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Immunotherapy as an effective tool in allergy treatment

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Immunotherapy in the treatment of allergic diseases

Allergen-specific immunotherapy and allergen reduction are the only interventions in allergic diseases with the potential to reduce symptoms in the long term. The clinical value of specific immunotherapy in the treatment of allergic diseases has been questioned for the last 20 years in spite of substantial documentation of efficacy. In the evaluation of the relative advantages of immunotherapy compared to exclusively pharmacologic treatment of allergic diseases, several aspects such as the magnitude of efficacy (short term and long term), practical applicability, side-effects, and costs and durations are important factors. The present review will focus on the magnitude of efficacy and side-effects.

In Hymenoptera venom allergies, immunotherapy represents the only curative treatment, and the only real option for protection of patients against life-threatening, sting-induced anaphylaxis (1). Drug treatment in allergic rhinitis and asthma is widely used and is clinically effective. However, pharmacotherapy has limitations, as its long-term efficacy in relation to preventing the development of chronic, irreversible destruction of mucous membranes is almost unknown.

Estimation of clinical efficacy

Allergic patients suffer from the clinical manifestations of the disease; i.e., rhinitis, conjunctivitis,

and asthma. Consequently, the only parameters indicating efficacy of a treatment are reduction in symptoms and/or drug intake (2). 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 morbidity of allergic disorders (3). This can be estimated either by investigating the reduction in symptom/medication scores in relation to a pre-treatment observation period (a season for seasonal allergies or a sufficiently long comparative period in the case of perennial allergies), or by comparing matched groups treated by active immunotherapy and by placebo. Changes in immunologic parameters and challenge tests may be of interest in elucidating mechanisms, but cannot replace the clinical evaluation (2). The magnitude of efficacy is rarely dealt with in clinical studies. Usually, only data on the statistical significance are provided. Of course, a statistically significant difference between the active group and the placebo group is critical for the documentation of efficacy, but *P* values do not, *per se*, guarantee the applicability of a specified treatment. A 10% reduction in drug intake may be statistically significant, but clinically irrelevant for the patient. As most DBPC (double-blind, placebo-controlled) immunotherapy studies provide longitudinal data on symptom/medication scores, the percentage reduction of symptom/medication scores in the actively treated group as compared with the placebo group could be used to calculate the magnitude of clinical efficacy.

Efficacy is estimated by mean symptom/medication scores or by measuring the AUC (area under the curve) of symptom/medication scores as compared with time for the active group and the placebo group, respectively. The magnitude of improvement induced by active treatment is calculated as the percent reduction of disease severity compared with placebo treatment (Fig. 1). In combination with the statistical evaluation of the difference between active and placebo treatment, this gives useful information on the degree of efficacy. This concept represents a very conservative estimate of efficacy, as only the additional effect, compared with the possible beneficial effect of placebo treatment (optimal care and adjustment of drugs), is taken into consideration. In daily life, this estimate gives a realistic depiction of the applicability of the treatment.

An arbitrary grading of the magnitude of efficacy could be as follows:

- 1) no efficacy (symptom/medication scores improved by <30%)
- 2) low efficacy (improvement 30–44%)
- 3) moderate efficacy (improvement 45–59%)
- 4) high efficacy (improvement of $\geq 60\%$).

Of course, this grading is arbitrary and controversial, but, in daily clinical practice, it is more operational than statistical *P* values. Compared with the efficacy of drug treatment of allergic diseases, the grading seems sensible. A symptom/medication score amelioration of <30% does not seem to justify a treatment involving a potential risk of side-effects, and will probably not be considered worthwhile by patients. Most studies provide data on a combined symptom/medication score and do not involve logistic problems. The interpretation of studies presenting separate data on symptom scores and medication scores may be distorted, due to the relative "weight" of these parameters. Improvement in symptoms and no change in drug scores, or vice versa, still represent an improvement of the total disease severity. Problems arise when symptoms and drug score show discordant changes. In these cases, it must be concluded that no significant and indisputable clinical efficacy has been induced by the treatment.

Inclusion of studies for the evaluation of clinical efficacy

The documentation of the clinical effect of injection immunotherapy is based on 43 DBPC rhinitis studies and 25 DBPC (16 providing symptom/medication scores) asthma studies, published since

1980, obtained by literature search (MEDLINE); it includes only peer-reviewed full papers in English. The reason for including only studies published after 1980 is that this was the period of a more general use of adequately standardized extracts. Allergen extracts are provided by various allergen producers, who apply different methods of standardization, and no attempts to validate the quality of the extracts used have been made. It is assumed that international guidelines for allergen standardization and manufacturing have been followed in most studies (4). Different formulations of allergen extracts have been used. Most studies use native aqueous or slow-release extracts, but some studies investigate the efficacy of chemically or physically modified allergoids. Comparing the doses of allergen extracts administered is not possible, as, in most studies, the potency is given only in arbitrary units designed by the manufacturer, which do not provide relevant information on potency or composition. As the allergen extracts and dosage regimens are those recommended by the manufacturer, the usefulness of the allergen extract is based on presented data. In most studies, the duration of treatment was rather short; i.e., a few months. The treatment was rarely continued more than 1 year. The rather short duration of treatment may be related to some studies using preseasonal immunotherapy. The duration of treatment was not considered when analyzing the documentation of clinical efficacy, although it is well known that the efficacy of immunotherapy improves with the duration of treatment.

Clinical efficacy of immunotherapy in rhinitis

Some characteristics of rhinitis studies included in this review (5–47) are summarized in Table 1. Most immunotherapy studies investigated the efficacy of pollen allergies. These studies can be subdivided into 13 studies (5, 7, 9, 11, 12, 15, 17, 19, 22, 32, 35, 36, 39) investigating ragweed allergy (nine showing clinically relevant efficacy, i.e., symptom/medication scores diminished by $\geq 30\%$ in the actively treated). Fifteen studies investigated the efficacy of immunotherapy in grass-pollen allergy (8, 13, 16, 18, 20, 21, 23, 25, 30, 34, 37, 38, 40, 44, 47), of which 14 proved efficacy. Nine studies investigated other pollen allergens: mountain cedar (10, 27, 29), *Parietaria* (42, 43, 46), *Cupressus* (45), *Cocos* (41), and mixtures (6); efficacy was demonstrated in six. The efficacy of house-dust-mite immunotherapy (14, 24, 26, 28, 33) was based on five studies (three showing efficacy). In mold allergies, efficacy was documented in one study investigating *Alternaria* (31). In the case of animal dander, no study in

Estimation of clinical efficacy

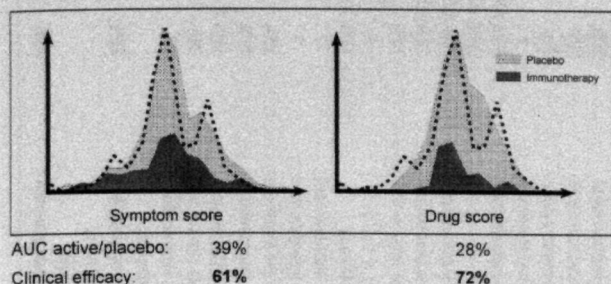


Fig. 1. Magnitude of clinical efficacy visualized by measuring area under curve (AUC) of immunotherapy group (darkly shadowed area) in percentage of placebo group (lightly shadowed area). Median symptom score and medication score of immunotherapy group amounted to 39% and 28%, respectively, of placebo-treated groups, resulting in mean total improvement (reduction) in symptom/medication score of 67% by active treatment. Dotted line represents grass-pollen counts. Clinical data adapted from Varney et al. (38).

patients with exclusively rhinitis symptoms has been done.

In the 43 DBPC rhinitis immunotherapy studies published since 1980, no efficacy was documented in 10 studies, low efficacy in 13 studies, moderate efficacy in 14 studies, and high efficacy in six studies (Fig. 2). The mean clinical improvement was a 45% reduction in symptom/medication scores compared with placebo. The best results were obtained in grass-pollen immunotherapy. Immunotherapy in ragweed allergy is fairly well documented, although the magnitude of efficacy is modest. The clinical efficacy of immunotherapy, based on DBPC studies, with other pollens, house-dust mite, animal dander, and molds is insufficiently documented. Furthermore, it has to be noted that most of the studies documenting efficacy have been performed in adult patients (75%). Only eight studies have involved children, so that the evidence of the beneficial

effect of immunotherapy in this particular age group is limited.

Clinical efficacy in asthma

The characteristics of studies evaluating immunotherapy in asthma (37, 48–62) by symptom/medication scores are shown in Table 2. The efficacy of grass-pollen immunotherapy has been investigated in six studies (37, 48, 52, 54–56) and documented in five. Mite immunotherapy was investigated in four studies (49, 57, 60, 62) with documented efficacy in two of these. Among animal danders, cat allergen is the only one showing efficacy in both studies (58, 61), as one dog study did not document efficacy (53). With respect to molds, one out of two *Cladosporium* studies documented efficacy (50, 51). In DBPC asthma studies assessing efficacy on bronchial challenge (BPT) or exposure tests (63, 71) (Table 3), one grass-pollen study noted a reduction in BPT sensitivity (68), as was also the case for one out of three mite studies (65, 70, 71). Five studies have investigated the efficacy of cat and/or dog immunotherapy (63, 64, 66, 67, 69), and three documented a reduction in challenge test or improvement in exposure tests. A recently published study investigating the effectiveness of immunotherapy in children (72) was excluded from this review because mixtures of allergens were used. The study did not document efficacy, indicating that the concept of mixing allergens may not prove useful.

According to the 16 asthma studies providing symptom/medication scores, the grading of efficacy showed no efficacy in five studies, low efficacy in three studies, moderate efficacy in four studies, and high efficacy in four studies (Fig. 3), with a mean efficacy of 40% reduction in disease severity of active treatment compared with placebo. The results indicate that immunotherapy is effective in

DBPC rhinitis studies providing symptom/medication scores

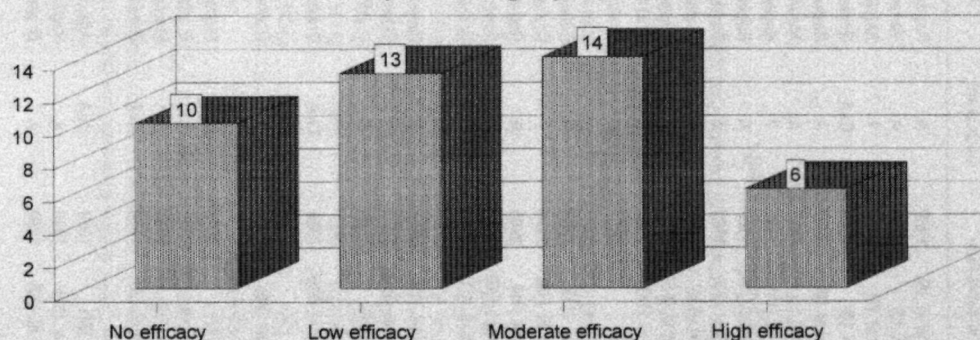


Fig. 2. Magnitude of clinical efficacy in DBPC rhinitis immunotherapy studies published in 1980–97, graded as no efficacy (<30% improvement), low efficacy (30–44% improvement), moderate efficacy (45–59% improvement), and high efficacy (≥60% improvement).

Table 1. DBPC rhinitis immunotherapy studies 1980-97

Author/year of publication	Age group (A=adults, C=children)	Allergen	Type of extract	Duration (M=month; W=week, Y=year)	No. of patients		Significance	Clinical effect	Systemic side-effects (% patients)
					Immunotherapy group	Placebo			
van Metre et al. (5)	A	Ragweed	Aqueous	5 M	12	12	NS	No effect	No
Hirsch et al. (6)	A	Various	Aqueous	13 W	81	74	NS	No effect	?
Metzger et al. (7)	?	Ragweed	Glutaraldehyde	5 W	43	49	P<0.02	Minor improvement	5% U
Weyer et al. (8)	C+A	Grass	Aqueous and alum	6 M	17	16	P<0.03	Minor improvement	?
Grammer et al. (9)	?	Ragweed	Polymerized	15 W	21	19	P<0.02	40% improvement	No
Lee et al. (10)	A	Mountain cedar	Aqueous	8 W	48	28	NS	No effect	13%
Norman et al. (11)	?	Ragweed	Allergoid	17 W	22	22	P<0.01	40% improvement	65%
van Metre et al. (12)	A	Ragweed	Aqueous	5 M	33	11	P<0.01	50% improvement	97%
Grammer et al. (13)	A	Grass	Polymerized	12 W	10	13	P<0.05	50% improvement	No
Blainey et al. (14)	A	<i>D. pteronyssinus</i>	Tyrosine	14 M	17	18	P<0.05	Efficacy?	6%
Grammer et al. (15)	?	Ragweed	Polymerized	15 W	19	31	P<0.04	40% improvement	?
Ortolani et al. (16)	A	Grass	Aqueous	10 M	8	7	P<0.001	70% improvement	25% U
Juniper et al. (17)	A	Ragweed	PEG	2 Y*	24	25	P<0.05	Minor improvement	13% A
Grammer et al. (18)	?	Grass	Polymerized	9 W	20	15	P<0.05	60% improvement	17%
Meriney et al. (19)	A	Ragweed	Allergoid	20 W	10	10	P<0.01	55% improvement	No
Bousquet et al. (20)	C+A	Grass	Allergoid	9 W	40	19	P<0.01	45% improvement	15%
Bousquet et al. (21)	C+A	Grass	Allergoid	6 M	19	19	P<0.05	45% improvement	37%
Grammer et al. (22)	?	Ragweed	Aqueous	15 W	15	11	P<0.01	65% improvement	20%
Bousquet et al. (23)	A	Grass	Polymerized	8 M	34	34	P<0.02	40% improvement	No
Ewan et al. (24)	A	<i>D. pteronyssinus</i>	Allergoid	3 M	15	10	P<0.005	55% improvement	?
Bousquet et al. (25)	C+A	Grass	Aqueous	8 M	19	19	P<0.01	50% improvement	42% AX
Corrado et al. (26)	A	<i>D. pteronyssinus</i>	Alginates	15 M	15	14	NS	40% improvement	121% mild
Fling et al. (27)	A	Mountain cedar	Aqueous	?	12	7	NS	No efficacy	7% AX
McHugh & Ewan (28)	A	<i>D. pteronyssinus</i>	Aqueous	12 M	19	28	P<0.01	35% improvement	?
Parker et al. (29)	A	Mountain cedar	Aqueous	?	26	25	P<0.0001	55% improvement	?
Bousquet et al. (30)	C+A	Grass	Allergoid	5 M	20	18	P<0.01	40% improvement	15%
Horst et al. (31)	C+A	<i>Alternaria</i>	Aqueous	12 M	13	11	P<0.005	45% improvement	11%
Juniper et al. (32)	A	Ragweed	Tyrosine	6 W	30	30	—	75% improvement	15% A
McHugh et al. (33)	A	<i>D. pteronyssinus</i>	Aqueous	12 M	30	30	P<0.01	Nasal steroid better	No
Bousquet et al. (34)	A	Grass	Alum	9 M	20	30	NS	35% improvement	?
Iliopoulos et al. (35)	?	Ragweed	Aqueous	8 M	21	20	P<0.04	50% improvement	22%
					32	34	NS	No efficacy	?
							NS	No efficacy	22%
								(multiple)	
								40% improvement	33%

Table 1. cont. DBPC rhinitis immunotherapy studies 1980-97

Author/year of publication	Age group (A=adults, C=children)	Allergen	Type of extract	Duration (M=month; W=week, Y=year)	Maximum dose	No. of patients		Significance	Clinical effect	Systemic side-effects (% patients)
						Immunotherapy group	Placebo			
Litwin et al. (36)	1991	A	Peptide Aqueous	**	13 µg AgE 130 µg AgE	9	8	P=0.001 P<0.0001	30% improvement 40% improvement	11% 10%
Machiels et al. (37)	1991	C+A	Al-ag complex	3 M	?	10	12	P<0.01	>50% improvement	No
Varney et al. (38)	1991	A	Alum	7 M	30 000 BU	37	19	P<0.002	65% improvement	10%
Brunet et al. (39)	1992	A	Alum	2 M	3000 PNU	21	14	P<0.05	40% improvement	?
Pastorello et al. (40)	1992	A	Allergoid	4 M	20 000 PNU	13	9	P<0.01	45% improvement	10%
Karmakar et al. (41)	1994	C+A	Aqueous	9 M	?	10	18	P<0.005	35% improvement	4%
Ortolani et al. (42)	1994	A	Alginate	11 M	800 U	18	17	P<0.05	40% improvement	28%
D'Amato et al. (43)	1995	A	Alum	24 M	12 500 BU	12	15	P<0.01	55% improvement	No
Dolz et al. (44)	1996	A	Aqueous and alum	36 M	100 000 SQ	18	10	NS [*] P<0.001 ^{**}	10% improvement 30%? improvement	39%
Ariano et al. (45)	1997	A	Aqueous	12 M	10 000 PNU	10	10	P<0.001 ^{***}	>90% improvement	?
Tari et al. (46)	1997	A	Allergoid	12 M	10 000 TU	20	19	P<0.05	35% improvement	10%
Zenner et al. (47)	1997	A	Alum	7 W	1.5 µg g5	45	41	P<0.05 P<0.02	45% improvement	20%

A: asthma; AX: anaphylaxis; U: urticaria; PEG: polyethylene glycol.

* Preseasonal treatment for 2 years.

** Preseasonal immunotherapy.

1st year.

2nd year.

3rd year.

DBPC asthma studies providing symptom/medication scores

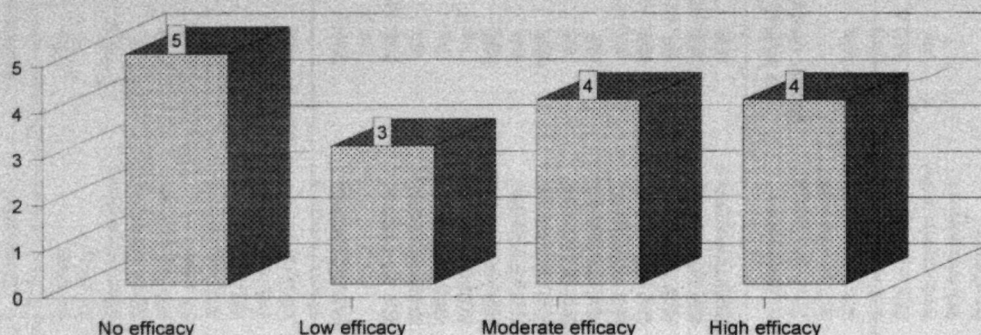


Fig. 3. Magnitude of clinical efficacy in DBPC asthma immunotherapy studies published in 1980-97, graded as no efficacy (<30% improvement), low efficacy (30-44% improvement), moderate efficacy (45-59% improvement), and high efficacy ($\geq 60\%$ improvement).

grass-pollen-induced asthma and in asthma caused by cat. The efficacy of mite immunotherapy is less convincingly documented, probably because it included patients with irreversible disease and there was difficulty in clearly identifying patients with primarily mite-induced asthma. The efficacy of mold asthma is based on a single study. No studies have shown efficacy of immunotherapy in dog allergy. In the case of asthma, several studies done in children indicate that immunotherapy may be of value in this age group.

Efficacy compared with drugs

Critical questions that arise when discussing the clinical applicability of immunotherapy in inhalant allergies concern efficacy in relation both to optimal pharmacologic treatment (topical or inhaled corticosteroids) and to the justification for treatment implying a potential risk of inducing life-threatening systemic reactions in patients suffering from mostly rather harmless, but inconvenient diseases. No studies using an appropriate allergen extract have investigated efficacy in comparison to topical steroids. The efficacy of immunotherapy in the rhinitis study by Varney et al. (38) is of special interest, as this study showed a reduction in symptoms and the use of drugs in actively treated patients to about one-third of the level in the placebo group in patients with severe hay fever uncontrolled by standard pharmacotherapy, including antihistamines and intranasal corticosteroids. The efficacy of immunotherapy in many studies was higher than for results obtained by antihistamines (73) and equivalent to the reduction in clinical symptoms obtained by standard doses of intranasal or inhaled corticosteroids (74-80). In asthmatic patients (77), the total symptom score after 1 year of treatment with inhaled corticosteroids was

reduced by 10% (nonsignificant), and another study (80) showed a reduction in symptoms by 25%. The dose-response curve for inhaled corticosteroids was extremely flat. During an 8-week observation period, the placebo-treated group experienced a nonsignificant deterioration from the baseline of -0.1 score points (on a scale of 0-3), while significant improvement was observed in the actively treated group. The group receiving a daily dose of 50 μg fluticasone improved by 0.14 in score, the 200- μg group by 0.21, and the 1000- μg group by 0.22 (78).

Side-effects

The risk of inducing systemic side-effects is the principal argument against immunotherapy. It is important to distinguish between annoying, but harmless reactions such as rhinitis, asthma, and urticaria responding well to treatment, and severe life-threatening anaphylactic reactions (2). Deaths have been caused by immunotherapy (81), and although most deaths were due to ignoring safety instructions and, especially, inadequate early treatment of anaphylactic shock, they serve as a warning not to perform immunotherapy without strict monitoring of safety (82). Nonspecific reactions, such as excessive tiredness and headache, and extremely rare symptoms consistent with immune complex disease have been reported. It has been shown that the risk of inducing anaphylactic systemic reactions is smaller in hay fever patients than in asthmatics (83). The rate of severe systemic reactions in rhinitic patients treated with high potency extracts is approximately 5% of the injections (84), primarily in the dose-escalation phase (2). However, systemic reactions represent a general limitation in the use of immunotherapy; therefore, the indication and possibly also the

Table 2. DBPC asthma immunotherapy studies 1980-97 providing symptom/medication scores

Author/year of publication	1984	1984	A	Grass	Type of extract	Duration (months)	Maximum dose*	No. of patients		Significance	Clinical effect**	Systemic side-effect (% patients)
								IT	PL			
Ortolani et al. (48)		1984	A	Grass	Aqueous	10	MD 6000 U CD 18700 U	8	7	<0.01	Asthma and rhinitis not separate	25% U 13% A 13% AX 33% A
Pauli et al. (49)		1984	A	Mite	Tyrosine	12	MD 400 Noon U	9	9	S NS M<0.05	S 20% deterioration M 40% improvement	80%#
Dreborg et al. (50)		1986	C	<i>Cladosporium</i>	Aqueous	10	MD 100 000 BU	16	14	S NS M<0.01	S unchanged M 25% improvement	100%# A 9% AX 9% AE 9% U
Malling et al. (51)		1986	A	<i>Cladosporium</i>	Aqueous	12	MD 100 000 BU CD 444 000 BU	11	11	<0.03	IT 80% patients improved PL 30% patients improved	44%
Reid et al. (52)		1986	A	Grass	Aqueous	7	CD 34.8 µg	9	9	<0.05	45% improvement	No
Valovirta et al. (53)		1986	C+A	Dog	Aluminum	12	MD 100 000 SQ	15	12	NS	No efficacy	20%
Bousquet et al. (54)		1989	C+A	Grass	GOLD	6	MD 1500 PNU CD 9100 PNU	15	14	S NS M NS	S 45% improvement M 60% improvement	7% AX
					HMW-GOLD		MD 2000 PNU CD 14 000 PNU	13		S<0.05 M<NS	S 60% improvement M 65% improvement	No
Kuna et al. (55)		1989	A	Grass	GOLD	1.5	MD 2000 Noon U	12	12	<0.02	30% improvement	No
Bousquet et al. (56)		1990	C+A	Grass	HMW-GOLD	3	MD 2000 PNU CD 10 600 PNU	19	18	S<0.001 M?	75% improvement	11% 5% AX
							MD 10 000 PNU CD 45 400 PNU	20		S<0.01 M?	65% improvement	15%
Machiels et al. (57)		1990	A	Mite	Ag-Ab complexes	24	MD 640 ng CD 15 400 ng	13	13	S<0.001 M<0.001	S 40% improvement M 20% improvement	No
							MD 80 ng CD 2500 ng	13		S<0.001 M<0.001	S 50% improvement M 20% improvement	No
Machiels et al. (37)		1991	C+A	Grass	Ag-Ab complexes	3	MD 1600 µg CD 5600 µg	13	12	<0.01	>80% improvement	
							MD 160 µg CD 560 µg	13		<0.01	>80% improvement	

Table 2. cont. DBPC asthma immunotherapy studies 1980-97 providing symptom/medication scores

Author/year of publication	Age group (A=adults, C=children)	Allergen	Type of extract	Duration (months)	Maximum dose*	No. of patients		Significance	Clinical effect**	Systemic side-effects (% patients)
						IT	PL			
Alvarez-Cuesta et al. (58)	1994	A	Cat	12	MD 13.2 µg Fel d 1 ICD 170 µg Fel d 1	14	14	<0.001	IT 80% improvement PL 20% improvement	21%
Creticos et al. (59)	1996	A	Ragweed	24	MD 10 µg Amb a 1	29	24	NS	No efficacy	19%
Pickler et al. (60)	1997	A	Mite	12	MD 1000 000 SQ	16	14	NS	S 50% improvement M?	31% AX 6%
Varney et al. (61)	1997	A	Cat	12	MD 15 µg Fel d 1	13	15	<0.001	70% improvement	23%
Olson et al. (62)	1997	A	Mite	12	MD 7 µg Der p 1	17	6	S<0.001 M<0.05	S 60% improvement M 40% improvement	No

Only studies providing data on indication, appropriate randomization, blinding of placebo, and statistical analysis are included.

IT: immunotherapy group; PL: placebo-treated group; S: symptom score; M: medication score; A: asthma; AE: angioedema; AX: anaphylaxis; U: urticaria - stated as percentage of patients with systemic reactions.

* Allergen doses are stated as maximal dose (MD) and, if possible, as cumulative dose (CD). Different potency units make comparison impossible.

** Estimated by AUC of symptom/medication score during allergen season; mean symptom/medication score in immunotherapy vs placebo group; improvement from pretreatment monitoring period.

More than one systemic reaction in individual patients.

practical treatment have to be performed by a specialist who is aware of the risks of immunotherapy, and who can deal with systemic reactions (2).

Analysis of the frequency of systemic side-effects in the 68 papers included in this review (Tables 1-3) showed that 15% of the papers failed to supply information on this extremely important aspect of immunotherapy. In the remaining studies, systemic side-effects were recorded to a highly varying degree. Fifteen papers (26%) report that no systemic side-effects were elicited by injection of allergens. Systemic side-effects of varying degree of severity were observed in 24% (mean value) of the patients. Most of the reactions were mild, requiring either no treatment or only minor treatment. However, a few reactions were rather severe, including anaphylaxis necessitating the administration of epinephrine. The data on systemic side-effects do not indicate that some allergen species, types of extracts (aqueous, depot, or modified), or dosage regimens result in a higher frequency of side-effects than others.

Conclusion

Based on both the number of DBPC studies and the number of patients included in these studies, the clinical efficacy of immunotherapy in rhinitis and asthma, when potent and standardized extracts were applied in carefully selected patients, was well documented. Although some studies demonstrated no or a low degree of clinical efficacy, most demonstrated efficacy equivalent to that obtained with pharmacologic treatment. Immunotherapy has the potential to reduce symptoms and the need for drugs significantly, and, furthermore, possibly to prevent progression into more severe disease. The most important aspect in successful immunotherapy is to select those patients most likely to respond adequately. This means identifying patients with symptoms primarily induced by allergens, patients with sensitivity to a single allergen or a few allergens, and young patients without chronic irreversible changes in the airways. To meet these requirements, the indication for immunotherapy should be made by an allergist.

Systemic side-effects induced by immunotherapy represent the primary argument against this type of specific treatment of allergic diseases. Although severe anaphylactic reactions may be induced, the risk of life-threatening side-effects is low. Most systemic reactions are rather mild, requiring no or minor treatment. To minimize the risk of side-effects, the patient should be assessed carefully, and the appropriate dose decided before the injection is given. Meticulous care should be taken to avoid

Table 3. DBPC asthma immunotherapy studies 1980-97 not providing symptom/medication

Author/year of publication	Age group (A=adults, C=children)	Allergen	Type of extract	Duration (M: months; W: weeks)	No. of patients				Allergen exposure**	Systemic side-effects (% patients)
					Maximum dose*	IT	PL	BPT		
Ohman et al. (63)	1984	A	Cat	3 M	MD 3.9 U cat 1 CD 10.9 U cat 1	9	8	PD ₂₀ ↑	S delay ↑ S score ↓	111% [†]
Valovirta et al. (64)	1984	C	Dog	12 M	MD 100 000 SQ	15	12	NS	NS	No
Bousquet et al. (65)	1985	A	Mite	7 W	MD 3000 BU	20	10	PD ₂₀ ↑	ND	20%
Sundin et al. (66)	1986	C+A	Cat	12 M	MD 100 000 SQ	15	18	PD ₂₀ ↑	NS	Children 100%
			Aqueous		CD 1 000 000 SQ					Adults 100%
			Adults		MD 100 000 SQ	7		NS	NS	36%
van Metre et al. (67)	1988	A	Aluminum		CD 1 000 000 SQ					18%
			Aqueous	12 M	MD 21 µg Fel d 1	11	11	PD ₂₀ ↑	NS	
Armentia-Medina et al. (68)	1989	C+A	Grass	7 W	CD 213 µg Fel d 1 MD 60 BU	19	11	PD ₂₀ ↑	ND	A 28% AE 6% AX 6% A 73% [†] 7% AX
Haugaard & Dahl (69)	1992	A	Cat	5 M	MD 200 µg Fel d 1 CD 460 µg Fel d 1	15	9	NS	ND	
			Dog		MD 100 000 BU CD 185 000 BU			NS		
van Bever & Stevens (70)	1992	C+A	Mite	12 M	MD 1000 BU CD 16500 BU	9	12	IAR NS LAR ↓	ND	?
Peroni et al. (71)	1995	C	Mite	12 M	MD 800 U	11	12	NS	ND	No

Only studies providing data on indication, appropriate randomization, blinding of placebo, and statistical analysis are included.

IT: immunotherapy group; PL: placebo-treated group; PD₂₀: allergen dose resulting in 20% decrease in lung function (FEV₁) in bronchial provocation test; IAR: immediate asthmatic reaction; LAR: late asthmatic reaction. A: asthma; AE: angioedema; AX: anaphylaxis – stated as percentage of patients with systemic reactions.

*Allergen doses are stated as maximal doses (MD) and, if possible, as cumulative dose (CD). Different potency units make comparison impossible.

**Effect on symptoms of allergen exposure under standardized conditions.

[†]More than one systemic reaction in individual patients.

mistakes involving patients, allergen extracts, allergen concentration, and volume injected. Adequate training of the staff administering immunotherapy and instantaneous and appropriate treatment of systemic reactions will reduce the problem of side-effects.

References

- Müller U, Mosbech H, editors. EAACI position paper. Immunotherapy with Hymenoptera venoms. Allergy 1993; 48 Suppl 14:37-46.
- Malling H-J, Weeke B, editors. EAACI position paper. Immunotherapy. Allergy 1993;48 Suppl 14:9-45.
- Malling H-J. New ideas in allergen-specific immunotherapy. Am J Rhinol 1990;4:155-8.
- Dreborg S, Frew A, editors. Allergen standardization and skin tests. Allergy 1993;48 Suppl 14:49-82.
- van Metre TE, Adkinson NF, Lichtenstein LM, et al. A controlled study of the effectiveness of the Rinkel method of immunotherapy for ragweed pollen hay fever. J Allergy Clin Immunol 1980;65:288-97.
- Hirsch SR, Kalbfleisch JH, Golbert TM, et al. Rinkel injection therapy: a multicenter controlled study. J Allergy Clin Immunol 1981;68:133-55.
- Metzger WJ, Dorminey HC, Richerson HB, Weiler JM, Donnelly A, Moran D. Clinical and immunologic evaluation of glutaraldehyde-modified, tyrosine-absorbed short ragweed extract: a double-blind, placebo-controlled trial. J Allergy Clin Immunol 1981;68:442-8.
- Weyer A, Donat N, L'Heritier C, et al. Grass pollen hyposensitization versus placebo therapy. I. Clinical effectiveness and methodological aspects of a pre-seasonal course of desensitization with a four-grass pollen extract. Allergy 1981;36:309-17.
- Grammer LC, Zeiss CR, Suszko IM, Shaughnessy MA, Patterson R. A double-blind, placebo-controlled trial of polymerized whole ragweed for immunotherapy of ragweed allergy. J Allergy Clin Immunol 1982;69:494-9.
- Lee LK, Kniker WT, Campos T. Aggressive coseasonal immunotherapy in mountain cedar pollen allergy. Arch Otolaryngol 1982;108:787-94.
- Norman PS, Lichtenstein LM, Kagey-Sobotka A, Marsh DG. Controlled evaluation of allergoid in the immunotherapy of ragweed hay fever. J Allergy Clin Immunol 1982;70: 248-60.
- van Metre TE, Adkinson NF, Amodio FJ, et al. A comparison of immunotherapy schedules for injection treatment of ragweed pollen hay fever. J Allergy Clin Immunol 1982;69:181-93.
- Grammer LC, Shaughnessy MA, Suszko IM, Shaughnessy JJ, Patterson R. A double-blind histamine placebo-controlled trial of polymerized whole grass for immunotherapy of grass allergy. J Allergy Clin Immunol 1983;72: 448-53.
- Blainey AD, Phillips MJ, Ollier S, Davies RJ. Hyposensitization with a tyrosine adsorbed extract of *Dermatophagoides pteronyssinus* in adults with perennial rhinitis. Allergy 1984;39:521-8.
- Grammer LC, Shaughnessy MA, Shaughnessy JJ, Patterson R. Asthma as a variable in a study of immunotherapy for allergic rhinitis. J Allergy Clin Immunol 1984; 73:557-60.
- Ortolani C, Pastorello E, Moss RB, et al. Grass pollen immunotherapy: a single year double-blind, placebo-controlled study in patients with grass pollen-induced asthma and rhinitis. J Allergy Clin Immunol 1984;73: 283-90.
- Juniper EF, Roberts RS, Kennedy LK, et al. Polyethylene glycol-modified ragweed pollen extract in rhinoconjunctivitis. J Allergy Clin Immunol 1985;75:578-85.
- Grammer LC, Shaughnessy MA, Finkle SM, Shaughnessy JJ, Patterson R. A double-blind placebo-controlled trial of polymerized whole grass administered in an accelerated dosage schedule for immunotherapy of grass pollinosis. J Allergy Clin Immunol 1986;78:1180-4.
- Meriney DK, Kothari H, Chinoy P, Grieco MH. The clinical and immunologic efficacy of immunotherapy with modified ragweed extract (allergoid) for ragweed hay fever. Ann Allergy 1986;56:34-8.
- Bousquet J, Frank E, Soussana M, Hejjaoui A, Maasch HJ, Michel FB. Double-blind, placebo-controlled immunotherapy with a high-molecular-weight, formalinized allergoid in grass pollen allergy. Int Arch Allergy Appl Immunol 1987;82:550-2.
- Bousquet J, Hejjaoui A, Skassa Brociek W, et al. Double-blind, placebo-controlled immunotherapy with mixed grass-pollen allergoids. I. Rush immunotherapy with allergoids and standardized orchard grass-pollen extract. J Allergy Clin Immunol 1987;80:591-8.
- Grammer LC, Shaughnessy MA, Bernhard MI, et al. The safety and activity of polymerized ragweed: a double-blind, placebo-controlled trial in 81 patients with ragweed rhinitis. J Allergy Clin Immunol 1987;80:177-83.
- Bousquet J, Maarch H, Martinot B, Hejjaoui A, Wahl R, Michel FB. Double-blind, placebo-controlled immunotherapy with mixed grass-pollen allergoids. II. Comparison between parameters assessing efficacy of immunotherapy. J Allergy Clin Immunol 1988;82:439-46.
- Ewan PW, Alexander MM, Snape C, Ind PW, Agrell B, Dreborg S. Effective hyposensitization in allergic rhinitis using a potent partially purified extract of house dust mite. Clin Allergy 1988;18:501-8.
- Bousquet J, Maasch HJ, Hejjaoui A, et al. Double-blind, placebo-controlled immunotherapy with mixed grass-pollen allergoids. III. Efficacy and safety of unfractionated and high-molecular-weight preparations in rhinoconjunctivitis and asthma. J Allergy Clin Immunol 1989;84:546-56.
- Corrado OJ, Pastorello E, Ollier S, et al. A double-blind study of hyposensitization with an alginate conjugated extract of *D. pteronyssinus* (Conjuvac®) in patients with perennial rhinitis. I. Clinical aspects. Allergy 1989;44:108-15.
- Fling JA, Ruff ME, Parker WA, et al. Suppression of the late cutaneous response by immunotherapy. J Allergy Clin Immunol 1989;83:101-9.
- McHugh SM, Ewan PW. Reduction of increased serum neutrophil chemotactic activity following effective hyposensitization in house dust mite allergy. Clin Exp Allergy 1989;19:327-34.
- Parker WA, Whisman BA, Apaliski SJ, Reid MJ. The relationships between late cutaneous responses and specific antibody responses with outcome of immunotherapy for seasonal allergic rhinitis. J Allergy Clin Immunol 1989;84: 667-77.
- Bousquet J, Hejjaoui A, Soussana M, Michel F-B. Double-blind, placebo-controlled immunotherapy with mixed grass-pollen allergoids. IV. Comparison of the safety and efficacy of two dosages of a high-molecular-weight allergoid. J Allergy Clin Immunol 1990;85:490-7.
- Horst M, Hejjaoui A, Horst V, Michel F-B, Bousquet J. Double-blind, placebo-controlled rush immunotherapy with a standardized *Alternaria* extract. J Allergy Clin Immunol 1990;85:460-72.

32. Juniper EF, Kline PA, Ramsdale EH, Hargreave FE. Comparison of the efficacy and side effects of aqueous steroid nasal spray (budesonide) and allergen-injection therapy (Polinex-R) in the treatment of seasonal allergic rhinoconjunctivitis. *J Allergy Clin Immunol* 1990;85:606-11.
33. McHugh SM, Lavelle B, Kemeny DM, Patel S, Ewan PW. A placebo-controlled trial of immunotherapy with two extracts of *Dermatophagoides pteronyssinus* in allergic rhinitis, comparing clinical outcome with changes in antigen-specific IgE, IgG, and IgG subclasses. *J Allergy Clin Immunol* 1990;86:521-32.
34. Bousquet J, Becker WM, Hejjaoui A, et al. Differences in clinical and immunologic reactivity of patients allergic to grass pollens and to multiple-pollen species. II. Efficacy of a double-blind, placebo-controlled, specific immunotherapy with standardized extracts. *J Allergy Clin Immunol* 1991;88:43-53.
35. Iliopoulos O, Proud D, Franklin Adkinson N, et al. Effects of immunotherapy on the early, late, and rechallenge nasal reaction to provocation with allergens: changes in inflammatory mediators and cells. *J Allergy Clin Immunol* 1991;87:855-66.
36. Litwin A, Pesce AJ, Fischer T, Michael M. Regulation of the human immune response to ragweed pollen by immunotherapy. A controlled trial comparing the effect of immunosuppressive peptic fragments of short ragweed with standard treatment. *Clin Exp Allergy* 1991;21:457-65.
37. Machiels JJ, Somville MA, Jacquemin MG, Saint-Remy JMR. Allergen-antibody complexes can efficiently prevent seasonal rhinitis and asthma in grass pollen hypersensitive patients. *Allergy* 1991;46:335-48.
38. Varney VA, Gaga M, Frew AJ, Aber VR, Kay AB, Durham SR. Usefulness of immunotherapy in patients with severe summer hay fever uncontrolled by antiallergic drugs. *BMJ* 1991;302:265-9.
39. Brunet C, Bédard P-M, Lavoie A, Jobin M, Hébert J. Allergic rhinitis to ragweed pollen. I. Reassessment of the effects of immunotherapy on cellular and humoral responses. *J Allergy Clin Immunol* 1992;89:76-86.
40. Pastorello EA, Pravettoni V, Incorvaia C, et al. Clinical and immunological effects of immunotherapy with alum-absorbed grass allergoid in grass-pollen-induced hay fever. *Allergy* 1992;47:281-90.
41. Karmakar PR, Das A, Chatterjee BP. Placebo-controlled immunotherapy with *Cocos nucifera* pollen extract. *Int Arch Allergy Immunol* 1994;103:194-201.
42. Ortolani C, Pastorello EA, Incorvaia C, et al. A double-blind, placebo-controlled study of immunotherapy with an alginate-conjugated extract of *Parietaria judaica* in patients with *Parietaria* hay fever. *Allergy* 1994;49:13-21.
43. D'Amato G, Kordash TR, Liccardi G, Lobefalo G, Cazzola M, Freshwater LL. Immunotherapy with Alpare® in patients with respiratory allergy to *Parietaria* pollen: a two year double-blind placebo-controlled study. *Clin Exp Allergy* 1995;25:149-58.
44. Dolz I, Martínez-Cócerca C, Bartolomé JM, Cimarra M. A double-blind, placebo-controlled study of immunotherapy with grass-pollen extract Alutard SQ during a 3-year period with initial rush immunotherapy. *Allergy* 1996;51:489-500.
45. Ariano R, Panzani RC, Augeri G. Double-blind placebo controlled specific immunotherapy with mixed Cupressaceae Taxodiaceae pollens in respiratory allergy to *Cupressus sempervirens*. *Allergol Immunopathol (Madr)* 1997;25:23-9.
46. Tari MG, Mancino M, Ghezzi E, Frank E, Cromwell O. Immunotherapy with an alum-adsorbed *Parietaria*-pollen allergoid: a 2-year, double-blind, placebo-controlled study. *Allergy* 1997;52:65-74.
47. Zenner HP, Baumgarten C, Rasp G, et al. Short-term immunotherapy: a prospective, randomized, double-blind, placebo-controlled multicenter study of molecular standardized grass and rye allergens in patients with grass pollen-induced allergic rhinitis. *J Allergy Clin Immunol* 1997;100:23-9.
48. Ortolani C, Pastorello E, Moss RB, et al. Grass pollen immunotherapy: a single year double-blind, placebo-controlled study in patients with grass pollen induced asthma and rhinitis. *J Allergy Clin Immunol* 1984;73:283-90.
49. Pauli G, Bessot JC, Bigot H, et al. Clinical and immunologic evaluation of tyrosine-absorbed *Dermatophagoides pteronyssinus* extract: a double-blind placebo-controlled trial. *J Allergy Clin Immunol* 1984;74:524-35.
50. Dreborg S, Agrell B, Foucard T, Kjellman N-IM, Koivikko A, Nilsson S. A double-blind, multicenter immunotherapy trial in children using a purified and standardized *Cladosporium herbarum* preparation. *Allergy* 1986;41:131-40.
51. Malling H-J, Dreborg S, Weeke B. Diagnosis and immunotherapy of mould allergy. V. Clinical efficacy and side effects of immunotherapy with *Cladosporium herbarum*. *Allergy* 1986;41:507-19.
52. Reid MJ, Moss RB, Hsu Y-P, Kwasnicki JM, Commerford TM, Nelson BL. Seasonal asthma in northern California: allergic causes and efficacy of immunotherapy. *J Allergy Clin Immunol* 1986;78:590-600.
53. Valovirta E, Viander M, Koivikko A, Vanto T, Ingeman L. Immunotherapy in allergy to dog. Immunologic and clinical findings of a double-blind study. *Ann Allergy* 1986;57:173-9.
54. Bousquet J, Maasch H, Hejjaoui A, et al. Double blind, placebo-controlled immunotherapy with mixed grass-pollen allergoids. III. Efficacy and safety of unfractionated and high-molecular-weight preparations in rhinoconjunctivitis and asthma. *J Allergy Clin Immunol* 1989;84:546-56.
55. Kuna P, Alam R, Kumanska B, Rozniecki J. The effect of preseasonal immunotherapy on the production of histamine-releasing factor (HRF) by mononuclear cells from patients with seasonal asthma: results of a double-blind, placebo-controlled, randomized study. *J Allergy Clin Immunol* 1989;83:816-24.
56. Bousquet J, Hejjaoui A, Soussana M, Michel FB. Double blind, placebo-controlled immunotherapy with mixed grass-pollen allergoids. IV. Comparison of the safety and efficacy of two dosages of a high-molecular-weight allergoid. *J Allergy Clin Immunol* 1990;85:490-7.
57. Machiels JJ, Somville MA, Lebrun PM, Lebecque SJ, Jacquemin MG, Saint-Remy J-MR. Allergic bronchial asthma due to *Dermatophagoides pteronyssinus* hypersensitivity can be efficiently treated by inoculation of allergen-antibody complexes. *J Clin Invest* 1990;85:1024-35.
58. Alvarez-Cuesta E, Cuesta-Herranz J, Puyana-Ruiz J, Cuesta-Herranz C, Blanco-Quirós A. Monoclonal antibody-standardized cat extract immunotherapy: risk-benefit effects from a double-blind placebo study. *J Allergy Clin Immunol* 1994;93:556-66.
59. Creticos PS, Reed CE, Norman PS, et al. Ragweed immunotherapy in adult asthma. *N Engl J Med* 1996;334: 501-6.
60. Pickler CE, Marquardsen A, Sparholt S, et al. Specific immunotherapy with *Dermatophagoides pteronyssinus* and *D. farinae* results in decreased bronchial hyperreactivity. *Allergy* 1997;52:274-83.
61. Varney VA, Edwards J, Tabbah K, Brewster H, Mavroleon G, Frew AJ. Clinical efficacy of specific immunotherapy to cat dander: a double-blind placebo-controlled trial. *Clin Exp Allergy* 1997;27:860-7.
62. Olsen OT, Larsen KR, Jacobsen L, Svendsen UG. A 1-year,

- placebo-controlled, double-blind house-dust-mite immunotherapy study in asthmatic adults. *Allergy* 1997;52:853-9.
63. Ohman JL, Findlay SR, Leitermann KM. Immunotherapy in cat-induced asthma. Double-blind trial with evaluation of *in vivo* and *in vitro* responses. *J Allergy Clin Immunol* 1984;74:230-9.
64. Valovirta E, Koivikko A, Vanto T, Viander M, Ingeman L. Immunotherapy in allergy to dog: a double-blind clinical study. *Ann Allergy* 1984;53:85-8.
65. Bousquet J, Calvayrac P, Guérin B, et al. Immunotherapy with a standardized *Dermatophagoides pteronyssinus* extract. I. *In vivo* and *in vitro* parameters after a short course of treatment. *J Allergy Clin Immunol* 1985;76:734-44.
66. Sundin B, Lilja G, Graff-Lonnevig V, et al. Immunotherapy with partially purified and standardized animal dander extracts. I. Clinical results from a double-blind study on patients with animal dander asthma. *J Allergy Clin Immunol* 1986;77:478-87.
67. van Metre TE, Marsh DG, Adkinson NF, et al. Immunotherapy for cat asthma. *J Allergy Clin Immunol* 1988;82:1055-68.
68. Armentia-Medina A, Blanco-Quiros A, Martin-Santos JM, et al. Rush immunotherapy with a standardized Bermuda grass pollen extract. *Ann Allergy* 1989;63:127-35.
69. Haugaard L, Dahl R. Immunotherapy in patients allergic to cat and dog dander. I. Clinical results. *Allergy* 1992;47:249-54.
70. van Bever HP, Stevens WJ. Effect of hyposensitization upon the immediate and late asthmatic reaction and upon histamine reactivity in patients allergic to house dust mite (*Dermatophagoides pteronyssinus*). *Eur Respir J* 1992;5:318-22.
71. Peroni DG, Piacentini GL, Martinati LC, Warner JO, Boner AL. Double-blind trial of house-dust mite immunotherapy in asthmatic children resident at high altitude. *Allergy* 1995;50:925-30.
72. Adkinson FN, Eggleston PA, Eney D, et al. A controlled trial of immunotherapy for asthma in allergic children. *N Engl J Med* 1997;336:324-31.
73. Grant JA, Nicodemus CF, Findlay SR, et al. Cetirizine in patients with seasonal rhinitis and concomitant asthma: prospective, randomized, placebo-controlled trial. *J Allergy Clin Immunol* 1995;95:923-32.
74. Bronsky WA, Dockhorn RJ, Meltzer EO, et al. Fluticasone propionate aqueous nasal spray compared with terfenadine tablets in the treatment of seasonal allergic rhinitis. *J Allergy Clin Immunol* 1996;97:915-21.
75. Scadding GK, Lund VJ, Jacques LA, Richards DH. A placebo-controlled study of fluticasone propionate aqueous nasal spray and beclomethasone dipropionate in perennial rhinitis: efficacy in allergic and non-allergic perennial rhinitis. *Clin Exp Allergy* 1995;25:737-43.
76. Haahtela T, Järvinen M, Kava T, et al. Comparison of a β_2 -agonist, terbutaline, with an inhaled corticosteroid, budesonide, in newly detected asthma. *N Engl J Med* 1991;325:388-92.
77. Dompeling E, van Schayck CP, Molema J, Folgering H, van Grunsven PM, van Weel C. Inhaled beclomethasone improves the course of asthma and COPD. *Eur Respir J* 1992;5:945-52.
78. Chervinsky P, van As A, Bronsky EA, et al. Fluticasone propionate aerosol for the treatment of adults with mild to moderate asthma. *J Allergy Clin Immunol* 1994;94:676-83.
79. Ayres JG, Bateman ED, Lundbäck B, Harris TAJ. High dose fluticasone propionate, 1 mg daily, versus fluticasone propionate, 2 mg daily, or budesonide, 1.6 mg daily, in patients with chronic severe asthma. *Eur Respir J* 1995;8:579-86.
80. König P, Schaffer J. The effect of drug therapy on long-term outcome of childhood asthma: a possible preview of the international guidelines. *J Allergy Clin Immunol* 1996;98:1103-11.
81. Reid MJ, Lockey RF, Turkeltaub PC, Platts-Mills TAE. Survey of fatalities from skin testing and immunotherapy 1985-1989. *J Allergy Clin Immunol* 1993;92:6-15.
82. Stewart GE II, Lockey RF. Systemic reactions from allergen immunotherapy. *J Allergy Clin Immunol* 1992;90:567-78.
83. Hejjaoui J, Ferrando R, Dhivert H, Michel FB, Bousquet J. Systemic reactions occurring during immunotherapy with standardized pollen extracts. *J Allergy Clin Immunol* 1992;89:925-33.
84. Tabar AI, García BE, Rodríguez A, Olaguibel JM, Muro MD, Quirce S. A prospective safety-monitoring study of immunotherapy with biologically standardized extracts. *Allergy* 1993;48:450-3.

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