

EDITORIAL

Sublingual immunotherapy

The concept of treating allergic diseases by oral ingestion of allergens dates back to the beginning of this century [1], and may be classified into two categories: (a) oral immunotherapy, i.e. swallowing the extract (either in the form of aqueous extract or by ingesting powdered extracts in enterosoluble capsules); and (b) sublingual immunotherapy, i.e. retaining the extract for a defined period of time in the mouth. Sublingual immunotherapy could be subdivided into either exclusively sublingual therapy, i.e. allowing absorption of the extract from the oral mucous membranes and then spitting out the extracts, or a combined sublingual/oral therapy whereby the extract is subsequently swallowed. The scientific basis for oral immunotherapy is based on the high number of immunocompetent cells which are located in intestinal lymph nodes [2]. The absolute prerequisite for sublingual immunotherapy is the penetration of sufficient amounts of allergens through the oral mucosa. Based on studies on exclusively sublingual immunotherapy like the study in this issue by Quirino *et al.* [3], one might question the absorption of allergen through the oral mucosa, as these studies were not able to demonstrate any increase in specific IgG.

The role of specific IgG as being directly involved in reducing the release of allergic mediators from mast cells and thereby in the clinical efficacy of injection immunotherapy is unlikely [4], but on the other hand, an increase in IgG indicates activation of immunocompetent cells and thereby a systemic administration of a significant amount of allergen. Experiments with radiolabelled allergen extracts (Canonica, personal communication) do not indicate any absorption in the oral cavity, thereby raising doubt about the rationale for this form of allergen administration. The degradation of aqueous allergen extract before reaching the small intestine results in reducing the allergenicity by 90%, as estimated by RAST-inhibition [5]. The degradation into peptides and subsequent stimulation of immunocompetent cells with these peptides might, however, represent an advantage in the form of an unintended peptide treatment [6].

Documentation about the clinical efficacy of sublingual (or sublingual/oral) immunotherapy includes nine published papers concerning placebo-controlled double-blind studies. The validation of the quality of the papers is hampered by a great variability in the amount of allergen extract administered, the duration of the treatment, and the criteria for concluding a clinical efficacy (Table 1). Six of the nine studies evaluate the efficacy after less than 1 year of treatment in spite of the possibility that a longer duration of treatment might improve the clinical efficacy.

The amount of allergen extract administered also differs over a wide range, from homeopathic doses used in the study by Scadding [7], to cumulative doses twice those used in injection immunotherapy [3]. The greatest dilemma in elucidating the clinical value of sublingual immunotherapy is related to the criteria used for concluding a clinical efficacy. It is my opinion that the only parameters indicating efficacy are a reduction in symptoms and/or drug intake, that from a clinical point of view significantly reduce the morbidity of allergic disorders [8]. Changes in immunological parameters and challenge tests may be of interest in elucidating mechanisms, but cannot constitute clinical evaluation [9]. The optimal study design for investigating clinical efficacy includes a pre-treatment monitoring of symptoms and drug score for a season [9]. This gives the advantage of elucidating the clinical relevance of allergen exposure in eliciting symptoms (critically important for the indication of immunotherapy), and represents the only possible way of ensuring an equal balance of disease severity in the active and control groups.

The study by Quirino *et al.* [3] is a carefully designed (double-blind, double-dummy) study, following international guidelines for 'good clinical practice' by pre-treatment monitoring of disease severity and evaluating clinical efficacy by a reduction in symptoms and drug intake, comparing the efficacy of sublingual immunotherapy with the traditional injection treatment. The conclusions of the study would have been improved by including a placebo group (to investigate the variation in symptom and drug scores not caused by active treatment), but comparison with a well-documented treatment is acceptable in elucidating efficacy. The magnitude of the clinical improvement is also important. It is of course critical to document a statistically significant difference between the active group and the placebo group, but 'P-values' do not *per se* guarantee the applicability of a specified treatment. A 10% reduction in drug intake might be statistically significant but for the patient clinically irrelevant.

When optimally performed, traditional injection immunotherapy has a documented clinical capacity to reduce, in actively treated patients, symptoms and drug intake to about 20% of symptoms and drug score of the placebo-treated group [10]. In the Quirino study [3], the average efficacy implies a reduction of 50% in symptoms and drug score in the treatment grass pollen season as compared to the pre-treatment season (being exposed to identical allergen load?). The lack of difference between the injection group

Table 1. Published placebo controlled double blind sublingual immunotherapy studies

Reference	Disease	No. of patients Active/Placebo	Allergen extract	Duration of treatment	Allergen dose*	Clinical efficacy†	Side effects‡
Scadding 1986 Van Niekerk 1987	Rhinitis Rhinitis	20 19/21	Mites 14 grasses	2 weeks 2 years§	Low dose ?	Subjective ↓ Symptoms ? Drugs	No No severe
Tari 1990	Rhinitis/Asthma	30/28	Mites	18 months	MD 3.75 BU	↓ Symptoms ↔ Drugs	32 episodes 3 severe asthma
Novembre 1991	Asthma	13	Mites	1 year	MD 3750 UN	? Symptoms ↓ Drugs	23% A = P
Nelson 1993	Rhinitis/Asthma	20/21	Cat	105 days	MD 100,000 AU CD 4,500,000 AU	No	No severe
Sabbah 1994	Rhinitis	29/29	5 grasses	17 weeks	MD 100 IR	↓ Symptoms ↓ Drugs	A 34% P 24%
Casanovas 1994	Rhinitis	9/6	Olea	2 months	MD 0.5 HEP	↓ Asthma symptoms	A 33% P 33%
Troise 1995	Rhinitis	15/16	Parietaria	10 months	MD 1.25 BU CD 105 BU	↔ Symptoms ↓ Drug score	A 7% P 6%
Feliziani 1995	Rhinitis/Asthma	18/16	5 grasses	3½ months	MD 25 BU	↓ Symptoms ↓ Drugs	No severe

* Allergen doses are stated as maximal dose (MD) and if possible as cumulative dose (CD). The different potency units makes comparison impossible.

† Clinical efficacy is based on a statistically significant reduction in symptoms and/or drugs.

‡ Side effects calculated as percentage of patients experiencing systemic side effects (A = active group; P = placebo group), and the severity of side effects.

§ 1st year placebo-controlled double-blind, 2nd year open study.

and the sublingual group might, by sceptics, be interpreted purely as a placebo effect, although a placebo effect of this magnitude is rare. The inclusion of a placebo group would have solved that problem!

The major objection to injection immunotherapy is the frequency of systemic side effects [9]. In sublingual immunotherapy, the most frequently noted side effect is related to the exposure of the oral mucosa to the allergen extract, i.e. itching and irritation. Nasal and intestinal symptoms are rarely reported. Urticaria and asthma have been elicited, but no cases of anaphylaxis have been described. In contrast to most other injection immunotherapy studies, the parenteral administration of grass pollen in the study by Quirino *et al.* [3] did not induce systemic side effects, and only a few minor local side effects were reported. The complete lack of systemic side effects and the limited local reactions might, by chance, be caused by the limited number of patients, but the use of low-potency extracts could also be the explanation (the Abellò biological units do not give any information on the amount of major grass pollen allergen). A higher maximum administered single dose in injection immunotherapy compared to sublingual immunotherapy (and *vice versa* for cumulative doses) might also explain the difference in systemic side effects. The actual data from the Quirino study [3] related to this issue are: injection 20 BU; sublingual ~6 BU. A study exposing patients to identical allergen doses would be of interest.

In conclusion, as long as injection immunotherapy is still considered controversial in spite of the clinical documentation for efficacy (and side effects), one has to be extremely cautious in recommending sublingual/oral immunotherapy for routine treatment of allergic diseases. Of the nine published studies, one [11] has not been able to document efficacy of cat sublingual immunotherapy. The Scadding study [7] could, due to the homeopathic dose of allergen and exceptional study design, be excluded from studies included in the evaluation of efficacy. Two studies (using mite and olea allergens) include too few patients to allow conclusions to be drawn [12,13]. There is only one study which includes an acceptable number of patients using mite allergen [14] with some efficacy (reduced symptoms), and one *Parietaria* and three grass pollen studies showing efficacy [15,16,17,18].

I agree with the conclusion of Quirino *et al.* [3] that 'the safety of an alternative therapy is a real advantage only if it is not counterbalanced by a loss of clinical efficacy'. In my opinion, sublingual immunotherapy is without doubt a safe treatment, but the clinical efficacy — especially in relation to injection immunotherapy — is only documented by a few studies and only for mite, *Parietaria* and grass allergens. Before recommending this alternative specific treatment for routine use, we need more documentation of efficacy (and the magnitude of the reduction in symptoms and drugs) both

in comparison to placebo and in relation to injection immunotherapy.

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