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Rush immunotherapy for wasp venom allergy seems safe and effective in patients with mastocytosis

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Key words

Immunotherapy; mastocytosis; tryptase; urticaria pigmentosa; yellow jacket venom allergy; wasp venom allergy.

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Summary

Background. *Patients with mastocytosis and wasp venom allergy (WA) may benefit from venom immunotherapy (VIT). However, fatal insect sting reactions have been described in mastocytosis patients despite previous immunotherapy. We investigated the safety and efficacy of (rush) VIT in patients with mastocytosis and WA.* ***Objective.*** *To investigate the safety and efficacy of (rush) VIT in patients with mastocytosis and WA.* ***Methods.*** *We describe nine patients with cutaneous mastocytosis and WA who received VIT. Cutaneous mastocytosis was confirmed by histopathology and systemic mastocytosis was diagnosed according to World Health Organization criteria. VIT was given according to a rush protocol. Given the difference in safety and efficacy of VIT in patients with WA and honeybee venom allergy, we reviewed the literature for VIT with the focus on WA patients with mastocytosis and addressed the difference between patients with cutaneous versus systemic mastocytosis.* ***Results.*** *Nine patients had WA and mastocytosis, of whom six had cutaneous mastocytosis, two combined cutaneous and systemic mastocytosis and one systemic mastocytosis. All patients received rush IT with wasp venom. Most patients had only mild local side effects, with no systemic side effects during the course of VIT. One patient had a systemic reaction upon injection on one occasion, during the updosing phase, with dyspnoea and hypotension, but responded well to treatment. Immunotherapy was continued after temporary dose adjustment without problems. Two patients with a previous anaphylactic reaction were re-stung, without any systemic effects.* ***Conclusions.*** *VIT is safe in cutaneous mastocytosis patients with WA, while caution has to be made in case of systemic mastocytosis. VIT was effective in the patients who were re-stung.*

Introduction

Mastocytosis is a disease characterized by the proliferation of mast cells in skin and/or bone marrow and/or other tissues. The symptoms are the consequence of the release of histamine and other mediators from mast cells and can vary from itching and flushing to anaphylactic shock. Clinical presentations can be cutaneous (urticaria pigmentosa, diffuse cutaneous mastocytosis, mastocytoma) but systemic disease with or without skin involvement may also occur (indolent/aggressive systemic mastocytosis, mast cell leukemia) (1). Mastocytosis patients have an increased risk of a severe allergic reaction following hymenoptera stings compared to patients without mastocytosis. An immunoglobulin E (IgE)-mediated mechanism has been postulated, and although specific IgE could not be detected in some mastocytosis patients with a reaction to hymenoptera venom (2), IgE was detected in all but one patient when using the basophil activation test in the diagnostic work-up, making an IgE-mediated mechanism likely in most if not all patients (3).

Immunotherapy is a well-accepted treatment for patients with wasp (yellow jacket) venom allergy (WA) without mastocytosis. It prevents a systemic reaction in 90-98% of cases (4).

Table 1 *- Safety and efficacy according to protocol followed during up-dosing phase.*

Author	C/R	SSE	Re-stung	SS Re-stung
Bonnadonna[9]	15 C	2	13	2
Gonzalez de Olano[11]	10 C	1	5	1
Total	25 C	3	18	3
Gonzalez de Olano[11]	5R	2	4	1
Total	5R	2	4	1
Our data	9R	1	2	0
Oude Elberink[7]	2 nd	1	2	0
Müller[6]	1 nd	0	0	-
Fricker[10]	4 nd	0	3	1

C/R: conventional/rush immunotherapy; nd: not determined; SSE: systemic side effects; SS: systemic symptoms.

Table 2 *- Safety and efficacy depending of type of mastocytosis.*

Author	Number of patients	SSE IT	Re-stung	SS Re-stung
Systemic mastocytosis				
Bonnadonna[9]	15	2	13	2
Gonzalez de Olano[11]	15	3	9	2
Oude Elberink[7]	2	1	2	2
Fricker[10]	1	0	1	0
TOTAL	33	6	25	6
Our data	3	1	1	0
Cutaneous mastocytosis				
Fricker[10]	3	0	2	0
Müller[6]	1	0	0	-
TOTAL	4	0	2	0
Our data	6	0	1	0

SSE: systemic side effects; IT: immunotherapy; SS: systemic symptoms.

H1 antihistamines were reported to reduce local and systemic reactions related to immunotherapy with hymenoptera venom (5). VIT in hymenoptera venom allergy (HVA) patients with (cutaneous) mastocytosis was first described in 1983 in one patient with yellow jacket anaphylaxis. This patient had no systemic side effects during the course of VIT (6). In 1997 two fatal reactions were described in mastocytosis patients with yellow jacket anaphylaxis, both from The Netherlands, after a field sting 1 and 9 years respectively after stopping VIT (duration 2.5 and 5 years) and despite emergency treatment (7). In the first patient VIT was stopped because of systemic side effects. These fatalities raised questions regarding the safety and efficacy of VIT in mastocytosis patients. To date studies are limited to case reports and small observational studies, reflecting the fact that HVA and mastocytosis occur infrequently in combination. Two studies reported a high frequency of systemic side effects during VIT and limited efficacy: 86 to 100% systemic reactions following a re-sting (7,8). Other studies reported encouraging results with regard to safety and efficacy (4,9-11). VIT in WA is safer and more effective than in honeybee allergy (HA) (12). Whether this is similar in patients with co-existing mastocytosis is unknown. However, in a multicenter trial by Ruëff et al. there was a significant association between side effects during VIT and elevated baseline serum tryptase concentration (BTC, a marker for SM) in patients with WA but not with HA (13). So there may be a difference in the efficacy and safety of VIT in HA and WA patients with and without mastocytosis. Most studies, however, do not distinguish between HA and WA in patients with mastocytosis and hymenoptera venom allergy. Moreover studies on patients with urticaria pigmentosa-type mastocytosis are rare.

We report on nine mastocytosis patients (six with urticaria pigmentosa-type mastocytosis) with WA to add to the limited and sometimes conflicting experience with this type of therapy in this rare disease. Moreover we summarize the most important patient characteristics in the studies published to date (**table 1 and 2**).

Methods

Patient characteristics

Between 1990 and 2009, nine patients with yellow jacket venom allergy and mastocytosis were treated with immunotherapy. Inclusion criteria were: 1) severe WA grade IV according to Müller, 2) cutaneous and/or systemic mastocytosis. WA was confirmed by positive intracutaneous (IC) tests and/or venom-specific IgE. Cutaneous mastocytosis was confirmed by skin biopsy and systemic mastocytosis was confirmed according to WHO criteria (1). IC tests, baseline serum tryptase concentration (BTC) and venom-specific IgE were assessed before and

during VIT. IC tests were performed with ten-fold increasing doses of yellow jacket venom ranging from 0.0001 to 0.1 microgram/ml. Testing was conducted on the volar surface of either forearm, with yellow jacket dilutions in conjunction with a normal saline solution as the negative control and histamine hydrochloride as the positive control. Intracutaneous test results were measured with calipers and were considered positive if the intracutaneous skin test with yellow jacket venom (or bee venom, as a control) resulted in a wheal diameter of 5 mm or more and was at least 3 mm larger than the negative control. Venom-specific IgE antibodies in the serum were measured by CAP-FEIA, Phadia, The Netherlands. A value of > 0.35 kU/L was considered positive. Serum BTC levels were measured and a value above 13.5 ng/ml was considered as elevated (2). Patients with systemic symptoms and/or a BTC > 20 ng/ml were referred to the hematologist to consider a bone marrow biopsy. The study was approved by the ethics committee. Informed consent was not required given the retrospective design.

Venom immunotherapy and follow-up

The updosing phase of VIT was administered according to a 3-day rush protocol with Pharmalgen yellow jacket venom (ALK-Abelló, Nieuwegein, The Netherlands). This VIT protocol was the same as for HVA patients without mastocytosis. Ten milligrams cetirizine was routinely given as pre-medication one hour before each dose. On day 1 doses of 0.01 µg, 0.1 µg, 1 µg and 2 µg were given. On the second day, 5 µg, 10 µg, 20 µg and 40 µg were given. On the last day two doses of 50 µg were given. The treatment was continued with 100 µg Alutard SQ 802 (ALK-Abelló, Nieuwegein, The Netherlands). The interval between injections was gradually increased to 6 weeks after the first year and to 8 weeks after the second year. Patients were admitted for the 3-day rush VIT to our inpatient clinic. The patients were continuously monitored for local and systemic symptoms by trained personnel. Maintenance therapy was given in our outpatient clinic for at least the first year. Subsequent maintenance treatment was given by the referring specialist or by the general practitioner in the case of patients residing far away from the clinic.
Safety was evaluated by carefully assessing any local or systemic allergic symptoms. All patients were supplied with emergency medication including an epinephrine auto-injector, prednisolone and antihistamines. Patients were re-evaluated annually.

Literature review

A thorough review of the literature was conducted. The PubMed database was searched using the following terms: mastocytosis, immunotherapy, urticaria pigmentosa, hymenoptera venom allergy. We specifically searched for patients with (any type of) mastocytosis with sensitization and immunotherapy for wasp venom.

Results

Patient characteristics

Nine patients, four female and five male, with mastocytosis and WA were included (**table 3**). All had had a severe systemic reaction with cardiovascular symptoms within 15 minutes of a wasp sting. Six of the patients had cutaneous mastocytosis only, two had combined indolent systemic and cutaneous mastocytosis, and one had indolent systemic mastocytosis only. The median specific IgE at baseline was 18 kU/L (range < 0.35 - >100 kU/L) and positive in 7/8 patients (missing in one patient). An intracutaneous test with yellow jacket venom was positive in all patients tested. Honeybee venom allergy (HA) was excluded in all patients. For details see **table 3**.

Safety of immunotherapy

The median duration of immunotherapy was 6.1 years (range 0.1-19 years). All patients are still on immunotherapy. Patient 9 had a systemic reaction on one occasion at a dose of 40 µg/ml, during the up-dosing phase. Symptoms started with erythema on the chest, which subsequently spread over the arms, followed by chest pain, palpitations, dyspnea, nausea and a decrease in blood pressure (from 120/80 to 99/53) with a tachycardia of 97 beats per minute. The patient responded rapidly to treatment. VIT was continued after dose adjustment, without any further systemic side effects during follow-up. There were no systemic side effects in any of the patients during the maintenance phase.

Efficacy of VIT

Two patients had a field sting during the maintenance phase of venom immunotherapy, in both cases 2 years after the start of VIT treatment. They experienced a local reaction for which treatment was unnecessary. Both had been diagnosed with a severe WA with respiratory as well as cardiovascular symptoms including loss of consciousness, within 15 minutes of a yellow jacket sting, requiring treatment (before the start of VIT) with epinephrine, prednisolone and antihistamines in the ambulance and in the emergency department.

Discussion

We report the successful treatment of nine patients with WA and mastocytosis, using WA IT with a rush protocol. Most patients had no side effects at all. One patient had a systemic

Table 3 *- Safety and efficacy of IT in our study population.*

							sIgE		Tryptase			
No	**Age**	**Sex**	**Type mastocytosis**	**BM**	**SRS**	**IC[1] t = 0**	**t = 0**	**t = IT**	**t = 0**	**t = IT**	**Duration IT (years)**	**Symptoms IT**
1	59	m	CM	-	4	0.0001	20.4	5.3	28	22	5	-
2	54	f	CM	nd	4	0.0001	> 100	29.3	5	6.3	4	-
3	71	m	CM	nd	4	0.0001	11	5	nd	nd	19	-
4	67	m	CM	nd	4	nd	26	nd	nd	26	3	-
5	64	f	CM+SM	pos	4	0.0001	6	1.3	13	31,7	6	Numbness hand/feet/tongue
6	39	m	CM	neg	4	0.0001	3.8	nd	12.5	nd	0.1	Nausea, headache
7	56	f	SM	pos	4	0.01	0.4	< 0.35	38	31	3	-
8	41	f	CM	neg	4	0.01	< 0.35	< 0.35	22.3	20.1	2	-
9	67	m	CM+SM	pos	4	0.01	1.17	nd	nd	43	7	Urticaria, oedema, erythema, dyspnea, drop blood pressure

IT: immunotherapy; BM: bone marrow biopsy; SRS: systemic reaction score; CM: cutaneous mastocytosis; SM: systemic mastocytosis; nd: not done; NA: not applicable.

[1]positive at dilution (in mcg/ml).

reaction following one injection, during the up-dosing phase, with a rapid response to treatment. After dose adjustment VIT was continued without problems. Ruëff et al. found that the two greatest risk factors for a systemic reaction during VIT were elevated BTC, bee venom allergy and (ultra) rush VIT (13). When evaluating the literature with respect to VIT in patients with mastocytosis and WA, we calculated that 23% of the WA patients had a systemic reaction during the up-dosing phase (see **table 1** and **2**). Note that we excluded the studies of Dubois et al. and Ruëff et al. from our review, since it was not clear which patients had HA or WA (2,8). However, as most of their patients had WA, Dubois et al. questioned the safety of VIT given their findings of a systemic reaction during VIT in 6/7 patients with mastocytosis (8). This high number of side effects might be explained by differences in dosing schemes or patient selection. Ruëff et al. supported the relative safety of VIT. They found a systemic reaction during VIT in 9/48 patients (2).

The WA VIT rush protocol seems to be associated with a higher percentage of systemic side effects compared to conventional protocols (table 1) (14). This is consistent with the findings of Przybilla and Ruëff in patients with HA and WA. There are however no comparative studies between HA and WA in mastocytosis patients. Our study revealed systemic side effects in one patient (11%) despite the fact that we used a rush protocol, thus contrasting with previous studies (table 1). This might be due to the fact that all our patients had pre-treatment with antihistamines. The beneficial effect of pre-treatment with antihistamines in VIT has previously been reported (5). The other studies gave no indication of any pre-treatment (table 1 and 2). With regard to the potential influence of the type of mastocytosis on the occurrence of side effects, the only systemic reaction occurred in one of the three patients diagnosed with systemic mastocytosis. In the literature systemic side effects were reported in 30% of patients with SM (table 2), which is a significantly higher percentage than that observed in patients without mastocytosis. The group of patients with CM and WA reported in the literature to date is small (n = 4, table 2). No systemic side effects of VIT were recorded in this group (table 2). Although the patient numbers are small, the results suggest that patients with systemic mastocytosis are at greater risk for systemic reactions.

Two patients had a field sting during the maintenance phase of VIT, 2 years after the start of VIT treatment, while still on therapy. They experienced a local reaction, without the need for treatment, illustrating the efficacy of the protocol, although patient numbers are limited. The efficacy of VIT in patients with mastocytosis has been debated, especially since two patients died after VIT for WA (7). In both cases this occurred following the cessation of VIT, respectively 1½ and 5 years previously. To date no fatalities have been reported in mastocytosis patients while still on VIT. Only 2/9 patients were re-stung during VIT without any systemic reaction. This supports the findings of other studies (table 1 and 2).

In conclusion, (rush) VIT in patients with WA and cutaneous mastocytosis is safe, while extra caution has to be made in patients with systemic mastocytosis. VIT was effective in two patients who were re-stung. Efficacy might be lower than that in patients without mastocyosis, and might disappear upon discontinuation. Therefore, lifelong treatment should be considered, as well as prescription of an epinephrine auto-injector.

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