

ORIGINAL ARTICLE

Dosing and efficacy in specific immunotherapyP. Demoly¹ & M. A. Calderon²¹University Hospital of Montpellier – Inserm U657, Montpellier, France; ²Section of Allergy and Clinical Immunology, Imperial College, NHLI, Royal Brompton Hospital, London, UK**To cite this article:** Demoly P, Calderon MA. Dosing and efficacy in specific immunotherapy. *Allergy* 2011; **66** (Suppl. 95): 38–40.**Keywords**

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Abstract

Allergen-specific immunotherapy is used to treat allergic rhinoconjunctivitis and asthma worldwide. The clinical efficacy of the most common routes, subcutaneous (SCIT) and sublingual (SLIT) immunotherapy, is documented for respiratory allergy by double-blind, placebo-controlled, randomised clinical trials (DB PC RCT). However, dose-effect relationships are not available for all extracts. The 1998 WHO Consensus Report on Allergen Immunotherapy found SCIT ineffective at low doses, with high doses more likely to result in an unacceptably high level of systemic reactions. Recent large well-designed DB PC RCTs using SLIT grass pollen tablets have undergone phase II–III studies in adults with allergic rhinitis, yielding proper dose-response studies. These were analysed by the European Academy of Allergy and Clinical Immunology Immunotherapy Interest Group task force on dose effect. In general, low doses (5–7 µg of allergen Phl p 5 per day) are ineffective. Daily doses of 15–25 µg of the major allergen protein are required for significant clinical improvement measured by symptom scores. A higher dose (33–40 µg of Phl p 5 per day) was not more effective than 15–25 µg. Optimization of the allergen/adjuvant ratio may allow for lower allergen doses, increase the safety/efficacy profile and allow for shorter up dosing. However, our analysis of the available studies concluded that every product requires its own dose-response relationship study.

This presentation is on behalf of the European Academy of Allergy and Clinical Immunology Immunotherapy Interest Group (EAACI ITIG) task force on dose effect. According to the World Health Organization (WHO) 1998 consensus report, and the Allergic Rhinitis and its Impact on Asthma (ARIA) 2008 report (1, 2), specific immunotherapy (SIT) is efficacious in allergic rhinoconjunctivitis and asthma from grass, birch, ragweed and parietaria pollen. It is also efficacious in house dust mite-induced rhinoconjunctivitis and asthma and in cat dander-induced allergic rhinoconjunctivitis and asthma, although the results are controversial for dog dander and certain fungi. As an empiric principle, the highest tolerated dose for an individual is considered the most effective. However, medical registration requires proper phase II dose-finding studies. In 2010 in Europe, only three SIT products are registered as a pharmaceutical treatment by the European Medicines Agency (3, 4). Other products are registered nationally but with no dose-effect studies. All other formulations worldwide are used as named patient products with no dose-effect studies. In the United States, 95% of allergen extracts are prepared in a doctor's office.

Development of SIT is not possible with conventional phase I trials, which are performed in healthy subjects. For

SIT, allergic patients must be included. Pharmacokinetic and pharmacodynamic studies are also not possible because the products are not detectable in serum. For SIT, specific biological surrogate tests do not always correlate with clinical response and therefore cannot replace clinical evaluations. Nonetheless, phase II trials for SIT are possible, and dose-effect must be investigated and demonstrated (5).

Findings of the European Academy of Allergy and Clinical Immunology task force on dose effect

The EAACI task force aims to collect and compare clinical and immunological data on the dose-efficacy of SCIT and sublingual immunotherapy (SLIT) for the treatment of allergic rhinoconjunctivitis and asthma; analyse dose-efficacy and dose-safety of venom SCIT; and define optimal doses regarding systemic adverse reactions. Our methods were a draught paper in June 2009, four meetings from 2009–2010, and extensive email exchanges. A medical writer was enlisted to help meet the EAACI strategy of communication in the immunotherapy field with a peer-reviewed consensus paper in 2011. Our members are M Calderon (Chair), D Larenas (Secretary), G Passalacqua, E Varga, C Andre, L Jacobsen, P

Eng, J Kleine-Tebbe, H-J Mallng, E Alvarez-Cuesta, D Barber, C Moreno, E Valovirta, SR Durham and P Demoly.

We searched and evaluated all relevant published controlled studies, comprising more than 1700 papers, using keywords related to multiple-dose SIT for allergic rhinitis, asthma and venom anaphylaxis. We found 15 of 1379 studies that used multiple doses. Nine were SCIT for respiratory allergies, four for SLIT in respiratory allergy and two for SCIT for venom allergy. Nine were double-blind placebo-controlled (DB PC). For each study, we evaluated participant characteristics; allergen used, including doses and duration; methodology; clinical, safety and surrogate outcomes; immunologic data; and report quality, although Consolidated Standards of Reporting Trials (CONSORT) is not applicable before 1996 (6).

Among the best three examples is a randomised DB PC study by Frew et al. (7) for SCIT in 26 centres in the United Kingdom for seasonal allergic rhinoconjunctivitis in adults. The allergen extract was adjuvanted Alutard SQ[®] *Phleum pratense* (ALK, Denmark), and the groups were placebo and two dose groups: 10 000 and 100 000 SQ-U. Treatment duration was average 6.4 months. Outcomes of symptom/medication scores over the whole season and in peak season showed a significant difference in peak season, with significant differences in quality-of-life between doses. An evaluation of bad days did not differ between doses. Safety outcomes showed more adverse events in the high-dose group, with 14% in the 100 000 SQ-U group, 4% in 10 000 SQ-U group, 2% in the placebo group, and grade 3 systemic adverse events were observed in nine subjects in the highest dose group. Efficacy showed a clear dose dependence.

Another SLIT-randomised DB PC study on seasonal allergic rhinoconjunctivitis in adults was performed at 55 centres in Europe and Canada by Durham et al. (8). Groups were placebo, 2500 SQ-T (0.5 µg Phl p 5), 25,000 SQ-T (5 µg) and 75,000 SQ-T (15 µg). The extract was nonadjuvanted Grazax[®] tablets (ALK, Denmark) containing a *Phleum pratense* grass pollen extract. Treatment duration was 8 weeks before pollen season and 18 weeks throughout the season. Outcomes of symptom and medication scores showed a clear dose-response effect in the 15 µg group, with quality-of-life and well days significantly increased in the 15 µg group compared with other groups. Safety outcomes included an increase in mild adverse events between the 0.5 and 5.0 µg groups, but not between the 5 and 15 µg groups, so the significant effect in dose outcomes did not parallel with safety outcomes. A dose-dependent increase was seen in specific IgE and IgG₄, with a clear dose- and time-dependent increase in specific IgG₄, and a response relationship with quality-of-life and rhinoconjunctivitis symptoms.

The third example is a randomised DB PC SLIT therapy trial of 42 European centres (9), again for seasonal allergic rhinoconjunctivitis in adults, with groups of placebo, 100 IR,

300 IR (25 µg Phl p5) and 500 IR. The allergen extract was the Oralair tablet from Stallergènes, which is a nonadjuvanted mixture of pollen extract from five different temperate grasses. Treatment was 8 weeks before pollen season and 4–6 months throughout the season with a 5-day updosing phase. A significant reduction in symptom and medication scores and an improvement in quality-of-life were seen when the 300 and 500 IR groups were compared to placebo, but no significant differences were seen between 300 and 500 IR. No significant dose-dependent increase in side effects was observed, but a dose-dependent increase in specific IgG₄ was evident. A significant reduction in rhinoconjunctivitis score was seen with 500 IR, which was not significantly different from 300 IR, although both were significantly different from 100 IR. This paralleled results for days without rescue medication.

The necessity of dose-response relationship studies

To summarize, 15 studies analysed overall dose-effect results for clinical efficacy. Of these, 12 clearly found a dose-response relationship. Ten analysed immunological responses, and nine found a dose-response relationship. Safety was analysed in seven studies, and 5 found a dose-response relationship. It is absolutely not possible to compare one study or compound with another. Every product must have its own dose-response relationship assessment.

In conclusion, a dose effect on SIT efficacy is seen with both clinical and surrogate immunological markers. Increases in adverse effects of SIT are observed, but are not always dose dependent, so the mechanisms for clinically effective SIT and safety must be different. Dose-response data will enable clinicians to determine the correct dose for patients with the most favourable risk-to-benefit ratio and permit product registration. Direct comparisons cannot be made between studies using products from different manufacturers. Our analysis showed the need for standardisation of allergen content measurements and immunoassays for surrogate markers, especially specific IgG₄. Investigating the role of the nature and dose of adjuvant and allergen may lead to allergen/adjuvant ratio optimization. Together with this, animal studies during preclinical development may help to better design future phase II trials.

Conflict of interest

Pascal Demoly has received consultancy fees from ALK-Abelló, BioXtract, Crucell, Schering-Plough, Stallergènes and Thérabel as well as lecture fees from ALK-Abelló, GSK, MSD, Schering-Plough, Stallergènes and Thérabel.

Moises A Calderon has received honorarium lecture fees from ALK-Abello.

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