

The allergen specificity of allergen immunotherapy—doubt no more

1 | INTRODUCTION

The ARIA-GA2LEN collaboration published a guide for the design and evaluation of randomized controlled trials of allergen immunotherapy for allergic rhinitis.¹ Several problems were identified. For example, mean seasonal symptom scores in subjects during allergen immunotherapy trials were noted to be much lower than in trials of pharmacotherapy. The dropout rates were higher. Seasonal pollen counts varied markedly between study centres and year-on-year during long-term trials thereby confounding the ability to detect treatment effects during “low” pollen seasons. Placebo unmasking occurred due to the local side effects of allergen immunotherapy in actively treated participants. Possible solutions raised included use of allergen exposure chambers rather than relying on seasonal pollen exposure and a design that included participants with dual allergen sensitivity, with randomization to treatment with one allergen with the other acting as an untargeted allergen control. The study by Wagenmann et al.² reported in this issue of the journal tests these concepts and additionally addresses the question whether allergen immunotherapy may be allergen-specific.

Ninety-five participants with dual allergy to birch and grass pollen were randomized to 9 months' subcutaneous immunotherapy with either a grass or a birch pollen allergoid extract. Birch pollen challenge was followed by grass pollen challenge, sequentially, with a >5-day interval in a standardized allergen exposure chamber before and after completion of immunotherapy. The primary outcome demonstrated approximate 40% reductions compared to baseline (both $P < 0.001$) in nasal symptom scores within groups for both grass and tree pollen exposures, confirming the efficacy of both treatments. These differences were also significant for both targeted allergens when compared to exposure to the same (untargeted) allergen (both $P < 0.02$) between groups thereby confirming the utility of an active allergen placebo group. It is not possible to draw firm conclusions on safety from a trial of 95 participants although the occurrence of only 3 very mild treatment-related immediate systemic reactions with these extracts represents an acceptable level of adverse events.

Strengths of the study include the lower numbers of participants needed for adequate power using the allergen exposure chamber compared to the use of conventional seasonal outcomes, the adequate blinding afforded by the study design and the observed low dropout rate. The groups were well matched for demographics, rhinitis severity and presence of asthma, polysensitization rates, skin test results and

serum allergen-specific IgE levels.² Limitations include the absence of a true placebo such that it is not clear to what extent the 40% reduction within groups could be true placebo effect and as such is not comparable to the World Allergy Organization (WAO)'s (empirical) cut-point of 20% for a minimal clinically important difference. The placebo effect could also have accounted for the minor observed effects of treatment on untargeted allergen exposures (Figure 1B-G and G-B comparisons).² The order of the sequential challenges before and after treatment was not randomized, and this could explain why there was an apparent nonspecific effect of successful birch allergen immunotherapy on the second grass challenge because the diminished “priming inflammation” by birch exposure would have resulted in a diminished response to the second grass pollen challenge compared to the first prebirch immunotherapy grass pollen challenge (Figure 1G-B).² Before treatment, the level of symptoms during chamber exposure was well matched for each allergen between groups although was different for the grass compared to tree pollen exposures (Figure 1).²

A previous study by Winther et al incorporated a similar design in dual grass and birch-allergic participants but using natural seasonal symptoms as the primary outcome.³ Pre-co-seasonal birch pollen immunotherapy during the first year suppressed birch but not grass-related seasonal symptoms, whereas the effect of grass pollen immunotherapy was uninterpretable due to low seasonal grass pollen counts—thereby illustrating the advantage of the chamber exposure method used in the present study. Dreborg et al studied dual grass and mite allergic subjects using the same design with alum-based vaccines.⁴ Over the 3 years of the trial, there was a consistent significant decrease in immediate conjunctival allergen sensitivity to the targeted but not untargeted allergens (Figure 2) that was accompanied by marked increases in allergen-specific IgG4 to the relevant allergen only.

Allergen immunotherapy is generally regarded as allergen-specific although apart from the clinical trials described above, few studies have directly addressed this issue. Lowell et al⁵ employed an aqueous multi-allergen mix in a double-blind randomized controlled trial of patients with seasonal pollen allergy where omission of ragweed pollen from the mix resulted in higher levels of seasonal symptoms compared to the mix that included ragweed pollen. Norman et al⁶ treated patients with multiple pollen allergies with an aqueous allergen extract of ragweed. There was a marked decrease in symptoms during the ragweed season but no impact on symptoms during the ensuing tree and grass pollen seasons. Lack et al performed rush allergen immunotherapy

FIGURE 1 Targeted and untargeted effects of allergen immunotherapy on total nasal symptom score (full analysis set). Reproduced from Wagenmann et al.². ACC, allergen challenge chamber; AIT, allergen immunotherapy; AUC, area under the curve; n, number of participants with data; TNSS, total nasal symptom score. B-B, birch on birch treatment effect (targeted); B-G, birch on grass treatment effect (untargeted). CI, confidence interval; G-B, grass on birch treatment effect (untargeted); G-G, grass on grass treatment effect (targeted). The first letter of each abbreviation refers to the pollen species used in the ACC exposure and the second letter to the allergen preparation used for AIT (G, grass pollen, B, birch pollen)

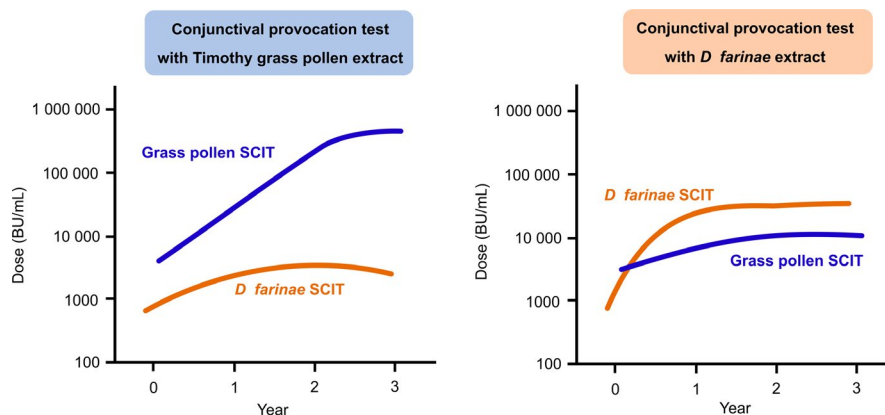
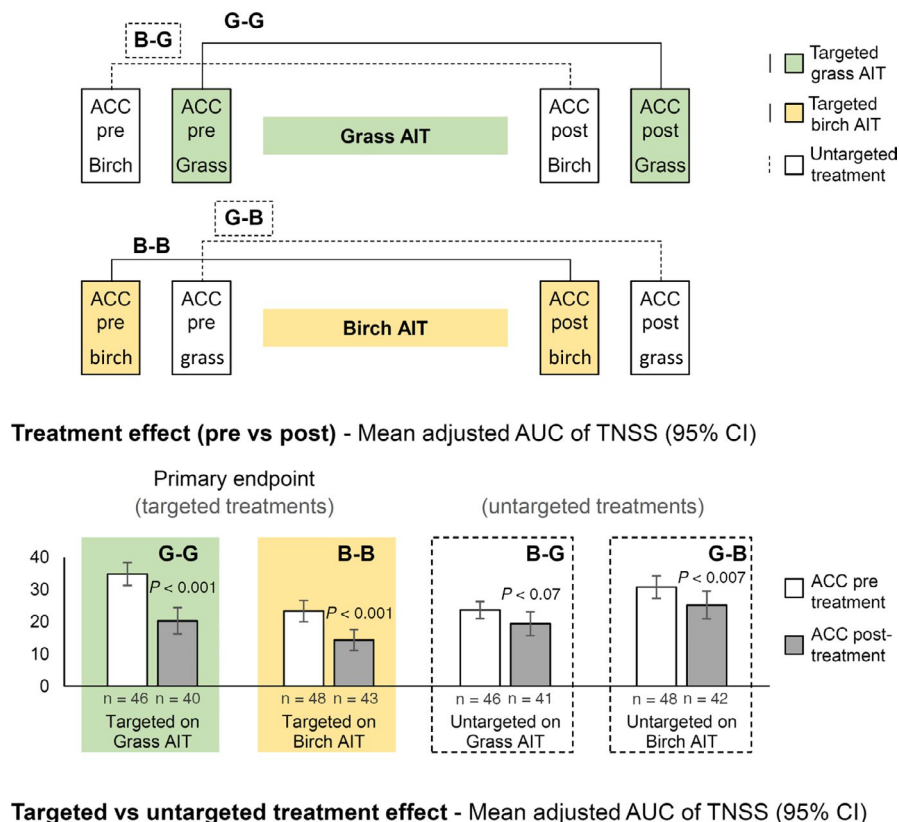


FIGURE 2 Targeted and untargeted effects of allergen immunotherapy on conjunctival provocation test. Modified from ref⁴. Conjunctival provocation test (CPT) thresholds for Timothy grass pollen extract and *D. Farinae* allergen extract before and after 1, 2 and 3 y immunotherapy with subcutaneous alum-based extracts of *D. Farinae* (*D. fariniae* SCIT,) and Timothy grass pollen (Grass pollen SCIT). There were significant differences in the change in CPT threshold concentration between groups from pretreatment to after years 1, 2 and 3 y of immunotherapy (all $P < 0.05$, Kolmogorov-Smirnov test)

with an aqueous house dust mite extract in children with dual allergy to mite and cat.⁷ There were significant reductions in immediate nasal and skin responses only after house dust mite challenge.

2 | CONCLUSIONS

There are notable implications of the study by Wagenmann et al. Firstly, the incorporation of an allergen placebo in immunotherapy trials avoids “placebo unmasking” and enables all trial

participants to receive an active treatment for their allergies. The caveat is that it does not enable an estimation of the true placebo effect that is known to be substantial in true placebo-controlled trials. The two approaches should therefore be regarded as complementary.

Secondly, the study supports other trials cited³⁻⁷ in providing a strong consensus in favour of the allergen specificity of allergen immunotherapy. This highlights the need for obsessional care in our selection of patients for immunotherapy, according to current guidelines.⁸

Thirdly, it is the property of allergen specificity of immunotherapy that underlies durable alterations in immunologic memory within T- and B-cell compartments that persist after treatment discontinuation and result in long-term disease remission.⁹

ACKNOWLEDGMENT

The author thanks Dr Guy Scadding and Dr Despo Ierodiakonou for their helpful comments on the manuscript.

CONFLICTS OF INTEREST

SD has received consultancy fees from manufacturers of allergy vaccines - Adiga, ALK, Allergopharma, Anergis, Biomay and Torii Pharmaceuticals - unrelated to the current work.

KEYWORDS

active allergen placebo, grass pollen and birch pollen subcutaneous immunotherapy, specificity of allergen immunotherapy, trial design

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REFERENCES

1. Bousquet J, Schünemann HJ, Bousquet PJ, et al. How to design and evaluate randomized controlled trials in immunotherapy for allergic rhinitis: an ARIA-GA2LEN statement. *Allergy*. 2011;66:765-774.
2. Wagenmann M, Worm M, Akboga Y, Karajainen M, Hohlfeld J. Randomized immunotherapy trial in dual-allergic patients using "active allergen placebo" as control. *Allergy*. 2019;000:000-000.
3. Winther L, Malling HJ, Moseholm L, Mosbech H. Allergen-specific immunotherapy in birch- and grass-pollen-allergic rhinitis. I. Efficacy estimated by a model reducing the bias of annual differences in pollen counts. *Allergy*. 2000;55:818-826.
4. Dreborg S, Lee TH, Kay AB, Durham SR. Immunotherapy is allergen-specific: a double-blind trial of mite or timothy extract in mite and grass dual-allergic patients. *Int Arch Allergy Immunol*. 2012;158:63-70.
5. Lowell FC, Franklin W. A double blind study of the effectiveness and safety of injection therapy in ragweed hay fever. *N Engl J Med*. 1965;273:675-679.
6. Norman PS, Lichtenstein LM, Tignall J. The clinical and immunologic specificity of immunotherapy. *J Allergy Clin Immunol*. 1978;61:370-377.
7. Lack G, Nelson HS, Amran D, et al. Rush immunotherapy results in allergen-specific alterations in lymphocyte function and interferon-gamma production in CD4+ T cells. *J Allergy Clin Immunol*. 1997;99:530-538.
8. Roberts G, Pfaar O, Akdis CA, et al. Guidelines on allergen immunotherapy: allergic rhinoconjunctivitis. *Allergy*. 2018;73:765-798.
9. Shamji MH, Durham SR. Mechanisms of allergen immunotherapy for inhaled allergens and predictive biomarkers. *J Allergy Clin Immunol*. 2017;140:1485-1498.