

Position paper*

Local immunotherapy

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The term “local immunotherapy” (LIT) is proposed for the noninjective administration of specific immunotherapy in allergic disorders such as rhinitis and asthma. Local immunotherapy includes local nasal (LNIT), local bronchial (LBIT), oral (OIT), and sublingual (SLIT) administration of allergen extracts. The term “alternative immunotherapy” should be abandoned, since it may generate misleading associations and confusion with other, scientifically undocumented therapies used in allergic diseases; e.g., acupuncture, hypnosis, homeopathy, and other methods (1).

The rationale for using local routes as alternatives to the classical injection immunotherapy is based on scientific data primarily obtained from animal experiments. The arguments are an attempt to improve patient compliance and to reduce the risk of systemic side-effects that restricts the usefulness of injection immunotherapy.

*Position paper by the working group on local immunotherapy of the European Academy of Allergology and Clinical Immunology (EAACI) Immunotherapy Subcommittee and the European Society of Pediatric Allergy and Clinical Immunology (ESPACI) Immunotherapy Committee.

Immunologic aspects

The experimental evidence of local administration of allergen extracts on airway mucosa is based on the concept of inducing local tolerance. In IgE high-responder mice, partial inhibition of IgE has been obtained by inhalation of allergens (2–5). Oral and sublingual immunotherapy originates from experimental animal studies indicating that ingestion of antigens may induce tolerance (6–8). Hypothetically, the effect of sublingual immunotherapy might be explained by several mechanisms. The mucosa of the mouth is particularly rich in dendritic cells, known for their strong expression of MHC class II molecules (9). Dendritic cells process allergens and antigens and migrate to local lymph nodes where they are transformed into antigen-presenting cells. Animal models used in investigating the mechanisms involved in tolerance induction by the oral mucosa showed that dendritic cells derived from the oral mucosa act as antigen-presenting cells (10, 11), indicating that clonal anergy of specific T cells might be the mechanism of oral mucosa-induced tolerance. Dendritic cells also produce interleukin (IL)-12, which favors the

development of Th1 rather than Th2 cells (12, 13). The possible involvement of local immunity was confirmed in a recent study of the kinetics of allergen absorption (14). The purified major allergen of *Parietaria judaica* was demonstrated to persist adsorbed to the sublingual mucosa for up to 12 h after its administration, although in non-allergic persons, radiolabeled allergens were not absorbed at the oral mucosal level.

Clinical aspects

Poor compliance may limit the applicability of allergen-specific injection immunotherapy (15). As local immunotherapy is usually taken by the patients at home, eliminating the need for injections in the doctor's office, local immunotherapy is generally more favorably accepted by patients. However, the actual adherence to dosage regimens has not been studied; therefore, the actual patient compliance with local immunotherapy is unknown.

Systemic side-effects may limit the use of injection immunotherapy (16). The risk is less in hay-fever patients than with asthmatics (17). When the therapy is properly performed, the rate of severe systemic reactions in patients with rhinitis treated with potent extracts is approximately 5% of the injections (18). According to the published data, local immunotherapy seems rarely to evoke severe systemic side-effects, and no life-threatening nor fatal events have, until now, been reported.

Early attempts to treat allergic diseases by nasal, bronchial, and oral allergens dates back to the first decades of this century (19–21). The use of local immunotherapy gradually decreased until the 1980s, when some reports of severe reactions questioned the safety of subcutaneous immunotherapy (22–24) and consequently raised an interest in alternative forms of specific immunotherapy.

The present EAACI/ESPACI position paper analyzes the available documentation of clinical efficacy and safety of nasal, bronchial, oral, and sublingual immunotherapy, and discusses the rationale for using these specific treatments in clinical practice. Due to the rapidly growing number of studies on local immunotherapy, frequent revision and updating of this position paper will be needed.

Inclusion of papers

To eliminate any doubt of the validity of the papers included in this review, the review panel have used strict criteria. Inclusion criteria were as follows:

- 1) placebo-controlled, double-blind (PCDB) studies
- 2) allergen extracts and doses defined

- 3) treatment protocol and statistical analysis appropriate including an adequate sample size (over seven patients per group)
- 4) studies published in peer-reviewed journals in English
- 5) symptom/medication scores provided.

Allergen extracts, formulations, and duration of treatment

In 23 out of 31 studies of local immunotherapy included in this review, pollen allergen extracts (birch, grass, *Parietaria*, and ragweed) were employed. House-dust-mite and cat extracts have been less extensively studied. Allergen extracts were provided by various manufacturers, who have applied different methods for standardization, and validation of the quality of the extracts has not been attempted. As most studies were conducted over the past 15 years, we assume that international guidelines for allergen standardization and manufacturing were followed by the manufacturers (25), even if this was not always stated.

Both aqueous and powder extracts have been employed in local nasal and bronchial immunotherapy. Most studies employed nonmodified extracts, but some studies investigated modified allergoids. Extracts used for oral immunotherapy either consisted of aqueous solutions or were dispensed in enteric-coated capsules to prevent the degradation of allergens in the stomach. Aqueous extracts were employed in all studies of sublingual immunotherapy. Comparing the doses of allergens administered has not been possible, as, in most studies, the amount of major allergens or the potency of the extracts was given only in arbitrary units designed by the manufacturer, which do not provide relevant information regarding potency or composition. As the allergen extracts and dosage regimens were those recommended by the manufacturer, the assessment of the clinical usefulness was based on data presented in the studies.

In most studies, the duration of treatment was short, ranging from a few weeks to a few months of preseasonal immunotherapy. In only five out of 31 studies was the treatment extended more than 1 year. The duration of treatment was not considered when analyzing the documentation of clinical efficacy, although it is well known that in injection immunotherapy the efficacy improves with the duration of treatment (16). In a study employing oral immunotherapy, the intensity of clinical efficacy was clearly related to the length of the treatment (26). This could not be used as an argument that the lack of efficacy of a short-time treatment would automatically imply that a longer treatment period would be efficacious.

Table 1. PCDB local nasal immunotherapy studies

Author(s) and year of publication		Age range (years)	Allergen	Type of extract	Duration	Maximum dose*	No. patients			Significance <i>P</i>	Systemic side-effects
							IT	PI	Disease		
Johansson et al. (28)	1979	Adults	Grass	Aqueous (glutaraldehyde)	14 weeks	MD? CD 450000 Noon	12	11	Rhinitis	<0.001	12 R No severe
Nickelsen et al. (29)	1981	16–66	Ragweed	Aqueous modified (glutaraldehyde)	3 months	CD 59 µg AgE	38	34	Rhinitis	<0.01	38 R
						CD 315 µg AgE	35			<0.03	34 R No severe
Welsh et al. (30)	1981	13–58	Ragweed	Aqueous	20 weeks	CD 6–694 µg AgE	18	15	Rhinitis	<0.004	?
Schumacher & Pain (31)	1982	20–53	Grass	Powder (glutaraldehyde)	10 weeks	MD 320 µg	8	7	Rhinitis	NS	?
						CD 3.68 mg					No severe
Georgitis et al. (32)	1983	16–67	Grass	Aqueous allergoid	10 weeks	CD 0.6–44 kPNU	16	13	Rhinitis	<0.005	No severe
Georgitis et al. (33)	1984	Adults	Grass	Aqueous allergoid	10 weeks	CD 12–192 kPNU	15	16	Rhinitis	<0.01	No severe
						CD 32000 PNU	14			NS	No severe
Andri et al. (34)	1992	14–54	<i>Parietaria</i>	Powder modified	18 weeks	MD 240 AU	8	8	Rhinitis	S NS	No
							8			D<0.05	
Andri et al. (35)	1993	Adults	Mite	Powder	12 months	MD 1800 IU	11	10	Rhinitis	<0.05	No
						CD 164456 IU					
Passalacqua et al. (36)	1995	20–56	<i>Parietaria</i>	Powder	5 months	MD 240 AU	9	9	Rhinitis**	<0.01	No
D'Amato et al. (37)	1995	13–37	<i>Parietaria</i>	Powder	8 months	MD 240 AU	10	10	Rhinitis	<0.05	3 A
Andri et al. (38)	1995	Adults	Birch	Powder	22 weeks	MD 240 AU	14	14	Rhinitis	S NS	No severe
						CD 5607 AU				D<0.05	
Andri et al. (39)	1996	Adults	Grass	Powder	26 weeks	MD 240 AU	13	15	Rhinitis	<0.05	No
						CD 6567 AU					
Cirila et al. (40)	1996	17–44	Birch Alder	Powder	4 months	MD 240 AU	11	11	Rhinitis	<0.01	No severe
						CD 2950 AU					
Bardare et al. (41)	1996	5–15	Grass	Powder	12 weeks	MD 240 AU	19	20	Rhinitis	<0.05	No severe
						CD 2140 AU					

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

**Asthmatic patients not excluded.

Abbreviations – IT: immunotherapy; PI: placebo; A: asthma; R: rhinitis; S: symptom score; D: drug score; NS: nonsignificant.

Estimation of efficacy

As allergic patients suffer from the clinical manifestations of the disease, the efficacy of a treatment should be based on a reduction of symptoms and/or drug intake. Changes in immunologic parameters and challenge test results may be of scientific interest for elucidating mechanisms, but do not constitute a basis for the evaluation of clinical efficacy (16). Furthermore, the degree of reduction in symptoms and/or drug intake should be of a magnitude that, from a clinical point of view, significantly reduces the severity of the allergic diseases (27). The clinical efficacy can be estimated by comparing matched groups treated with active immunotherapy and placebo. This is best done by investigating the reduction in symptom/medication scores in relation to a pre-treatment observation period; i.e., over a season for seasonal allergy or a sufficiently long comparative period of time in the case of perennial allergies (16). The magnitude of efficacy was not discussed in most clinical studies, as only data supporting a statistically significant difference between the two groups were provided. Although such differences are essential, this does not guarantee that a particular treatment is clinically useful. For example, a 10% reduction in

drug intakes could be statistically significant, yet be clinically irrelevant to the patient. As with most other studies on antiallergic treatment, the magnitude of efficacy, and consequently the clinical relevance of local immunotherapy could not be fully appreciated.

Most studies investigating the clinical efficacy of immunotherapy provide a combined symptom-medication score, and consequently do not involve logistic problems. The interpretation of efficacy in studies providing segregated data on symptom scores and medication scores is more complicated due to the relative weighting of these parameters. Improvement in symptoms and no change in drug scores, or vice versa, still represent an improvement of the total disease severity. The problems arise when symptoms and drug score show discordant changes. In these cases, it must be concluded that no important and indisputable clinical efficacy was induced by the treatment.

Nasal immunotherapy

Clinical documentation of efficacy

Nasal immunotherapy may be performed as pre-seasonal or perennial treatment. The allergens are

dispensed in powder form or as an aqueous solution and are self-administered. During the application of the allergen extract, the patient vocalizes to avoid deposition of the extract in the bronchial tree. Extracts are administered daily or on alternate days during the induction phase and then weekly during maintenance treatment. Premedication with cromoglycate is recommended by some authors, but scientific support for this is lacking.

The clinical documentation of efficacy in nasal immunotherapy is based on 14 studies fulfilling the criteria for inclusion in this analysis (Table 1) (28–41). Seven studies were excluded because symptom/medication scores were not presented (42), a placebo group was not included (43–46), statistical methods were not defined (47), the randomization of patients was not satisfactory (48), and the allergen extract was insufficiently described (49).

Thirteen out of 14 papers on nasal immunotherapy found a statistically significant clinical efficacy primarily in adults. The numbers of actively treated patients were 252 in the “positive efficacy” studies and 22 in the “no efficacy” study. The long-term efficacy was considered in one study (50), which suggested that for preseasonal nasal immunotherapy the efficacy is dependent on the administration of the treatment before each pollen season. Two preseasonal courses of nasal immunotherapy with *Parietaria* did not prevent a relapse of symptoms in the third season in patients with a relevant reduction in symptoms during the two preceding seasons.

Safety

No severe systemic side-effects were observed in any of the studies evaluated. In most studies on nasal immunotherapy, local symptoms from the nose (sneezing and irritation) were reported by most patients, especially when aqueous extracts were used. Local nasal immunotherapy may induce asthmatic symptoms; thus, in one study, three patients in the active group withdrew from treatment because of bronchospasm after allergen administration (37). This may be due to incorrect administration technique, since no bronchial deposition of allergen has been shown *in vivo* (14). Finally, the frequency of local side-effects was identical in patients receiving either histamine placebo or allergen (29).

Critics of nasal immunotherapy have claimed that the treatment induces local symptoms for a prolonged period of time, i.e., during both the updosings phase and the pollen season. This may be of minor importance, however, since the higher preseasonal symptom scores in actively treated patients did not result in a higher drug score, indicating that patients accepted the relatively mild symptoms and did not use rescue medication (38).

Generally, the local nasal symptoms induced by immunotherapy were relatively short-lasting.

Paraclinical effects

In vivo. A reduction in nasal challenge test sensitivity has been shown in several studies (28, 31, 34–41). Skin test sensitivity does not seem to be influenced by nasal immunotherapy (28, 34, 35, 38, 39, 41).

In vitro. In most studies, there were no appreciable changes in the serum levels of allergen-specific IgE or IgG, while one study indicated a significant increase in both serum and nasal secretion allergen-specific IgG and IgA (28). In one study, stable values of serum soluble ICAM-1 levels during the pollen season were observed in actively treated patients, in contrast to increasing levels in the placebo group, as well as a significant reduction of ICAM-1 positive cells, and reduced eosinophil counts in the actively treated patients after nasal challenge. (36). These changes were not accompanied by any changes in serum IgE, IgG, or soluble ECP (eosinophil cationic protein) levels.

Conclusion: nasal immunotherapy

Thirteen of 14 PCDB studies (Table 5) on nasal immunotherapy have documented a statistically significant reduction in symptoms and/or the need for medication in adult patients with rhinitis. The allergen extracts used in studies showing clinical efficacy include grass allergens in five studies (28, 32, 33, 39, 41), ragweed in two (29, 30), *Parietaria* in three (34, 36, 37), birch in two (38, 40), and house-dust-mite extract in one (35). Only one study has documented efficacy and safety in pediatric patients (41). The side-effects do not appear to present a significant problem.

Bronchial immunotherapy

Clinical documentation of efficacy

The efficacy of bronchial immunotherapy has been evaluated in two studies using mite allergens (Table 2) (51, 52). In one of the studies, clinical efficacy was shown by progressive improvement in symptom and medication scores over a 24-month treatment period (51).

Safety

In both studies, bronchospasm was induced in most patients. In most cases, the immediate decline in lung function was less than 85% of pretreatment

Table 2. PCDB local bronchial immunotherapy studies

Author(s) and year of publication	Age range (years)	Allergen	Type of extract	Duration	Maximum dose*	No. patients		Disease	Significance <i>P</i>	Systemic side-effects	
						IT	PI				
Crimi et al. (51)	1991	13–57	Mite	Powder	9–13 weeks	MD 1000 AU	11	11	Asthma	NS	9 A
Tari et al. (52)	1992	10–50	Mite	Powder	24 months	MD 7500 IU	14	10	Asthma	<0.001	Mild A

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

Abbreviations – IT: immunotherapy; PI: placebo; A: asthma; NS: nonsignificant.

Table 3. PCDB oral immunotherapy studies

Author(s) and year of publication		Age range (years)	Allergen	Type of extract	Duration	Maximum dose*	No. patients		Disease	Significance <i>P</i>	Systemic side-effects
							IT	PI			
Cooper et al. (57)	1984	5–15	Grass	Aqueous	4 months	No data	22	22	Rhinitis**	NS	No severe 8 R 1 A
Taudorf et al. (58)	1985	11–44	Grass	Enteric-coated	6 months	MD 50000 PNU CD 8.9 mio PNU	25	27	Rhinitis	NS	No severe
Möller et al. (59)	1986	9–17	Birch	Enteric-coated	10 months	MD 1.4 mio BU	14	16	Rhinitis	S <0.04 D NS	No severe
Mosbech et al. (60)	1987	15–38	Grass	Enteric-coated	1 year	MD 10 mio BU	24	27	Rhinitis	NS	5 U
Taudorf et al. (61)	1987	16–47	Birch	Enteric-coated	18 months	MD 1.2 mio BU CD 280 mio BU	18	21	Rhinitis**	Nose S NS Eye S <0.05 D NS	1 U 9 GI
Oppenheimer et al. (62)	1994	24–72	Cat	Aqueous	3 months	MD 33333 AU CD 2580000 AU	23	25	Rhinitis**	NS	2 severe?
Giovane et al. (26)	1994	3–13	Mite	Aqueous	3 years	MD 1500 TU CD 800000 TU	10	8	Rhinitis**	R ¹ NS R ² <0.05 R ³ <0.05 A ¹ NS A ² NS A ³ <0.05	No
van Deusen et al. (64)	1997	19–49	Ragweed	Encapsulated	14 weeks	MD 24 µg Amb a 1	12	11	Rhinitis	NS	No severe
Litvin et al. (65)	1997	21–50	Ragweed	Encapsulated	16 weeks	MD 24 µg Amb a 1 CD 659 µg Amb a 1	20	21	Rhinitis	NS	No severe

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

**Asthmatic patients not excluded.

Abbreviations – IT: immunotherapy; PI: placebo; A: asthma; GI: gastrointestinal; R: rhinitis; U: urticaria; S: symptom score; D: drug score; NS: nonsignificant.

¹1st year; ²2nd year; ³3rd year.

value, but a delayed asthmatic reaction (below 75% of pretreatment value) was also induced in some patients.

Paraclinical effects

In vivo. In the study showing clinical efficacy, no effect was observed on methacholine sensitivity, but there was a significant increase in the bronchial tolerance of allergen in the actively treated group (52). Skin test sensitivity was unchanged.

In vitro. Significant increase in total IgG, IgG1, and IgG4 levels, but no change in allergen-specific IgE and lymphocyte subpopulations during the treatment period, was reported in one study (52), while these parameters showed no change in the other study (51).

Conclusion: bronchial immunotherapy

The clinical efficacy of bronchial immunotherapy is not sufficiently documented (Table 5), and there is concern about potentially serious immediate and delayed side-effects.

Oral immunotherapy

Clinical documentation of efficacy

The efficacy of oral immunotherapy has been investigated in 13 studies. Four studies were excluded from the survey because too few patients were included (53, 54), data were only presented as an abstract (55), or no efficacy data were presented (56). Some characteristics of the nine studies included are summarized in Table 3 (26, 57–62, 64, 65).

Seven out of nine studies did not show any efficacy (Table 3). A reduction in symptom/medication scores was reported in two studies, using birch and mite allergens, respectively (26, 59). In a third study in which efficacy was claimed, the only significant difference between the treated group and the placebo group was a decrease in eye symptoms in the treated group (61). Since no significant difference was observed in nasal symptoms and the use of rescue drugs, efficacy was only marginal in relation to the inconvenience for the patients and the cost of treatment, since very high doses of allergen were used. In contrast to those on birch pollen (59), studies using grass pollen in enteric-coated capsules have not shown efficacy. The reason could not be related to differences in degradation of the major birch- and grass-pollen allergens, as these are both degraded rapidly by duodenal juice *in vitro* (63). In the only study showing strong clinical efficacy, a fivefold higher dosage than in subcutaneous immunotherapy of an aqueous extract of house-dust mite was used for 3 years (26). The possible beneficial effect of a prolonged treatment was reflected in a gradual improvement in symptom/medication scores. No differences in rhinitis symptoms were observed during the first year of treatment, while during the second and third years, disease severity was significantly reduced. Asthma symptoms were not improved until the third year. In all, 126 actively treated patients were included in the negative studies, and 42 patients in the studies indicating efficacy (Table 5).

Safety

Oral administration of high doses of allergen may induce systemic side-effects, some of which may be severe. In one study involving 22 patients, eight cases of rhinitis and one case of asthma were reported. However, the incidence was similar in the placebo group (57). In a study involving 24 patients, five cases of urticaria were observed (60), and in another study involving 18 patients, one case of urticaria (61). In a study of oral immunotherapy with cat allergen, two patients had severe side-effects which were probably not related to treatment (62). Insignificant gastrointestinal side-effects appeared in a study using a maximum dose tenfold higher than that used in subcutaneous immunotherapy (61).

Paraclinical effects

In vivo. In most studies, there were no changes in nasal provocation tests or skin sensitivity. In one study, a reduction in nasal challenge sensitivity was

observed (59), and two other studies reported a reduced conjunctival challenge test (26, 61).

In vitro. A significant increase in allergen-specific IgE antibody levels and blunting of the postseasonal increase were observed after 1 month of oral immunotherapy (59, 66). Furthermore, the allergen-specific IgG levels (but not IgA antibody levels) increased in the actively treated compared to placebo-treated groups. Increasing IgG1 and IgG4 antibody levels were observed during treatment in the mite study (26), and of IgG and IgG4 in a ragweed study (64). In another ragweed study (65), low levels of nasal IgA antibodies appeared. These observations have not been substantiated in other studies (53, 58, 60, 62), or the effects were not studied (56, 57).

Conclusion: oral immunotherapy

The documentation of the clinical efficacy and safety of oral immunotherapy is not adequate for its recommendation for clinical use (Table 5). Only two studies indicate clinically relevant efficacy with either birch pollen administered in enteric-coated capsules or after treatment with aqueous mite extract for at least 1 year.

Sublingual immunotherapy

Clinical documentation of efficacy

Sublingual immunotherapy can be divided into the exclusively sublingual form, i.e., allowing only the interaction of the extract on the oral mucous membranes and then having the subject spit out the extract (sublingual-spit), and the combined sublingual/oral treatment, in which the extract, after being retained sublingually, is subsequently swallowed (sublingual-swallow).

Sublingual immunotherapy may be performed as either preseasonal or perennial treatment. The allergens are dispensed as aqueous solutions and are self-administered. Extracts are administered daily or on alternate days during the induction phase, and weekly or twice a week during maintenance treatment (schedules may vary slightly from one manufacturer to another).

Sublingual immunotherapy has been investigated in 13 studies. Seven of the studies were excluded for the following reasons: the use of low-allergen doses and not providing symptom/medication scores (67, 68); not supplying data on allergen doses (69); not including a placebo group (70); no data on medication scores and methodological problems (71); including too few patients (72); and an open study design (73). Some characteristics of

Table 4. PCDB sublingual immunotherapy studies

Author(s) and year of publication	Age range (years)		Allergen	Type of extract	Duration	Maximum dose*	No. patients			Significance <i>P</i>	Systemic side-effects
							IT	PI	Disease		
Tari et al. (74)	1990	5–12	<i>D. pteronyssinus</i>	Aqueous	18 months	MD 375 STU	30	28	Rhinitis Asthma	R <0.001 C NS A <0.001	32 episodes 3 U 3 severe A
Sabbah et al. (75)	1994	13–51	5 grasses	Aqueous (glycerin)	17 weeks	MD 100 IR CD 4500 IR	29	29	Rhinitis	<0.05	10 episodes No severe
Feliziani et al. (76)	1995	14–48	5 grasses	Aqueous (glycerin)	3½ months	MD 25 BU	18	16	Rhinitis**	<0.01	No severe
Troise et al. (77)	1995	17–60	<i>Parietaria</i>	Aqueous (glycerin)	10 months	MD 1.25 BU CD 105 BU	15	16	Rhinitis	<0.05	1 episode No severe
Hirsch et al. (78)	1997	6–16	<i>D. pteronyssinus</i> (glycerin)	Aqueous	12 months	MD 3.75 µg Der p 1 CD 570 µg Der p 1	15	15	Rhinitis Asthma	R NS A S <0.05 A D NS	1 episode No severe
Passalacqua et al. (79)	1998	15–46	<i>D. pteronyssinus</i> <i>D. farinae</i>	Allergoid	24 months	MD 1000 AU	10	9	Rhinitis**	<0.001	No severe

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

**Asthmatic patients not excluded.

***Abbreviations – IT: immunotherapy; PI: placebo; A: asthma; C: conjunctivitis; R: rhinitis; U: urticaria; S: symptom score; D: drug score; NS: nonsignificant.

Table 5. Clinical efficacy of local immunotherapy based on PCDB studies

	Efficacy		No efficacy	
	No. of studies		No. of studies	
Nasal immunotherapy	13		1	
	No. of patients	Children	No. of patients	Children
	252	19	22	0
Bronchial immunotherapy	No. of studies		No. of studies	
	1		1	
	No. of patients	Children	No. of patients	Children
	14	?	11	?
Oral immunotherapy	No. of studies		No. of studies	
	3		6	
	No. of patients	Children	No. of patients	Children
	42	24	126	22?
Sublingual immunotherapy	No. of studies		No. of studies	
	6		0	
	No. of patients	Children	No. of patients	Children
	117	45	0	0

the studies included in this survey (74–79) are given in Table 4. Efficacy was reported only with the sublingual-swallow method using extracts of mite allergens (74, 78, 79), grass pollen (75, 76), and *Parietaria* (77). In total, 117 patients were treated with active allergen extracts in the studies showing efficacy.

Safety

No systemic side-effects in adults have been reported in sublingual immunotherapy; in most studies, there was no difference between actively

treated and placebo-treated subjects. In the first study performed in children suffering from rhinitis and asthma, significant side-effects included 32 episodes of systemic reactions (three patients with urticaria, 11 cases of asthma including three severe, and four patients with diarrhea) (74). The severity of side-effects in six patients (20%) in this study corresponded to grade III of the EAACI recommendations (systemic non-life-threatening reactions) (16). In the other study in children, one patient developed symptoms of weakness and one episode of bronchial obstruction (78).

Paraclinical effects

In vivo. A significant reduction in skin test sensitivity and an increased nasal provocation threshold dose were recorded in the actively treated patients in one study (74), while there were no important changes in bronchial challenge sensitivity to allergen and methacholine. In another study, a significant increase in the tolerated dose in nasal challenge was reported (77), while the other two studies showed no changes in any of the investigated parameters (75, 76).

In vitro. Allergen-specific IgE antibody levels were not affected by sublingual immunotherapy in most studies (71, 72, 74, 77), but increased significantly in actively treated subjects in one study (78). Allergen-specific IgG antibody levels increased significantly in actively treated patients in one study (74), but not in another study (77). Significant increases in IgG subclasses have been observed for IgG1 (74), IgG4 (74, 77), and the IgG4/IgG1 ratio (74). Conjunctival challenge showed a significant reduction in the number of eosinophils and ICAM-1-positive cells over a 2-year treatment (79).

Conclusion: sublingual immunotherapy

Sublingual immunotherapy has been shown to reduce rhinitis symptoms and/or medication needs in six PCDB studies, using grass pollen extract in two studies (75, 76), *Dermatophagoides pteronyssinus* in three studies (74, 78, 79), and *Parietaria* in one study (77). The allergen doses administered were 5–20 times higher than in subcutaneous immunotherapy. Two of the studies were carried out in children, and in one of these, systemic side-effects were common (74). In adults, side-effects do not appear to represent a significant problem. The documentation of efficacy is based on a limited number of studies including around 120 patients (Table 5).

Efficacy of local immunotherapy compared to injection immunotherapy

Since no appropriate PCDB, double-dummy studies have been performed, it is difficult to compare the efficacy of local and injection immunotherapy. However, there are some mostly open studies comparing injection and local immunotherapy (80–86). In one of the studies, local nasal immunotherapy for 24 months showed no significant reduction in symptoms, in contrast to injection immunotherapy, which was effective (85). In two

studies, the efficacy of bronchial immunotherapy was compared to injection immunotherapy (83, 84). One of the studies indicated that bronchial immunotherapy was superior to injection immunotherapy in reducing bronchial hyperresponsiveness (84), while the other study observed the reverse (83). Oral and subcutaneous immunotherapies have been compared in three studies. In two of these, oral immunotherapy in children was inferior to injection immunotherapy (80, 81), and in one, performed in children, the efficacy was similar (82). In a study of mite immunotherapy, subcutaneous immunotherapy was more effective than sublingual immunotherapy (85), whereas in an open study comparing injection and sublingual immunotherapy in *Alternaria tenuis*-allergic patients, a significantly better efficacy of sublingual immunotherapy (60% mean improvement in patients' assessment vs 45% in subcutaneous immunotherapy) was shown (86). In a recently published double-blind, double-dummy study comparing the efficacy of sublingual and injection immunotherapy, a decrease in total symptom-medication score of 50% from the pre-treatment monitoring grass-pollen season was demonstrated in both groups (87).

A study investigating the effect of initial parenteral priming by injections and extension treatment with either placebo or oral immunotherapy showed a significant reduction in rhinitis symptoms in actively treated patients, but there was no reduction in drug scores (88). However, another comparable study did not substantiate the efficacy of oral grass-pollen "boosters" (89).

Long-term efficacy

The long-term efficacy of local immunotherapy has not been sufficiently studied. Only one paper (50) has investigated the long-term efficacy after two preseasonal courses of nasal immunotherapy with *Parietaria*, and this study did not document any persistent efficacy after terminating immunotherapy. As long-term efficacy and preventive aspects are the major aims of injection immunotherapy (16), the possible advantages of local immunotherapy performed over several years should be investigated.

Conclusions

Allergy diagnosis and treatment, including local immunotherapy, should be in the hands of physicians adequately trained in allergology. The evaluation of diagnostic tests, the appropriate education of patients in allergen avoidance, and the possible indications for immunotherapy call for an experienced, multidisciplinary team (16). Widespread use

of local immunotherapy without proper allergologic supervision should be discouraged because efficacy and side-effects are less documented than with subcutaneous immunotherapy. Improper use of local immunotherapy will result in poor management of allergic disease (treatment failures), which in turn will worsen the reputation of specific allergy treatment. Regular controls should be carried out by the specialist undertaking the evaluation of the efficacy of the treatment by appropriate methods.

Bronchial and oral immunotherapy are not recommended for clinical practice, except as part of controlled studies, due to insufficient documentation of efficacy and the risk of severe side-effects (bronchial immunotherapy).

Special recommendations for adults

Local nasal immunotherapy may be indicated in carefully selected adult patients with rhinitis caused by pollen allergy (grass, ragweed, birch, and *Parietaria*). Efficacy in mite allergy has been documented in only one study. Potential candidates for local nasal immunotherapy include patients who cannot be properly controlled by conventional pharmacotherapy (16), those who have presented with systemic reactions during injection immunotherapy, or those who show poor compliance and refuse injections. However, the potential risk of inducing asthma represents a relative contraindication, as the allergen extracts are self-administered without the supervision of a physician. Patients have to be carefully informed of the risk and what to do if systemic side-effects should occur.

Sublingual (swallow) immunotherapy with pollen extracts (grass and *Parietaria*) and mite has shown efficacy in six PCDB studies in patients suffering primarily from rhinitis, although the documentation was based only on nearly 120 patients. The documentation in asthma is inadequate. The overall safety has been documented in adults. Further studies with standardized extracts are needed to define better the most appropriate patients for this form of therapy, the optimal allergen dose, and its effectiveness as compared to conventional injection immunotherapy.

Special recommendations for children

Nasal and sublingual (swallow) immunotherapy is not indicated for normal clinical use in children. More studies are needed until these forms of local immunotherapy can be recommended in children for general use as an alternative to subcutaneous immunotherapy. More data have to be obtained about local immunotherapy from controlled studies

in children documenting the degree of efficacy, dose regimens, top doses, safety aspects during long-term treatment, and long-term efficacy.

Directions for future research

- The clinical documentation of the efficacy of local immunotherapy (nasal and sublingual) is still based on a limited number of studies and, in most cases, a rather short treatment period, and further substantiation of the applicability in daily clinical practice is needed.
- The efficacy of local immunotherapy is based mostly on adult patients. Its usefulness in children needs to be documented by proper studies; i.e., a placebo-controlled, double-blind design.
- The magnitude of the clinical efficacy of local immunotherapy and its duration of effect, as well as the secondary preventive capacity, requires further investigation.
- The efficacy and side-effects of local immunotherapy should be compared with injection immunotherapy in placebo-controlled, double-blind, double-dummy studies.
- Cost-effectiveness studies of local and injection immunotherapy are needed.
- The optimal allergen dose in relation to efficacy and side-effects, and the duration of treatment to maintain lasting efficacy should be investigated.
- The compliance of patients undergoing local immunotherapy and whether they prefer a specific treatment to pharmacologic intervention should be clarified.
- Institution of local immunotherapy early in the course of allergic disease (children) may possibly modify the natural progression of disease. This prospect should be explored.
- Elucidating the mechanisms of local immunotherapy might improve the applicability of this special treatment.

References

1. Watkins AD. The role of alternative therapies in the treatment of allergic diseases. *Clin Exp Allergy* 1994;24:813-25.
2. Holt PG, Batty JE, Turner KJ. Inhibition of specific IgE responses in mice by pre-exposure to inhaled antigen. *Immunology* 1981;42:409-17.
3. Holt PG, Sedgewick JD. Suppression of IgE responses following inhalation of antigen. A natural homeostatic mechanism which limits sensitization to aeroallergens. *Immunol Today* 1987;8:14-26.
4. Holt PG, Britten D, Sedgewick JD. Suppression of IgE responses by antigen inhalation: studies on the role of genetic and environmental factors. *Immunology* 1987;60:97-102.
5. Holt PG, McMenamin C. Defence against allergic sensi-

- zation in healthy lung: the role of inhalation tolerance. Clin Exp Allergy 1989;19:55-62.
6. Mowart AM. The regulation of immune response to dietary proteins. Immunol Today 1987;8:93-6.
7. Holt PG, Vines J, Britten D. Sublingual allergen administration. I. Selective suppression of IgE production in rats by high allergen doses. Clin Allergy 1988;18:229-34.
8. Chen Y, Kuchroo VK, Inobe J, Hafler DA, Weiner HL. Regulatory T cell clones induced by oral tolerance: suppression of autoimmune encephalomyelitis. Science 1994; 265: 1237-40.
9. Eriksson K, Ahlfors E, George-Chandy A, Kaiserlian D, Czerkinsky C. Antigen presentation in the murine oral epithelium. Immunology 1996;88:147-52.
10. van-Wilsem EJ, van-Hoogstraten IM, Breve J, Scheper RJ, Kraal G. Dendritic cells of the oral mucosa and the induction of oral tolerance. A local affair. Immunology 1994;83:128-32.
11. Hasseus B, Dahlgren U, Bergenholtz G, Jontell M. Antigen presenting capacity of Langerhans cells from rat oral epithelium. J Oral Pathol Med 1995;24:56-60.
12. Manetti R, Parronchi P, Giudizi MG, et al. Natural killer cell stimulatory factor (interleukin 12 [IL-12]) induces T helper type 1 (Th1)-specific immune responses and inhibits the development of IL-4-producing Th cells. J Exp Med 1993;177:1199-1204.
13. Macatania SE, Hosken NA, Litton M, et al. Dendritic cells produce IL-12 and direct the development of Th1 cells from naive CD4+ T cells. J Immunol 1995;154:5071-9.
14. Bagnasco M, Mariani G, Passalacqua G, et al. Absorption and distribution kinetics of the major *Parietaria judaica* (Par j 1) allergen administered by noninjectable routes to healthy human beings. J Allergy Clin Immunol 1997;100: 122-9.
15. Cohn JR, Pizzi A. Determinants of patient compliance with allergen immunotherapy. J Allergy Clin Immunol 1993;91: 734-7.
16. Malling H-J, Weeke B. Immunotherapy. EAACI Position paper. Allergy 1993;38 Suppl 14:9-45.
17. Hejjaoui J, Ferrando R, Dhiwert H, Michel FB, Bousquet J. Systemic reactions occurring during immunotherapy with standardized pollen extracts. J Allergy Clin Immunol 1992;89:925-33.
18. Tabar AI, Garcia BE, Rodriguez A, Olaguibel JM, Muro MD, Quirce S. A prospective safety-monitoring study of immunotherapy with biologically standardized extracts. Allergy 1993;48:450-3.
19. Curtis HH. The immunizing cure of hay fever. Med News (NY) 1900;77:16-18.
20. Black JH. The oral administration of pollen. J Lab Clin Med 1927;12:1156-9.
21. Feinberg SM, Foran FL, Lichtenstein MR. Oral pollen therapy in ragweed pollinosis. J Am Med Assoc 1940;115: 23-9.
22. Committee on the Safety of Medicine. CSM update. Desensitizing vaccines. BMJ 1986;293:948.
23. Greenberg MA, Kaufman CR, Gonzales GE. Late and immediate systemic allergic reactions to inhalant allergen immunotherapy. J Allergy Clin Immunol 1986; 77:865-70.
24. Lockey RF, Benedict LM, Turkeltaub PC, Bukantz SC. Fatalities from immunotherapy and skin testing. J Allergy Clin Immunol 1987;79:660-77.
25. Dreborg S, Frew A, editors. Allergen standardization and skin tests. Allergy 1993;48 Suppl 14:49-82.
26. Giovane AL, Bardare M, Passalacqua G, et al. A three-year double-blind placebo-controlled study with specific oral immunotherapy to *Dermatophagoides*: evidence of safety and efficacy in paediatric patients. Clin Exp Allergy 1994;24:53-9.
27. Malling H-J. New ideas in allergen-specific immunotherapy. Am J Rhinol 1990;4:155-8.
28. Johansson SGO, Deuschl H, Zetterström O. Use of glutaraldehyde-modified timothy grass pollen extract in nasal hyposensitisation treatment of hay fever. Int Arch Allergy Appl Immunol 1979;60:447-60.
29. Nickelsen JA, Goldstein S, Mueller U, Wypych J, Reisman RE, Arbesman CE. Local intranasal immunotherapy for ragweed allergic rhinitis. I. Clinical response. J Allergy Clin Immunol 1981;68:33-40.
30. Welsh PW, Zimmermann EM, Yunginger JW, Kern EB, Gleich GJ. Preseasonal intranasal immunotherapy with nebulized short ragweed extract. J Allergy Clin Immunol 1981;67:237-42.
31. Schumacher MJ, Pain MC. Intranasal immunotherapy and polymerized grass pollen allergens. Allergy 1982;37:241-8.
32. Georgitis JW, Reisman RE, Clayton WF, Mueller UR, Wypych JI, Arbesman CE. Local intranasal immunotherapy for grass-allergic rhinitis. J Allergy Clin Immunol 1983;71:71-6.
33. Georgitis JW, Clayton WF, Wypych JI, Barde SH, Reisman RE. Further evaluation of local intranasal immunotherapy with aqueous and allergoid grass extracts. J Allergy Clin Immunol 1984;74:694-700.
34. Andri L, Senna GE, Betteli C, et al. Local nasal immunotherapy in allergic rhinitis to *Parietaria*. A double-blind controlled study. Allergy 1992;47:318-23.
35. Andri L, Senna G, Betteli C, Giovanni S, Andri G, Falagiani P. Local nasal immunotherapy for *Dermatophagoides*-induced rhinitis: efficacy of a powder extract. J Allergy Clin Immunol 1993;91:987-96.
36. Passalacqua G, Albano M, Ruffoni S, et al. Nasal immunotherapy to *Parietaria*: evidence of reduction of local inflammation. Am J Respir Crit Care Med 1995;152:461-6.
37. D'Amato G, Lofefalo G, Liccardi G, Cazzola M. A double-blind, placebo-controlled trial of local nasal immunotherapy in allergic rhinitis to *Parietaria* pollen. Clin Exp Allergy 1995;25:141-8.
38. Andri L, Senna G, Andri G, et al. Local nasal immunotherapy for birch allergic rhinitis with extract in powder form. Clin Exp Allergy 1995;25:1092-9.
39. Andri L, Senna G, Betteli C, et al. Local nasal immunotherapy with extract in powder form is effective and safe in grass-pollen rhinitis. A double blind study. J Allergy Clin Immunol 1996;97:34-41.
40. Cirila AM, Sforza N, Roffi GP, et al. Preseasonal intranasal immunotherapy in birch-alder allergic rhinitis. A double-blind study. Allergy 1996;51:299-305.
41. Bardare M, Zani G, Novembre E, Vierucci A. Local nasal immunotherapy with a powder extract for grass pollen induced rhinitis in pediatric ages: a controlled study. J Invest Allergol Immunol 1996;6:359-63.
42. Metha SB, Morrison Smith J. Nasal hyposensitization and hay fever. Clin Allergy 1975;5:279-84.
43. Georgitis JW, Nickelsen JA, Wypych JI, Kane JH, Reisman RE. Local nasal immunotherapy. Efficacy of low-dose aqueous ragweed extract. J Allergy Clin Immunol 1985;75: 496-500.
44. Georgitis JW, Nickelsen JA, Wypych JI, Barde SH, Clayton WF, Reisman RE. Local intranasal immunotherapy with high-dose polymerized ragweed extract. Int Arch Allergy Appl Immunol 1986;81:170-3.
45. Ariano R, Panzani RC, Chiapella M, Augeri G, Falagiani P. Local immunotherapy of seasonal allergic rhinitis in children due to *Parietaria* pollen. A preliminary report. Pediatr Asthma Allergy Immunol 1993;7:227-37.

46. Welsh PW, Butterfield JH, Yunginger W, Agarwal MK, Gjeich GJ. Allergen controlled study of intranasal immunotherapy for ragweed hay fever. *J Allergy Clin Immunol* 1983;71:454-60.
47. Gasparini A, Di Franco G, Malavenda A. Preliminary evaluation of the nasal local specific immunotherapy in mite-sensitive respiratory patients. *Perspect ENT Immunol* 1991;5:29-33.
48. Filiaci F, Zambetti G, Lo Vecchio A. Specific local immunotherapy with macronized dust in the treatment of seasonal allergic rhinopathy caused by Gramineae. *Perspect ENT Immunol* 1989;3:170-6.
49. Gaglani B, Borish L, Bartelson BL, Buchmeier A, Keller L, Nelson HS. Nasal immunotherapy in weed-induced rhinitis. *Ann Allergy Asthma Immunol* 1997;79:259-65.
50. Passalacqua G, Albano M, Pronzato C, et al. Long-term follow-up of nasal immunotherapy to *Parietaria*: clinical and local immunological effects. *Clin Exp Allergy* 1997;27:904-8.
51. Crimi E, Voltolini S, Troise C, et al. Local immunotherapy with *Dermatophagoides* extract in asthma. *J Allergy Clin Immunol* 1991;87:721-8.
52. Tari MG, Mancino M, Monti G. Immunotherapy by inhalation of allergen in powder in house dust allergic asthma: a double-blind study. *J Investig Allergol Clin Immunol* 1992;2:59-67.
53. Taudorf E, Weeke B. Orally administered grass pollen. *Allergy* 1983;38:561-4.
54. Björkstén B, Möller C, Broberger U, et al. Clinical and immunological effects of oral immunotherapy with a standardized birch pollen extract. *Allergy* 1986;41:290-5.
55. Creticos PS, Naclerio RM, Adkinson F, Norman PS. Efficacy, safety and kinetics of oral ragweed immunotherapy in the treatment of seasonal allergic rhinitis. *J Allergy Clin Immunol* 1990;85:165.
56. Leng X, Fu YX, Ye ST, Duan SQ. A double-blind trial of oral immunotherapy for *Artemisia* pollen asthma with evaluation of bronchial response to pollen allergen and serum-specific IgE antibody. *Ann Allergy* 1990;64:27-31.
57. Cooper PJ, Darbyshire J, Nunn AJ, Warner JO. A controlled trial of oral hyposensitization in pollen asthma and rhinitis in children. *Clin Allergy* 1984;14:541-50.
58. Taudorf E, Laursen LC, Djurup R, et al. Oral administration of grass pollen to hay fever patients. An efficacy study in oral hyposensitization. *Allergy* 1985;40:321-35.
59. Möller C, Dreborg S, Lanner Å, Björkstén B. Oral immunotherapy of children with rhinoconjunctivitis due to birch pollen allergy. A double blind study. *Allergy* 1986;41:271-9.
60. Mosbech H, Dreborg S, Madsen F, et al. High dose grass pollen tablets used for hyposensitization in hay fever patients. A one-year double blind placebo controlled study. *Allergy* 1987;42:451-5.
61. Taudorf E, Laursen LC, Lanner Å, et al. Oral immunotherapy in birch pollen hay fever. *J Allergy Clin Immunol* 1987;80:153-61.
62. Oppenheimer J, Areson JG, Nelson HS. Safety and efficacy of oral immunotherapy with standardized cat extract. *J Allergy Clin Immunol* 1994;93:61-7.
63. Einarsson R, Renck B, Taudorf E. *In vitro* studies of degradation of birch and timothy pollen allergen preparations by human duodenal juice. *Allergy* 1988;43:469-72.
64. van Deusen MA, Angelini BL, Cordoro KM, Seiler BA, Wood L, Skoner DP. Efficacy and safety of oral immunotherapy with short ragweed extract. *Ann Allergy Asthma Immunol* 1997;78:573-80.
65. Litwin A, Flanagan M, Entis G, et al. Oral immunotherapy with short ragweed extract in a novel encapsulated preparation: a double-blind study. *J Allergy Clin Immunol* 1997;100:30-8.
66. Taudorf E, Laursen L, Lanner A, Björkstén B, Dreborg S, Weeke B. Specific IgE, IgG, and IgA antibody response to oral immunotherapy in birch pollinosis. *J Allergy Clin Immunol* 1989;83:589-94.
67. Scadding K, Brostoff J. Low dose sublingual therapy in patients with allergic rhinitis due to dust mite. *Clin Allergy* 1986;16:483-91.
68. Reilly D, Taylor MA, Beattie NGM, et al. Is evidence for homeopathy reproducible? *Lancet* 1994;344:1601-6.
69. van Niekerk CH, De Wet JI. Efficacy of grass-maize pollen oral immunotherapy in patients with seasonal hay fever: a double blind study. *Clin Allergy* 1987;17:507-13.
70. Feliziani V, Marfisi RM, Parmiani S. Rush immunotherapy with sublingual administration of grass allergen extract. *Allergol Immunopathol (Madr)* 1993;21:173-8.
71. Nelson HS, Oppenheimer J, Vatsia GA, Bucheimer A. A double blind placebo controlled evaluation of sublingual immunotherapy with standardized cat extract. *J Allergy Clin Immunol* 1993;92:229-36.
72. Casanovas M, Guerra F, Moreno C, Miguel R, Maranon F, Daza JC. Double blind placebo controlled clinical trial of preseasonal treatment with allergenic extracts of *Olea europaea* pollen administered sublingually. *J Investig Allergol Clin Immunol* 1994;4:305-14.
73. D'Ambrosio FP, Ricciardi L, Isola S, Puccinelli P, Musarra A. Rush sublingual immunotherapy in *Parietaria* allergic patients. *Allergol Immunopathol (Madr)* 1996;24:146-51.
74. Tari MG, Mancino M, Monti G. Efficacy of sublingual immunotherapy in patients with rhinitis and asthma due to house dust mite. A double blind study. *Allergol Immunopathol (Madr)* 1990;18:277-84.
75. Sabbah A, Hassoun S, Le Sellin J, André C, Sicard H. A double blind placebo controlled trial by the sublingual route of immunotherapy with a standardized grass pollen extract. *Allergy* 1994;49:309-13.
76. Feliziani V, Lattuada G, Parmiani S, Dall'Aglio PP. Safety and efficacy of sublingual rush immunotherapy with grass allergen extracts. A double blind study. *Allergol Immunopathol (Madr)* 1995;23:224-30.
77. Troise C, Voltolini S, Canessa A, Pecora S, Negrini AC. Sublingual immunotherapy in *Parietaria* pollen induced rhinitis: a double blind study. *J Investig Allergol Clin Immunol* 1995;5:25-30.
78. Hirsch T, Sahn M, Leupold W. Double-blind placebo-controlled study of sublingual immunotherapy with house dust mite extract (D.pt.) in children. *Pediatr Allergy Immunol* 1997;8:21-7.
79. Passalacqua G, Albano M, Fregonese L, et al. Randomised controlled trial of local allergoid immunotherapy on allergic inflammation in mite-induced rhinoconjunctivitis. *Lancet* 1998;351:629-32.
80. Reben W, Puttonen E, Maasch HJ, Stix E, Wahn U. Clinical and immunological response to oral and subcutaneous immunotherapy with grass pollen extracts. A prospective study. *Eur J Pediatr* 1982;138:341-4.
81. Palacios AS, Medina FS, Rua-Figueroa AL, Millares CB, Santos SR, Marrero JAG. Comparative clinical-immunological study of oral and subcutaneous immunotherapy in children with extrinsic bronchial asthma. *Allergol Immunopathol (Madr)* 1989;17:323-9.
82. Urbanek R, Bürgelin KH, Kahle W, Wahn U. Oral immunotherapy with grass pollen in enterosoluble capsules. *Eur J Pediatr* 1990;149:545-50.
83. Moscato G, Rossi G, Dellabianca A, Pisati A, Vinci G,

- Biale C. Local immunotherapy by inhalation of a powder extract in asthma due to house dust mite *Dermatophagoides pteronyssinus*: a double-blind comparison with parenteral immunotherapy. *J Investig Allergol Clin Immunol* 1991; 1:383-94.
84. Corbetta L, Pesiri P, Ferro G, Mander A. Improvement of fog and exercise induced asthma after local and subcutaneous immunotherapy in mite asthma. *Allergol Immunopathol (Madr)* 1992;20:60-6.
85. Piazza I, Bizzaro N. Humoral response to subcutaneous, oral, and nasal immunotherapy for allergic rhinitis due to *Dermatophagoides pteronyssinus*. *Ann Allergy* 1993;71:461-9.
86. Bernadis P, Agnoletto M, Puccinelli P, Parmiani S, Pozzan M. Injective versus sublingual immunotherapy in *Alternaria tenuis* allergic patients. *J Investig Allergol Clin Immunol* 1996;6:55-62.
87. Quirino T, Iemoli E, Siciliani E, Parmiani S, Milazzo F. Sublingual versus injective immunotherapy in grass pollen allergic patients: a double blind (double dummy) study. *Clin Exp Allergy* 1996;26:1253-61.
88. Horak F, Wheeler AW. Oral hyposensitisation with enteric-coated allergens as extension therapy following a basic subcutaneous course of injections. *Int Arch Appl Immunol* 1987;84:74-8.
89. Trede NS, Urbanek R. Combination of parenteral and oral immunotherapy in grass pollen-allergic children. A double-blind controlled study of clinical and immunological efficacy. *Allergy* 1989;44:272-80.

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