

Immunotherapy in children and adolescents with allergic rhinoconjunctivitis: a systematic review

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Allergen-specific immunotherapy is one of the cornerstones of allergic rhinoconjunctivitis treatment. Since the development of non-invasive administration forms with better safety profiles, there is an increasing tendency to prescribe immunotherapy in youngsters. However, no overview is available on the efficacy of immunotherapy in all its different administration forms in youngsters. Therefore, we systematically reviewed randomized controlled trials (RCTs) to evaluate the effect of immunotherapy with inhalant allergens on symptoms and medication use in children and adolescents with allergic rhinoconjunctivitis.

Medline, EMBASE, the Cochrane Controlled Clinical Trials Register and reference lists of recent reviews and published trials were searched. RCTs including youngsters aged 0–18 yr with allergic rhinoconjunctivitis and comparing immunotherapy with placebo, symptomatic treatment or a different administration form of immunotherapy were included. Primary outcome measures were rhinoconjunctivitis symptom and/or medication scores. Methodological quality was assessed using the validated Delphi list. A method of best evidence synthesis, a rating system with levels of evidence based on the overall quality and the outcome of the trials, was used to assess efficacy. Six subcutaneous (SCIT), four nasal (LNIT), seven oral (OIT) and 11 sublingual (SLIT) immunotherapy trials, comprising 1619 youngsters, were included. Only 39% of the trials were of high methodological quality. For the SCIT and OIT subgroups the level of evidence for efficacy was conflicting. Moderate evidence of effect was found for LNIT. Analysis of the SLIT subgroup showed no evidence of effect. The evidence for the perennial and seasonal allergen trials within the subgroups varied from moderate evidence of effect to no evidence of effect. In conclusion, there is at present insufficient evidence that immunotherapy in any administration form has a positive effect on symptoms and/or medication use in children and adolescents with allergic rhinoconjunctivitis.

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The cornerstones of allergic rhinoconjunctivitis treatment are allergen avoidance, symptomatic drug therapy and specific immunotherapy. Allergen-specific immunotherapy, i.e. the administration of increasing amounts of allergen, in the

traditional subcutaneous immunotherapy form (SCIT) prevents symptoms by altering the natural course of the disease (1). The reduction of both symptoms and medication requirements even persists after discontinuation of treatment

(2). SCIT is an attractive treatment option for children, because it might also prevent the onset of asthma and the development of new sensitizations (3, 4). Unfortunately, SCIT has several disadvantages. The inconvenience of injection therapy hampers the administration to children, whereas the risk of serious adverse events restricts administration to experienced physicians or specialized centres (1, 5). Consequently, alternative routes of administration have been developed to make immunotherapy more acceptable and safer, particularly for children. So far, articles have been published on nasal (LNIT), oral (OIT) and sublingual immunotherapy (SLIT). However, no overview is available on the efficacy of immunotherapy in all its administration forms in children. Therefore, we performed a systematic review of the literature to evaluate the effect of immunotherapy with inhalant allergens on symptoms and medication use in children and adolescents with allergic rhinoconjunctivitis.

Methods

Search strategy

One of the reviewers (ER) searched Medline, EMBASE and the Cochrane Controlled Clinical Trials Register. The search strategy combined disease and therapy specific terms, [(rhin* OR hay fever) AND (immunotherap* OR desensiti*)], with the optimal search strategy for controlled trials (6). Additionally, reference lists of recent reviews and published trials were searched. Only full text articles were considered and language was not restricted. The search was completed in June 2006.

Study selection

Two reviewers (ER and MB) independently selected the trials, initially based on title and abstract. Of the selected abstracts the full text article was retrieved. Final selection was independently performed using a standardized form. Disagreement was resolved in a consensus meeting.

We selected randomized controlled clinical trials (RCTs) including youngsters aged 0–18 yr with allergic rhinoconjunctivitis, with or without asthma. Trials using inhalant allergens were considered irrespective of route, dose or duration of treatment. We included only trials comparing immunotherapy with placebo or symptomatic treatment and trials comparing different administration forms of immunotherapy. Trials exclu-

sively comparing different doses of the same product were excluded. Sensitivity to the administered allergen had to be confirmed by a positive skin test and/or serum allergen-specific IgE. Our primary outcome measures were rhinoconjunctivitis symptom and/or medication scores. Therefore, at least one of the following outcomes had to be presented: a rhinoconjunctivitis symptom score, a (anti-allergic) medication score and/or a composite symptom-medication score. If a separate rhinitis score was absent, a total symptom score including a rhinitis score was evaluated. In case, an overall evaluation of the treatment was presented but no composite symptom-medication score, the former was evaluated instead. Secondary outcome measures in this review were quality of life, adverse events and compliance with medication intake.

Methodological quality assessment

Two reviewers (ER and either MB, HG or RG) independently assessed the methodological quality using the Delphi list (7). Two items were added concerning the drop-out rate (Table 1).

Each item (D1–D11) was scored as yes (= 1), no (= 0) or unclear (= 0). Disagreement between the two reviewers was resolved in a consensus meeting. The overall methodological quality of a trial was computed by counting the number of positive scores, with equal weights applied on all items. We arbitrarily regarded trials with a score ≥ 6 (range 0–11) of high quality.

The inter-assessor agreement on the methodological quality was calculated using Cohen's Kappa scores, ranging from –1 (perfect disagreement) to +1 (perfect agreement) (8). A $\kappa > 0.7$, between 0.5 and 0.7 or < 0.5 corresponded with a high, moderate or poor level of agreement between assessors respectively.

Table 1. Items of the Delphi-list for the assessment of the methodological quality of the articles

D1	Was a method of randomization performed?
D2	Was the treatment allocation concealed?
D3	Were the groups similar at baseline regarding the most important prognostic indicators?
D4	Were both inclusion and exclusion criteria specified?
D5	Was the outcome assessor blinded?
D6	Was the care provider blinded?
D7	Was the patient blinded?
D8	Were point estimates and measures of variability presented for the primary outcome measures?
D9	Did the analysis include an intention-to-treat analysis?
D10	Was the withdrawal/drop-out rate $< 20\%$ of the total study population?
D11	Was the withdrawal/drop-out rate unlikely to cause bias?

Data extraction and analysis

Two reviewers (ER and either MB, HG or RG) independently extracted data on a standardized form regarding trial design, treatment, participants and outcome measures. In principle, the last treatment period was evaluated, unless the data presented for this period were insufficient or a control group was no longer present.

Considering the outcome measures, our initial intention was to extract means and SDs or RRs and 95% CIs to pool the data. In case of a statistical significant difference between treatment groups, the clinical relevance of this difference would be assessed. A difference in symptom/medication scores between treatment groups of at least 30% was considered the minimal clinical important difference (9). However, the description of the various scores was often insufficient as for instance information on the range and composition of the score was lacking. Different point estimates (e.g. mean or ranks) were presented and the measures of variability (e.g. SD or 95% CI) were not always stated. Moreover, the trials were heterogeneous concerning participants, allergen (type and dose) and duration of treatment. Therefore, the results could not be pooled.

Instead, for each trial we present the presence or absence of a positive effect of the intervention on the symptom/medication scores compared with the control group. An effect was considered positive, if a statistically significant difference was presented between intervention and control group. If a positive effect was found for at least one of the three scores (symptom score, medication score and composite symptom-medication score) efficacy was considered demonstrated.

To analyse the efficacy for different subgroups we used the method of best evidence synthesis, a rating system with levels of evidence based on the overall quality and the outcome of the trials (10). First, the total number of high-quality trials within each group was evaluated. In case of at least two high-quality RCTs, only these trials would provide the evidence. All trials were considered if no or only one high-quality RCT was available. Secondly, the consistence of the findings was calculated. Findings were considered consistent if $\geq 75\%$ of the trials reported comparable results (i.e. positive or negative effect) on the demonstrated efficacy. A score $< 75\%$ was considered inconsistent. Lastly, the level of evidence (conflicting/strong/moderate/limited) was determined. Conflicting evidence existed, if multiple RCTs showed inconsistent findings. Strong evidence was defined by consistent findings among at least two

high-quality RCTs. Moderate evidence existed, if one high-quality RCT and/or at least two low-quality RCTs showed consistent findings. If only one low-quality RCT was found, the evidence was considered limited. This method of best evidence synthesis was applied to each administration form subgroup separately. Within these subgroups, the best evidence synthesis was also applied to the seasonal and perennial trials separately.

Results

Identification and selection of the literature

The search strategy resulted in 1629 titles and abstracts. The majority ($n = 1274$) did not meet the inclusion criteria, mainly because 1040 articles did not refer to RCTs. A total of 23 potentially eligible manuscripts were excluded because of language barriers (10 Polish, 6 Russian, 4 Spanish, 2 Romanian and 1 Croat). We retrieved 332 full text articles for detailed evaluation. Another 304 trials were excluded, mainly because they included only adults ($n = 125$) or a mixed adult-child population from which the data for children could not be extracted ($n = 85$). Eventually 28 RCTs were included in this review (3, 11–37).

Description of the included trials

All trials were performed in referral centres and all except two were carried out in Europe (12, 13). Eleven trials reported financial or intellectual support from a pharmaceutical company (3, 14, 19, 22, 24, 27, 28, 30–33). Study medication was supplied by the manufacturer in four trials (11, 16, 17, 35).

Treatment. Six SCIT, four LNIT, seven OIT and 11 SLIT trials were included. In the majority of trials ($n = 19$) a seasonal allergen, mainly grass pollen ($n = 13$), was used. Nine trials used a perennial allergen, i.e. house dust mite (15, 19, 25, 26, 34–37) and mould (14). Only nine trials, all within the SLIT subgroup, stated the cumulative dose of allergen in micrograms (27, 28, 30–36). The duration of treatment varied from 1 to 36 months. Most trials ($n = 23$) were placebo-controlled. In four trials the control group received symptomatic treatment (3, 15, 18, 30) and in one trial OIT was compared with SCIT (21). All children were allowed to use rescue medication in addition to their study medication. Allergen exposure was measured in 17 trials (11–14, 17, 20–22, 24, 27, 28, 30–33, 36, 37), but only five trials incorporated allergen exposure in their analysis (12, 17, 20, 24, 28) (Table 2).

Participants. A total of 1619 children (ranged: 15–205) were included. Seventeen trials included < 50 participants (11, 13, 14, 16–20, 23–26, 29, 31, 32, 35, 36) and only four trials comprised ≥100 children (3, 12, 27, 30). The participants were aged between 3 and 18 yr. Generally more boys were included. All trials, except for five (16, 18, 19, 24, 30), included a mixed rhinitis–asthma

population. One trial did not state whether participants with asthma were included (21) (Table 3).

Methodological quality assessment

Eleven trials were of high methodological quality (11, 19, 20, 25, 27, 30, 32–36) of which the

Table 2. Treatment characteristics

	Article	Allergen	Control group	Cum dose (μg)	Duration	Time	Exposure measured
SCIT	Sanders (1966) (11)	Grass pollen	Placebo	NS	NS	Pre-seasonal	Yes
	Möller et al. (2002) (3)	Grass pollen and/or birch pollen	Symptomatic treatment	NS	36 months	All year	No
	Fontana et al. (1966) (12)	Ragweed pollen	Placebo	NS	±6 months†	Pre-seasonal	Yes
	Weisnagel (1979) (13)	Ragweed pollen	Placebo	NS	1 month	Pre-seasonal	Yes
	Dreborg et al. (1986) (14)	Mould (<i>Cladosporium herbarum</i>)	Placebo	NS	10 months	Pre-, co- and post-seasonal	Yes
	Urbanek et al. (1991) (15)	House dust mite	Symptomatic treatment	NS	12 months	All year	No
LNIT	Bardare et al. (1996) (16)	Grass pollen	Placebo	NS	3 months*	Pre-seasonal	No
	Mehta and Smith (1975) (17)	Grass pollen	Placebo	NS	±3 months	Pre-seasonal	Yes
	Cserhati and Mezei (1997) (18)	Group 1-Grass pollen-Group 2/Ragweed pollen	Symptomatic treatment	NS	12 months†	Pre-seasonal	No
	Marcucci et al. (2002) (19)	House dust mite	Placebo	NS	18 months	All year	No
OIT	Caffarelli et al. (2000) (20)	Grass pollen	Placebo	NS	3 months	Pre-seasonal	Yes
	Urbanek et al. (1990) (21)	Group 1-Low dose-Group 2/High dose grass pollen	SCIT	NS	24 months	All year	Yes
	Cooper et al. (1984) (22)	Grass pollen	Placebo	NS	at least 3.5 months	Pre-seasonal and early co-seasonal	Yes
	Reinert and Reinert (1983) (23)	Pollen (grass/rye)	Placebo	NS	24 months	All year	No
	Möller et al. (1986) (24)	Birch pollen	Placebo	NS	10 months	Pre- and post-seasonal	Yes
	Giovane et al. (1994) (25)	House dust mite	Placebo	NS	36 months	All year	No
	Urbanek and Gehl (1982) (26)	House dust mite	Placebo	NS	10.5 months	NS	No
	Bufe et al. (2004) (27)	Grass pollen	Placebo	9600 (Ph1 p 5)	12 months*	All year	Yes
	Rolinck-Werninghaus et al. (2004) (28)	Grass pollen	Placebo	188 (major grass pollen allergen)	32 months	All year	Yes
	Yuksel et al. (1999) (29)	Grass pollen	Placebo	NS	12 months	All year	No
SLIT	Novembre et al. (2004) (30)	Grass pollen	Symptomatic treatment	120 (major allergen group 5)	4 months/yr during 3 years	Co-seasonal	Yes
	La Rosa et al. (1999) (31)	Parietaria pollen	Placebo	52500 (Par j 1)	24 months	All year	Yes
	Pajno et al. (2003) (32)‡	Parietaria pollen	Placebo	20.3 (Par j 1)	13 months	All year	Yes
	Vourdas et al. (1998) (33)	Olive pollen	Placebo	8100 (Ole e 1)	6 months/yr during 2 years	Pre- and co-seasonal	Yes
	Ippoliti et al. (2003) (34)	House dust mite	Placebo	90 (60 Der p1 /30 Der p2)	6 months	NS	No
	Bahceciler et al. (2001) (35)	House dust mite	Placebo	1540 (560 D. pter/980 D. far)	6 months	NS	No
	Hirsch et al. (1997) (36)	House dust mite	Placebo	570 (Der p1)	12 months	All year	Yes
	Tari et al. (1990) (37)	House dust mite	Placebo	NS	18 months	All year	Yes

SCIT, subcutaneous immunotherapy; LNIT, nasal immunotherapy; OIT, oral immunotherapy; SLIT, sublingual immunotherapy; NS, not stated.

*Only the first year of the study was double-blind placebo-controlled.

†Sufficient data are only presented for the first year.

‡Both the intervention and the control group used inhaled fluticasone.

Table 3. Participant characteristics (demographic data of analysed population unless otherwise stated)

	Article	n included verum/control	Drop-out (%)	n analysed verum/control	Age-range (yr) verum/control	Male (%) verum/control	Rhinitis (rh), asthma (a) verum/control
SCIT	Sanders (1966) (11)	32 (16/16)	0	32 (16/16)	4–15*	78*	Rh and/or A 16/16
	Möller et al. (2002) (3)	205 (103/102)	7	191 (97/94)	6–15*	67*	Rh 163; Rh + A 42*
	Fontana et al. (1966) (12)	101 (51/50)	9	91 (47/44)	6–17§	64*	Rh and/or A 47/44
	Weisnagel (1979) (13)	34 (17/17)	21	23 (8/15)	NS	71/71†	Rh 1215; Rh + A 5/2†
	Dreborg et al. (1986) (14)	30 (16/14)	0	30 (16/14)	5–17*	47*	Rh and/or A 16/14
	Urbanek et al. (1991) (15)	57 (26/31)	14	49 (24/25)	NS	NS	Rh or A 24/25
LNIT	Bardare et al. (1996) (16)	40 (NS/NS)	3	39 (NS/NS)	5–15*	70*	Rh 40; A 0/0*
	Mehta and Smith (1975) (17)	46 (23/23)	9	42 (21/21)	6–18+¶	NS	Rh 21/21; A NS**
	Cserhati and Mezei (1997) (18)	36 (grass 12/ragweed 12/control 12)	0	36 (12/12/12)	4–18§	50/83/75†	Rh 12/12/12; A 0/0/0
	Marcucci et al. (2002) (19)	32 (16/16)	19	26 (12/14)	5–14/4–14*	63/44*	Rh 12/14; A 0/0
OIT	Caffarelli et al. (2000) (20)	48 (24/24)	8	44 (24/20)	4–14*	50/65	Rh 1/0; Rh + A 16/17; A 7/3
	Urbanek et al. (1990) (21)	60 (low-dose NS/high-dose NS/control NS)	25	45 (16/14/15)	6–15‡	31‡	Rh 60; A NS*
	Cooper et al. (1984) (22)	54 (28/26)	13	47 (25/22)	5–15§	NS	Rh 28; Rh + A 16; A 3‡
	Reinert and Reinert (1983) (23)	20 (10/10)	30	14 (7/7)	4–11*	NS	Rh 14; Rh + A 6*
	Möller et al. (1986) (24)	30 (14/16)	0	30 (14/16)	8–16/10–15†	57/50†	Rh 14/16; A 0/0
	Giovane et al. (1994) (25)	18 (10/8)	0	18 (10/8)	4–11/3–9†	70/88	Rh + A 10/8
	Urbanek and Gehl (1982) (26)	32 (17/15)	16	27 (15/12)	4–13‡	NS	Rh and/or A 17/15 50/43
	Bufe et al. (2004) (27)	161 (83/78)	18	161 (83/78)	NS	NS	Rh + A 33/35
	Rolinck-Werninghaus et al. (2004) (28)	97 (49/48)	23	77 (39/38)	3–14*	61/73	Rh 29/29; Rh + A 20/19†
SLIT	Yüksel et al. (1999) (29)	39 (21/18)	0	39 (21/18)	6–15/8–15	NS	Rh 10/10; A 11/8
	Novembre et al. (2004) (30)	113 (54/59)	14	97 (47/50)	5–14/4–16	70/70	Rh 47/50; A 0/0
	La Rosa et al. (1999) (31)	41 (20/21)	20	33 (16/17)	6–14/7–13†	65/57†	Rh ± A 16/17
	Pajno et al. (2003) (32)‡	30 (15/15)	10	27 (14/13)	8–14/8–14†	47/40†	Rh + A 14/13
	Vourdas et al. (1998) (33)	66 (34/32)	3	64 (33/31)	8–17/7–17†	74/75†	Rh 1/3; Rh + A 33/29†
	Ippoliti et al. (2003) (34)	86 (47/39)	0	86 (47/39)	5–12/7–11	60/56	Rh + A 18/15; A 29/24
	Bahceciler et al. (2001) (35)	15 (8/7)	0	15 (8/7)	7–18/7–15	50/57	Rh + A 8/7
	Hirsch et al. (1997) (36)	30 (15/15)	3	30 (15/15)	6–15/6–14	67/67	Rh 3/5; Rh + A 9/5; A 3/5
	Tari et al. (1990) (37)	66 (34/32)	12	58 (30/28)	5–12§	64*	Rh + A 30/28

SCIT, subcutaneous immunotherapy; LNIT, nasal immunotherapy; OIT, oral immunotherapy; SLIT, sublingual immunotherapy; NS, not stated.

*Total included participants.

†Included participants.

‡Total analysed participants.

§Inclusion criterium.

¶Two participants were 18+.

**The exact number was not stated, however, a comment was made that most patients had some degree of seasonal asthma.

majority was found within the SLIT subgroup. The description of ‘treatment allocation’ (D2), ‘similarity of the treatment groups at baseline’ (D3), ‘blinding of the outcome assessor/care provider’ (D5/D6) and ‘inclusion of an intention-to-treat-analysis’ (D9) was insufficient in most trials, resulting in a low score of these items. The overall Cohen’s κ was 0.785, corresponding with high agreement between both reviewers (Table 4).

Data extraction and analysis

Primary outcome. Only nine trials stated a primary outcome. A symptom/medication score (23, 27, 28, 31, 33, 36), the development of asthma (3, 30)

or a combined patient–doctor evaluation (17) was used to evaluate efficacy (Table 5).

Demonstrated efficacy. In four cases our conclusion on the effects of the intervention differed from the original conclusion. Ippoliti et al. (34) concluded that rhinitis symptom scores decreased significantly. However, only intra-group p-values for the symptom scores were presented. No measure of variability was stated, making it impossible to calculate the inter-group p-value (SLIT vs. placebo) and to draw a conclusion on the effect of the intervention. Vourdas et al. (33) concluded that SLIT had a positive effect on the conjunctivitis score, but we classified the results as ‘not stated’ because only one of the three eye

Table 4. Results of the methodological quality assessment

Article	D1	D2	D3	D4	D5	D6	D7	D8	D9	D10	D11	Total Delphi*	Cohen's κ †
SCIT	Sanders (1966) (11)	1	0	0	0	1	1	1	1	1	1	8	0.744
	Möller et al. (2002) (3)	1	0	0	1	0	0	0	1	0	1	5	0.814
	Fontana et al. (1966) (12)	1	1	0	0	0	0	0	0	0	0	2	0.744
	Weisnagel (1979) (13)	1	1	0	0	1	0	1	0	0	0	5	0.814
	Dreborg et al. (1986) (14)	1	0	0	1	0	0	1	0	0	1	5	0.814
	Urbanek et al. (1991) (15)	1	0	0	0	0	0	1	0	1	0	3	1.000
LNIT	Bardare et al. (1996) (16)	1	0	0	0	0	0	1	0	0	1	4	0.814
	Mehta and Smith (1975) (17)	1	0	0	0	0	0	0	0	1	1	3	0.792
	Cserhati and Mezei (1997) (18)	1	0	0	1	0	0	0	0	1	1	4	0.792
	Marcucci et al. (2002) (19)	1	0	1	1	0	0	1	1	0	1	7	1.000
OIT	Caffarelli et al. (2000) (20)	1	0	0	1	1	1	1	0	1	0	7	0.298
	Urbanek et al. (1990) (21)	1	0	0	0	0	0	1	0	0	0	2	0.744
	Cooper et al. (1984) (22)	1	0	0	1	0	0	1	0	0	1	5	1.000
	Reinert and Reinert (1983) (23)	1	0	0	0	1	1	1	0	0	0	5	0.645
	Möller et al. (1986) (24)	1	0	0	1	0	0	1	0	0	1	5	0.814
	Giovane et al. (1994) (25)	1	1	1	0	1	1	1	0	1	1	9	0.744
	Urbanek and Gehl (1982) (26)	1	0	0	0	0	0	0	0	1	1	3	0.421
SLIT	Bufe et al. (2004) (27)	1	0	0	1	0	0	1	1	1	1	6	0.814
	Rolinck-Werninghaus et al. (2004) (28)	1	0	1	1	0	0	1	0	0	0	4	0.621
	Yuksel et al. (1999) (29)	1	0	0	0	0	0	1	1	0	0	3	0.560
	Novembre et al. (2004) (30)	1	0	1	1	0	0	1	0	1	1	6	0.633
	La Rosa et al. (1999) (31)	1	0	0	1	0	0	1	1	0	0	4	0.792
	Pajno et al. (2003) (32)	1	1	0	1	1	1	1	0	1	1	9	0.621
	Vourdas et al. (1998) (33)	1	0	1	0	0	0	1	1	0	1	6	0.633
	Ippoliti et al. (2003) (34)	1	0	1	1	0	0	1	1	1	1	7	0.814
	Bahceciler et al. (2001) (35)	1	0	1	0	0	0	1	1	1	1	6	0.814
	Hirsch et al. (1997) (36)	1	1	1	1	1	1	1	0	0	1	9	0.560
	Tari et al. (1990) (37)	1	0	0	1	0	0	1	0	1	1	5	1.000
	Total Item	28	5	8	15	7	6	15	18	5	21	19	
	Cohen's κ †	1.000	0.661	0.578	0.469	0.909	0.900	0.858	0.643	0.700	0.909	0.673	Overall κ

SCIT, subcutaneous immunotherapy; LNIT, nasal immunotherapy; OIT, oral immunotherapy; SLIT, sublingual immunotherapy; 0 = no or unclear; 1 = yes.

*Total Delphi (range 0–11): total score ≥ 6 = high quality; < 6 = low quality.

†Cohen's κ (range 0–1): ≥ 0.7 = high agreement, 0.5 – 0.7 = moderate agreement, < 0.5 = low agreement between reviewers.

symptoms was presented. Dreborg et al. (14) reported a significant difference in rescue medication scores. As this difference was found in 2 weeks of the 10-week evaluation period only, we concluded that there was no positive effect present. Rolinck-Werninghaus et al. (28) calculated the difference in rescue medication scores after 1 and 3 yr of treatment and compared these differences between both treatment groups. They concluded that a significant difference was found between the treatment groups regarding medication scores (28). However, the medication scores of the SLIT-group after 1 yr of treatment were much higher than the scores of the placebo group and a correction for this difference between both groups should have been incorporated in the analysis. We analysed the difference in medication scores after 3 yr of treatment and found no statistically significant difference between both treatment groups ($p = 0.72$) (Table 6).

Level of evidence. The SCIT and LNIT subgroups contained only one high-quality RCT (11, 19), therefore all trials were considered. The findings within the SCIT and OIT groups were not consistent, resulting in conflicting evidence. Although $\geq 75\%$ of the trials demonstrated efficacy in the LNIT group, the level of evidence was considered moderate because only one high-quality trial was available. In 83% of the high-quality trials within the SLIT group efficacy was not demonstrated (27, 32, 33, 35, 36), resulting in no evidence of effect. Only for the perennial allergen trials within the SCIT subgroup and the seasonal allergen trials within the OIT subgroup, the conclusion differed from the overall conclusion for the administration form subgroup. In both cases, the evidence changes from conflicting evidence to no evidence of effect (Table 6).

In consideration of the data, we decided to perform three sensitivity analyses. First, we

Table 5. Data extraction

	Article	Primary outcome stated	Symptoms recorded	Rescue medication recorded	Positive effect on symptoms	Positive effect on rescue medication	Positive effect on symptom-medication score
SCIT	Sanders (1966) (11)	No	ND	No	Yes	NA	No*
	Möller et al. (2002) (3)	Yes	N + O (separate)	No	Yes	NA	NS
	Fontana et al. (1966) (12)	No	N + O (separate)	Yes	No	No	NS
	Weisnagel (1979) (13)	No	N + O (separate)	Yes	No	No	No
	Dreborg et al. (1986) (14)	No	N–O–B (total score)	Yes	No	No†	NS
	Urbanek et al. (1991) (15)	No	ND	Yes	No	NS	NS
LNIT	Bardare et al. (1996) (16)	No	N + O (separate)	Yes	Yes	Yes	NS
	Mehta and Smith (1975) (17)	Yes	ND	No	NS	NA	Yes*
	Cserhati and Mezei (1997) (18)	No	N + O (separate)	Yes	Grass - Yes; Ragweed - No	No	NS
	Marcucci et al. (2002) (19)	No	N + O (separate)	Yes	N - Yes/O - NS	Yes	NS
OIT	Caffarelli et al. (2000) (20)	No	N + O (separate)	Yes	No	No	No
	Urbanek et al. (1990) (21)	No	N + O (separate)	Yes	No	No	No
	Cooper et al. (1984) (22)	No	N + O (separate)	Yes	No	No	No
	Reinert and Reinert (1983) (23)	Yes	ND	No	No	NA	No*
	Möller et al. (1986) (24)	No	N + O (separate)	Yes	No	No	Yes
	Giovane et al. (1994) (25)	No	N + O (separate)	Yes	NS	NS	N - Yes/O - NS (NS)
	Urbanek and Gehl (1982) (26)	No	ND	Yes	NS	NS	No*
SLIT	Bufe et al. (2004) (27)	Yes	N–O–B (total score)	Yes	NS	NS	No
	Rolinck-Werninghaus et al. (2004) (28)	Yes	N + O (separate)	Yes	No	No†	No†
	Yuksel et al. (1999) (29)	No	N	Yes	Yes	Yes	NS
	Novembre et al. (2004) (30)	Yes	N–O–B (total score)	Yes	No	Yes	No
	La Rosa et al. (1999) (31)	Yes	N + O (separate)	Yes	N - Yes/O - NS	No	NS
	Pajno et al. (2003) (32)	No	N + O (separate)	Yes	No	No	NS
	Vourdas et al. (1998) (33)	Yes	N + O (separate)	Yes	N - No/O - NS†	No	No*
	Ippoliti et al. (2003) (34)	No	N	No	NS†	NA	NS
	Bahceciler et al. (2001) (35)	No	N	Yes	No	No	NS
	Hirsch et al. (1997) (36)	Yes	N + O (separate)	Yes	N (no)/O (NS)	No	No*
	Tari et al. (1990) (37)	No	N + O (separate)	Yes	Yes	NS	NS

SCIT, subcutaneous immunotherapy; LNIT, nasal immunotherapy; OIT, oral immunotherapy; SLIT, sublingual immunotherapy; N, nasal; O, ocular; B, bronchial; NA, not applicable; ND, not defined; NS, not stated.

*Only an overall evaluation (benefit–no benefit) was available.

†Revised conclusion, differs from conclusion authors, see text for details.

included the trial by Caffarelli et al. (20) in the SLIT subgroup, as several systematic reviews classified this trial as SLIT instead of OIT (38–42). Inclusion of this trial in the SLIT subgroup, however, did not change the conclusion on the demonstrated efficacy for the SLIT and OIT subgroups. Secondly, we reanalysed all subgroups using the original conclusions stated by the authors. Compared with our initial analyses, the only difference was found in the SLIT subgroup, changing the conclusion from no evidence of effect to conflicting evidence. Thirdly, we excluded all trials sponsored by a pharmaceutical company. As a result the conclusion for the SCIT subgroup changed from conflicting evidence to no evidence of effect.

Secondary outcomes. Quality of life was not investigated in any of the trials included in this review.

Data on adverse events were presented in 86% of the trials (11–14, 16–25, 27, 28, 30–36). The definition of an adverse event was often unclear. For instance, in one trial the authors stated that no side-effects occurred, but some patients suffered from nasal complaints after the LNIT application (18). Local side-effects were more frequently reported in the intervention groups. Systemic side-effects (e.g. asthma) were rare and mild. One SLIT trial reported a serious adverse event, an acute asthma exacerbation requiring hospitalization, in the active group (28). Although the same event was described in the placebo group in another SLIT trial, the authors concluded that no major adverse events were reported (31). Systemic anaphylactic reactions did not occur.

It was often unclear whether results on compliance represented compliance to medication intake or to the study protocol. Only one

Table 6. Level of evidence

Article	Efficacy demonstrated	Methodological quality	Level of evidence	
Subcutaneous immunotherapy				
Sanders (1966) (11)	Yes	H*	Conflicting evidence	
Möller et al. (2002) (3)	Yes	L*		
Fontana et al. (1966) (12)	No	L*		
Weisnagel (1979) (13)	No	L*		
Dreborg et al. (1986) (14)	No	L*		
Urbanek et al. (1991) (15)	No	L*		
Nasal immunotherapy				
Bardare et al. (1996) (16)	Yes	L*	Moderate evidence of effect	
Mehta and Smith (1975) (17)	Yes	L*		
Cserhati and Mezei (1997) (18)	Grass - Yes; Ragweed - No	L*		
Marcucci et al. (2002) (19)	Yes	H*		
Oral immunotherapy				
Caffarelli et al. (2000) (20)	No	H*	Conflicting evidence	
Urbanek et al. (1990) (21)	No	L		
Cooper et al. (1984) (22)	No	L		
Reinert and Reinert (1983) (23)	No	L		
Möller et al. (1986) (24)	Yes	L		
Giovane et al. (1994) (25)	Yes	H*		
Urbanek and Gehl (1982) (26)	No	L	No evidence of effect	
Sublingual immunotherapy				
Bufe et al. (2004) (27)	No	H*		
Rolinck-Werninghaus et al. (2004) (28)	No	L		
Yuksel et al. (1999) (29)	Yes	L		
Novembre et al. (2004) (30)	Yes	H*		
La Rosa et al. (1999) (31)	Yes	L		
Pajno et al. (2003) (32)	No	H*		
Vourdas et al. (1998) (33)	No	H*		
Ippoliti et al. (2003) (34)	Insufficient data†	H		
Bahceciler et al. (2001) (35)	No	H*		
Hirsch et al. (1997) (36)	No	H*		
Tari et al. (1990) (37)	Yes	L		

H, high-quality RCT; L, low-quality RCT.

*Trials providing the evidence.

†Insufficient data to draw conclusion.

trial pre-defined compliance to medication intake (19). Some trials presented the results only in the form of general comments like 'compliance was good' (16, 20, 34). Others reported the number of participants excluded because of 'poor compliance' or 'irregular

intake' (23, 27, 28, 30). Four trials mentioned the number of participant reaching the maximal dose (12, 14, 19, 33). Two studies gave a detailed description of the medication intake. In the trial of Hirsch et al. (36) 53% and 67% of the participants in the SLIT and placebo group, respectively, reported complete regular intake. Weisnagel (13) described that 59% of the participants in the intervention and 100% of the participants in the placebo group received all injections.

Discussion

Methodological quality

The overall quality of the trials was low. Even in studies published after the introduction of the CONSORT statement in 1996 (43) one of the most important items for the assessment of quality, i.e. concealment of treatment allocation, was often insufficiently described. As the lack of adequate allocation concealment is associated with exaggerated estimates of treatment effect and bias (44, 45), inadequate description of this item hampers the interpretation of the results.

Demonstrated efficacy

We did not find conclusive evidence of the efficacy of immunotherapy in any administration form. Several explanations for this finding can be discussed. First, although only two trials presented a power calculation (28, 36), the power in most trials seems to be insufficient to detect a statistical significant difference (38). A clinical relevant difference might be present, but because of inadequate description of the data we could only assess whether a statistical significant difference between treatment groups was found.

Secondly, efficacy could vary for different allergens. Summarizing the efficacy for an administration form could conceal such differences. Although numbers were small, the sensitivity analyses did not show convincing evidence of efficacy for the seasonal and perennial allergen trials within each administration form subgroup.

Thirdly, the dosages used may have been suboptimal. Unfortunately, there are no placebo-controlled dose-finding studies in children available for SCIT, LNIT and OIT. After the inclusion of the trials a placebo-controlled dose-response study with SLIT was published, showing dose-dependent effects (46). Furthermore, the duration of treatment might have been too short in some trials. It has been reported for SLIT that

trials with a duration < 18 months did not show a significant effect on symptom scores (42).

Lastly, compliance to medication intake is important for efficacy to emerge. Only a few trials presented data on compliance making it difficult to interpret the influence of this factor.

To our knowledge, there are no systematic reviews on the efficacy of SCIT, LNIT and OIT in children available. SCIT has been used for a long time and probably because of the fact that positive effects were found in studies performed in adults, trials in children were no longer performed. LNIT and OIT were never used on a large scale, mainly because of side-effects.

Several overviews on the efficacy of SLIT have been published. However, the majority are not systematic reviews and many are written by the same authors. Taking only systematic reviews for allergic rhinitis that included children into account (38–42, 47–49), these reviews differed from our overview on several points. Some only selected English publications in peer-reviewed journals (38, 40). Others restricted the selection to placebo-controlled studies (38, 42, 47, 48) or excluded children > 14 yr (48) or with other clinically relevant sensibilizations (47, 48). In several reviews (38–42) the study by Cafferelli et al. (20) was classified as a SLIT instead of an OIT trial. Our definition of SLIT was that a sublingual phase should be present. The authors described the administration form used as oromucosal-swallow immunotherapy and the tablets were held in the mouth and not under the tongue. Inclusion of this trial in the SLIT subgroup did not alter the conclusion in our analysis. Other reviews (41, 42, 48, 49) included the trial by Wüthrich et al. This trial was excluded from our review because the children were not reported to be randomized. The trial by Yuksel et al. (29) was only considered in one review (41), probably because the focus was on immunological parameters. However, symptom and medication scores were also reported.

The methodological quality of the included trials was assessed in three reviews, using different validated lists (39, 42, 47). All lists included the important quality item ‘concealment of treatment allocation’, but the assessment of this item varied. Wilson et al. (47) concluded that concealment of treatment allocation was adequate in all studies, but Sopo et al. (39) and Penagos et al. (42) stated that the randomization method was not always reported.

A meta-analysis was performed in three reviews (42, 47, 48). Pooling of the data, however, seems inappropriate. All meta-analyses showed a substantial statistical heterogeneity

among trials. If statistical heterogeneity is present and can be explained, meta-analysis – and consequently random effect meta-analysis – should not be considered (45) and as stated, the heterogeneity among SLIT trials can be explained by the clinical diversity (variability in participants, intervention and outcomes) and methodological differences (variability in trial design and quality) presented in the trials.

Although the conclusion on the efficacy of SLIT in these previous systematic reviews varied, the authors were unanimous in their recommendation that more adequately designed studies were needed (38–42, 47–49).

Strengths and weaknesses

We had to exclude a few manuscripts because of language barriers and we cannot rule out that possible relevant trials were not included in this review. As trials from 1966 onward were selected, we decided not to collect additional information from the authors in case of insufficient or missing data. It is conceivable that as data from older studies could probably not be provided a selection would be created. Besides being unable to pool the data, we were also unable to perform all intended analyses, because of insufficient description of the data. As it is suggested that multi-sensitized patients might not benefit from specific immunotherapy as much as mono-sensitized patients, our intention was to perform a sensitivity analysis. However, it was often unclear which allergens were tested to exclude multi-sensitization and/or if additional sensitizations were clinically relevant, making it difficult to classify the included population as mono- or multi-sensitized.

So far, this is the only review presenting an overview on the efficacy of immunotherapy in all its administration forms in children. Furthermore, we included the methodological quality of the trials in the overall evaluation of efficacy.

Interpretation

In spite of the accepted position of immunotherapy in guidelines (50) there is at present insufficient evidence that immunotherapy in any administration form has a positive effect on symptoms and/or medication use in children and adolescents with rhinoconjunctivitis.

Future research

As only SCIT and SLIT are used in clinical practice, future research should focus on these

administration forms. First, the optimal but still safe dose needs to be determined, using randomized placebo-controlled dose-finding studies. Subsequently, trials with adequate design (randomized, placebo-controlled, double-blind, sufficient number of participants, adequate duration of treatment, etc) should establish efficacy. These trials should also include assessment of quality of life and compliance to medication intake. If efficacy is demonstrated cost-effectiveness ought to be assessed.

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