[17]. Demoly, et al.[9] advised that the mixing of allergens may be considered in two-allergen SCIT or SLIT immunotherapy.

4.3. Multi-allergen immunotherapy

Despite the common use of multi-allergen immunotherapy, a recent review highlighted the low level of evidence for the safety and efficacy in SCIT or SLIT. Nelson[18] completed an exhaustive review on the multi-allergen immunotherapy for patients with rhinitis and asthma from the scientific literature published between 1961 and 2007. He assessed 13 studies (some of them were double-blind, placebo-controlled trials) where two or more allergens were used at the same time, but there were some with a full comparison with single-allergen immunotherapy. Population size in these trials ranged from 24-208. Nelson speculated that treatment of polysensitized patients using combined exposure to multiple allergens might be clinically relevant, but that there is a need for further research of treatment with more than two allergens in SCIT and SLIT.

4.4. SLIT

A study by Amar et al.[19] looked at the use of allergen mixtures for 10 months of SLIT in 54 polysensitized patients who were randomised into three groups; treatment with the timothy extract (19 mg of Phl p 5 daily), or the same amount of timothy extract mixed with nine pollens, or placebo. The results were assessed during the 2008 grass pollen season

Table 2
Clinical trials for sublingual multi-allergen immunotherapy

Authors	Trial	Subjects	Treatment	Main outcomes
Amar, et al.[19] USA, 2009	A single-center, randomized, double-blind, placebo-controlled trial with SLIT	54 patients	Placebo, timothy extract (19 microg Phl p 5 daily) as monotherapy, or the same dose of timothy extract plus 9 additional pollen extracts.	Results for symptom and medication scores were not significant or either group versus placebo, perhaps because of a low pollen season. Improvement in multiple relevant laboratory outcomes suggests that SLIT with timothy extract alone was effective. The differences between multiple allergen SLIT and placebo in skin sensitivity to timothy only suggests a reduction in SLIT efficacy in this group.

Table 3
Clinical trials for subcutaneous multi-allergen immunotherapy

Authors	Trial	Subjects	Treatment	Main outcomes
Bousquet et al.[20] France, 1991	A double-blind, placebo-controlled study	70 patients	A standardized orchard grass-pollen extract or with a standardized mixed-pollen extract prepared, depending on the sensitivity of the patients	The response toward specific IT differs in patients only allergic to grass pollens by comparison to polysensitized patients
Kim, et al.[21] Korea, 2006	The clinical trial including monosensitized and polysensitized groups	130 patients who underwent SCIT 68 patients belonged to the monosensitized group (6.3±0.3 yr) and 62 patients to the polysensitized group (7.6±0.3 yr).	Monosensitized subjects received immunotherapy with house dust mite vaccines and polysensitized subjects with mixed vaccines depending on the sensitivity of the subjects. Both groups had the same dosage of house dust mite antigen in the vaccines.	Monosensitized groups and polysensitized groups are immunologically different, and these differences are most likely controlled by the secretion pattern of various cytokines, as allergic indices are more severe and immunotherapy might be less effective in the polysensitized group.

in Denver, Colorado. There was no significant difference between placebo and the treatment groups. Pollen counts were very low, during this study, which may have affected the results[19] (Table 2).

4.5. SCIT

Bousquet et al.[20] performed a double-blind, placebo-controlled trial of a rush SCIT protocol in 70 adults with AR, with or without asthma. Patients monosensitized to grass pollen received SCIT with grass extract or a placebo, and polysensitized patients received SCIT with the same grass extract mixed with up to three other common allergens. The trial showed a significant clinical effect in monosensitized patients, but the effect was less in polysensitized patients, which led the authors to conclude that higher doses of all allergens might be required to achieve the equal effect. Kim et al.[21] compared SCIT in polysensitized patients (with allergic asthma) and monosensitized patients. Out of 130 children, 62 were polysensitized to HDM and four other allergens, and 68 children were monosensitized to HDM. Both groups received the same dose of HDM vaccine. Polysensitized patients had a significantly greater baseline symptom scores compared to the monosensitized group. In this study, immunotherapy in the polysensitized group was less effective compared to monosensitized patients[21] (Table 3).

4.6. Single versus multi-allergen immunotherapy

Few studies have directly compared single versus multi-allergen AIT. One study focused on grass and/or birch IT in patients sensitized to the two allergens, and found that the effect of treatment with two allergens was better compared to treatment with a single allergen.[22] Nelson[23] compared 13 studies that included 900 patients who received separately two allergens (seven studies) or a mix of four or more allergens (six studies). Five of these studies showed the efficacy of using mixtures in comparison with placebo (three of them were completed before 1968).

The dose of allergen given in multi-allergen preparations may be too low for efficacy, however, a recent review of the allergen content of various SLIT vaccines was very variable, with one manufacturer providing consistently low levels (monthly SLIT dose 1-5 times the SCIT dose). However, this low dose was clinically effective in some trials, suggesting that factors other than dose may be relevant.[24]

5. Conclusions

The comparison of the efficacy of multiple- compared with single-allergen AIT should be based on well-designed, large-scale clinical trials. Multi-allergen immunotherapy was less effective in polysensitized patients than single-allergen immunotherapy in monosensitized patients[25], however, there is a need for further research in polysensitized patients, including determination of underlying cross-reactive molecules. Polyallergy may require the use of more than one allergen for AIT, whereas polysensitization probably frequently does not. Based on current evidence, multi-allergen immunotherapy gives variable results in polysensitized patients.

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References

1. Bousquet J, Lockey R, Malling HJ. Allergen immunotherapy: therapeutic vaccines for allergic diseases. A WHO position paper. *J Allergy Clin Immunol.* 1998;102(4 Pt 1):558-562.
2. Sastre J. Molecular diagnosis in allergy. *Clin Exp Allergy.* 2010;40(10):1442-1460.
3. Cox L. The role of allergen immunotherapy in the management of allergic rhinitis. *Am J Rhinol Allergy.* 2016;30(1):48-53.
4. Migueres M, Dávila I, Frati F, Azpeitia A, Jeanpetit Y, Lhéritier-Barrand M, Incorvaia C, Ciprandi G. Types of sensitization to aeroallergens: definitions, prevalences and impact on the diagnosis and treatment of allergic respiratory disease. *Clin Transl Allergy.* 2014;4:16.
5. Calderón MA, Cox L, Casale TB, Moingeon P, Demoly P. Multiple-allergen and single-allergen immunotherapy strategies in polysensitized patients: looking at the published evidence. *J Allergy Clin Immunol.* 2012;129(4):929-934.
6. Bousquet PJ, Castelli C, Daures JP, Heinrich J, Hooper R, Sunyer J, Wjst M, Jarvis D, Burney P. Assessment of allergen sensitization in a general population-based survey (European Community Respiratory Health Survey I). *Ann Epidemiol.* 2010; 20(11):797-803.
7. Arbes SJ Jr, Gergen PJ, Elliott L, Zeldin DC. Prevalences of positive skin test responses to 10 common allergens in the US population: results from the third National Health and Nutrition Examination Survey. *J Allergy Clin Immunol.* 2005;116(2):377-383.
8. Malling HJ, Montagut A, Melac M, Patriarca G, Panzner P, Seberova E, Didier A. Efficacy and safety of 5-grass pollen sublingual immunotherapy tablets in patients with different clinical profiles of allergic rhinoconjunctivitis. *Clin Exp Allergy.* 2009;39(3):387-393.
9. Demoly P, Passalacqua G, Pfaar O, Sastre J, Wahn U. Management of the polyallergic patient with allergy immunotherapy: a practice-based approach. *Allergy Asthma Clin Immunol.* 2016;12:2.
10. Nyembue TD, Vinck AS, Corvers K, Bruninx L, Hellings PW, Jorissen M. Sensitization to common aeroallergens in patients at an outpatient ENT clinic. *B-ENT.* 2011;7(2):79-85.
11. Devey ME, Wilson DV, Wheeler AW. The IgG subclasses of antibodies to grass pollen allergens produced in hay fever patients during hyposensitization. *Clin Allergy.* 1976;6(3):227-236.
12. Jeannin P, Lecoanet S, Delneste Y, Gauchat JF, Bonnefoy JY. IgE versus IgG4 production can be differentially regulated by IL-10. *J Immunol.* 1998;160(7):3555-3561.
13. Lima MT, Wilson D, Pitkin L, Roberts A, Nouri-Aria K, Jacobson M, Walker S, Durham S. Grass pollen sublingual immunotherapy for seasonal rhinoconjunctivitis: a randomized controlled trial. *Clin Exp Allergy.* 2002; 32(4):507-514.
14. Didier A, Malling HJ, Worm M, Horak F, Jäger S, Montagut A, André C, de Beaumont O, Melac M. Optimal dose, efficacy, and safety of once-daily sub-lingual immunotherapy with a 5-grass polen tablet for seasonal allergic rhinitis. *J Allergy Clin Immunol.* 2007;120(6):1338-1345.
15. Passalacqua G, Pasquali M, Ariano R, Lombardi C, Giardini A, Baiardini I, Majani G, Falagiani P, Bruno M, Canonica GW. Randomized double-blind controlled study with sublingual carbamylated allergoid immunotherapy in mild rhinitis due to mites. *Allergy.* 2006;61(7):849-854.
16. Ciprandi G, Cadario G, Di Gioacchino M, Gangemi S, Minelli M, Ridolo E, Valle C, Verini M, Boccardo R, Incorvaia C, Puccinelli P, Scurati S, Frati F. Sublingual immunotherapy in polysensitized allergic patients with rhinitis and/or asthma: allergist choices and treatment efficacy. *J Biol Regul Homeost Agents*. 2009;23(3):165-171.
17. de Jong AB, Dikkeschei LD, Brand PL. Sensitization patterns to food and inhalant allergens in childhood: a comparison of non-sensitized, monosensitized and polysensitized children. *Pediatr Allergy Immunol.* 2011;22(22):166-171.
18. Nelson HS. Multiallergen immunotherapy for allergic rhinitis and asthma. *J Allergy Clin Immunol.* 2009; 123(4):763-769.

19. Amar SM, Harbeck RJ, Sills M, Silveira LJ, O'Brien H, Nelson HS. Response to sublingual immunotherapy with grass pollen extract: monotherapy versus combination in a multiallergen extract. *Allergy Clin Immunol.* 2009;124(1):150-156.
20. Bousquet J, Becker WM, Hejjaoui A, Chanal I, Lebel B, Dhivert H, Michel FB. Differences in clinical and immunologic reactivity of patients allergic to grass pollens and to multiple-pollen species. II. Efficacy of a double-blind, placebo-controlled, specific immunotherapy with standardized extracts. *J Allergy Clin Immunol.* 1991;88(1):43-53.
21. Kim KW, Kim EA, Kwon BC, Kim ES, Song TW, Sohn MH, Kim KE. Comparison of allergic indices in monosensitized and polysensitized patients with childhood asthma. *J Korean Med Sci.* 2006;21(6):1012-1016.
22. Marogna M, Spadolini I, Massolo A, Zanon P, Berra D, Chiodini E, Canonica WG, Passalacqua G. Effects of sublingual immunotherapy for multiple or single allergens in polysensitized patients. *Ann Allergy Asthma Immunol.* 2007;98(3):274-280.
23. Nelson HS. Specific immunotherapy with allergen mixes: what is the evidence? *Curr Opin Allergy Clin Immunol.* 2009;9(6):549-553.
24. Larenas-Linnemann DE, Mösges R. Dosing of European sublingual immunotherapy maintenance solutions relative to monthly recommended dosing of subcutaneous immunotherapy. *Allergy Asthma Proc*. 2016;37(1):50-56.
25. Lombardi C, Gargioni S, Cottini M, Canonica GW, Passalacqua G. The safety of sublingual immunotherapy with one or more allergens in adults. *Allergy.* 2008; 63(3):375-376.

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