

Comparison of the clinical efficacy and safety of subcutaneous and sublingual immunotherapy: methodological approaches and experimental results

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Purpose of review

Sublingual immunotherapy has been documented as clinically effective in controlled studies. Some concerns about the magnitude of disease severity reduction in relation to standard subcutaneous immunotherapy have been raised. The comparison with subcutaneous immunotherapy is important for giving recommendations on the use of sublingual immunotherapy in daily clinical practice.

Recent findings

Only three controlled comparative studies of sublingual and subcutaneous immunotherapy have been published. The methodology of the studies indicated that some study design deficiencies limited the interpretation of efficacy. Only one study used an optimal placebo-controlled, double-blind, double-dummy and randomized design. The studies are assessed with respect to a sufficient number of patients to detect statistically possible differences, the inclusion of patients, clearly defined outcome measures, doses of extract administered, and duration of treatment. In all three studies the reduction in disease severity was of the order of 50% with no significant difference between the two treatments.

Summary

The clinical efficacy of sublingual immunotherapy is based on three studies only, and a limited number of patients equal to the efficacy obtained by subcutaneous immunotherapy. Only limited information on long-term efficacy and preventative capacity are available. More data on these aspects are needed, but the restraint in using sublingual immunotherapy in the treatment strategy of allergic diseases does not seem to be evidence based. Future research should also focus on identifying which subsets of patients would most benefit from either of the two routes of immunotherapy administration.

Keywords

clinical efficacy, comparative studies, study design, subcutaneous immunotherapy, sublingual immunotherapy

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Abbreviations

SCIT subcutaneous immunotherapy
SLIT sublingual immunotherapy

Introduction

Sublingual immunotherapy (SLIT) has become increasingly popular, and in some countries more allergic patients are treated by the sublingual than the subcutaneous route. Evaluation of the scientific documentation for clinical efficacy is important before a treatment is used unrestrictedly. Selection of the right treatment for different diseases is a cornerstone in the work of the allergist. This implies a knowledge of the advantages and disadvantages of available treatment modalities. Allergen-specific subcutaneous immunotherapy (SCIT) is the only treatment that may alter the natural course of the disease, with documentation of long-term effectiveness (after termination of treatment) and preventative capacity [1]. Sublingual immunotherapy, as a result of the almost non-existing risk of severe systemic side-effects and the possibility of home administration, has attracted considerable interest. International position papers have not recommended sublingual immunotherapy [2], stated that it may be a viable alternative to subcutaneous immunotherapy [1], and recommended that it may be considered in selected patients with systemic side-effects, who refuse injection treatment, and in children [3]. Recent reviews and a meta-analysis have confirmed the clinical efficacy [4,5••].

Methodological aspects

The validity of clinical studies making the basis for selecting a specified treatment is closely related to the quality and methodology of the study design. The Consolidated Standards of Reporting Trials (CONSORT) guidelines [6] stipulate study planning for conclusive trials. A summary of these guidelines is presented, and the published comparative studies evaluating the relative advantages of subcutaneous and sublingual immunotherapy will be assessed in relation to these guidelines: (1) The study should be a placebo-controlled, double-blind, double-dummy, randomized trial; (2) the sample size should be large enough to detect statistically significant and clinically relevant changes in disease severity; (3) Patients should be selected according to predefined clinical criteria; (4) the primary and secondary outcome measures should be clearly defined; (5) allergen extracts and maintenance doses should be defined; and (6) the duration of treatment should be sufficient to allow clinical improvement to occur.

Comparative studies of sublingual and subcutaneous immunotherapy

Two uncontrolled studies comparing the sublingual and the subcutaneous route will not be discussed in this review [7,8]. A controlled comparative evaluation of sublingual and subcutaneous treatment is limited to three published papers [9,10,11••]. The study by Quirino *et al.* [9] evaluated the clinical efficacy of grass pollen immunotherapy by the two routes of administration. The main methodological limitation is that the study did not include a placebo group, and the crucial question not answered in the study is whether a change in symptom-medication scores are different from placebo, i.e. does active treatment change the disease severity favourably to placebo treatment? The study was double-blinded, and patients were randomly selected in blocks on the basis of age, sex and disease severity, including pollen-induced asthma. An appropriate double-dummy technique was used, but the success of blinding is not presented. Another methodological problem is the size of the study groups. No information on the expected magnitude of efficacy was provided, and no calculation of the number of patients to be included in each treatment arm to ensure the probability (power) to detect statistical significance was presented. The inclusion of an insufficient number of patients (10 patients in each treatment arm) implies a high risk of statistical type II errors (not being able to detect a factual difference between the two treatment options). The patients were selected appropriately, being monosensitive to grass and not presenting generally accepted contraindications for immunotherapy [2]. A clear differentiation in primary and secondary outcomes is not perceptible from the methodological information, although indirectly symptom and medication scores represent the primary outcome. No information was given as to the recommended introduction of different drugs, or to compensate for the relative antiallergic potency of available drugs. The allergen extracts used were labelled in arbitrary units and no information on the content of major allergens in mass units is provided. The cumulative dose in patients receiving sublingual immunotherapy over the one year treatment period was approximately 2.4 times the dose administered subcutaneously. The clinical results related to efficacy imply a reduction in symptom and medication scores of approximately 50% in both groups (not significant) evaluated over two comparable grass pollen seasons (pretreatment and treatment seasons). Skin reactivity was reduced during treatment in the subcutaneous immunotherapy group but not the sublingual immunotherapy group. Likewise, only the SCIT group demonstrated an increase in total IgG and IgG4. Neither of the treatments induced clinically relevant systemic side-effects. In summary, the study did not reveal significant advantages of either treatment, either with respect to clinical

efficacy or safety, but because of the number of patients included, this was not to be expected, taking the magnitude of the clinical effect of published studies into consideration [12,13]. The study does not demonstrate that the downregulation of clinical symptoms with SLIT is caused by immunological mechanisms. The absence of an IgG response to SLIT might be interpreted as a deficiency of a systemic immune response to SLIT compared with SCIT.

The study by Mungan *et al.* [10] included a placebo group, but treatment was not administered in a double-blind fashion using the double-dummy technique as only the sublingual treatment was placebo controlled and double blinded. Consequently, drawing conclusions about the magnitude of clinical efficacy of the two treatment options is difficult. The criterion for randomization is not stated. The study population included seven men and 29 women. Patients were included on a well-established diagnosis of mite-induced rhinitis and asthma and were monosensitized. The primary outcome was a reduction in clinical symptoms and the use of anti-allergic drugs in the first 6 months and the second 6 months of treatment compared with a one-month pretreatment baseline. SCIT-treated patients were not balanced with respect to asthma scores at baseline, which might have biased the outcome. The allergen extract employed was a commercial mite extract standardized in biological units, but with no information on the content of major allergens. The cumulative dosage of allergen in the sublingual group was 86 times the dose administered in the subcutaneous group. The mean rhinitis symptom score decreased significantly in the sublingual group (reduction 43%) and the subcutaneous group (reduction 47%). Regarding the asthma symptom score, only the subcutaneous group experienced a significant reduction of 51%. No significant change in the placebo group was observed. No comparisons between the groups are presented. Regarding medication scores, a significantly reduced use of anti-allergic drugs was observed in both the sublingual (reduction 60%) and the subcutaneous group (reduction 43%). No significant change was observed in the placebo group. Regarding immunological parameters, a reduced skin sensitivity was found only in the subcutaneous group, and likewise a relevant IgG4 response was observed in this group. Side-effects in both groups were negligible, with only one systemic reaction (mild bronchospasm) in the subcutaneous group and a local reaction in the sublingual group. In summary, sublingual immunotherapy was clinically effective in downregulating rhinitis symptoms and the use of drugs, but not for asthma symptoms, in contrast to subcutaneous immunotherapy, which worked on symptom manifestations from both the upper and lower airways. Only subcutaneous immunotherapy seemed to have an effect on immunological parameters.

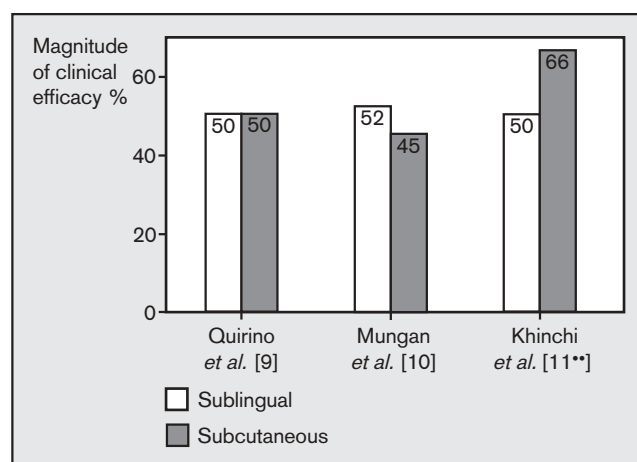
The only adequate methodological trial (placebo-controlled, double-blind, double-dummy) is the study by Khinchi *et al.* [11**]. Based on an estimate of responders, screening included almost 90 patients, but only 71 were allocated (minimization based on symptom medication scores during a pretreatment season) to the three treatment arms (25 in each arm were required to give a 5% risk of statistical type 1 error and 10% type 2 error). As a result of dropouts only approximately 20 in each arm completed the first year of treatment and only 48 the second year. Concluding about clinical efficacy in the second year of treatment could have been problematical because of the inadequate number of patients, but another problem in pollen allergy, i.e. a poor pollen season resulting in an almost complete lack of clinical symptoms, excluded the evaluation of efficacy in year two of the treatment. The success of blinding was documented by a questionnaire asking the patients to identify which kind of active treatment they had received before breaking the code. Patients included in the study had experienced rhinoconjunctivitis during the two preceding birch pollen seasons, and were uncontrolled by conventional anti-allergic pharmacotherapy. Mild asthma was accepted. The stratification of the different treatment arms ensured equivalence with respect to sex, sensitization especially to grass, and the frequency of asthma. Despite dropouts, no significant difference in symptom and medication scores was observed among the groups, although a higher medication scoring was observed in the SLIT group. The primary outcome measure was to compare SLIT with SCIT in relation to clinical efficacy and side-effects. The secondary outcome was to evaluate the magnitude of the efficacy of active treatment versus placebo. The allergen extract employed was a commercial birch-pollen extract administering 49.2 μ g Bet v 1 every second day in the SLIT group and 3.28 μ g Bet v 1 every 4 weeks in the SCIT group. The cumulative dose in SLIT-treated patients after one year of treatment was 175 times the dose administered subcutaneously. The study clearly documented the value of estimating clinical efficacy based on changes in disease severity compared with the pretreatment period. Looking exclusively at differences between the groups during the first treatment season, a reduction in disease severity of 42% was observed in the SCIT group, but as a result of the individual variation in scoring this was not statistically significant. Comparing results from the pretreatment to the first treatment season, the 2.3 times higher pollen load in the first treatment season resulted in a significant deterioration in scores in the placebo-treated group in contrast to an improvement in the actively treated groups (most obvious for symptom scoring). Symptoms and medication scoring in SCIT-treated patients was only a third of the placebo group, indicating a reduction in disease severity of 66% (comparing first treatment season with

pre-treatment). In SLIT-treated patients the reduction was approximately 50%. In spite of intending to include a sufficient number of patients to detect the likely differences between SLIT and SCIT this was not statistically possible. As a result of the notable risk of statistical type 2 errors caused by the limited number of patients completing the study, it is not possible to state that the two treatments are equally effective. Regarding side-effects, the study confirmed the safety of SLIT, as only mild local mouth/throat reactions occurred predominantly during the induction phase. In the SCIT group five grade III and one grade IV reaction was induced. Changes in immunological parameters have not yet been analysed. In summary, this methodologically optimal study confirms previous studies that indicated that the downregulating capacity of sublingual immunotherapy with respect to disease severity is equivalent to the gold standard subcutaneous immunotherapy.

Conclusion

Based on a very limited number of patients and three studies only (of which two used an inadequate methodological study design) sublingual immunotherapy in pollen rhinitis (birch and grass pollen) and mite asthma seems to be clinically effective compared with placebo (Fig. 1). Furthermore, if a difference exists in the magnitude of clinical efficacy between sublingual and subcutaneous immunotherapy, this difference is limited, and large study groups would be required to detect it. A major limitation to the use of sublingual treatment in routine clinical practice is the insufficient documentation of long-term clinical effectiveness [14*] and preventative capacity. A number of studies addressing these issues are

Figure 1. Clinical efficacy obtained in comparative studies of sublingual and subcutaneous immunotherapy



Efficacy is estimated as changes from baseline in disease severity (symptom and medication scores). The difference between the two treatments is not statistically significant in any of the three studies.

in progress [15•]. The ease of administration and the almost non-existent risk of systemic side-effects adds to the advantages of sublingual immunotherapy. However, the rather limited impact on immunological parameters might indicate that the clinical effect might be caused by a local downregulation of the sensitivity of the mucous membranes rather than a systemic target organ independent of disease-modifying capacity. The dose of allergen needed to induce clinical efficacy varies considerably [13], with doses administered ranging from 3 to 300 times the corresponding dose used in subcutaneous immunotherapy.

Further large scale, properly randomized and controlled studies are needed to define the role of sublingual immunotherapy in the treatment strategy of allergic diseases. Future research should concentrate on identifying candidates for the two treatments. Our current knowledge does not determine whether special age groups, sensitizations, or disease manifestations are better suited to subcutaneous or sublingual immunotherapy. Comparative studies are needed that focus not only on clinical efficacy but also on the clinical characteristics of the patients responding to treatment. Based on the available literature, sublingual immunotherapy seems to be a viable alternative to subcutaneous immunotherapy, especially taking the safety aspects into consideration.

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