

Safety of allergen-specific immunotherapy. Relation between dosage regimen, allergen extract, disease and systemic side-effects during induction treatment

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Summary

Background Allergen-specific immunotherapy is a well-documented treatment for allergic rhinitis, asthma, and allergy to *Hymenoptera* venoms. The drawbacks of injection immunotherapy are related to the risk of inducing systemic side-effects (especially during the induction phase), the time used to reach the maintenance dose, and the percentage of patients completing the induction phase).

Objective To investigate the practicability and safety of three different patient-friendly induction regimens of clustered immunotherapy (several injections administered during each visit).

Methods Since 1990, three different clustered induction regimens (regimen 1 = exclusively aqueous extracts; regimen 2 = a combination of aqueous and alum depot extracts; and regimen 3 = induction using exclusively alum depot extracts) have been investigated in 657 patients (10 369 injections).

Results A total of 454 systemic (immediate and late) reactions were observed in 257 patients corresponding to 4.4% of the injections and 39.1% of the patients. Most of the systemic reactions were of little or no clinical importance (93% grade 1 and grade 2) and < 1% anaphylactic reactions. The 8-week induction regimen using exclusively alum depot extracts showed a statistical significant lower frequency and severity of systemic side-effects. Immunotherapy with cat and mite allergen extracts showed the highest frequency of severe side-effects, which may be related to these extracts being used predominantly in asthmatic patients. The lowest frequency of systemic side-effects was observed in patients allergic to *Hymenoptera* venoms and these patients furthermore showed the highest number of patients (97%) completing the induction phase.

Conclusion An 8-week clustered induction regimen using alum depot extract seems an acceptable compromise in relation to a reduction in the time used to reach maintenance dose and the risk of inducing clinically relevant systemic side-effects, and consequently imply a reduction in the costs of the treatment.

Keywords: allergen-specific immunotherapy, allergic diseases, allergen extracts, compliance, induction regimens, systemic side-effects

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Introduction

The clinical efficacy of allergen-specific immunotherapy in the treatment of allergies is well documented [1–3].

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Immunotherapy implies, however, a risk of inducing side-effects [1–3]. The frequency and severity of systemic reactions (SR) vary between studies, depending on patient selection, disease, allergen extract and formulation, and induction regimens. Evidence indicates that the patients most likely to react anaphylactic are highly allergic patients with more severe pretreatment disease, i.e. asthma is a

particular risk factor for systemic side-effects [4], and that SR occur more often during induction treatment [2,5,6]. Some studies report a lower frequency of SR with the use of standardized aluminium extracts compared with aqueous extracts, and a reduction in the number of injections required to reach maintenance dose [2,6].

The present study reports the frequency of side-effects during the induction phase in daily routine immunotherapy using different clustered induction regimens and allergen extract formulations. The study include retrospective data from three different induction regimens, and are a part of an immunotherapy quality assurance programme. The paper gives information based on a continuous work with induction regimens to make the treatment more users friendly in daily clinical practice. To obtain the same degree of information in a formal randomized trial would imply the inclusion of an inadmissible large number of patients.

Materials and methods

Patients

A total of 657 patients (307 females and 350 males) referred to our department were included in the study. The distribution of allergic disease involved rhinitis (309), asthma (47), rhinitis and asthma (184), or hymenoptera venom sensitivity (117) treated with immunotherapy in the period 1990–97. The patients were, based on skin tests, determination of specific IgE, and in patients with inhalation allergies conjunctival or bronchial challenge, allergic to at least one of the following allergens: *Betula* (171), *Phleum pratense* (272), cat (32), dog (9), horse [2], house dust mite (54), bee venom (13) and wasp venom (104). The mean age of the patients was 33 years ranging from 14 to 76 years.

Immunotherapy

The indication and contraindications for immunotherapy followed the recommendations of the European Academy of

Allergy and Clinical Immunology (EAACI) [2]. According to the routine of the Department, patients were treated with only one allergen extract during the induction phase. Patients with a need for treatment with more than one allergen extract received induction treatment with a second extract during maintenance phase with the primary extract. The patients were monitored before each injection according to EAACI Immunotherapy position papers [2]. After each injection, patients were observed by nurses and physicians in the clinic for at least 30 min. Allergen extract dosages, local and systemic reactions, and the treatment of such reactions was registered in a patient record form. Allergen dosing was omitted in patients with recent infections or exacerbations of allergic symptoms (increased need for drugs). The dose was reduced accordingly in the case of systemic reactions, unpleasant large delayed local reaction, and exceeding interval between two series of injections. No increment in patients with large immediate (within 30 min after injection) local reaction >5 cm in diameter. Immunotherapy was discontinued in most patients with severe SR (grade 3 & 4) except in Hymenoptera venom-allergic patients. Patients presenting SR were observed, and rescue treatment instituted by the responsible physician, who also graded the systemic reaction based on symptoms, and the patient's response to rescue treatment.

The patients received clustered immunotherapy with standardized aqueous extracts (Aquagen SQ[®] ALK, Denmark) or depot preparations (ALK Alutard SQ[®]) in three different regimens (Table 1).

Regimen 1 (101 pts) comprises patients receiving exclusively aqueous extracts during the induction phase. In regimen 2 (49 pts) aqueous extracts were administered in the initial phase followed by a depot preparation starting with injection no. 12 before reaching maintenance dose. In regimen 3 (507 pts) depot extracts were used during the entire clustered induction phase.

The dosage schedules involved administration of incremental doses at 1 week intervals, followed by maintenance

Table 1. Induction dosage regimens

	Regimen 1	Regimen 2	Regimen 3
Cluster 1	<i>10–50–100–300</i>	<i>10–100–300–600</i>	10–100–1000
Cluster 2	<i>500–800–1000–2000</i>	<i>600–1000–2000–3000</i>	2000–4000
Cluster 3	<i>4000–6000–8000–10 000</i>	<i>3000–4000–6000</i>	6000–10,000
Cluster 4	<i>10,000–20,000–40 000</i>	10,000–20 000	10,000–10,000
Cluster 5	<i>50,000–50 000</i>	20,000–40 000	20,000–20,000
Cluster 6	100000	40,000–60 000	30,000–30,000
Cluster 7		100000	50,000–50,000
Cluster 8			100000

Allergen dosages (SQ-U) administered at each individual cluster. Figures in italics represent aqueous extracts.

injections given at intervals of 2 months. Intended maintenance doses were 100 000 SQ-U/mL or the maximum tolerated dose, e.g. the highest dose not resulting in systemic side-effects. If no side-effects occurrence, and therefore no dose modifications, the patients in regimens 1 and 2 would reach maintenance dose in 18 injections (6 and 7 weeks, respectively). Patients in regimen 3 reached maintenance dose in 16 injections if the schedule were followed as planned (8 weeks) (Table 1).

Side-effect monitoring

Systemic reactions were categorized into immediate SR (occurring within 30 min) and late SR (debut >30 min after injection). They were graded according to the EAACI Immunotherapy Position Paper [2]:

- Grade 0 No symptoms.
- Grade 1 Nonspecific symptoms probably not IgE-mediated, i.e. discomfort, headache, arthralgia, etc.
- Grade 2 Mild systemic reactions, e.g. mild rhinitis or asthma responding adequately to antihistamines or inhaled β_2 -agonist.
- Grade 3 Non-life-threatening systemic reactions, e.g. urticaria, angioedema, or severe asthma, responding well to treatment.
- Grade 4 Anaphylactic shock, e.g. rapidly evoked reaction of itching, flushing, erythema, bronchial obstruction, etc. requiring intensive treatment.

Recording of data

For each of the 657 patients the following data were recorded: a patient identification number; gender; year of

birth; year of treatment start; allergen; disease; regimen; number of injections to reach maintenance dose; and whether or not the patient terminated treatment before reaching maintenance dose. Only data related to the dose escalation phase are reported in this study.

If the patient had presented any SR during the dose increase phase this was separately recorded as follows: Time courses of reaction (immediate or late, or both immediate/late); grading the severity of SR; the allergen dose that elicited the SR; and whether or not adrenalin was administered.

Statistics

Comparisons were made by chi-square analysis for categorical data. An alpha level of 0.05 was considered statistically significant.

Results

The number of patients included in this survey was 657, and the total number of injections administered during the induction phase was 10 369. In total 4.4% (454) of the injections induced SR in 257 patients corresponding to 39.1% of the patients. As some patients experienced more than one different grade of SR, the number of reactors with SR in the statistical analysis is 300 (even though it does not reflect individual patients, this figure depicts better the frequency of SR). According to type, 47.8% of SR were of the immediate type, 50% late SR and 2.2% both immediate and late type. Graded according to severity, 21% of patients presented SR grade 1, 20% grade 2, 4% grade 3, and 0.6% grade 4 (Table 2). The relation between dosage regimens and the grading of SR (Table 2) showed a significant ($P < 0.01$) reduction of SR grade 1–4 in regimen 3 compared

Table 2. Systemic reactions (immediate, i.e. within 30 min after injection and late, i.e. developing >30 min after injection) in relation to regimen

	Total	Regimen 1	Regimen 2	Regimen 3
No. of patients	657	101	49	507
No. of SR (grade 1)	217	39	23	155
No. of patients with SR (grade 1)	141 (21%; 18–25%*)	24 (24%; 16–33%)	13 (27%; 15–41%)	104 (21%; 17–24%)
No. of SR (grade 2)	206	32	16	158
No. of patients with SR (grade 2)	131 (20%; 17–23%)	22 (22%; 14–31%)	8 (16%; 7–30%)	101 (20%; 17–24%)
No. of SR (grade 3)	27	7	2	18
No. of patients with SR (grade 3)	24 (4%; 2–5%)	5 (5%; 2–11%)	2 (4%; 0.5–14%)	17 (3%; 2–5%)
No. of SR (grade 4)	4	2	1	1
No. of patients with SR (grade 4)	4 (0.6%; 0.2–1.6%)	2 (2%; 0.2–7%)	1 (2%; 0.1–10.9%)	1 (0.2%; 0–1.1%)

*The observed mean rate of graded SR and 95% confidence intervals.

with regimens 1 and 2. SR grade 4 (anaphylactic reactions) in regimen 3 occurred less frequently compared with regimen 1 and 2 (1/507 vs 3/150) (NS).

In regimen 3, where patients were treated exclusively with depot allergen extracts, a significantly lower frequency of immediate SR (41% [136/332] vs 63% [50/80] and 74% [31/42], respectively) compared with regimen 1 and 2 was observed ($P < 0.01$) (data not shown). A high percentage of patients in regimen 1 and 2 presented immediate SR of grade 2–4: 28% (28/101) and 33% (16/49), respectively, compared with 14% (69/507) of the patients in regimen 3 ($P < 0.01$). On the other hand, patients treated in regimen 3 showed slightly more late SR than the other groups. Late SR were generally mild and seldom required other interventions than increased self-medication.

The relation between allergen extracts and SR (the dog and horse group includes too few patients to allow statistical analysis) showed that 42% (71/171) of birch allergic patients, 53% (143/272) of grass allergic patients, 59% (19/32) of cat allergic patients, and 57% (31/54) of mite allergic patients experienced one or more SR, and a significant reduced frequency for Hymenoptera venom allergies (28% [33/117]; $P < 0.01$). Looking at severe SR, birch pollen and Hymenoptera venom allergic patients experienced significantly fewer grade 2–4 reactions per patient (20% [34/171]; $P < 0.05$, and 9% [11/117]; $P < 0.01$, respectively) compared with cat, mite and grass allergic patients (41% [13/32], 35% [19/54] and 29% [80/272]).

Maintenance phase was reached by 90% of the patients (594), whereas 10% (63) patients terminated immunotherapy and did not complete the induction phase. Patients who reach maintenance phase presented an average of 0.66 (395–594) SR per patient, whereas those who stopped immunotherapy had an average of 0.94 (59/63) SR per patient ($P < 0.01$). This difference was mainly due to a single patient who on 13 different occasions exhibited a SR. Compliance with immunotherapy (patients reaching maintenance dose) was highest in regimen 3: 92.3% (468/507) of the patients completed treatment and reached the maintenance dose compared with 84.2% (85/101) of the patients in regimen 1 ($P < 0.05$) and 83.7% (41/49) in

regimen 2 (NS). Patients in regimen 3, scheduled to receive 16 injections to reach maintenance dose, required an average of 16.5 injections, whereas patients in regimen 1 and 2, though scheduled to receive 18 injections, received an average of 21.1 and 20.5 injections, respectively, before reaching maintenance dose.

The relation between allergen extract and compliance is shown in Table 3. About 90% (402/443) of patients treated with pollen extracts reached the maintenance dose, compared with 72% (23/32) and 81% (44/54) treated with cat and house dust mite extracts. The highest compliance (97% [114/117]) was found in Hymenoptera venom allergic patients ($P < 0.01$) compared with cat and mite allergic patients and ($P < 0.05$) compared with birch and grass pollen-allergic patients.

The relation between the pretreatment clinical manifestations of the allergic disease and the allergens used for immunotherapy showed that cat and house dust mite allergic patients constituted a significant higher proportion of asthmatics (81% and 73%) compared with patients allergic to birch and grass pollen (34% and 36%), respectively. Overall the compliance was higher ($P < 0.02$ and $P < 0.001$) and SR less pronounced among patients with rhinitis and Hymenoptera venom allergy ($P < 0.005$ and $P < 0.001$), respectively, compared to exclusively asthmatic patients (Table 4). Patients suffering from both rhinitis and asthma showed almost the same frequency of SR and figures for compliance as patients with rhinitis as the only clinical manifestation.

Four of the 454 SR that occurred during immunotherapy induction phase were of grade 4 (anaphylactic shock) corresponding to 0.9% of systemic side-effects, a rate of 0.6% of patients or 0.04% of injections. On these occasions' adrenaline was administered as part of the standard rescue treatment. However, adrenaline was administered on three other occasions, which retrospectively showed not to be grade 4 SR. Totally seven patients received treatment with adrenaline. The characteristics of these are listed in Table 5.

Out of the 257 patients exhibiting SR, 138 were females and 119 males, giving a reaction rate of 45% (138/307) in females vs 34% (119/350) in males ($P < 0.01$). Looking only at clinically relevant SR (grade 2–4) no significant difference

Table 3. Patients completing the induction phase in relation to allergen extract

	Total	Birch	Grass	Cat	Mites	<i>Hymenoptera</i>
No. of patients	657	171	272	32	54	117
No. of patients reaching maintenance dose	594	155	247	23	44	114
Completing induction phase	90% (88–93%*)	91% (85–95%)	91% (87–94%)	72% (53–86%)	81% (69–91%)	97% (92–99%)

*Stated as mean percentage and 95% confidence intervals.

Table 4. Relation between pretreatment disease, serious systemic reactions (immediate and late), and the percentage of patients completing the induction phase

	Total	Rhinitis	Asthma	Rhinitis & asthma	Hymenoptera
No. of patients	657	309	47	184	117
No. of SR (grade 2–4)	237	108	37	78	14
	36% (32–40%*)	35% (30–41%)	79% (64–89%)	42% (35–50%)	12% (7–19%)
No. of patients reaching maintenance dose	594	279	37	164	114
Completing induction phase	90% (88–93%*)	90% (86–93%)	79% (64–89%)	89% (84–93%)	97% (93–99%)

*Number of serious systemic reactions and patients completing induction phase stated as mean percentage and 95% confidence intervals.

between females and males was observed. Likewise, no significant relation between age and SR was observed. However, patients allergic to Hymenoptera venom were on average 43 years of age, which is more than 10-year-old the mean age of the other patients (rhinitis: 31 years; asthma: 31 years; asthma/rhinitis: 30 years). Concerning the number of injections needed to reach maintenance dose, there was little or no difference regarding gender, disease, allergen extract or dosage regimen.

Discussion

The frequency of side-effects in immunotherapy is related to the severity of the disease treated, the degree of sensitivity of the patients, the induction regimen used, and the potency and formulation of the allergen extract [2,3]. Several studies have documented a higher frequency of SR in asthmatics compared with patients with exclusively rhinitis [1]. The intensity of the induction regimen (classical = one injection per week, clustered or rush) has similarly been documented to influence the risk of systemic side-effects, but this may also be related to the formulation of the allergen extract

(aqueous vs. depot) [2,3]. A key measure in reducing side-effects is to undertake pre-injection monitoring of patients to exclude those patients who are unfit to receive injections and to identify those patients in whom the dose should be reduced [2,3].

An important aspect in the discussion of the safety of immunotherapy is the grading of SR. A tremendous difference exists in the impact of a grade 1 nonspecific reaction like tiredness or headache vs a full blown grade 4 anaphylactic shock. Consequently, precise recording and grading of SR are essential for meaningful scientific communication. The grading system proposed by the EAACI [2] and adopted by WHO [3] is a useful instrument for grading side-effects [5].

This retrospective study confirms some findings of other studies reporting systemic side-effects and patient compliance during immunotherapy. Looking at controlled studies published since 1980 [1] supplying data on safety aspects' sometimes fails as 15% of 68 papers did not provide any information on side-effects. No immunotherapy-related side-effects were observed in 26% of the studies. In the remaining studies, a mean value of 24% of the patients

Table 5. Characteristics of seven cases where adrenaline was administered

Case no.	1	2	3	4	5	6	7
Gender	F	F	M	F	M	F	F
Age	32	28	23	18	68	51	17
Allergen	Mite	Cat	Grass	Grass	Bee	Wasp	Grass
Disease	A & R	A	R	R	H	H	A & R
Regimen	1	1	1	1	2	3	3
Completed immunotherapy	no	no	no	yes	yes	yes	yes
Immediate/late SR	Imm	Imm	Imm	Imm	Imm	Imm	Imm + Late
Severity of SR (grade)	4	3	4	2	4	4	2
Dose eliciting SR (SQ-U)	1000	1000	10 000	40 000	100 000	30 000	4000

F = female; M = male; A = asthma; R = rhinitis; H = hymenoptera allergy; Imm = immediate reaction.

experienced various degree of side-effects, mostly mild. Generally, but not consistently, aqueous extracts elicited more systemic side-effects than depot preparations [1–9].

The present study compares three different induction regimens using either aqueous extracts, combined aqueous and depot extracts, or only depot extracts in patients recruited from a comparable population, and using identical indication and monitoring of immunotherapy. The three different regimens are a consequence of an ongoing strategy to improve patient satisfaction by reducing the number of injections and time consumption during induction treatment without increasing the risk of side-effects to an unacceptable level (maintaining safety aspects). Taking all SR, the reaction rate is high compared with published data [1]. Half of all recorded systemic reactions are however, symptoms not recorded and considered as SR in most studies (grade 1), thus reducing the incidence of clinically important side-effects to that of other studies [1]. Furthermore, the frequency of life-threatening side-effects (grade 3 & 4) constitutes <7% of all side-effects. The reaction rate in regimen 3 documented in this study (Table 2) is comparable to other studies on immunotherapy with depot preparations [5,9].

Fewer patients experienced SR when treated with depot preparations (regimen 3) compared with aqueous extracts (Table 2). Tabar *et al.* reported 82.8% of all SR to be late reactions during immunotherapy with an aluminium hydroxide adsorbed extract [5]. Similarly we found a significantly higher proportion of late reactions in regimen 3. We have registered no serious, life-threatening late SR, and most late reactions were managed by the patient without a need for seeking medical help. Using an allergen formulation reducing the risk of immediate systemic side-effects (potentially life-threatening) therefore seems appropriate on the cost of a slight increase in late reactions.

The risk of inducing clinically important side-effects are significantly related to the allergen used for immunotherapy. Especially cat and mite extracts showed a high frequency of grade 2–4 SR. This may be related to differences in potency but more likely caused by a higher proportion of patients allergic to these allergens being asthmatics.

Asthmatic patients presented a great portion of SR grade 2–4 (79% compared with 35% in the rhinitis group, 42% in the group with both rhinitis and asthma, and 12% in the Hymenoptera venom group, Table 4). When immediate reactions are considered 74% of the SR presented by asthmatics, were grade 2 (mild SR). The majority of SR for rhinitis (50%), rhinitis/asthma (52%) and hymenoptera (52%) were all graded as grade 1 (unspecific symptoms). This difference also applies to the late reactions, where 64% of the late SR presented by asthmatics were graded as grade 2, compared with only 44%, 47%, and 9% for rhinitis, rhinitis/asthma, and Hymenoptera, respectively. Therefore, it may be concluded that asthmatics exhibit more frequent

and more severe SR compared with patients suffering from rhinitis and Hymenoptera venom allergy. The group of both rhinitis and asthma include a high proportion of pollen-allergic patients with pulmonary symptoms during intense pollen exposure. The dose induction phase was not performed during the pollen season, which may explain why this group showed SR of the same magnitude as the rhinitis group.

We found a significantly higher proportion of females exhibiting overall SR compared with males. However, this difference was no longer significant, when reactions grade 1 were excluded suggesting an equal distribution of serious side-effects in females and males. Since grade 1 reactions are exclusively subjective symptoms, detecting these reactions causal relationship to immunotherapy is sometimes difficult as an equivalent frequency in placebo-treated patients is observed in many studies. Another study [9] found a similar difference but it is also reported not to be statistically significant. Therefore we conclude that females do not exhibit more severe SR than males.

This study has not investigated why some patients terminated the treatment before reaching maintenance dose. Life-threatening allergic conditions like allergy to Hymenoptera venoms showed a completing rate close to 100%. The lowest percentage of patients completing the induction phase was in the group of asthmatics and the elevated frequency of side-effects seems the most obvious explanation for this. An overall completing rate of 90% seems acceptable in an unselected group of allergics, and the rather high frequency of side-effects does not seem to have a major impact on patients terminating the induction phase before reaching the maintenance dose. The study investigates different induction regimens, and we have only focused on the number of patients completing the induction phase. Failures to complete the whole treatment is another important aspect however, beyond the scope of this study.

In conclusion, the presently used regimen (regimen 3) for immunotherapy induction seems a useful compromise between the time used to reach maintenance dose and the risk of clinically important systemic side-effects. The presented 8-week induction regimen does not seem to have an unacceptable high frequency of side-effects and have the advantage of a fast induction regimen being a benefit for the patients, and furthermore reduces the costs of the treatment. As the safety monitoring is important for reducing side-effects, extrapolating the results to other settings is only valid in combination with the pre-injection monitoring of patients used in this study.

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