Alergologia Polska – Polish Journal of Allergology 2023; 10, 3: 180–186
DOI: https://doi.org/10.5114/pja.2023.131707
Received: 13.08.2023, Accepted: 7.09.2023.

Alergologia POLSKA
Polish Journal of Allergology

ORIGINAL PAPER/*PRACA ORYGINALNA*

Role of premedication to prevent reactions in cluster immunotherapy

Rola premedykacji w zapobieganiu reakcjom w immunoterapii klastrowej

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ABSTRACT

Introduction: The clinical efficacy of allergen immunotherapy is well documented, but the treatment always involves a risk of adverse reactions. Although premedication is not routinely performed, it has been shown to reduce the adverse reactions.

Aim: To evaluate the contribution of premedication to prevent hypersensitivity reactions during cluster immunotherapy.

Material and methods: 253 patients receiving a total of 290 cluster immunotherapy protocols to house dust mites, pollens, and venoms were recruited in the study. Patients were randomized into 5 groups according to the premedication status as follows: daily antihistamine, antihistamine only 2 h prior to injections, daily montelukast, combination of montelukast and antihistamine and the control group including patients without premedication. Patients were followed during up-dosing and maintenance phases of immunotherapy. Systemic and local reactions were reported.

Results: Most of the patients were female (61.7%), the most frequent allergen was house dust mites (56.9%). 67.2% of patients had premedication and 20.6% of patients had reactions during the up-dosing phase. Reactions were more frequent in patients who received pollen immunotherapy. The total frequency of the hypersensitivity reaction was significantly higher in the control group. When evaluated seperately, local reactions were more frequently observed in the control group, while no difference in the frequency of systemic reactions was detected.

Conclusions: Our study suggests that the reaction risk is increased in pollen immunotherapy. Premedication does not seem to prevent the frequency or severity of systemic reactions. However premedication, daily AH intake in particular, decreases the frequency of local reactions.

KEY WORDS

premedication, allergen immunotherapy, systemic hypersensitivity reactions, local hypersensitivity reaction, cluster immunotherapy, antihistamine.

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INTRODUCTION

Allergen immunotherapy (AIT) is a specific treatment that has the potential to change the natural course of allergic disease. Its antigen-specific immunomodulatory tolerance is manifested by a relative decrease in antigen-specific responsiveness that might be accompanied by immune deviation, T-cell anergy and/or T-cell apoptosis. There exists an allergen-specific immune deviation from Th2 to Th1 responses and a clonal deletion of sensitized cells that reduces the hyperreactivity of the recipient to those allergens [1–3].

The aim of immunotherapy is to reach an optimum clinical effect with as few adverse reactions as possible. The adverse reactions of AIT may be local or systemic. Local reactions (LR) are limited to the site of injections, while systemic reactions (SR) can range from mild to severe reactions of the skin, upper and lower airway, gastrointestinal system and cardiovascular system. In a real-life US survey researching the adverse reactions of subcutaneous immunotherapy (SCIT) which evaluated 64.5 million doses of injection visits, SR occurred in 8.8 per 10,000 injections [4]. A European real-life prospective survey performed by the EAACI Interest group evaluated 4316 AIT patients and demonstrated that systemic reactions occurred in 2.1% of the patients [5].

The majority of patients receive AIT without any serious complications, but still a minority of patients may experience adverse reactions. According to characteristics of adverse reactions, different variations of dose adjustments and/or premedication may be implemented to overcome the complications. These adjustments not only prevent the adverse reactions but also provide other benefits, such as increasing patients' comfort and adherence to the immunotherapy. But still the main intention of dose adjustment is to reduce the risk of systemic reactions. When 1 or more SRs occur, the physician should reevaluate the risks and benefits of AIT with the patient and decide whether or not to continue AIT [6, 7].

Although premedication is not routinely performed in allergen-specific immunotherapy, it has been shown to reduce SRs in patients using rush, cluster and conventional schedules. Premedication in immunotherapy with antihistamines (AH) is shown to reduce the systemic reaction rate during rush immunotherapy in studies. But the efficacy of premedication in cluster immunotherapy is lacking [8].

AIM

The aim of our study was to evaluate the contribution of premedication protocols to prevent local and systemic hypersensitivity reactions during cluster immunotherapy.

MATERIAL AND METHODS

PATIENT RECRUITMENT

Adult patients with proven aeroallergen or venom hypersensitivity were enrolled to the study before initiation of cluster AIT. Patients suffering from mastocytosis (as determined by elevated serum tryptase), patients requiring β-blockers or ACE inhibitors, pregnant women, noncompliant patients and patients who received immunotherapy within 5 years and patients who did not give informed consent were excluded.

STUDY DESIGN

Patients were randomized into 5 different groups according to the premedication status as follows: Group 1: daily antihistamine, Group 2: antihistamine only 2 hours prior to injections, Group 3: daily montelukast, Group 4: combinations of montelukast and antihistamine and Group 5: control group including patients without premedication.

The patients received immunotherapy with either house dust mite (HDM), wall pellitory, birch, grass pollen extracts**,** venom or two of these. Before each injection the physician evaluated the patient's condition and assessed the patient's suitability for immunotherapy. The patients received the injections at 30-minute intervals and stayed in the clinic for at least 30 min after the last injection, systemic and local reactions were reported. Reactions are reported according to the World Allergy Organization Subcutaneous Systemic Reaction Grading System [9]. To assess delayed LR, the patients were asked to report any swelling, erythema and itching at the site of injection for the next 2 days after each injection series.

Dose modifications were made if reactions occurred. Patients who experienced systemic reactions or inconvenient large local reactions during cluster immunotherapy were transferred to the conventional schedule (one injection in a week). The patients were planned to be excluded from the study, in case of persistently occurring reactions despite modifications. Splitting doses or adding AH treat-

ment were made if local reactions occurred according to the reaction and premedication status.

STATISTICAL ANALYSIS

Statistical analyses were performed by the IBM Statistical Package for the Social Sciences version 25.0 (SPSS Inc., Chicago, IL, USA) for MacOS. Categorical variables were summarized as frequencies and percentages. Continuous variables were given as mean values and standard deviations or median (min.–max.) values according to the distribution of the data. The Wilcoxon test was used for comparison of data that were not normally distributed. Mann-Whitney *U* test and Kruskal-Wallis test was conducted to evaluate the different groups. The two-sided p-value < 0.05 determined the statistical significance.

ETHICS

This study was conducted in accordance with the World Medical Association Declaration of Helsinki. Ethical approval was obtained from the Istanbul Faculty of Medicine Ethics Committee and written informed consent forms were collected from all study participants.

RESULTS

DEMOGRAPHIC FEATURES AND CLINICAL CHARACTERISTICS OF THE PATIENTS

253 patients were recruited to the study. The ages of patients ranged from 18 to 71 years (mean: 37.57 ±12.15 years) and the majority (61.7%) of the patients were female. Of the 253 patients, 186 (73.5%) had allergic rhinitis, 20 (7.9%) had allergic rhinitis and asthma, 4 (1.6%) had asthma, and 43 17%) had venom hypersensitivity.

A total of 290 cluster immunotherapy protocols with a total of 4001 injections were performed. 165 (56.9%) HDM, 61 (21%) pollen, 64 (22.1%) venom immunotherapy (VIT) was administered. 216 patients received single immunotherapy, 37 patients received double immunotherapy with 2 different allergen content of immunotherapy making a total of 290 cluster immunotherapy protocols.

All of the patients reached the scheduled maintenance dose and completed the study.

PATIENT DISTRIBUTION ACCORDING TO PREMEDICATION

170 (67.2%) of the patients were given premedication, 83 (32.8%) were not given any premedication and were recruited to the control group.

Of the 170 patients who were given premedication, 51 (20.2%) had daily antihistamine, 28 (11.1%) had antihistamine only 2 h prior to injections, 40 (15.8%) had daily montelukast, 51 (20.2%) had a combination of montelukast and antihistamine.

CHARACTERISTICS OF HYPERSENSITIVITY REACTIONS (HSRS) AMONG ALL PATIENTS

52 (20.6%) patients had HSR during the up-dosing phase, with a total of 58 reactions. 12 (4.7%) patients had SR, 36 (14.2%) had delayed LR, and 5 (2%) had early LR. One patient with delayed LR experienced SR during incremental doses. None of the SRs re-occurred during the up-dosing phase while 4 of 36 delayed LRs, 1 of 5 early LRs re-occurred in the next injections during the up-dosing phase. All of the HSRs were treated accordingly, dose adjustments for the next injection were done according to the reaction severity.

However, one patient re-experienced SR during the maintenance phase. In line with the suggestion of the EAACI guidelines [7], we re-evaluated the risks and benefits of AIT with the patient. Since the patient experienced grade 2 SR and had a will to continue treatment due to favorable response to AIT, we continued AIT with dose adjustment and the patient had no HSR thereafter.

When HSRs are evaluated according to the allergen content of immunotherapy, no difference was detected in the frequency of local LRs. But SRs were reported more frequently in patients receiving pollen specific immunotherapy ($p = 0.004$, OR = 5.8, 95% CI: 1.7–19.00).

Female patients experienced HSRs together with local HSRs more frequently ($p = 0.01$, $p = 0.002$, respectively). But the frequency of SRs did not vary significantly by gender.

Presence of another AIT (double AIT) and polysensitization are not associated with the frequency of HSRs.

Characteristics of each patient with systemic HSRs are demonstrated in Table 1.

CHARACTERISTICS OF HSRS ACCORDING TO PREMEDICATION GROUPS

Premedication significantly reduced the frequency of HSRs ($p = 0.009$). Of the HSRs, LRs were more frequently observed in the control group ($p = 0.017$), while premedication did not affect the frequency of SRs.

When HSRs are assessed according to premedication groups, lower frequency of LR was detected in each premedication group, but only the daily AH premedication group and daily AH + montelukast premedication group were statistically significant ($p = 0.007$, $p = 0.017$, respec-

TABLE 1. Characteristics of patients who experienced systemic hypersensitivity reactions

Patient no.	Sex	Age	Premedication status	AIT type	AIT no.	Symptoms/Findings (SR grade)	Treatment of SR	Week of SR	AIT dose at SR (SQ)	Protocol/ Dose adjustment	SR after adjustment	Other sensitization
1	F	51	Control	Wasp	2	Flushing (1)	Sys CS + AH	3	6 000	Switch to conventional protocol, AH	–	Bee
2	M	60	Control	Bee	1	Flushing itchy throat (1)	Sys CS, + AH	2	2 000	Switch to conventional protocol	–	–
3	M	40	Control	Bee	1	Flushing, itchy throat (1)	Sys CS + AH	3	16 000	Switch to conventional protocol	–	–
4	F	31	Daily AH	HDM	1	Urticaria (1)	Sys CS + AH	4	10 000	Daily AH added	–	–
5	F	36	Daily montelukast	HDM	1	Urticaria (1)	Sys CS + AH	3	16 000	Daily AH added	+*	–
6	M	24	Control	Pollen	1	Rhinitis (1)	Sys CS + AH	2	2 000	Daily AH added	–	–
7**	F	30	Control	Pollen	1	Urticaria (1)	Sys CS + AH	6	100 000	AH 2 h before injection added	–	HDM
8	M	31	control	Pollen	2	Bronchospasm (2)	Sys CS + AH IM Adrenaline	2	6 000	Switch to conventional protocol	–	HDM
9	M	21	AH 2 h prior to injection	Pollen	1	Cough (2)	Sys CS + AH	2	6 000	Daily AH added	–	–
10	M	33	Daily AH	Pollen	1	Anaphylaxis (3)	Sys CS + AH IM Adrenaline	3	16 000	Switch to conventional protocol	–	HDM
11	F	19	Daily AH	Pollen	1	Hypotension (4)	Sys CS + AH IM Adrenaline	3	6 000	Switch to conventional protocol	–	–
12	M	34	Daily montelukast	Pollen	1	Bronchospasm urticaria (4)	Sys CS + AH IM Adrenaline	3	16 000	Switch to conventional protocol	–	–

*Patient re-experienced a systemic reaction during the maintenance phase, immunotherapy continued with a lesser dose (20 000SQ). **Patient had also a delayed local reaction in week 4. AH – antihistamine, AIT – allergen immunotherapy, F – female, HDM – house dust mite, IM – intramuscular, M – male, SR – systemic reaction, SysCS – systemic corticosteroid.

tively). Although the frequency of SRs was lower in each premedication group, statistical significance was not detected.

According to allergen contents of AIT, SR and LR were both more frequently observed in control groups for each AIT, but were statistically non-significant (Table 2).

As stated in the previous section, SRs were significantly higher in patients receiving pollen immunotherapy. When HSRs were evaluated according to the allergen content of AIT together with premedication presence, it was found that patients receiving pollen immunotherapy have a significantly higher risk of SR independent of

TABLE 2. Comparison of hypersensitivity reactions with premedication according to the allergen content of immunotherapy

AIT type	HSR type	Premedication group, *n* (%)	Control group, *n* (%)	*P*-value
HDM IT	Total HSRs	9 (34.6)	17 (65.4)	NS
	LR	9 (37.5)	15 (62.5)	NS
	SR	0	2 (100)	NS
Pollen IT	Total HSRs	4 (36.4)	7 (63.6)	NS
	LR	3 (50)	3 (50)	NS
	SR	2(33.3)	4 (66.6)	NS
VIT	Total HSRs	8 (72.7)	3 (27.3)	NS
	LR	5 (62.5)	3 (37.5)	NS
	SR	3 (100)	0	NS

AIT – allergen immunotherapy, HSR – hypersensitivity reaction, IT – immunotherapy, LR – local reaction, SR – systemic reaction, VIT – venom immunotherapy.

premedication. However, patients receiving pollen immunotherapy without premedication experienced LRs more frequently.

DISCUSSION

The clinical efficacy of AIT has been shown in many studies [10–16]. Besides the clinical efficacy, AIT is a safe and well-tolerated method when patients are selected properly and injections are given in a medical setting by experienced personnel. Although the number of practicing allergists is increasing, the concerns on adverse reactions restricts AIT from being a more widely used therapy [7, 8, 17].

LR due to AIT is fairly common [10]. In our study, 16.2% of patients had LR which is less frequent than in the literature. We also detected that local reactions are significantly less frequent in patients who had premedication ($p = 0.017$). Since more than half of our patients had premedication, a lower frequency of LR in our patients is relevant.

According to the LOCAL study, 27% of the patients who experienced an LR during AIT experiences another LR at the next injection [18]. In our study only 5 (12%) patients re-experienced LR at the next injections. The LOCAL study and the present study are different in methodology as the LOCAL study was performed in a non-dose adjustment manner. The lower frequency of LRs at the next injections in our study might be explained by performing appropriate dose adjustments for the next injection. These findings point out to the importance of dose adjustments to prevent further LRs as well as the favorable effect of premedication on the prevention of LRs.

Two retrospective studies by Kelso and Tankersley *et al.* reported that most of the SR were not preceded by any LR and a LR is not a risk factor for SR. Kelso also stated that dose adjustments after a local reaction is unnecessary [19, 20]. In accordance with these studies, in our study only one patient with LR experienced SR during incremental doses, which is of insignificance. Considering our above-mentioned finding that dose adjustments lower LR frequency at the next injections, it is noteworthy to mention that dose adjustments after a LR are not completely unnecessary.

In our study, 12 (4.7%) patients had SR and no difference in frequency was detected between premedication groups and control group, revealing that premedication does not lower the risk of SRs in the up-dosing phase of AIT.

In a recent study, meta-analysis of 11 randomized-controlled trials with a total of 609 patients was performed to determine the contribution of premedication to the safety of AIT. This meta-analysis revealed that premedication with AH in AIT can reduce the frequency and severity of SRs [8]. Of these 11 trials analyzed, the rush protocol was most commonly performed in the up-dosing phase (8 rush, 1 cluster, 1 conventional, 1 oral immunotherapy) [7, 20–30]. Accelerated protocols, such as the rush schedule, result in higher frequency of HSR than the conventional protocols. Since there is an increased frequency of allergen exposure during the up-dosing phase of rush schedules, it is consequently expected to lead an increased incidence of HRs [1, 31]. In line with that, frequency of SRs in these 11 studies is much higher than our 4.7% of SR rate. This difference in frequency of SRs between our study and aforementioned studies is considered as a probable explanation of our finding that premedication did not significantly lower the risk of SRs in the up-dosing phase contrary to other trials.

The theoretical approach of AH masking mild HSRs, which an increased exposure to allergen could result in a more serious reaction, limits the usage of premedication in AIT. As consistent with the other studies evaluating effects of premedication in AIT, we found no evidence

of premedication masking the early warning signs and of delaying the onset of SRs [8].

In our study we evaluated the contribution of premedication to prevent HSRs according to the allergen content of AIT, such as HDM immunotherapy, pollen immunotherapy and VIT, we found that HSRs were less frequent in the premedication group for each type of allergen specific immunotherapy, although none was statistically significant (Table 2). Statistical non-significance might be attributed to the inadequate sample size for each AIT group.

We also determined that patients receiving pollen immunotherapy have a significantly higher risk of SR independently of premedication. This finding is in line with the findings of the EAACI Immunotherapy Interest group that pollen hypersensitivity was indicated as an independent risk factor for systemic reactions during allergen immunotherapy [5].

When HSRs are assessed according to premedication groups, lower frequency of LR was detected in each premedication group, but only daily AH premedication group and daily AH + montelukast premedication group were statistically significant, reflecting the preventive effect of AH on LRs, which is comparable with the literature [24–26, 29, 30]. In the literature most of the studies are conducted in rush protocols of AIT. In these studies premedication was given each day 1–2 h prior to injections, which may also be considered as daily AH intake. In regard to the present study, the patient group who had AH 1 h prior to injections had AH only once a week as we followed the cluster schedule. The nonsignificant preventive effect of AH to LRs when given only prior to injection in the cluster protocol might be explained by less cumulative effect of AH.

Lower frequency of LR was detected in the montelukast premedication group compared to the control group, although it was not statistically significant. In addition, montelukast had no prior effect over antihistamine to prevent LR unlike the study by Wöhrl *et al.* [22].

Although the present study has the largest sample size compared to other studies investigating the contribution of premedication to HSRs, a multicenter study including a higher sample size is needed to evaluate the different premedication protocols within each allergen specific immunotherapy. This might be a potential limitation of our study.

Due to ethical considerations, dose modifications were made when a HSR occurred. This might be another limitation of our study that dose modifications might have obscured the potential future HSRs during incremental doses.

CONCLUSIONS

Our study suggests that the reaction risk is increased in pollen immunotherapy. Premedication does not seem to prevent the frequency or severity of systemic reactions. However premedication, daily AH intake in particular, decreases the frequency of local reactions.

CONFLICT OF INTEREST

The authors declare no conflict of interest.

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