



The use of single versus multiple antigens in specific allergen immunotherapy for allergic rhinitis: review of the evidence

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Purpose of review

Allergen-specific immunotherapy (AIT) targets the IgE-mediated response to specific allergen(s). Accordingly, a monosensitized patient would be the ideal candidate for AIT. However, most patients are polysensitized; thus, two main problems emerge: first, whether AIT with a clinically relevant allergen is effective in polysensitized patients, and second, whether the use of a few allergens (European approach) or of mixtures containing all the possibly sensitizing allergens (USA approach) should be used. Of note, only in recent years has the so-called 'component resolved diagnosis' introduced new diagnostic opportunities. In the present article, the available experimental data concerning the controversial aspects of single versus multiallergen AIT are reviewed.

Recent findings

Some data are only available from isolated studies, which are often not controlled, and few trials on the argument have been recently conducted. Main findings are that AIT can be effective in both monosensitized and polysensitized patients, as shown by large trials with grass extracts.

Summary

The evidence for the efficacy of allergen mixes is still weak, but component-resolved diagnosis could represent a valuable help in selecting the allergen. As a matter of fact, comparative trials on multiple versus single allergen immunotherapy would be expensive and time-consuming: this justifies the paucity of data.

Keywords

allergen mixtures, allergen-specific immunotherapy, component-resolved diagnosis, monosensitization, polysensitization

INTRODUCTION

Allergen immunotherapy (AIT), as a matter of fact (and as an act of faith), is a treatment that specifically modifies the immune response to a single allergen [1,2] or, better, to an allergen component, usually a protein contained in 'allergenic sources' (e.g. mite, grass, trees) [3]. According to the available data in literature, the effect of allergen administration evokes a specific immune response that can be documented, for instance, by the appearance of allergen-specific IgG4 interfering with the IgE-facilitated antigen presentation or by the reduction of symptoms or drug intake in allergic rhinitis and asthma [4,5^{6,7}]. Based on the available mechanistic data, AIT is expected to be highly effective when the IgE-mediated reaction is predominant, as it happens in hymenoptera venom immunotherapy [8⁹], and when the patient is monosensitized [1]. It is well ascertained that atopic patients suffering

from allergic rhinitis/asthma are usually polysensitized, and produce specific IgE against different allergens. According to epidemiological data [10–12], about 80% of the allergic patients are polysensitized, with their pattern of sensitization varying with the geographical region. In this context, it has been claimed that AIT is especially effective in monosensitized individuals [1], whereas its clinical efficacy can be reduced when multiple sensitizations are present.

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KEY POINTS

- Polysensitization is often an obstacle to the correct prescription of allergen immunotherapy; in fact, the European and USA approaches profoundly differ on this aspect.
- The currently available evidence suggests that allergen immunotherapy with one or few clinically relevant allergens is effective in both monosensitized and polysensitized patients.
- The evidence for the effectiveness of allergen mixtures is weakly positive.
- The component-resolved diagnosis approach could be helpful in more accurately defining the sensitization profile, thus allowing a more appropriate AIT prescription.

The aforementioned aspects raise two main problems: the usefulness of AIT for a given allergen in polysensitized individuals and the rationale for using multiple-allergen AIT. This is especially related to the different AIT approaches in Europe (vaccination with only one or few allergens) and in the USA (vaccination with mixtures) [13] (Fig. 1). In recent years, critical appraisals of the experimental data were carried out, generally suggesting that the presence of multiple sensitizations does not necessarily represent a limitation to the efficacy of AIT [14²²], that component-resolved diagnosis can be of help selecting the allergens, and that multiallergen

AIT can be satisfactorily effective, although the latter aspect is less robustly supported [15].

ALLERGEN IMMUNOTHERAPY IN THE POLYSENSITIZED PATIENT

As mentioned above, the monosensitized patient would be the ideal candidate for an AIT course to the sensitizing agent. Nonetheless, looking at the available literature, it appears that polysensitized patients would also benefit from an appropriately prescribed AIT. This observation is mainly based on the results of the 'big trials' conducted with sublingual (sublingual immunotherapy, SLIT) grass tablets for allergic rhinitis. For instance, Emminger *et al.* [16], in a post-hoc analysis of a large clinical trial with SLIT grass pollen extract separately analyzed monosensitized patients, pollen polysensitized patients, and those polysensitized to other pollen allergens. As a result, the three sensitization groups showed a significant reduction in symptoms and medication scores, as compared with the placebo group, thus demonstrating that the clinical efficacy of AIT does not depend on the sensitization profile. Similar results were reported by Malling *et al.* [17], who separately analyzed the rhinitis/conjunctivitis symptom scores in polysensitized versus grass-monosensitized patients against the placebo group; evidence showed no difference relating to the sensitization asset. Several Italian trials [18–20], though not double blinded, further confirmed that SLIT with the clinically relevant allergen (one or two) was equally effective in monosensitized and

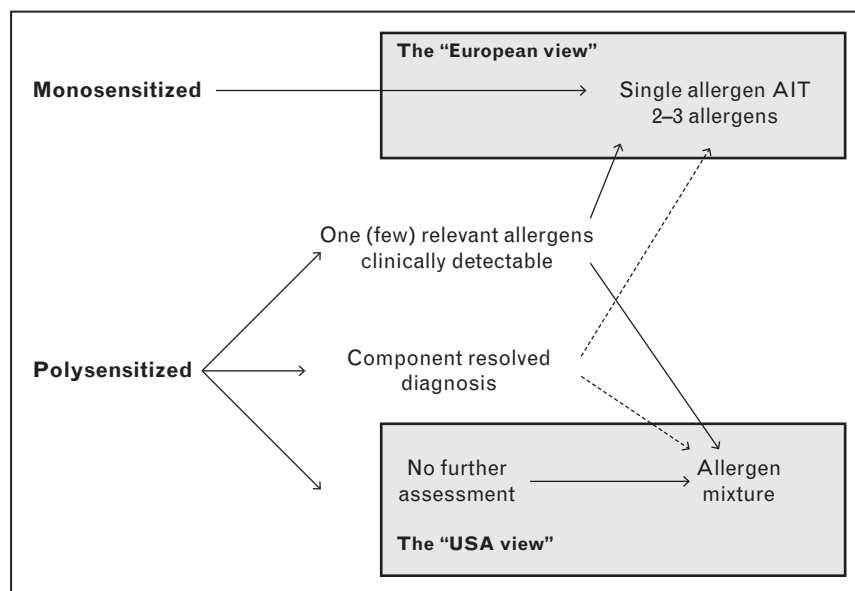


FIGURE 1. The possible approaches to allergen-specific immunotherapy prescription according to sensitization profile and cultural background. AIT, allergen-specific immunotherapy.

polysensitized patients. Nonetheless, one of those studies only considered the quality of life parameter as the main variable, without any objective assessment of clinical symptoms. Lee *et al.* [21], in a comparative study on 134 individuals, demonstrated that mite-SLIT is equally effective in monosensitized and polysensitized patients. Also in a previous study [22], conducted with a robust experimental design, with subcutaneous immunotherapy (SCIT) for grass pollen, the efficacy of the treatment was apparent, despite approximately 80% of patients being polysensitized. So far, according to the available data, it appears that the presence of multiple sensitizations is not necessarily a limitation in the use of AIT with the clinically relevant allergen(s). In this regard, it has to be considered that in the majority of the available trials, a detailed assessment of genuine sensitizations was not done. This latter approach is now achievable with the use of recombinant/purified allergenic components, which may allow a more precise definition of the sensitization profile of patients, thus avoiding the intrinsic diagnostic bias due to the use of whole 'natural' extracts commonly employed for diagnosis [23[■],24[■]]. In particular, some of the polysensitizations observed with the standard diagnostic methods, and due to cross-reacting molecules could be ruled out [25]. Indeed, a truly 'component-resolved' AIT seems, so far, difficult to achieve, both for the large variability of sensitization profiles among individuals [26], and for the regulatory obstacles in registering single recombinant molecules, as required by the European Medicine Agency [27].

THE PROBLEM OF MULTIALLERGEN IMMUNOTHERAPY (MIXTURES)

As mentioned before, one of the most striking differences between the European and USA approach to AIT is the use of allergen mixtures, which is common practice in USA, and usually not applied in European countries [13,28,29]. The European view is favored by the relative paucity of unrelated allergenic sources and by the consideration that if multiple allergens are administered, in the case of adverse events it is not possible to identify the culprit allergen. On the contrary, in the USA approach, in which all diagnosis-positive allergens are used, economic and convenience factors are involved. This still remains a matter of debate, both from a clinical and immunological viewpoint, also considering the composition/potency of the extracts used, which vary greatly in standardization [13,30]. In addition, a well controlled head-to-head comparison of the two forms of treatment (multiple versus single) would be expensive, time-consuming,

and difficult to perform from a methodological viewpoint.

In fact, there are few studies directly comparing single versus multiallergen AIT. One study [31] compared the administration of extracts of grass, birch or both to patients sensitized to those two allergens, and found that the association of the two extracts was on average more efficacious than the single allergens given alone. Another study [32] compared the clinical efficacy of a single allergen SCIT to mite in 68 monosensitized children and a multiallergen SCIT in 62 polysensitized, and found that there was no difference between the two groups versus baseline, although the monosensitized patients had a greater benefit. This study was flawed by the patients' selection, and by the poorly detailed symptoms' assessment used. Two other studies with SLIT directly compared the safety of single versus multiallergen administration, one in 159 adults [33] and one in 433 children [34], finding no difference between the groups. Nonetheless those studies were open, nonrandomized, and only evaluated the occurrence of adverse events, without any assessment of the efficacy.

Thus, our knowledge on the efficacy of multiple versus single allergen AIT should be based only on a rough and distant comparison of clinical trials with single and multiple allergens, which obviously makes no scientific sense, given the heterogeneity of the trials. Some more information can be derived from the few controlled studies in which multiple-allergen AIT was at least compared with a control group, as recently reviewed by Nelson [35]. In this review, 13 studies are quoted for a total of about 900 patients receiving either two unrelated allergens (seven studies) or a complex mixture (four or more unrelated allergens, six studies). Out of the 13 studies, four did not separately report the outcome of the different treatments. Focusing on the five studies conducted with complex mixtures and reporting results versus placebo, three were published before 1968, and all were in favor of multiallergen AIT. Of the two remaining studies, published after 1990, one showed that grass monotherapy was superior to multiallergen therapy, and the other (including 121 children) failed to show any clinical difference between the active and placebo group. Overall, there are numerous biases in those trials, including study design, doses of allergens, inclusion criteria, duration, and outcome. According to those considerations, the evidence for the efficacy of allergen mixtures in polysensitized patients remains experimentally weak.

CONCLUSION

The use of multiallergen immunotherapy (in particular with allergen mixtures) still remains

one of the greater debates in current allergy practice, mainly due to the historical and cultural reasons separating the USA and European countries, and also due to the fact that there is no clear experimental datum supporting the superiority of one approach versus the other. It is clear that a single AIT in a monosensitized patient would be the ideal situation. It is also acceptably clear that the administration of a single (or few) clinically relevant extract is equally effective in both monosensitized and polysensitized patients [36[■]]. What still remains unclear, with only weak experimental evidence, is whether multiple-allergen AIT can be recommended in patients with multiple sensitizations. In this context (allergen mixtures), there are still unsolved problems concerning the dilution, the compatibility of products, and the possible degradation of allergens [37–41], in addition to the problem of side-effects.

Of note, the relatively recent introduction of the component-resolved diagnosis (either single or multiplexed) has suggested the possibility to better dissect the individual sensitization profile, avoiding possible biases due to pan-allergens, which are largely represented in commercially available extracts [42[■]]. This approach, when used in a balanced way, could help to harmonize the use and prescription of AIT.

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Conflicts of interest

There are no conflicts of interest.

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- of special interest
- of outstanding interest

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