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OTOLARYNGIC ALLERGY (SK WISE AND C DAMASK, SECTION EDITORS)

Single, Pauci, and Multi-allergen Testing and Immunotherapy

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Abstract

Purpose of Review Allergy immunotherapy has been a mainstay of treatment of inhalant allergy for years. Controversy still exists regarding best methods of allergy testing and immunotherapy. We aim to review the evidence supporting single-, pauci-, and multi-allergen testing and immunotherapy.

Recent Findings The efficacy of immunotherapy has been well-established. The majority of research regarding allergy immunotherapy has focused on single-allergen treatment for mono- or poly-sensitized patients. There is a small heterogeneous group of studies that evaluate the efficacy of multi-allergen immunotherapy. There is a need for further research comparing single- and multi-allergen immunotherapy in poly-sensitized patients.

Summary We review the efficacy, relevant immunology, and persistent benefits of immunotherapy. We also review the most recent research examining the efficacy of single-allergen and multi-allergen immunotherapy in mono-, pauci-, and poly-allergic patients.

Keywords Allergy · Asthma · Allergy testing · Immunotherapy · Sensitization

Introduction

Allergic rhinitis (AR) and allergic asthma (AA) are prevalent conditions with a significant societal healthcare burden and impact on individual quality of life. The prevalence of asthma is increasing with 25.7 million people, or 8.7% of the US population, affected in 2010. [1] The total cost of the US asthma in 2013, including costs incurred by absenteeism and mortality, has been estimated at $81.9 billion [2•]. Allergic rhinitis affects 30–60 million people in the USA annually. It is estimated that 10–30% of the US adults may be affected, and the cost of AR treatment is estimated at $3.4 billion [3].

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There are different approaches to testing for sensitivity to inhalant allergies. Skin-prick testing (SPT) for immunoglobulin E (IgE)-mediated hypersensitivity is a commonly utilized technique. Intradermal testing (ID) or serum immunoglobulin E testing (sIgE) are also used in the evaluation of allergy. Allergic patients may be mono-sensitized (testing positive for just one allergen), pauci-sensitized (testing positive for 2–4 allergens), or poly-sensitized (testing positive to multiple allergens) [4]. Allergy immunotherapy can be administered as subcutaneous immunotherapy (SCIT), aqueous sublingual immunotherapy (aqSLIT), or sublingual tablets (tabSLIT) with the number of allergens that could be delivered differing among these techniques. There is no clinical dilemma when treating a mono-allergic patient with single-allergen immunotherapy. However, there is debate as to whether poly-sensitized or poly-allergic patients can be effectively treated with immunotherapy directed at only one or a few allergens, regardless of technique. This manuscript will review the topic and the current evidence, practices, and recommendations of mono- or pauci-immunotherapy in poly-sensitized and poly-allergic patients.

Sensitization Versus Allergy

There is an accepted distinction between an individual being sensitized and being allergic. Sensitization refers

to positive allergy testing, either sIgE or skin testing. It has been shown that those without allergic symptoms can commonly have positive allergy tests. For example, a recent study of 100 healthy volunteers without known allergic symptoms found that 42 had a positive skin prick test for at least one allergen using a 16 allergen panel. The median number of sensitized allergens was 2 (range 1–7) [5]. It has also been observed that individuals with allergic symptoms can have negative allergy testing. Some allergists utilize intradermal (ID) skin testing if clinical suspicion is high after negative skin prick testing (SPT). In one study, 34 patients underwent SPT followed by ID testing for 12 inhalant allergens; of 339 negative SPT results, 56.3% (191/339) were positive on ID testing [6]. There are multiple theories for these false positive and false negative results including the similarity between allergic and nonallergic rhinitis, local allergy (sIgE in the respiratory system not represented in the skin), and variations between the allergens used for testing and those occurring naturally. In this manuscript, allergic individuals are defined as those having allergic symptoms that plausibly correlate with their allergy testing results.

Definitions and Epidemiology of Mono-, Pauci-, and Poly- sensitization and Allergy

Prior to discussing the current evidence supporting mono-, pauci-, or poly-allergen testing and immunotherapy, it is important to define key terms. An allergen is a protein or glycoprotein capable of binding IgE. A biologic source, e.g., cat or short ragweed, usually has multiple allergens, and each allergen may have different epitopes that bind different IgEs. Often the term allergen refers to allergens from single biologic source, such as "cat allergens" which can be a source of confusion but is generally decipherable from context.

Mono-sensitization is defined as a response or sIgE elevation to one allergen test. The European and the US studies estimate 15.5–19.6% of the general population is mono-sensitized. Poly-sensitization is defined as sensitization to more than one allergen and is believed to affect 12.8–38.8% of the general population [7]. Of poly-sensitized patients, those demonstrating sensitivity to 2–4 allergens are more specifically characterized as pauci-sensitized. Sensitization itself, as defined by skin testing or sIgE assay, is common but provides no information on symptomatology in patients. Poly-allergy is the term that describes one who is both poly-sensitized and who reports symptoms upon exposure to multiple offending antigens of interest (Table 1) [4].

Evidence of Allergen-Specific Immunotherapy

Historical Evidence

Allergen-specific immunotherapy has a history spanning more than a century with substantial evidence demonstrating its value in treating inhalant allergy. In 1911, Noon performed a landmark study in which 28 patients were treated with preseasonal and co-seasonal subcutaneous injection of boiled grass pollen extract. He observed, "that the sensibility of hay fever patients may be decreased, by properly directed dosage, at least a hundredfold, while excessive or too frequent inoculations only serve to increase the sensibility" [8].

In 1949, the first controlled study in immunotherapy was performed by Bruun [9]. In 1963, Lowell and Franklin performed the first double-blind randomized study of immunotherapy against ragweed – the best defined pollen season in New England from mid-August to mid-September [10]. All subjects were symptomatic and had skin testing consistent with ragweed allergy but were also treated for other pollens. Subjects were then paired by severity of symptoms and randomized to immunotherapy with or without ragweed extract (but continued with the non-ragweed pollen immunotherapy). Those in the group that continued to receive immunotherapy to ragweed had significant symptomatic improvement during ragweed season, and, as ragweed extract was the variable between groups, the authors concluded that the effect was specific [11].

In 1967, Lowell and Franklin studied the effect of extract concentration using a double-blind study. Twenty-five patients receiving a mixture of pollen extracts were paired and separated into two groups, with one receiving a ragweed extract dosage 20 × that of the other group. The higher-dose group was noted to have fewer symptoms, and again this effect was concluded to be specific to the concentration of ragweed extract [12].

In 1978, Norman and Lichtenstein showed that ragweed sensitivity was due to Amb a 1 – the major ragweed allergen. They also demonstrated that subcutaneous injection of purified Amb a 1 had similar clinical efficacy to treatment with whole-plant extract [13]. In 1999, Durham et al. showed the persistent immunologic benefits of immunotherapy even after cessation of treatment. Even 3 years following completion of a 3–4 year course of subcutaneous immunotherapy patients noted persistent reduction in symptom scores and skin lymphocyte infiltration following intradermal testing [14].

Immunologic Mechanisms

Patients suffering from inhalant allergies can have significant symptoms that are uncontrolled by medical therapy such as antihistamines and inhaled steroids. In such cases, allergen-specific immunotherapy has been shown to effectively reduce

symptom scores and medication use [15, 16]. Allergy immunotherapy is also the only treatment shown to have persistent effects well beyond completion of therapy [14]. The mechanism of these effects is poorly understood, but immunologic observations suggest that immunotherapy alters the underlying disease process through allergen-specific and allergen non-specific mechanisms. [17]

Allergy is characterized by a predominantly T-helper cell type 2 (Th2) rather than T-helper cell type 1 (Th1)-mediated immune response [18]. Activated Th2 cells secrete interleukin (IL)-4, IL-5, and IL-13, which induce class switching of B-cells to IgE production and eosinophil activation and recruitment [19]. These immune responses result in mucosal inflammation, mucus production, and the resultant symptoms of allergy [20]. Though the exact mechanism is unclear, studies indicate allergen-specific immunotherapy results in a down-regulation of the Th2 immune response [21]. Allergy immunotherapy facilitates this immunologic shift by activating T-regulatory cells that produce anti-inflammatory cytokines, including IL-10 and tumor growth factor-beta (TGF-β) that down regulate allergic inflammation to all sensitized allergens. IL-10 has generalized inhibition of inflammation and has been shown to inhibit B cell production of total and allergen-specific IgE [22], inhibit mast cell activation [23], suppress IL-5 production and subsequent eosinophil activation [24], and promote cell death of eosinophils [25]. Additionally, IL-10 stimulates production of IgG4, which is a protective, noninflammatory antibody isotype [26]. IgG4 may block the binding of allergen to IgE bound to mast cells, thus limiting the release of histamine through an allergen-specific mechanism [21]. Peripheral blood IgG4 memory B cells remain elevated long after the completion of treatment [27], which may contribute to the lasting clinical tolerance attributed to immunotherapy. [14]

Single- and Pauci-Allergen Versus Multi-allergen Immunotherapy

Despite years of research showing the benefits of allergy immunotherapy, currently debate exists among experts regarding the most appropriate method of allergy testing and immunotherapy. Worldwide, some practitioners support mono- or pauci-allergen testing and immunotherapy, and others support a multi-allergen approach.

Although many patients are sensitized to multiple allergens, there are geographic preferences regarding selection of extracts for use in immunotherapy. Practitioners from some countries may pursue subcutaneous mono-allergen immunotherapy or pauci-allergen immunotherapy. There are no large double-blinded controlled studies directly comparing the two approaches of mono/pauci-allergen immunotherapy versus poly-allergen immunotherapy in poly-allergic patients. There are, however, some studies that have examined whether immunotherapy limited to one or a few allergens can provide cross-benefit in poly-allergic patients beyond the allergens being targeted.

Table 1 Definitions

- •Allergen – a protein or glycoprotein capable of binding IgE
- •Mono-sensitization – sensitization (as confirmed by skin testing or sIgE assay) to 1 allergen
- •Poly-sensitization – sensitization to < 2 allergens
- •Pauci-sensitization – sensitization to 2–4 allergens
- •Poly-allergy – clinically confirmed allergy (positive skin/sIgE + symptoms on exposure) to > 5 allergens

Adapted from Migueres M, et al. Clin Transl Allergy. 2014;4:16. doi:https://doi.org/10.1186/2045-7022-4-16.; Creative Commons Attribution License [http://creativecommons.org/licenses/by/2.0 [5].

Effects of Single-Allergen Immunotherapy on Pauci-Allergic Patients

To initially investigate whether single allergen immunotherapy could provide benefit upon an unrelated allergen in pauci(dual)-allergic patients, Norman et al. performed a randomized, double-blind controlled trial on 87 patients allergic to both grass and ragweed pollen.[13]. One group received mono-immunotherapy directed towards ragweed pollen, while the other group served as the control and remained immunotherapy-naive. Upon allergen exposure, the ragweed-immunotherapy group demonstrated decreased symptoms in the setting of ragweed, but there was no cross-benefit demonstrated in this group upon exposure to grass. As expected, the control, immunotherapy-naive group continued to demonstrate symptoms to both conditions.

A more recent study, performed in 2012, further examined this question with similar findings. Dual-allergic patients to both *Dermatophagoides farinae* and Timothy grass were treated with mono-immunotherapy to one of the two allergens and assessed for cross-benefit to the untreated allergen. On yearly conjunctival provocation testing (CPT) over consecutive years, both the dust mite group and the timothy grass group demonstrated a decreased response to the respective allergen for which they had been treated, but neither group demonstrated a cross-benefit to the untreated allergen [28].

Cross-benefit of immunotherapy directed towards timothy grass was again tested in 2018 ($n = 87$); this study examined for cross-benefit in patients who were dual-allergic to both timothy grass and birch tree pollen. After 4 months of timothy grass sublingual immunotherapy, no cross-benefit was demonstrated upon birch pollen exposure [29••]. It was concluded that symptomatic benefits of grass immunotherapy are likely allergen-specific.

Effects of Single-Allergen Immunotherapy on Poly-sensitized Patients

There has also been an effort to demonstrate the benefits of single-allergen immunotherapy in poly-sensitized and poly-allergic patients. In a double-blind placebo-controlled study performed in 2006, Frew et al. investigated the efficacy and safety of 2 doses of single-allergen grass immunotherapy on patients with moderately severe seasonal allergic rhinitis with symptoms refractory to standard pharmacotherapy – including antihistamines, topical steroids, and/or cromoglycate eye drops. The 203 patients included in the study had a history of grass pollen-induced seasonal allergic rhinitis and grass pollen sensitivity confirmed with skin and blood testing. Patients with other sensitizations were included unless they had sinusitis, rhinoconjunctivitis, or asthma outside of grass season or daily symptomatic contact with animals.

Results showed that during the whole pollen season, mean symptom and medication scores were 29% and 32% lower in the treatment group than the control group. Quality of life measures also showed superior results of single-allergen immunotherapy to placebo [30].

The benefits of single-allergen immunotherapy on poly-sensitized patients were again investigated in a 2008 study by Malling et al. They performed a post hoc analysis of a multinational double-blind placebo-controlled trial of once daily sublingual grass pollen tablet immunotherapy. Both mono-sensitized and poly-sensitized patients were included. Poly-sensitized patients were included if their non-grass sensitivities did not present confounding symptoms during grass pollen season. Of the 628 patients included, over 51% were poly-sensitized. The average rhinoconjunctivitis total symptom score (RTSS) showed that symptoms were reduced by 27.4% and medication use by 46.1% in patients allocated the 300 IR grass pollen tablets compared with those given placebo. No differences in efficacy or safety were observed in patients who were poly-sensitized. Regardless of sensitization (mono-sensitized/poly-sensitized) or concomitant mild asthma, both the 300 IR and 500 IR doses resulted in a significantly improved RTSS compared with placebo. The authors concluded that sensitization status (mono- vs poly-sensitization) was not a necessary criteria for the use of single-allergen immunotherapy given its favorable risk-benefit ratio [7, 31].

Another post hoc analysis investigating the benefits of treating poly-sensitized allergic rhinitis patient with a single-allergen immunotherapy tablet treatment was performed by Emminger et al. in 2009 (published meeting abstract). 568 patients with skin prick testing confirmed sensitivities who participated in the first year of a double-blind placebo-controlled trial of mono-allergen treatment for grass allergy were included. Data were analyzed in patients sensitized to (a) grass only (mono-sensitized – 161 patients), (b) grass + tree + any other allergen (tree poly-sensitized – 191 patients), and (c) grass + any allergen except tree allergens (non-tree poly-sensitized – 216 patients). Single-allergen immunotherapy was found to reduce symptom and medication scores in mono- and poly-sensitized patients regardless of presence or absence of tree-related sensitivities [7, 32].

Evidence for the Efficacy of Multi-allergen Immunotherapy

There are very few studies looking at the efficacy of multi-allergen immunotherapy. In a 2009 review, Nelson et al. reviewed a total of 877 articles regarding allergen immunotherapy searching for studies simultaneously using 2 or more distinct allergen extracts. Thirteen studies were identified, and, of these, 7 studies used non-cross-reacting allergens. Four of these studies reported outcomes superior to placebo and comparable to single-allergen immunotherapy. The three remaining studies did not report multi-allergen and single-allergen treatment separately. In the five studies that used multiple allergens, 3 studies reported efficacy and 2 did not. The authors believed this "lack of efficacy might have been due to inadequate doses of extract or omission of clinically relevant allergens." There was significant heterogeneity between studies in the subjects, primary condition being treated, immunotherapy regimen, and outcome reporting.

Despite these differences, the authors still concluded that the review suggested simultaneous delivery of multiple unrelated allergens can be effective [33].

Discussion

The majority of patients with inhalant allergy are sensitized to multiple allergens. Most of the US patients are treated with multi-allergen immunotherapy with the mean number of extracts being eight [34]. The US consensus is that there may be benefit in treating as many actual or potential sensitizations as possible – especially given the time-consuming buildup phase of modern immunotherapy. European practice patterns are significantly different than the US, and patients are often treated with single-allergen immunotherapy. Less than 10% of European formulations contain more than 1 non-cross-reacting allergen. Usually treatment is focused on the most troublesome allergen. The practice in Europe is that poly-sensitized patients are not necessarily poly-allergic and that, depending on the seasonality of exposure, poly-allergy is not always clinically significant. This practice difference has led to a longstanding difference between the US and European allergy communities about the efficacy of multi-allergen immunotherapy [7, 35]. The majority of clinical immunotherapy trials have been investigations of single-allergen immunotherapy. More than a

century of historical data has shown the efficacy of single-allergen immunotherapy in reducing patient symptoms and medication use – both during treatment and persisting following cessation of immunotherapy. Basic science research has confirmed that specific allergen proteins are the targets of IgE that elicit an immune response.

Several studies have demonstrated the specific nature of single-allergen immunotherapy without noted cross-benefit in pauci-allergic patients [13, 28, 29••]. Despite the specificity of the immune response and single-allergen immunotherapy, there are noted benefits of single-allergen immunotherapy in poly-sensitized patient. Multiple studies have shown that poly-sensitized patients have symptomatic and quality of life benefit from single-allergen immunotherapy despite known sensitivities to different environmental allergens [30–32]. Some of these studies are difficult to interpret as poly-sensitized patients were limited to those without seasonal or perennial allergen sensitivities that might present confounding symptoms during the allergen season of interest – usually grass. It is difficult to elucidate if the benefit seen in poly-sensitized patients is due purely to the seasonal effects of treatment, efficacy against the most clinically relevant sensitivity, or some other cross-benefit occurring perhaps from T cell-mediated down-regulation of allergic inflammation. It has been shown that single-allergen immunotherapy can result in persistent immunologic changes that may benefit the allergic responses and symptoms of the patient in general.

As illustrated in the literature review above, the sparse studies investigating the efficacy of multi-allergen immunotherapy have produced conflicting results. Among this small heterogeneous group of studies, some have shown significant clinical improvement compared to placebo. Other studies have shown no benefit over that expected from environmental control measures and standard pharmacotherapy. This paucity of data has led to a recent practice parameter recommendation underlining the importance of treating patients "only with relevant allergens" (Statement 72) [36].

A review of this topic suggests a need for further research. The scientific basis for the current broad application of multi-allergen immunotherapy is largely extrapolated from data regarding single-allergen immunotherapy in mono- or poly-allergic patients. There are known risks of allergen immunotherapy, and it is used throughout the world to help patients with inhalant allergies. The choice of single- vs multi-allergen immunotherapy may be influenced by training and geography given the limited scientific comparisons. Further study focused on the efficacy of multi-allergen immunotherapy versus single-allergen immunotherapy in the treatment of poly-sensitized patients would be helpful in determining the safest and most efficacious approach for patients worldwide.

Conclusion

There is currently controversy whether to use single-allergen or multi-allergen immunotherapy in poly-allergic patients. While there are very few studies investigating the efficacy of multi-allergen immunotherapy, there is robust clinical experience. Further research into the efficacy of multi-allergen immunotherapy as compared to single-allergen or pauci-allergen immunotherapy in poly-allergic patients is needed. Variances involving shared patient decision-making and differences in provider practices are expected given the current state of the evidence.

Compliance with Ethical Standards

Conflict of Interest The authors declare that they have no conflict of interest.

Human and Animal Rights and Informed Consent This article does not contain any studies with human or animal subjects performed by any of the authors.

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