

Editorial

Sublingual immunotherapy: from proven prevention to putative rapid relief of allergic symptoms

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Allergen-specific immunotherapy (SIT) for the treatment of allergic rhinitis and asthma was first introduced in 1911. Although millions of patients have received this form of treatment, it has remained a controversial therapy since its inception. The vast majority of randomized double-blind, placebo-controlled trials have only been performed since the 1960s and standardized allergen vaccines have only been available for the past 25 years.

It is now recognized that subcutaneous SIT using appropriate doses, high-quality allergen vaccines and an appropriate indication is effective in rhinitis and asthma caused by pollens and mites (1). However, although sublingual immunotherapy (SLIT) using high-dose vaccines is widely used in many European countries (2), it is still controversial (3) and this form of therapy has gained little acceptance in the US.

'Evidence-based medicine' (EBM) is an increasingly important concept which has become a new paradigm in medicine. It is the ability to track down, critically appraise (for its validity and usefulness) and incorporate the information obtained from randomized trials to establish the clinical bases for diagnosis, prognosis and therapeutics (4). The increasing influence of EBM is due partly to the work of the Cochrane Collaboration which has led the way in setting new standards for preparing systematic reviews (5). Cochrane reviews are, on average, more systematic and less biased than systematic reviews published in paper journals. However, they have not yet all been perfected as errors and biases also occur in Cochrane reviews (6). For SLIT, there was, however, no pivotal controlled trial nor has a meta-analysis yet been

published. An evidence-based evaluation was therefore impossible.

In this issue of the journal, Wilson et al. (7) publish the Cochrane Collaboration meta-analysis of SLIT in rhinitis. Twenty-two trials involving 979 patients were included in the analysis. There were six trials of SLIT for house dust mite allergy, five for grass pollen, five for *Parietaria*, two for olive pollen and one each for, ragweed pollen, cat dander, and *Cupressus* pollen. Four studies exclusively tested children. The authors concluded that 'SLIT is a safe treatment which significantly reduces symptoms and medication requirements in allergic rhinitis. The size of this benefit compared to that of other available therapies, particularly injection immunotherapy, is not clear, having been assessed directly in very few studies. Further research is required concentrating on optimizing allergen dosage and patient selection.' This study therefore confirms the Allergic Rhinitis and its Impact on Asthma (ARIA) guidelines (1) which proposed that SLIT is one of the treatment options for allergic rhinitis in adults. However, more information is required on SLIT. Although the same conclusions will probably be arrived at, more data are needed to confirm the efficacy of SLIT in asthma and in children. The safety of SLIT in asthma and in children is now ascertained (8). Moreover, we need more data to find the relative indications of SLIT and subcutaneous SIT (9).

So, what may be the next step for SLIT? As SLIT is a safe treatment with doses currently administered, rush SLIT can be performed without the risk of serious systemic reactions observed with subcutaneous SIT. Can these high doses then be effective within minutes after

administration making it possible to rapidly relieve allergic symptoms? Although no clear answers can be given from clinical trials, there is sufficient evidence in the literature to suggest that this may be a possibility.

Rush SIT with inhalant allergens (grass pollen and house dust mites) leads, within days, to a reduction in skin test reactivity (10, 11). This decreased reactivity was invariably found 1 week after rush SIT initiation in over 500 patients and for a dose which was almost identical for all patients. The decrease in skin test reactivity was therefore dose- and not time-dependent. It is even possible that skin test reactivity could decrease earlier but only anecdotal data have been presented. During rush SIT, it was also found that patients had a relapse of allergic symptoms between 10 and 20 days after the last injection. However, within hours following the next injection, symptoms subsided (11). After 4–8 months of treatment, patients were able to increase the time between two injections and could be treated using a monthly maintenance dose (11).

In venom allergy, rush SIT is common practice and rapidly effective. However, it is not fully understood whether the treatment may be effective within a day or so. Beekeepers who do not work during the winter and early spring often present mild systemic reactions when they are stung at the beginning of the beekeeping season. These symptoms rapidly disappear after a few stings. The protection is obtained depending on the number of stings (dose-dependent) and may occur within days to a few weeks (time-independent) (12).

Although mechanisms of IgE-mediated drug allergy may differ from those of inhalant allergy, tolerance to the drug (e.g. β -lactam) can be achieved within a day (13).

These rapid clinical features cannot be explained by an adaptive immune response, but may be related to inflammatory cell downregulation (desensitization) occurring almost immediately after the injection of a high-dose vaccine (14). Basophil reactivity to allergen is reduced by SIT with inhalants and venoms. Several mechanisms may explain the rapid cell desensitization. Mast cells and basophils co-express Fc γ RIIb, a low-affinity receptor containing an immunoreceptor tyrosine-based inhibitory (ITIM) motif the co-aggregation of which with Fc ϵ RI can block Fc ϵ RI-mediated reactivity (15, 16). Another possible mechanism is the early production of interleukin (IL)-10 inducing T-cell allergy (17) and cell desensitization, and which may be an important early step in venom SIT (14). In venom SIT, platelets are less reactive to allergen within a week of treatment (18) and chemokine release *in vitro* is affected immediately after rush SIT (19), confirming, therefore, that cell desensitization can occur rapidly. In beekeepers, symptoms occurring at the onset of the beekeeping season are due to a lack of tolerance which may also be associated with cell re-sensitization or reduced venom-specific IgG levels. It is therefore possible that several mechanisms interact to explain the efficacy of

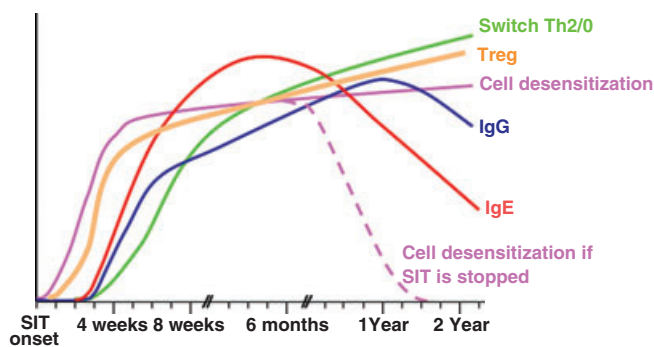


Figure 1. Early and late putative mechanisms of allergen specific immunotherapy.

SIT (Fig. 1). Early effects are likely to be associated with cell desensitization and are dose-dependent whereas long-term effects are associated with a switch of T-helper (Th)2 cells into Th1 cells and the occurrence of T-regulatory cells. The role of IgG is still unclear but this adaptive immune response needs some weeks to be fully effective.

We attempted to perform subcutaneous rush SIT during the pollen season to prove the possible rapid relief of allergic symptoms but, because of the high prevalence of systemic reactions (20), we were unable to confirm this hypothesis. It may be noted, however, that in the 1960s, many allergists in Europe were applying pollen extracts on scarifications during the pollen season and they claimed to ‘extinguish’ the allergic reaction within minutes. However, side effects were also common and these anecdotal observations have never been confirmed by a controlled trial. In SLIT, there is one study which approximates these methods. Although this trial was mainly carried out for safety purposes, this confirms the rapid effects of SLIT. In cypress pollen allergy, Vervloet et al. (21) started a rush SLIT protocol at the beginning of the pollen season. They were able to reach the maintenance dose of 300 IR within hours safely and found that medication scores were significantly reduced in the treated group in comparison with placebo. It is possible that the first doses of vaccines might have boosted the IgG immune response thereby inducing a more effective down regulation of mast cells at the peak of the pollen season.

Thus, by extending from asthma in which treatment is classified in controller and reliever therapy, it may be expected that future studies with SLIT may confirm that it is a rapid reliever for allergic symptoms in addition to current pharmacotherapy. A novel rapid treatment is required for many patients with severe persistent allergic rhinitis who are incompletely controlled with current pharmacological treatment and who do not want to have a long-term preventive treatment all year round, as severe allergic symptoms last only for some days, or in those who consult just before the start of the pollen season. We

are of course still facing many issues to prove this concept. These include the dose of the allergen vaccine to be administered, the dosage schedule of rush SLIT, whether it is an add-on treatment to medications or less

likely the only treatment, and more importantly, whether it is safe (probably) and effective (possibly). I am however confident that we are at the eve of a paradigm shift for SLIT.

References

1. Bousquet J, Van Cauwenberge P, Khaltaev N. Allergic rhinitis and its impact on asthma (ARIA)-executive summary. *Allergy* 2002;**57**:841-855.
2. Passalacqua G, Canonica GW. Sublingual or injection immunotherapy: the final answer? *Allergy* 2004;**59**:37-38.
3. Frew AJ, Smith HE. Sublingual immunotherapy. *J Allergy Clin Immunol* 2001;**107**:441-444.
4. Sackett DL, Rosenberg WM. The need for evidence-based medicine. *J R Soc Med* 1995;**88**:620-624.
5. Robinson A. Research, practice and the Cochrane Collaboration. *Cmaj* 1995;**152**:883-889.
6. Olsen O, Middleton P, Ezzo J, Gotzsche PC, Hadhazy V, Herxheimer A et al. Quality of Cochrane reviews: assessment of sample from 1998. *Bmj* 2001;**323**:829-832.
7. Wilson DR, Torres LI, Durham SR. Sublingual immunotherapy for allergic rhinitis. *Allergy* 2005;**60**:4-12.
8. Andre C, Vatrinet C, Galvain S, Carat F, Sicard H. Safety of sublingual-swallow immunotherapy in children and adults. *Int Arch Allergy Immunol* 2000;**121**:229-234.
9. Khinchi MS, Poulsen LK, Carat F, Andre C, Hansen AB, Malling HJ. Clinical efficacy of sublingual and subcutaneous birch pollen allergen-specific immunotherapy: a randomized, placebo-controlled, double-blind, double-dummy study. *Allergy* 2004;**59**:45-53.
10. Bousquet J, Guerin B, Dotte A, Dhivert H, Djoukhadar F, Hewitt B et al. Comparison between rush immunotherapy with a standardized allergen and an alum adjuved pyridine extracted material in grass pollen allergy. *Clin Allergy* 1985;**15**:179-193.
11. Bousquet J, Demoly P, Michel FB. Specific immunotherapy in rhinitis and asthma. *Ann Allergy Asthma Immunol* 2001;**87**(Suppl. 1):38-42.
12. Bousquet J, Menardo JL, Aznar R, Robinet-Levy M, Michel FB. Clinical and immunologic survey in beekeepers in relation to their sensitization. *J Allergy Clin Immunol* 1984;**73**:332-340.
13. Borish L, Tamir R, Rosenwasser LJ. Intravenous desensitization to beta-lactam antibiotics. *J Allergy Clin Immunol* 1987;**80**(3 Pt 1):314-319.
14. Ewan PW. New insight into immunological mechanisms of venom immunotherapy. *Curr Opin Allergy Clin Immunol* 2001;**1**:367-374.
15. Daeron M, Malbec O, Latour S, Arock M, Fridman WH. Regulation of high-affinity IgE receptor-mediated mast cell activation by murine low-affinity IgG receptors. *J Clin Invest* 1995;**95**:577-585.
16. Tam SW, Demissie S, Thomas D, Daeron M. A bispecific antibody against human IgE and human FcγRII that inhibits antigen-induced histamine release by human mast cells and basophils. *Allergy* 2004;**59**:772-780.
17. Jutel M, Akdis M, Budak F, Aebischer-Casaulta C, Wrzyszc M, Blaser K et al. IL-10 and TGF-β cooperate in the regulatory T cell response to mucosal allergens in normal immunity and specific immunotherapy. *Eur J Immunol* 2003;**33**:1205-1214.
18. Tsicopoulos A, Tonnel AB, Wallaert B, Joseph M, Ameisen JC, Ramon P et al. Decrease of IgE-dependent platelet activation in Hymenoptera hypersensitivity after specific rush desensitization. *Clin Exp Immunol* 1988;**71**:433-438.
19. Akoum H, Duez C, Vorng H, Fahy O, Wallaert B, Tonnel AB, et al. Early modifications of chemokine production and mRNA expression during rush venom immunotherapy. *Cytokine* 1998;**10**:706-712.
20. Hejjaoui A, Ferrando R, Dhivert H, Michel FB, Bousquet J. Systemic reactions occurring during immunotherapy with standardized pollen extracts. *J Allergy Clin Immunol* 1992;**89**:925-933.
21. Vervloet D, Birnbaum J, Laurent P, Hughes B, Fardau M, Massabie-Bouchat Y et al. Safety and clinical efficacy of rush sublingual *Juniperus ashei* immunotherapy. European Academy of Allergy and Clinical Immunology report. Paris, EAACI: 2003.