Monotherapy for the polysensitized patient

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Introduction.

Specific Immunotherapy (SIT) is the only therapeutic resource with curative effects in the management of allergic disorders.[1]

The effectiveness of allergen SIT by the injective (SCIT) and the sublingual (SLIT) routes has been proved in allergic rhinitis (AR), bee venom allergies, and allergic asthma. [2-5] SIT has been shown to be capable of modifying the natural history of allergic diseases, such as preventing the development of asthma in patients with allergic rhinitis and the development of new sensitizations.[6] SIT causes a significant reduction in symptom scores and use of medications in selected patients with seasonal allergic rhinitis and has long term effects after discontinuation.[7]

Most randomized controlled studies demonstrating efficacy with SCIT or SLIT have been conducted with single-allergen extracts but the majority of the allergic individuals are polysensitized as it was demonstrated in a multi-Centre international study involving more than11000 subjects, the estimated prevalence of sensitized subjects is 35.6% using a common standardized battery of seven SPT allergens enabled the identification of IgE-sensitized subjects with sufficient precision for most purposes.[8]

In a large study among US population aged 6 to 59 years, more than half of the population (54.3%) had positive test responses to one or more allergens. On average, an individual with a positive test response reacted to 3 to 4 allergens.[9] In other retrospective study of sIgE in 9044 children analyzing the characteristics of polysensitized, monosensitized or non-sensitized children shows that sensitization to multiple allergens is considerably more common (47.4%) than monosensitization (31.1%) in this population children with polysensitization had higher symptom scores and a poorer response to immunotherapy than monosensitized children.[10] Ciprandi in the POLISMAIL study demonstrated that polysensitized patients have more severe symptoms and poorer quality of life (QoL) than monosensitized children but treatment with SLIT for 2 years with only one or two allergens significantly reduced AR and asthma symptoms, the use of medications and improve QoL.[11] About patients with asthma, 51 to 95% of subjects from 12 to 65 years of age with mild to moderate disease are sensitive to at least one allergen. 14% have at least 1 or 2 positive responses but 81% are sensitive to 3 or more allergens (average 5 allergens) and correlate with markers of bronchial inflammation such as increased levels of eNO and bronchial hyperactivity by challenge tests (PC_{20}).[12] It seems that the majority of patients whit AR and allergic asthma are polysensitized and the majority of polysensitized patients have a moderate-severe intermittent or persistent manifestations of Allergy.

Is Immunotherapy with single allergen effective in polysensitized patients?

Sublingual Immunotherapy. (SLIT)

Sublingual immunotherapy has demonstrated to be effective in treating allergic rhinitis and allergic asthma in adults and children.[3-4]

Although some studies analyzed in meta-analysis include only monosensitized patients, the majority of the patients included in the studies that met the criteria for analysis were polysensitized.[4]

With the purpose of elucidate whether the efficacy of sublingual immunotherapy (SLIT) with standardized timothy extract will be reduced by combination with other allergen extracts a double blind, placebo controlled study was performed by professor HS Nelson and his group.[13] After an observational grass season, SLIT was administered for 10 months to 54 patients randomized to 1 of 3 treatment arms: placebo, timothy extract (19 mg Phl p 5 daily) as monotherapy, or the same dose of timothy extract plus 9 additional pollen extracts. They found in the timothy monotherapy group, thresholds for titrated nasal challenge and skin prick tests (P = .03 and P = .001, respectively), and serum-specific IgG4 levels (P = .005) significantly increased, and IFN- g levels decreased (P = .02), whereas in the multiallergen group, there was significant improvement only in the titrated skin prick tests (P = .04). Although the majority of patients on immunotherapy experience adverse reactions, no systemic adverse effects were reported.

This results support the evidence that SLIT with single allergen is more effective than SLIT with multiallergen in patients polysensitized with related allergens.

To compare the efficacy of SLIT with standardized HDM extract in monosensitized or polysensitized patients with allergic rhinitis. Lee and his group[14], in a prospective case series study, patients with Allergic rhinitis sensitized only to house dust mites were compared with patients simultaneously sensitized to house dust mites and other unrelated allergens. 134 patients received SLIT with HDM F/Pt 50% during one year. The total nasal symptoms and medication scores were decreased significantly after SLIT in both the monoallergen sensitized and polyallergen sensitized groups but did not differ significantly between the 2 groups (54.1 vs 46.1, P = .56). QoL also improved significantly in patients with AR after one year of treatment with SLIT. The use of just 1 or 2 allergen extracts seems to be sufficient and effective in terms of improving QOL. SLIT was performed in 123 patients (73.6%) with a single allergen extract, in 31 patients (18.6%) with 2 extracts, and in 13 patients (7.8%) with more than 2 extracts.[15] The mean QOL scores was assessed by the Rhinoconjunctivitis Quality of Life Questionnaire score decreased significantly in all cases (P<.01). Differences between the 2 groups were not significant.

In a large randomized placebo controlled trial, the efficacy the safety and the dependence on an appropriate dose of sublingual immunotherapy with grass tablets was confirmed in polysensitized patients.[16] 628 adults with grass pollen Allergic rhino-conjunctivitis (ARC) received 1 of 3 doses (100 IR, 300 IR, or 500 IR) of a standardized 5–grass pollen extract, or placebo, administered sublingually once daily in tablet. The 300-IR and 500-IR doses both demonstrated significant efficacy compared with placebo, although no systemic adverse effects were reported; the risk-benefit ratio favors the use of 300-IR (25mcg/mL of group 5 major allergen) tablets for clinical practice and the 100-IR proves to be ineffective. More than half of the patients in all 4 groups were polysensitized to other unrelated allergens.

The long lasting effect of SLIT was confirmed in a recently published randomized, double blind, placebo-controlled, phase III trial.[17] The authors included 257 polysensitized adults with a history of moderate- to-severe grass pollen induced Rhinoconjunctivitis inadequately controlled by symptomatic medications. Three

years of treatment with the SQ-standardized grass allergy immunotherapy tablet resulted in consistent clinical improvement and accompanying immunologic changes that were sustained 1 year after treatment, which is indicative of disease modification and associated long-term benefits in polysensitized patients treated with a single allergen sublingual tablet.

Injective Immunotherapy (SCIT)

Specific immunotherapy is most commonly administrated via subcutaneous injection and has being used and has demonstrated to be effective although empirical since 1911.[18] The first double-blind controlled trial of pollen immunotherapy published by Frankland in 1954, established a firm scientific foundation for the further development of allergen immunotherapy.[19]

Meta-analyses of SIT based on properly well-performed systematic reviews represent the highest level of evidence. Meta-analyses have shown that SCIT is effective in the treatment of allergic rhinitis and allergic asthma.

The recently published meta-analysis by Calderon[3] with Cochrane collaboration on SCIT for Allergic rhinitis examined 51 RCTs published between 1984 and 2006 and included a total of 2871 patients (1645 active, 1226 placebo). A wide range of allergens were administered, it was not specified if SIT with single allergen in polysensitized patients was used, however they included studies with monosensitized and polysensitized patients. The combined Standardized Mean Difference (SMD) for symptom scores after SCIT was -0.73 (95% CI -0.97 to -0.50, P < 0.00001), indicating a significant reduction in symptom scores. And the combined SMD for medication scores was -0.57 (95% CI -0.82 to -0.33, P < 0.00001) indicating a significant reduction in medication scores.

The clinical efficacy of SCIT in asthma was demonstrated by Abramson's meta-analysis[5] of eighty-eight trials (13 new trials added to previous meta-analysis). There were 42 trials of immunotherapy for house mite allergy; 27 pollen allergy trials; 10 animal dander allergy trials; two Cladosporium mold allergy, two latex and six trials looking at multiple allergens, but no study specified single allergen SIT in polysensitized patients. Overall, there was a significant reduction in asthma symptoms and medication, and improvement in bronchial hyper-reactivity following immunotherapy. There was a significant improvement in asthma symptom scores (SMD -0.59, 95%, CI -0.83 to -0.35) and it would have been necessary to treat three patients (95% CI 3 to 5) with immunotherapy to avoid one deterioration in asthma symptoms. Overall it would have been necessary to treat four patients (95% CI 3 to 6) with immunotherapy to avoid one requiring increased medication. Allergen immunotherapy significantly reduced allergen specific bronchial hyper-reactivity, and non-specific bronchial hyper-reactivity as well.

In a large study of SCIT in 410 patients with treatment resistant allergic rhinoconjuntivitis[20] were included and randomized in three treatment groups (203 to 100,000 standardized quality units [SQ-U] maintenance (20mcg of Phl p 5), 104 to 10,000 SQ-U (2mcg), and 103 to placebo). Over the peak pollen season, mean symptom and medication scores were 32% and 41% lower, respectively, than those in the placebo group. The 10,000–SQ-U group had 22% less symptoms than the placebo group over the whole season (P < .01), but medication scores reduced by

only 16% (P 5 .16). Quality-of-life measures confirmed the superiority of both doses to placebo. 276 out of 347 (78%) subjects were polysensitized. Both active doses were effective, but 100,000 SQ-U was more effective than 10,000 SQ-U, as confirmed by greater reductions in symptom scores, medication scores, and VAS scores and less seasonal change in RQLQ score. This dose-response effect is consistent with earlier findings with SIT and confirms its dependence on using an appropriate therapeutic dose.

Conclusion. The majority of allergic patients are polysensitized. and polysensitized patients with asthma and allergic rhinitis have a worse symptom and medication scores and also a poorer response to SIT. Single allergen SLIT and SCIT causes a stronger immune response, characterized by a reduction of allergen-specific T-cell proliferation and a suppressed secretion of TH1- and TH2-type cytokines and also causes an inhibition of the development of allergen-specific TH2 and TH1 cell responses by Treg cells. Because these immunologic changes are induced by allergen SIT with single or multiple airborne allergens, single-allergen SIT (SCIT and SLIT) is effective and safe in polysensitized patients and definitively dose dependent.

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