

Premedication with Montelukast Reduces Local Reactions of Allergen Immunotherapy

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Key Words

Allergen immunotherapy · Antihistamine premedication · Local reaction · Leukotriene antagonist · Montelukast

Abstract

Background: Local reactions (LRs) are a very frequent side effect of specific immunotherapy with allergens and can impair patients' adherence. Antihistamine pretreatment – originally introduced as a safety measure to reduce anaphylactic side effects – has been the only treatment option for LR so far, although these swellings usually do not appear immediately but after hours. We were interested whether pretreatment with the leukotriene antagonist montelukast would be better suited for preventing those reactions than pretreatment with the antihistamine desloratadine. **Methods:** Fifteen patients with a history of severe anaphylactic reactions to hymenoptera stings were enrolled into a prospective, double-blind, randomized, placebo-controlled pilot study. We selected a rush immunotherapy protocol consisting of 19 injections of hymenoptera venom administered over 5 consecutive days, where the majority is developing LR, and counted the number of injections until an LR of >3 cm occurred. The patients were randomized to 3 treatment groups: premedication with placebo, 10 mg montelukast and 5 mg of the antihistamine desloratadine. **Results:** Compared with

placebo, the occurrence of LR (>3 cm) was significantly delayed by montelukast ($p < 0.01$, analysis of variance) but not by desloratadine ($p = 0.19$). The difference between montelukast and desloratadine was close to significant ($p = 0.054$). Itching, recorded on a scale from 0 to 5, did not differ between the 3 groups. **Conclusion:** Montelukast can be useful in the prevention of LR after specific immunotherapy.

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Introduction

Specific immunotherapy (SIT) with purified venom is the only causal therapy in patients suffering from severe systemic reactions to bee and yellow jacket (YJ; hymenoptera) stings [1–4]. Conventional SIT requires a build-up phase of up to 4 months before reaching a maintenance level. To shorten the build-up phase for high-risk patients requiring SIT with hymenoptera venom, so-called rush SIT regimens have been developed and introduced [for review, see 5]. Although the risk-benefit ratios of conventional and rush SIT are excellent [6], side effects in these usually young and otherwise healthy patients have always been a matter of concern. Premedication with antihistamines (H1-RA) prior to each vaccination has been shown to significantly decrease the low rate of

severe anaphylactic or other systemic side effects in SIT with venom as well as pollen allergens [7–13]. However, local reactions (LRs) are common in SIT and can reduce the patient's compliance to this sometimes lifelong therapy [14–16]. Premedication with H1-RA was also shown to beneficially influence these LRs but usually did not prevent their upcoming [9, 11–13].

LRs at the injection sites of SIT seem to depend on pathophysiologic mechanisms different from the immediately appearing histamine-driven anaphylactic as well as 'wheal and flare' reactions. Probably, they rather depend on the newly synthesized late products of the activated mast cells such as leukotrienes and prostanoids [17] as well as the modulation of the mainly neutrophilic as well as eosinophilic infiltrate of type 1 late-phase reactions [18]. Consistently, the leukotriene antagonist (LT-A) montelukast was shown not to affect or influence the immediate response of skin tests with allergen [19], while repressing, for example, delayed pressure urticaria [20]. Nevertheless, LT-As have been introduced in a variety of diseases classically treated with H1-RA, such as chronic urticaria [21, 22] or allergic rhinoconjunctivitis [23], alone or in combination with H1-RA. In initial studies, Shultz and co-workers [24, 25] showed the beneficial effects of adding an LT-A such as montelukast to conventional H1-RA pretreatment for the reduction of SIT-associated LRs in outpatient settings. However, they had performed their studies on a nonsystematic basis.

In our study, we compared a premedication with montelukast as monotherapy with an H1-RA premedication represented by desloratadine as new generation H1-RA in patients submitted to rush SIT with hymenoptera venom.

Material and Methods

Study Design

We performed a prospective, double-blind, placebo-controlled, randomized rush SIT in hymenoptera venom-allergic patients. We used a locally developed variant of an inpatient rush SIT protocol successfully used at our department since 1997, where the full dosage is reached with the 19th vaccination on day 5 (table 1). We chose our protocol as a model to study local side effects because in historic patients we had observed a constant rate of LRs in 95.3% of the patients with a low rate of 6.8% of rather mild systemic reactions allowing us to include a placebo treatment group [unpubl. data].

The SIT was done with aqueous Alutard SQ® for the buildup and aluminum adsorbate depot Alutard SQ® (ALK-Abelló, Linz, Austria) for the maintenance phase. The maintenance dosage was 100,000 SQ units/ml.

Table 1. 5-day inpatient rush SIT protocol

Injection	Day	µg	SQ units
1	1	0.001	1
2		0.004	4
3		0.008	8
4		0.02	20
5		0.04	40
6	2	0.08	80
7		0.2	200
8		0.4	400
9		0.8	800
10	3	2	2,000
11		4	4,000
12		6	6,000
13		8	8,000
14	4	10	10,000
15		20	20,000
16		40	40,000
17		60	60,000
18	5	80	80,000
19		100 ¹	100,000
Maintenance	21	100 ¹	100,000
Maintenance	monthly	100 ¹	100,000

This is a local protocol introduced at our department in 1997 by one of the authors [T.K., unpubl. data]. Injection No. 19 was the last injection included in the analysis of this study.

¹ The SIT was performed with aqueous solution except for the marked concentrations where we delivered depot extracts.

The patients received the premedication on every of the 5 mornings (table 1) 1 h prior to the first vaccination. The 3 treatment groups were: pretreatment with placebo (lactose), 10 mg montelukast (LT-A group, Singulair®; MSD Austria, Vienna, Austria) or 5 mg desloratadine (H1-RA group, Aeries®; AESCA, Traiskirchen, Austria).

The 19 injections were administered in a clockwise fashion into the upper arms and thighs. We recorded 2 readout parameters: the objective parameter 'diameter of the outer border of the LRs' (skin infiltration and induration without the surrounding erythema) measured with a ruler in centimeters as described by Tankersley et al. [26] after 10 min, 6 h and 24 h, as well as the subjective 'itch' on a scale from 0 to 5 points resulting in 57 consecutive values. Cool packs were the only permitted local therapy. All patients who surpassed the cutoff of 3 cm and also those experiencing systemic reactions were unblinded and received intravenous H1-RA (diphenhydramine) treatment. All these patients were counted as having reached the cutoff reaction of >3 cm. Having finished the study period 24 h after injection No. 19, all patients received the standard maintenance injections as depicted in table 1.

Patients

From 12th January 2004 to 21st February 2005, we randomized 15 adult patients (6 female, 9 male, average age 44.4 ± 12.6

Table 2. Patients' characteristics

Medication	Patient	Sex	Age years	Venom	Initial reaction grade	Bee			YJ			Total IgE kU/l	Other sensitizations	Double therapy (bee and YJ)
						SPT μ g/ml	IDT μ g	sIgE kU/l	SPT μ g/ml	IDT μ g	sIgE kU/l			
Placebo	1	m	50	bee	III/IV	10	–	neg.	neg.	neg.	0	17.2	grass pollen	–
	2	m	52	YJ	III/IV	neg.	neg.	neg.	100	0.1	0.37	54.1		–
	3	f	37	YJ	III/IV	neg.	neg.	neg.	neg.	0.01	20.9	183		–
	4	f	53	YJ	III/IV	neg.	1	neg.	neg.	0.1	3.5	50		–
	5	f	43	YJ	III/IV	neg.	neg.	1.72	100	–	3.41	199		–
Desloratadine	6	f	40	bee	III/IV	300	0.01	31.7	100	0.01	28.6	176	grass, birch, mugwort pollen, dust mite	yes
	7	m	32	bee	III/IV	neg.	0.1	1.61	neg.	0.01	2.42	28.8	grass, birch, mugwort pollen	yes
	8	m	64	YJ	III/IV	neg.	neg.	neg.	100	0.01	1.51	61.3	grass, birch, mugwort pollen	–
	9	f	40	YJ	III/IV	neg.	10	neg.	300	0.01	10.1	21.7		–
	10	m	33	YJ	III/IV	neg.	0.1	5.31	neg.	0.01	7.4	143		yes
Montelukast	11	m	27	bee	II	100	0.1	1.05	100	0.01	0.94	107	grass, birch, mugwort pollen, dust mite	yes
	12	f	62	bee	III/IV	300	–	14.8	100	–	100	>2,000		yes
	13	m	38	YJ	III/IV	neg.	–	24.5	300	–	9.27	337		–
	14	m	65	YJ	III/IV	neg.	0.1	9.88	neg.	0.01	3.54	240		yes
	15	m	31	YJ	III/IV	neg.	0.1	20.2	300	0.1	16.8	518		yes

Venom is the type of venom used in the study. SPT = Skin prick test; IDT = intradermal test; sIgE = serum IgE; neg. = negative.

years) to the 3 treatment arms using the following inclusion criteria: proven hymenoptera venom allergy by a sting-specific history of a reaction of at least grade II according to the classification by Mueller [27], a venom-specific serum IgE and a positive venom-specific skin test performed at increasing dosages in skin prick tests with 10, 100 and 300 μ g/ml and, if remaining negative, in intradermal tests with 0.01, 0.1 and finally 1 μ g/ml. Patients with an indication for therapy with both venoms were only included during their first regimen. The randomization was stratified for the type of venom (YJ vs. bee) because of their known difference in side effects [28] and for the intensity of the initial reaction (grade II vs. grade III/IV). However, we enrolled only 1 patient with a grade II reaction who was randomized to the LT-A group (table 2). The patients had been stopped for any H1-RA and LT-A treatment as well as for corticosteroids for at least 1 month before inclusion to the study. We excluded patients suffering from mastocytosis as determined by elevated serum tryptase [29], patients requiring β -blockers or ACE inhibitors, pregnant women and noncompliant patients.

Ethical Considerations

All patients gave informed written consent for participating in this study. The study was approved by the local ethics committee.

Statistics

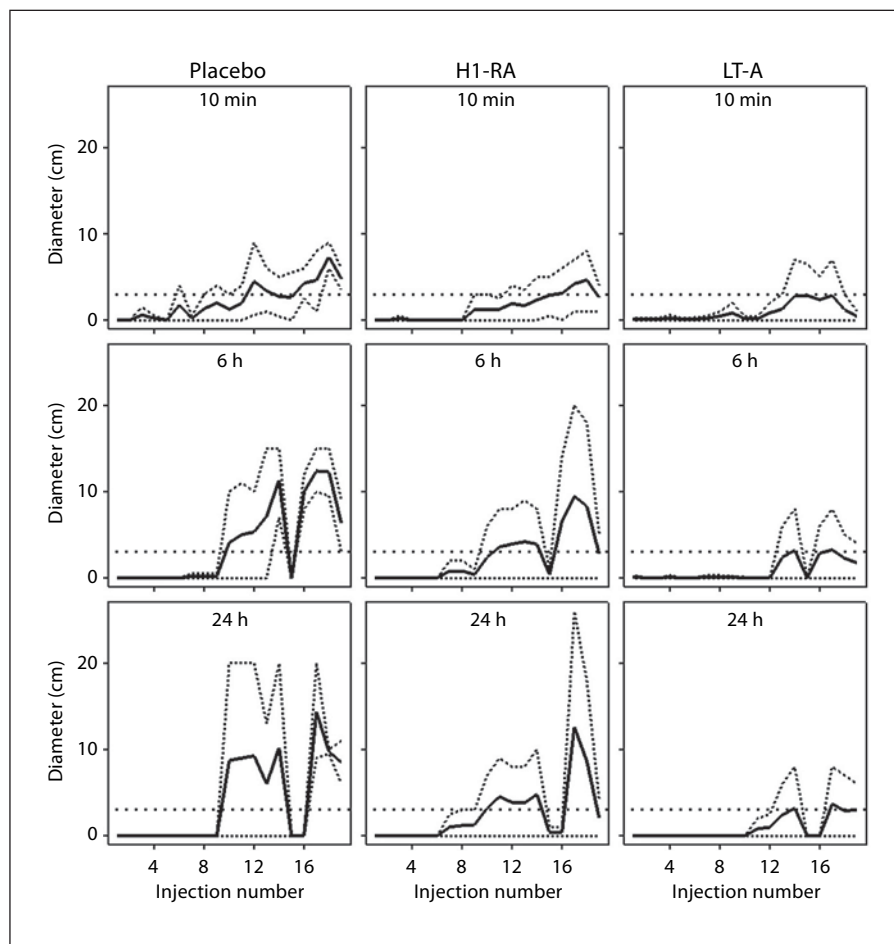
Continuous data are described by means. Categorical variables are described by frequency. The main outcome of the study was defined as the injection number at which a diameter of LR ≥ 3 cm was observed at either 10 min, 6 h or 24 h after infection. This summary measure was compared between the 3 study groups using two-way analysis of variance, adjusting the group comparison by the used venom for VIT (bee/YJ), which was used as stratification criterion during randomization, as second factor. The injection number at which the subjective itch score exceeded the value of 0.5 was compared similarly. Fisher's least significance difference procedure (considering pairwise comparisons only if the global F-test was significant) was used to correct for multiple testing. The SAS system (version 9.1; SAS Institute Inc., Cary, N.C., USA) was used for statistical computations.

Results

Patient Characteristics

We randomized 10 YJ-allergic (66.6%) and 5 bee-allergic (33.3%) patients (table 2), of whom all but 1 had experienced severe grade III or grade IV reactions. Seven patients were submitted to SIT with both venoms but

Fig. 1. The figure shows mean (solid line) as well as minimum and maximum (dotted lines) diameters of LRs of each patient group in centimeters as function of injection number, broken down by group (placebo, H1-RA, LT-A) and time of reaction (10 min, 6 h and 24 h after injection). Relevant local reactions (diameter >3 cm, horizontal dotted line) occurred significantly earlier in the placebo than in the LT-A group ($p = 0.0048$) but not in the H1-RA group ($p = 0.1904$). The difference between LT-A and H1-RA pretreatment was close to significance ($p = 0.0538$).



were only included during their first treatment. Another 7 individuals were 'atopics' as defined by the new World Allergy Organization criteria [30] with a total IgE >100 kU/l.

Skin test reactivity was equally distributed among the 3 treatment groups (3 patients in the placebo, 3 in the H1-RA and 4 in the LT-A group already had positive reactions in the skin prick test).

Local Reactions

The simultaneous 3-group comparison of the number of injections until the first occurrence of LRs with a diameter of >3 cm (global F-test, F-value 6.32, 2 degrees of freedom, $p = 0.0149$) was significant at the 5% level. Following the least significance difference principle, this significant p value allowed us to perform all 3 pairwise comparisons without further correction for multiple testing.

The occurrence of LRs of >3 cm was prolonged from an average of 9.9 injections upon pretreatment with pla-

cebo to 12.5 for H1-RA and 16.5 for LT-A. While the difference between placebo and LT-A was highly significant ($p = 0.0048$), this was not the case for the difference between placebo and H1-RA pretreatment ($p = 0.1904$). Interestingly, the more pronounced delay by LT-A pretreatment was close to significance when compared to H1-RA pretreatment ($p = 0.0538$).

Adjustment for stratification showed no influence of the venom used for treatment (F-value 1.31, 1 degree of freedom, $p = 0.2764$). The second stratification for the grade of initial reaction was not performed as there was only a single patient with a grade II reaction.

Premedication did not only delay the timing of the occurrence of LRs, it also decreased the size of LRs after 6 and 24 h (fig. 1). This effect was observed in comparison with placebo but also with H1-RA pretreatment. Although the shape of the curves of the LT-A group was flattened compared to the other groups, this effect did not reach significance.

Subjective Itch Score

Relevant itching (>0.5) appeared before the occurrence of visible LRs at all 3 time points between injections 6 and 7. Interestingly, although the objective parameter – the diameter of the LRs – was significantly reduced by pretreatment with LT-A and not significantly by H1-RA pretreatment, there were no differences in subjective itch scores between the 3 treatment groups (data not shown).

Systemic Reactions

We observed 2 mild anaphylactic reactions at injection No. 15 that led to unblinding and consecutive H1-RA premedication with intravenous diphenhydramine for the remaining SIT injections. Patient No. 1 of the placebo group experienced a grade II reaction with a drop in systolic blood pressure of >30 mm Hg, patient No. 9 from the desloratadine group a urticarial rash (grade I). Both were controlled within minutes after the intravenous administration of the H1-RA diphenhydramine. As described in Material and Methods, both events were counted as if the patients would have surpassed the cutoff of 3 cm for a positive LR.

Discussion

In this pilot study, we show that pretreatment with the LT-A montelukast is an effective therapy for the reduction of local side effects of SIT. Surprisingly, it is more effective than pretreatment with the H1-RA desloratadine. Although H1-RA pretreatment also delayed the occurrence of large LRs, this did not reach significance when compared with placebo. The H1-RA disadvantage in clinical effectiveness may be explained on the one hand by a slightly lower clinical potential of desloratadine and its predecessor loratadine in comparison to other newer antihistamines. On the other hand, previous reports dealing with premedication in SIT of which one employed loratadine [11] and the others other H1-RAs [7–10, 12, 13] were mostly designed to study the prevention of anaphylactic reactions as primary outcome.

There is only a single study directly comparing the effectiveness of LT-A and H1-RA in suppressing cutaneous reactions of allergic disease in aspirin- or food additive-sensitive chronic urticaria patients [21]. In their study, Pacor et al. [21] already suggested a more pronounced effectiveness of montelukast over cetirizine in this special subgroup of patients. Another study from the same group could, however, not find an additional effect of montelu-

kast when added to desloratadine in ‘classical’ chronic urticaria patients [31].

SIT is usually a safe therapy with low incidences of anaphylactic reactions [6]. As anaphylactic reactions are seldom occurring during SIT, studies about anaphylaxis demand large samples for examination of these rare events. As our study dealt with the frequently occurring LRs as primary outcome, we observed mild systemic reactions in only 2 patients (13.3%) in the placebo and the H1-RA group, a rate that was comparable to the historic controls of our center as already mentioned in Material and Methods. Due to the small sample, we cannot draw conclusions about the effect of LT-As on the prevention of systemic reactions. At the time of the writing of this manuscript, most of the patients were in their first to second year of maintenance therapy. Hence, we could not foresee whether the addition of LT-A to the SIT would have influenced the outcome of the SIT in the same beneficial way as reported for H1-RA by Müller et al. [32].

Conclusion

Premedication with montelukast can attenuate the size of LRs from SIT with hymenoptera venom and may be of value in patients suffering from such LRs.

Acknowledgements

The authors thank Karin Rainer for cooperation with the statistical analysis. This investigator-initiated study was supported by MSD Austria, Vienna (MSD Austria had no influence on study design, data collection, data analysis, data interpretation, or writing of the report).

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