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Side-effects of injective allergen immunotherapy administered to intermittent or persistent allergic rhinitis patients*

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SUMMARY

Aim: *Evaluation of the side-effects of conventional subcutaneous allergen immunotherapy in inhalant allergy.*

Material and methods: *Retrospective analysis of early and late, local and systemic, short-term and long-term side-effects of 4723 injections given to 224 patients suffering from intermittent or persistent allergic rhinitis.*

Results: *There were 65 systemic reactions in 48 patients (21%) after 61 injections (1.29%). Most of them were late, and included dyspnoea, rhinorrhoea, fever, fatigue and urticaria. Incidence of systemic reactions did not correlate to age or sex, but was higher in grass pollen than in house dust mite allergy and during the up-dosing phase of treatment. Late intense local reactions were observed after 1.6% of injections.*

Conclusions: *Allergen immunotherapy in inhalant allergy is a safe method of treatment.*

Key words: allergen immunotherapy, side-effects, intermittent allergic rhinitis, persistent allergic rhinitis

INTRODUCTION

Allergen immunotherapy (IT) is standard therapeutic management of patients suffering from allergic diseases. This method, besides avoidance of exposure to clinically significant allergens, is the only one possibility of causal treatment of IgE-mediated diseases. IT has immunomodulation activity and additionally, it also modifies the natural history of atopic allergy. Even though specific immunotherapy is considered to be a safe method of treatment, there is a risk of side-effects during its application [(1)].

The most frequent method of IT is subcutaneous injections of increasing doses of extracts of allergens of proven clinical relevance. Allergen vaccines should be administered in optimal doses to achieve clinical efficacy. However this method of treatment poses the risk of a life-threatening anaphylactic reaction that needs immediate medical intervention. Side-effects of allergen vaccines can occur locally and systemically. Local symptoms may be early (in <30 minutes) or late (after 30 minutes, the most frequently after 6-24 hours). They manifest as excessive oedema, reddening, pain and pruritus in the place of injection. Systemic symptoms may manifest as an intensification of allergic symptoms such as rhinitis, dyspnoea, urticaria, fatigue and shock. These symptoms can occur early and late. While late symptoms, both local and systemic, are not dangerous and can be controlled through changing the dose of allergen vaccine, systemic anaphylactic reaction is life-threatening and always needs immediate medical intervention [(2-5)].

It has been generally accepted that correct indications for immunotherapy and treatment by a specialist result in the optimal therapeutic index and the highest level of safety. Even

List of abbreviations:
IT – immunotherapy
IAR – intermittent allergic rhinitis
PAR – persistent allergic rhinitis
BA – bronchial asthma
AD – atopic dermatitis
SSE(s) – systemic side effects (effects)
LSE (s) – local side effect (effects)

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though IT has been accepted as a safe method of treatment, there is a risk of side-effects. Accordingly, constant observation for side-effects of this form of immunotherapy is necessary.
The aim of our study was to estimate the frequency and severity of side-effects of allergen immunotherapy in patients with intermittent or chronic allergic rhinitis.

MATERIAL AND METHODS

Material

In total, 224 patients (129 males, [57.6%], mean age 25.07 years, range 5-46), including 127 subjects with intermittent allergic rhinitis and 97 with persistent allergic rhinitis who underwent allergen immunotherapy from 1990 to 2001, were included in this retrospective study. The patients were treated in the following institutions in Poland: Out-patient Clinic of Allergology, Centre for Pulmonary Diseases in Bystra Śląska, Out-patient Laryngological Clinic, Hospital "Stalownik" in Bielsko-Biala, Out-patient Clinic of Allergology in Zabrze, and Chair and Clinical Department of Internal Diseases, Allergology and Clinical Immunology, Silesian University School of Medicine, Zabrze.
Patients were divided into four subgroups: a group IAR - 100 subjects with intermittent allergic rhinitis, a group IAR+BA – 27 subjects with intermittent allergic rhinitis coexisting with bronchial asthma, a group PAR - 51 patients with chronic allergic rhinitis, and a group PAR+BA - 46 patients with chronic allergic rhinitis coexisting with bronchial asthma. Patients in groups IAR and IAR+BA had clinical signs of sensitization to grass, rye, tree or weed pollen. All the patients in groups PAR and PAR+BA were sensitized to house dust mites. No patient with intermittent allergic rhinitis was sensitive to perennial allergens (house dust mites) and similarly no one with persistent allergic rhinitis suffered from sensitization to seasonal allergens.
There were 8 patients with atopic dermatitis: 2 subjects in the IAR group, 4 subjects in the PAR group, and 2 subjects in the PAR+BA group.

Type of immunotherapy

The decision to use immunotherapy was made on medical history regarding the appearance or increase in disease symptoms and the positive results of skin prick tests (wheal diameter >3 mm). A solution containing phenol, glycerol and natrium chloride was used as negative control and histamine diphosphate (5 mg/ml) as a positive control.
Before applying the vaccines the following procedures took place: (i) physical examination; (ii) measurement of peak expiratory flow, (iii) assessment of local early and late reaction after a previous injection according to recommendations by EAACI; (iv) assessment of systemic reaction after a previous injection. Antihistaminic preparations were not applied as a preventive method.
Allergen immunotherapy was conducted according to generally accepted rules and manufacturers' recommendations.
The following vaccines were applied:

1. Aqueous extracts of allergens:

a. **Catalet T or D** (Company of Serums and Vaccines, Kraków, Poland; T stands for grass pollens, and D stands for tree allergens), (aqueous extract of inhalant allergens precipitated with zinc chloride and tannin, modifying formalin and aluminum hydroxide-adsorbed; standardized in PNU units).
b. **Alutard SQ** (Alk Laboratories, Denmark) (aqueous allergen extract aluminum hydroxide- adsorbed and diluted in physiologic salt solution with 0.5% phenol as conserving agent).

2. Modified allergen extracts:

a. **Allergovit** (Allergopharma, Germany) (alergoids aluminum hydroxide- adsorbed), standardized in therapeutic units,
b. **Novo–Helisen Depot** (Allergopharma, Germany) (allergenic extract with buffered salt solution, aluminum hydroxide- adsorbed, in suspension of physiologic salt solution, preserved in 0.4% phenol) standardized in therapeutic units
c. **Alavac S** (Bencard, Brentford, England; now Allergy Therapeutics Poland) (standardized allergenic extract of house dust mite, extracted and modified by pyridine, and hydroxide- adsorbed, preserved in 0.5% phenol)

Catalet T was given to 74 subjects (33%), Catalet D to 5 subjects (2%), Alutard SQ to 36 subjects (16%), Allergovit to 47 subjects (21%), Novo – Helisen Depot to 26 subjects (12%), and Alavac S to 36 subjects (16%).

Assessment of side effects

Local and systemic, early and late side-effects were evaluated according to the European Academy of Allergology and Clinical Immunology (EAACI) scale with regard to the severity of syndrome (0- IV°) [6]:
Grade 0 – without symptoms; Grade 1 – non-specific symptoms, probably independent from IgE, such as headache, discomfort, arthralgia etc.; Grade 2 – mild, systemic reactions such as weak intensification of rhinitis or asthma, which respond well to drugs (antihistaminic drugs or short-acting β2-mimetics); Grade 3 – systemic non-life-threatening reactions such as urticaria, angioedema, symptoms of asthma, which respond well to drugs; Grade 4 – anaphylactic reaction.
The final analysis was based on observations of subjects by physicians who oversaw the whole course of immunotherapy and by patients who noted symptoms down in the patient's diary and in questionnaires recommended by the EAACI [6]. All symptoms remaining in cause and effect relationship with allergen injections were accepted as side-effects. Before starting treatment informed consent from all patients or their parents in the case where patients were under age of 18 was obtained.

Table 1. Local side-effects of immunotherapy - time of onset and method of management.

Type of side-effects	Number (%) of injections which induced LSE	Time of incidence	Management
Oedema 5- 10 cm	45 (0.95)	Late (after 6- 24 hours) -45	Spontaneous resolving
Oedema >10 cm	7 (0.15)	Late (after 6-24 hours) -7	Antihistaminic drugs, cold compress
Pruritus in the place of injection	7 (0.15)	Late (after 6-24 hours) -7	Ice compress
Pain of arm	18 (0.38)	Late (after 6-24 hours) -18	Antihistaminic drugs, cold compress
Lack of side-effects	4646 (98.37)		
Together	**4723 (100)**	**Early 0 Late 77**	

Table 2. Local side-effects of immunotherapy according to type of allergic disease.

Type of allergic disease	Number (%) of injections	Type of local side-effects	Time of incidence early	late
IAR	18 (23)	edema 5-10cm – after 9 injections; edema >10 cm – after 5 injections; pain – after 4 injections;	0	18
IAR+BA	10 (13)	edema 5-10 cm – after 9 injections; pain - after 1 injection;	0	10
PAR	15 (20)	edema 5-10 cm – after 5 injections; pruritus – after 6 injections; pain – after 4 injections;	0	15
PAR+BA	34 (44)	edema 5-10 cm – after 22 injections; edema >10 cm – after 2 injections; pruritus – after 1 injection; pain – after 9 injections	0	34
Together	**77**		**0**	**77**

IAR indicates a group of patients with intermittent allergic rhinitis, IAR+BA – a group of patients with intermittent allergic rhinitis and asthma, PAR - a group of patients with persistent allergic rhinitis, PAR+BA - a group of patients with persistent allergic rhinitis and asthma.

Statistical analysis

As data were mostly qualitative, statistic analysis was based on the Chi-square test with modifications if needed (Yates (Y) correction, V- square test). All analyses were performed with a software package (The Quick STATISTICA PL.) and p-values < 0.05 were considered significant.

RESULTS

In total, 4723 injections in 224 subjects were analyzed (average 21 injections per patient), of which 3327 injections were applied during the up-dosing phase and 1396 injections during the maintenance phase.

Local side-effects

Local side-effects occurred in 33 (14%) patients after 77 (1.6%) injections. All of them were late and manifested as oedema at the site of injection and / or brachialgia which needed anti-histamines and / or compress of ice. The more severe side effects occurred in the patients suffering from chronic rhinitis with bronchial asthma. The most common local side-effects were clinically insignificant and were treated with ice compress or local anti-histamines without modification of the consecutive dose of vaccine (Tables 1 and 2).

Systemic side-effects

Among 4723 injections of allergen vaccines, which were given to patients included in analysis, 61 (1.29%) induced systemic side-effects (SSEs). Only 3.1% of them were early and 96.9% were late. SSEs occurred in 48 (21%, 26 males) patients treated with allergen vaccines. Most of these symptoms were classified as mild (1st or 2nd grade according to EAACI). The most frequent SSEs included running nose, sneezing, lacrimation and did not need treatment. Urticaria occurred in 4.6% of cases as late symptoms by 3rd grade of seriousness and regressed after using an antihistamine. Systemic reaction (4th grade according to EAACI) was not observed in any case. Dyspnoea was observed after 15 (0.32%) injections, intense rhinitis after 37 (0.79%) injections, fever after 3 (0.06%) injections, and fatigue after 6 (0.13%) injections. Anxiety due to a sleepless night occurred in 1 patient after 1 injection. There was no correlation

between sex or age of patients and the incidence of side-effects. SSEs occurred significantly more often after vaccines containing pollen allergens than those house dust mite allergens ($p < 0.00001$). Systemic symptoms were preceded by local symptoms only in two cases; there were dyspnoea and fatigue occurring at the same time as edema and redness in a site of injection. These symptoms resolved after applying antihistaminic drug. The distribution of SSEs in all groups of patients has been shown in Table 3. The most SSEs occurred in patients suffering from intermittent allergic rhinitis (Chi-square test; $p = 0.002$). There were more SSEs in the group IAR+BA in comparison with the group PAR+BA (V test; $p = 0.001$).

In patients with bronchial asthma, dyspnoea was observed after 12 injections, whereas in the group of patients with IAR only 3 injections caused dyspnoea. Dyspnoea occurred three times in patients of the group IAR+BA sensitive to grass and rye, in the up-dosing phase. Dyspnoea was mild, occurred 20 minutes after injection, with no physical signs and spontaneously resolved. In 9 (4.0%) patients of the group PAR+BA dyspnoea with wheezing was observed in the up-dosing phase. In all cases the reactions were late in their nature and regressed after inhalations of short-acting β2-mimetics. No disturbances of ventilation were noticed during next visits and at home therefore IT was continued.

SSEs occurred more often in the up-dosing phase than in maintenance phase [53 SSEs, (86.8% of all SSEs) during the up-dosing phase and 8 SSEs (13.2%) during the maintenance phase ($p < 0.0001$).] The occurrence of SSEs was 1.12% (53 of 3327 all applied injections) in the up-dosing phase of treatment, and 0.17% (8 of 1396 all applied injections) in the maintenance phase (p=0.005, Chi-square test). The occurrence of SSEs in individual years of immunotherapy did not differ significantly (data not shown).

Table 3. Distribution of systemic side-effects of immunotherapy according to type of allergic disease.

Allergic disease	Number of patients	Number (%) of patients with SSEs	Number of injections administered	Number of injections inducing SSEs
IAR	100	24 (24%)	1458	30
IAR+BA	27	9 (33%)	329	12
PAR	51	3 (6%)	1494	2
PAR+BA	46	12 (26%)	1442	17
Total	**224**	**48 (100%)**	**4723**	**61**

SSE indicates systemic side effects, IAR – a group of patients with intermittent allergic rhinitis, IAR+BA – a group of patients with intermittent allergic rhinitis and asthma, PAR - a group of patients with persistent allergic rhinitis, PAR+BA - a group of patients with persistent allergic rhinitis and asthma.

DISCUSSION

In this paper safety of injective specific immunotherapy of inhalant allergy has been proved. Side-effects relevant to administration of allergen vaccines occurred rarely and were mostly mild. Observed side-effects were not life threatening. In individual cases it was necessary to modify the next dose of vaccine. The results confirm that specific immunotherapy is a safe method of treatment of correctly qualified patients suffering from atopic diseases. It is worth emphasizing that all patients in this study received allergen vaccines in professional medical settings and that they were under the close scrutiny of allergists during whole period of the treatment.

In this study we analyzed 224 patients. In total, 33 (13.7%) experienced local side effects, which occurred after 77 (1.6%) injections. The reactions like oedema (sized more than 5 cm) in the site of injection, pruritus or pain were qualified as late and safe symptoms, and resolved spontaneously or after applying antihistaminic drugs.

Other researchers have observed a higher incidence of LSEs of specific immunotherapy than in our study. Zenner et al. [7] analyzed safety of specific immunotherapy in patients suffering from IAR who were desensitized with allergoids of grass pollens. LSEs occurred after 9.7% of all injections. Frank et al. [8] reported early LSE after 0.6% of injections, and late LSE after 13% of injections in patients suffering from IAR. In another study [9] LSEs bigger than 5 cm occurred after 22.1% of injections in patients suffering from intermittent allergic rhinitis treated by depot vaccine containing allergoids of hazel, birch and alder pollens. LSEs were observed in the first year after 5.9% of injections, in the second year after 2.3% of injections and in the third year after 1% of injections, together after 189 (3%) among 6322 injections applied during three years.

Interestingly, Tamir et al. [10] indicated incidence of LSEs of 40% (average 3 LSEs per one patient) in patients suffering from inhalant allergy. Gawlik et al. [11] observed a significant decrease in number of local reactions like oedema bigger than 5 cm in successive years of immunotherapy of pollen allergy.

In the present study all systemic side-effects were late. These effects were noticed in 48 (21%) patients, after 1.29% of all injections. Administration of adrenalin was not necessary in any patient. Winter et al. noticed a similar frequency of SSEs (1.08% of injections) when usingAlutard in patients suffering from allergic rhinitis [12]. Rieckenberg et al. observed SSEs in 6.7% of 901 patients, and 1% of them needed administration of adrenalin. These reactions occurred in the maintenance phase and without any prodromal symptoms [13]. Zannino at el. evaluated risk of complications of injective IT in 1056 children aged 4-16 years. Mild systemic side-effects were observed in 3.7% of patients and one anaphylactic reaction [14]. Symptoms occurred more often in children treated with preparations containing house dust mite allergens than in those who received grass pollen extracts. Luigi et al. applied 300.086 injections of

allergens extracts to 6319 patients suffering from allergic rhinitis and/or asthma and observed only 0.061% SSEs (urticaria, mild aggravation of asthma and rhinitis) in 131 (2.1%) patients. Anaphylactic reactions did not occur [15]. It is hard to compare data concerning safety of IT because authors apply various vaccines and they use various methods of documentation. It is noteworthy that aqueous extracts of allergens used in the past were less effective and caused more side-effects as compared to extracts currently available [16-18].

Some authors draw attention to more frequent incidence of systemic side-effects in patients suffering from bronchial asthma and with high grade of sensitization. Stewart and Lockley [18] ascertained that the most dangerous were systemic side-effects occurring in less than 30 minutes after injection (so classified as early). These can precede anaphylactic reaction. The dose of vaccine should be increased carefully in patients who experienced dyspnoe after applying allergen vaccines. Kowalski et al. [19] recommended evaluation of peak expiratory flow value after applying each dose of vaccines in order to demonstrate bronchocontriction as early as possible

The same type of reactions in the same patients draws attention in the present study. It confirms the thesis that the incidence of side-effects during immunotherapy is individually variable. There was no relationship between SSEs and sex or age. In our study SSEs occurred in only 3 children under 10 years and in 3 adults above 35 years. Mean age of all patients experiencing SSEs was 25.1 years. Lin et al. [20] obtained similar results; they observed most SSEs in patients aged 16-39. Ragus et al. [21] also failed to show a relationship between systemic side-effects and sex or age, as well.

As in the present study more SSEs were observed after vaccines including grass pollens and in patients suffering from asthma, although 1/3 of all patients with SSEs suffered from IAR only. In Ragusa's study that lasted 10 years, systemic side-effects were less common during IT than whilst using pharmacotherapy. SSEs were noticed in 5.2% of patients after 0.06% of injections. This was in contrast to results by Buscino et al. [22] where SSEs occurred significantly more frequently in children desensitized with extracts of house dust mites than with extract of grass pollen. SSEs were observed in 3.7% of patients and after 0.09 % of injections. Karaayvaz et al. described 125 SSE in 109 patients among 1506 (8.3%) treated with aqueous extract of allergens for 12 years. Most of them (84.8 %) occurred early, in the maintenance phase (58.4%) and in the pollen season (60.8%). There was no correlation between SSEs and age, sex, incidence of asthma in desensitized patients [23].

In our study most complications occurred in the up-dosing phase, similar to the results obtained by others [13,23,24]. It is worth noting that 4 of our patients had side-effects after the very first dose of vaccine and 2 patients had SSE after 2 years of applying IT at monthly intervals. These practical valuable observations suggest that side-effects can occur whenever and irrespective of the concentration of allergens in preparation.

Concluding, analysis of our data confirmed that allergen immunotherapy conducted strictly according to the guidelines of EAACI is a safe method of treatment with only a few side-effects which are mostly mild in character.

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REFERENCES

1. Bousquet J, Lockey R, Malling HJ. Allergen immunotherapy: therapeutic vaccines for allergic diseases. A WHO position paper. J Allergy Clin Immunol 1998; 102: 558-562.
2. Stewart GE, Lockey RF. Systemic reactions from allergen immunotherapy. J Allergy Clin Immunol 1992; 90: 567-578.
3. Lower T, Henry J, Mandik L, Janosky J, Friday G. A compliance with allergen immunotherapy. Ann Allergy 1993; 70: 480-482.
4. Squillace DL, Yunginger JW. Systemic reaction (SR) rates in a multicenter, double-blind, placebo controlled study of standardized immunotherapy for short ragweed (SWR) or house dust mite (HDM)-induced asthma. J Allergy Clin Immunol 1991; 87: 193.
5. AAAI Board of Directors. Guidelines to minimize the risk from systemic reactions caused by immunotherapy with allergenic extracts. J Allergy Clin Immunol 1994; 93: 811-812.
6. Malling HJ, Weeke B. EAACI Position Paper on Immunotherapy. Allergy 1993; 48 Suppl 14: 9-35.
7. Bousquet J, Hejjaoui A, Soussana M and Michel FB. Double-blind, placebo-controlled immunotherapy with mixed grass-pollen allergoids: IV. Comparison of the safety and efficacy of two dosages of high-molecular-weight allergoid. J Allergy Clin Immunol 1990; 85:490-497.
8. Frank E. Fruhzeitige Veraenderungen klinischer und immunologischer Parameter waehrend der Hyposensibilisierung mit Depot-Allergoid. Allergologie; 1988; 11: 359-365.
9. Frank E, Joppich B, Distler A and Cromwell O. Kurz- und mittelfristige Erfolgskontrolle nach dreijaehriger Hyposensibilisierung mit Gramineenpollen-Depot-Allergoid (Allergovit). Allergologie 1996; 19: 277-281.
10. Tamir R, Levy I, Duer S, Pick AI. Immediate adverse reactions to immunotherapy in allergy. Allergy 1992; 47: 260-263.
11. Gawlik R. Powikłania w przebiegu swoistej immunoterapii. (Complications as result of specific immunotherapy). Pulmonologia 1997; 4: 201-203.
12. Winther L, Malling HJ, Mosbech H. Allergen-specific immunotherapy in birch and grass-pollen allergic rhinitis. II. Side-effects. Allergy 2000; 55:827-835.
13. Rieckenberg MR, Khan RH, Day JH. Physician reported patient response to immunotherapy: a retrospective study of factors affecting the response. Ann Allergy 1990; 64: 364-367.
14. Businco L, Zannino L, Cantani A, Corrias A, Fiocchi A, La Rosa M. Systemic reactions to specific immunotherapy in children with respiratory allergy. A prospective study. Pediatr Allergy Immunol 1995; 6: 44-47.
15. Luigi A. Senna G, Mezzelani P, Pappalard G. Safety of specific immunotherapy: a retrospective study. J Invest Allergol Clin Immunol 1994; 4: 250-254.
16. Bousquet J, Guerin B, Dotte A, et al. Comparison between rush immunotherapy with a standardized allergen and an alum adjuved pyridine extracted material in grass pollen allergy. Clin Allergy 1985; 15:179-193.
17. Vervloet D, Khairallah E, Arnaud A, Charpin J. A prospective national study of the safety of immunotherapy. Clin Allergy 1980; 10: 59-64.

18. Stewart GE, Lockey RF. Systemic reactions from allergen immunotherapy. J Allergy Clin Immunol 1992. 90: 567-578.
19. Kowalski ML, Buczyłko K, Jurkiewicz D, Kuna IAR, Małolepszy J, Rogala B et al. Objawy niepożądane w przebiegu przedsezonowej immunoterapii preparatem Pollinex® +Rye u pacjentów uczulonych na pyłki drzew i/lub traw - badanie wieloośrodkowe. Alergia, Astma, Immunologia 2001; 6: 45-50.
20. Lin MS, Tanner M, Lynn J, Friday GA. Nonfatal systemic reactions induced by skin testing and immunotherapy. Ann Allergy 1993; 71: 557-562.
21. Ragusa FV, Passalacqua G, Gambardella R, Campanari S, Barbieri MM, Scordamaglia A, Canonica GW. Nonfatal systemic reactions to subcutaneous immunotherapy: a 10-year experience. J Invest Allergol Clin Immunol 1997; 7:151-154.
22. Businco L, Zannino L, Cantani A, Corrias A, Fiocchi A, La-Rosa M. (1995) Systemic reactions to specific immunotherapy in children with respiratory allergy: a prospective study. Pediatr Allergy Immunol 1995; 6: 44-47.
23. Karaayvaz M, Erel F, Caliskaner Z, Ozanguc N. Systemic reactions due to allergen immunotherapy. J Invest Allergol Clin Immunol 1999; 9: 39-44.
24. Mellerup MT, Hahn GW, Poulsen LK, Malling HJ. Safety of allergen-specific immunotherapy. Relation between dosage regimen, allergen extracts, disease and systemic side-effects during treatment. Clin Exp Allergy 2000; 30: 1423-1429.

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