

Review article

Mastocytosis and insect venom allergy: diagnosis, safety and efficacy of venom immunotherapy

The most important causative factor for anaphylaxis in mastocytosis are insect stings. The purpose of this review is to analyse the available data concerning prevalence, diagnosis, safety and effectiveness of venom immunotherapy (VIT) in mastocytosis patients. If data were unclear, authors were contacted personally for further information. Quality of evidence (A: high, B: moderate, C: low and D: very low) and strength of recommendation (strong 1 and weak 2) concerning VIT in mastocytosis patients are assessed according to the Grading of Recommendations Assessment, Development and Evaluation and are marked in square brackets. Results of VIT were described in 117 patients to date. The mean rate of side-effects during treatment in studies published so far is 23.9% (7.6% requiring adrenaline) with an overall protection rate of 72%. Based on the review we conclude that (1) mastocytosis patients have a high risk of severe sting reactions in particular to yellow jacket, (2) VIT could be suggested [2] in mastocytosis, (3) probably should be done life long [2], (4) VIT in mastocytosis is accompanied by a higher frequency of side-effects, so (5) special precautions should be taken into account notably during the built up phase of the therapy [2], (6) VIT is able to reduce systemic reactions, but to a lesser extent compared to the general insect venom allergic population [2], so (7) patients should be warned that the efficacy of VIT might be less than optimal and they should continue carrying two adrenaline auto injectors [2].

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Mastocytosis is an uncommon disease resulting from a monoclonal proliferation of pathological mast cells in different tissues including skin, bone marrow, liver, spleen, lymph nodes and gastrointestinal tract (1–5). The clinical presentation of mastocytosis is heterogeneous, varying from a manifestation limited to skin in urticaria pigmentosa (UP), diffuse cutaneous mastocytosis and *mastocytoma*, to different forms of systemic diseases (extradermal tissue involvement) including indolent systemic mastocytosis (ISM), smoldering systemic mastocytosis, aggressive systemic mastocytosis and mast cell leukemia (3–5). In adult patients with systemic mastocytosis, the large majority (approx. 90%) has the indolent form of the disease (3–5). Mast cell infiltration leads to organ failure in rare forms of aggressive mastocytosis, whereas skin involvement and mast cell mediator release affect the majority of patients. Symptoms of mast cell degranulation may vary from itching and flushing to profound hypotension and anaphylaxis (1, 2, 4, 6). About half of the patients experience anaphylactic reactions (6). The most important trigger is insect venom. It is estimated that 30% of all mastocytosis

patients suffer from venom anaphylaxis (6), and these reactions are often more severe than in the general insect venom allergic (IVA) population (7). The treatment of choice in IVA patients is venom immunotherapy (VIT) with the relevant venom (honey bee, yellow jacket and/or *Polistes*) (8, 9). The opinions concerning VIT in mastocytosis patients with IVA are conflicting and range from considering it as a contraindication, to seeing these patients as the group who needs VIT most of all (8, 10, 11). These conflicting opinions were the reason to analyse the available data concerning diagnosis, safety and effectiveness of VIT among mastocytosis patients.

We analysed data both published in the journals listed in the Pubmed database (search terms: mastocytosis IVA, immunotherapy), as data presented at allergological congresses from 2003–2008. If data were unclear, authors were contacted personally for further information. Quality of evidence (A: high, B: moderate, C: low and D: very low) and strength of recommendation (strong 1 and weak 2) concerning VIT in mastocytosis patients was assessed according to the Grading of Recommendations

Assessment, Development and Evaluation (GRADE) (12, 13) and are marked in square brackets.

Epidemiology

Insect venom allergic (defined as at least one systemic IgE-mediated reaction in lifetime after an insect sting) is reported in approx. 1–3% of population (14). It is higher in beekeepers and reaches 14–43% (9, 15). The epidemiology of mastocytosis has not been properly studied so far. It is estimated that 1 in 1000 –1 in 8000 of dermatological patients suffer from urticaria pigmentosa (16). The prevalence of mastocytosis is higher in patients with IVA and varies from 0.9–2.6% (Table 1) (10, 11, 17, 18). In many centers, serum tryptase levels are not routinely measured which may lead to under diagnosis of the frequency of mastocytosis in IVA patients, especially in patients without skin involvement (19).

Compared to patients with IVA without mastocytosis and normal basal tryptase levels, the systemic sting reaction is usually more severe in patients with mastocytosis (7), as well as in those with increased levels of tryptase without diagnosed mastocytosis (20, 21).

In mastocytosis patients, IVA is the most important trigger factor for anaphylaxis (6, 22), the prevalence of IVA in this group is estimated between 20% and 30% (6, 19, 22, 23). In addition to Brockow and Florian we evaluated our own data and found about the same prevalence (Table 2). In the study by Haeberli et al. (where in general more patients with a honey bee venom allergy are referred to) it was remarkable that yellow jacket venom allergy was more prevalent in patients with

elevated tryptase compared to the general population of IVA patients (20).

Fatalities

At least six cases of patients with mastocytosis with a fatal reaction after an insect sting have been described to date. Three patients (10, 24, 25) had not been treated with VIT, in three others, treatment was stopped before the fatal sting occurred (25, 26). No fatalities were described in patients while on maintenance dose of VIT so far.

Concerning the patients who died despite VIT, Oude Elberink et al. (26) described two cases. The first patient was treated with VIT for 5 years without side-effects after suffering a severe systemic reaction. Four years after completion of VIT, systemic mastocytosis was diagnosed. The patient died after an accidental sting 9 years after the end of VIT in spite of immediate emergency treatment. The second patient described was treated with VIT for 4 years. The treatment was stopped because of side-effects at maintenance dose of VIT, after which the diagnosis of mastocytosis was established. This patient died 1 year later, after an insect sting. Both fatal reactions raise the question whether continuation of VIT would have been able to prevent these fatal reactions. A third patient described by Reimers and Müller (27) was treated with honey bee VIT after honey bee venom anaphylaxis, but died 10 years later due to a *Vespula* sting anaphylaxis. Both Rueff et al. (11) and Reimers and Müller (27) raise the question whether VIT should be performed both with honey bee and yellow jacket in mastocytosis patients even if there is a clinical relevant allergy to only one species. The natural history of IVA in mastocytosis patients is unknown, as is the natural history after stopping VIT (see Efficacy of treatment during venom immunotherapy). Despite this uncertainty, the guidelines of the European Academy of Allergology and Clinical Immunology (EAACI) advice life long treatment with VIT (8), but only with venom of the culprit insect.

Concerning the patients who were not treated with VIT, three patients with mastocytosis were described who died after an insect sting in whom this was probably the first systemic reaction in their life (10, 24, 26). In one patient, the diagnosis of mastocytosis was made post-mortem (28, 29). In two others, the diagnosis of mastocytosis was made before the fatal sting (24, 26). Therefore, Wagner et al. (24) suggested prophylactic VIT in all mastocytosis patients. However, the natural history of IVA in mastocytosis patients is presently not known sufficiently well to draw such a conclusion.

Pathogenesis of insect venom anaphylaxis in mastocytosis patients

The mechanism of IVA in mastocytosis is only partially understood. The first publications of coexistence of

Table 1. Epidemiology of mastocytosis in insect venom allergic (IVA) patients

Author (ref.)	Number of patients evaluated	n (%) of patients suffering from mastocytosis
Rueff F (11)	1102	2.6%
Dubois A (10)	2375	0.9%
Bonadonna P (17)	552	2.9%
Bonadonna P (18)	379	5.5%

Table 2. Epidemiology of insect venom allergy (IVA) among mastocytosis patients (disease diagnosed according to World Health Organization (WHO) criteria [3])

Author (ref.)	Studied mastocytosis patients	n (%) of patients suffering from IVA
Brockow K. (6)	46 children, 74 adults (59 ISM, 1 ASM, 1 SMAHD)	Children 0%, adults 27%
Florian S. (22)	40 adults (40 ISM)	20%
Van Doormaal J*	160 adults with ISM	30%
Niedoszytko M*	60 adults (35 ISM)	30%

ISM: indolent systemic mastocytosis; ASM aggressive systemic mastocytosis; SM-AHNMD: systemic mastocytosis associated hematological nonmast cell lineage disease.

*Unpublished data.

both diseases came from Müller et al. (30). They reported three patients with UP suffering from anaphylaxis following a *Hymenoptera* sting. Two had detectable sIgE and positive skin prick tests (SPT), whereas in one patient no specific IgE mediated allergy could be found. This raised questions concerning the IgE mechanisms. The authors concluded that the mediator release by a pharmacologic mechanism may be an alternative way of induction of anaphylaxis after *Hymenoptera* stings in mastocytosis (30). However, the introduction of the basophil histamine release test and the basophil activation test in the diagnostic work-up allows nowadays detecting IgE in most, if not all patients (11). Therefore, the non-IgE mediated IVA is regarded as a very rare reaction (20, 31), although the results of sIgE and skin test in mastocytosis patients are less pronounced compared to patients suffering reactions with a similar grade without mastocytosis (20). A suggested explanation for this phenomenon is the adsorption of circulating IgE on the abundant mass of tissue mast cells (30).

Also, alternative pathways of mast cell activation have been demonstrated, although none of them has been proven so far to play a crucial role in the mechanism of anaphylaxis in mastocytosis. In mouse models, activation of macrophages by IgG-antigen complexes cross-linking low-affinity IgG receptor (FcγRIII) has been demonstrated to induce anaphylaxis. No data so far have confirmed the relevance of this model to human anaphylaxis (23). Another element of anaphylaxis is the activation of mast cells by intracellular tyrosine kinase-mediated cascades especially via the well known Kit, but also Lyn, Syk and Fyn pathways (23). The presence of a *KIT* mutation, especially the D816V, is found in the large majority of patients with systemic mastocytosis (3–5). The D816V mutation might induce exaggerated mast cell stimulation, as is shown in *in vitro* studies (23). However, the presence of this mutation does not correlate with the severity and prevalence of anaphylaxis (6). Further, deregulation of the calcium influx for mast cell activation may also play a role in anaphylaxis susceptibility (23, 32, 33). Transient receptor potential membrane proteins (TRPM) channels are involved in the mast cell degranulation, compounds activating these channels can serve as drugs inhibiting allergic reactions (32).

There are also data indicating complement activation, calcitonine gene-related peptide overproduction, osteopontine pathway involvement and diminished function of angiotensinogen and renin-angiotensin system in IVA (34–39). It is not known to which extent these pathways could be relevant for mastocytosis and effectiveness of VIT in this disease.

Unfortunately, in spite of the findings mentioned above, still it is not known why one out of two patients with mastocytosis suffer from anaphylaxis and one out of three from IVA.

Diagnostic tests of insect venom allergy in mastocytosis patients

An elevated level of tryptase is an indicator of mastocytosis and should be measured in IVA patients, especially subjects with severe reactions after an insect sting and those who react abnormally to treatment (9, 40–44). In all patients with a history of a systemic allergic reaction to an insect sting before VIT specific IgE has to be demonstrated (9, 15, 31, 40), by SPT, intracutaneous tests and/or serological specific IgE in order to detect specific IgE and to identify the culprit insect (9, 15, 31, 40). It must be taken into account that skin tests in mastocytosis patients may provoke systemic reactions (10, 26). In the majority of patients, this set of tests is sufficient for a diagnosis (9, 21). In individual patients with negative results, the tests should be repeated after 1 or 2 months. If still no specific IgE can be demonstrated for all possibly relevant insects, additional examinations as basophil histamine release test, leukotriene release test or basophil activation test may be considered (9, 11, 31, 40, 41). With these novel diagnostic methods the diagnosis of IgE mediated IVA can be established in 99% patients (31, 40, 41, 43). The amount of specific IgE does not correlate with the severity of the preceding reaction.

In nonmastocytosis patients, sting challenges may also be considered, however in mastocytosis patients diagnostic challenges are considered contra-indicated [2] (10). It can not be excluded that in rare occasions patients with mastocytosis may have non-IgE-mediated anaphylaxis to an insect sting, but this diagnosis can only be made after all other methods described evaluating the existence of IgE are negative.

Immunotherapy

The review of the articles describing VIT in patients with mastocytosis reveals conflicting opinions. Data available so far come from case reports and observational studies, of which most are retrospective with a high risk of selection bias. Additionally, only the studies by de Olano (45) and Bonadonna (17) provide a complete diagnosis of mastocytosis in all patients. Therefore, the power of evidence is moderate [B] to very low [D] according to evidence based medicine guidelines (12, 13). Below, we describe the most relevant studies. None of the studies was a randomized trial.

De Olano et al. (45) examined 21 patients with IVA and mastocytosis treated in the centers cooperating within the Spanish Network on Mastocytosis [B]. The diagnosis of mastocytosis was made according to the World Health Organization (WHO) criteria (3). A total of 21 patients were treated (seven with *Polistes venom*, six with *Vespula*, five with *Apis venom*, and three with two venoms). Fourteen patients were treated according to conventional and seven according to cluster protocol. The

maintenance dose was 100 µg in 20 patients and in the remaining patient 300 µg mixed vespid together with 100 µg honey bee was used. Field stings in the study group were reported. There were no sting challenges performed.

Bonadonna et al. (17) retrospectively studied 16 patients treated in Verona (Italy) with IVA and mastocytosis diagnosed according to the WHO guidelines [C] (3). The patients were selected from 552 IVA cases treated in the years 2004–2007. Seven patients were treated with *Polistes*, eight with *Vespula* and one with *Apis* venom. A conventional protocol of VIT was used reaching maintenance dose of 100 µg of venom. The dose was increased to 200 µg in two patients who reacted to a field sting. Similarly to the previous study sting challenges were not performed, field stings occurred in 13 patients.

Fricker et al. (46) studied 10 patients with IVA and urticaria pigmentosa treated in the years 1980–1994 in Bern (Switzerland) [C]. Three patients were treated with honey bee, five with *Vespula* and two with both honey bee and *Vespula* venoms. The study was performed before the WHO criteria on the diagnosis of mastocytosis were established; it is unknown how many patients could have had a systemic mastocytosis. Seven patients were restung: three by a sting challenge and four experienced a field sting.

Dubois (10) described seven patients with systemic mastocytosis who were treated with VIT according to a semi rush protocol in the Netherlands [D]. The diagnosis of mastocytosis was made by histopathological examination of the bone marrow. The reaction to field stings was reported in six cases.

Rueff et al. (11) described 55 patients with mastocytosis and IVA. Honey bee venom allergy was diagnosed in seven (13%), yellow jacket venom allergy in 35 (66.7%)

and both yellow jacket and honey bee venom allergy in 11 (20.3%) of the patients [C]. About 48 patients were treated with VIT according to a rush protocol. Additionally, sting challenges were performed in 33 of them.

Haerberli et al. (20) treated 19 IVA patients with an elevated basal tryptase level (≥ 13.5 ng/ml), of whom 16 underwent the histopathological examination of the skin biopsies confirming urticaria pigmentosa [C]. Seven patients were treated with honey bee and 12 with *Vespula* venom. The treatment was performed according to an ultrarush, rush or conventional protocol. Sting challenges were performed in 10 patients.

Safety of treatment

The safety of VIT in mastocytosis patients could be evaluated in a total of 117 patients described in six retrospective analyses [C] (10, 11, 17, 20, 45, 46) and four case reports (26, 30, 47, 48) (Table 3). Side-effects were not described in all studies. Side-effects during VIT were documented in 28 (23.9%) patients and systemic side-effects in 24 (20.5%).

We compared these percentages with side-effects in the general population of IVA patients treated with VIT. Studies evaluating at least >100 patients were included for this analysis (Table 4). Both conventional, rush and ultrarush schedules were used. Side-effects are described in 20.3% (11.1–36%) of the population, which seems to be comparable with the percentage of side-effects in the mastocytosis patients. However, it is known that studies evaluating one *Hymenoptera* venom cannot be extrapolated to the other *Hymenoptera* venoms (49). In the general population side-effects due to honey bee venom occurred more frequently compared to yellow jacket venom allergic patients. In the studies we included side-

Table 3. Side-effects of venom immunotherapy (VIT) in mastocytosis patients

Author (ref.)	VIT	Number (%) of mastocytosis patients		
		All side-effects	Systemic side-effects	Adrenaline ¹ was used or caused discontinuation of treatment ²
Rueff F (11)	48 mastocytosis	9 (18.8%) built up phase of VIT	9 (18.8%) built up phase of VIT	2 ^{1*}
Dubois A (10)	7 ISM	6 (85%)	6 (85%)	4 ²
Bonadonna P (17)	16 ISM (2 UP+, 14 UP–)	2 (12.5%)	0	0
Haerberli (20)	10 patients with tryptase >13.5 µg/L and sting challenge performed	1 (10%)	1 (10%)	0
Fricker (46)	3 ISM + UP, 3 ISM – UP +, 4 UP no BM diagnosis	2 (20%)	1 (10%)	0
De Olano (45)	21 ISM (5 UP+, 16 UP–)	6 (29%) 3 built up, 3 maintenance phase of VIT	5 (24%)	1 ²
Engler, Müller, Oude Elberink (26, 30, 47, 48)	4 UP 1 ISM	2 (33%)	2 (33%)	2 ^{1,2}
Total	117	28 (23.9%)	24 (20.5%)	9 (7.6%)

ISM: indolent systemic mastocytosis; UP: urticaria pigmentosa.

*Unpublished data.

Table 4. Side-effects of venom immunotherapy (VIT) in general population of insect venom allergy (IVA) patients (papers with >101 patients published in English)

Author (ref.)	Characteristics of patients and VIT protocol	<i>n</i> (%) of patients with side-effects	Side-effects of Honey bee/ yellow jacket/ <i>Polistes</i> allergic patients (%)	<i>n</i> (%) of patients with systemic side-effects	<i>n</i> (%) of patients were adrenaline was used
Haeberli (20)	151 honey bee and yellow jacket allergic normal basal tryptase, ultrarush, rush conventional	21 (13.9%)	17 / 7	–	–
Górska L. (55)	118 honey bee and yellow jacket allergic 5 day rush	18 (15.2%)	28.6/11.1	7 (5.9%) III or IV Mueller (59)	6 (5%)
Mosbech H. (60)	840 honey bee and yellow jacket allergic ultrarush, rush, conventional	20%(24%rush/ultrarush; 12% conventional)	24/19/0	3%	3%
Wenzel J. (61)	178 honey bee and yellow jacket, rush protocol	(32) 17.9%	Not known	III or IV Mueller (59) 10 (5.6%)	0
Birnbaum (62)	325 patients 90 honey bee, 186 yellow jacket, 49 <i>Polistes</i> ultra-rush	33 (11.1%)	30/3.3/6.1	9 (2.7%)	2 (0.6%)
Müller (49)	205 patients honey bee 148, yellow jacket 57 rush and conventional VIT	74 (36%)	Objective side-effects 21/4	Objective side-effects 33 (16%)	Not known
Brehler (63)	1055 ultrarush VIT in 966 patients yellow jacket VIT in 933 honey bee VIT in 122 patients	224 (21.4%)	23.8/20.9	160 (15.2%)	0
Sturm (64)	101 patients 52 honey bee VIT, 47 yellow jacket VIT rush VIT	7 (6.9%)	12/2	2 (2%)	0

effects occur in 26.6% (12–30%) of the honey bee venom treated patients and in 11.2% (2–20.9%) of the yellow jacket treated patients. In the mastocytosis patients, VIT was performed with yellow jacket venom in 36, honey bee venom in 15, *Polistes* in 14, and with two venoms in four subjects, while in the study by Rueff the specific venom was not stated, but most were yellow jacket allergic patients (11).

Side-effects to yellow jacket venom VIT were present in 12 out of 34 (35%) patients, to honey bee venom VIT in five out of 13 (38%) and to *Polistes* venom VIT in two of 17 (12%). Thus, there is no difference in side-effects between yellow jacket and honey bee venom treated patients with mastocytosis. However, compared with the general IVA population, side-effects are more frequent, especially in yellow jacket allergic patients.

In addition, we evaluated the number of side-effects in which adrenaline was used or the reaction was so severe that therapy has been stopped. In the population of

nonmastocytosis patients treated with VIT, this varied from 3–7% vs 7.6% in patients with mastocytosis (Tables 3 and 4).

These results suggest [2] that side-effects of VIT are probably more frequent in mastocytosis patients, especially in patients with a yellow jacket allergy.

Efficacy of treatment during venom immunotherapy

The efficacy of VIT in mastocytosis was described in six review papers covering 81 patients [B, C, D] (10, 11, 17, 20, 45, 46) and one case report including one patient (47) by evaluating the outcome of sting challenges or reaction to field stings (Table 5). A systemic reaction was observed in 11 of 46 (23.9%) sting challenges described, whereas a systemic reaction to a field sting occurred in 12 of 36 (33.3%) patients during VIT (Table 4). The most severe reaction described (requiring resuscitation and intubation) was found in a patient who was not yet on

Table 5. Effectiveness of venom immunotherapy (VIT) in mastocytosis

Author (ref.)	Time of sting challenge	<i>n</i> (%) of patients with systemic reaction in sting challenge	<i>n</i> (%) of patients with systemic reaction on field sting	Cumulative number of reactions to re-sting
Rueff F (11)	6–12 months after reaching maintenance dose	7/33 (21.6%)	–	7/33 (21.6%)
Dubois A (10)	ND	–	6/7 (85%)	6/7 (85%)
Bonadonna P (17)	ND	–	2/13 (15%)	2/13 (15%)
Haeberli (20)	3–5 years of VIT maintenance dose	4/10 (40%)	–	4/10 (40%)
Fricker (46)	ND	0/3	1/3 (33%)	1/6 (16%)
De Olano (45)	ND	–	3/12 (25%)	3/12 (25%)
Engler (47)	ND	–	0/1	0/1
Total		11/46 (23.9%)	12/36 (33.3%)	23/82 (28%)

ND: not done.

maintenance phase of VIT (45). The cumulative (sting challenge and field stings) number of reactions was 23 in 82 (28%) patients, indicating a protection rate of 72%. However, individual studies show a large variation in protection rate varying from 15–85%. A protection rate of 72% is lower compared to patients without mastocytosis, where the protection is about 80% in honey bee allergic patients and about 95% in yellow jacket allergic patients during maintenance phase of VIT (41).

The assessment of efficacy of VIT however may be overstated due to the possibility of false negative sting reactions as the field sting could have been by an irrelevant insect or due to the relatively low predictive value of one single negative sting reaction in a patient (it is possible that patients with one negative sting reaction, still will react to a second sting) (50).

All patients with a reaction to a later sting in study by de Olano et al. had side-effects during build-up phase of VIT (45). The same has been demonstrated in the general population of patients treated with VIT, where half of the patients who experience sting reactions after stopping VIT have a history of previous systemic reactions during treatment due to a VIT injection or to a field sting (51). This may suggest that at least these patients should be warned that VIT might be less efficacious.

Rueff et al. (11) strongly recommend performing sting challenges to assess the efficacy of VIT in order to detect unprotected patients in whom the dose of venom should be increased to gain protection [B] (11, 51). They increased maintenance dose in 39 patients of which eight had elevated tryptase levels (> 13.5 ng/ml) after a positive challenge (52), and subsequently demonstrated that seven of these eight patients were protected at a subsequent sting challenge, whereas in one patient the sting challenge was not repeated. In another set of patients, the comparison of different maintenance doses of venom in mastocytosis patients revealed better protection of 200 μ g (all 17 patients had no reaction to sting challenge) in comparison to 100 μ g (five of 24 subjects developed systemic symptoms during the sting challenge) $P = 0.05$ (53). The 'effect' of a higher maintenance dose was also demonstrated in another study in two mastocytosis patients reacting to a field sting who tolerated subsequent stings after increasing the maintenance dose (17).

No data are available to date evaluating the long-term efficacy of VIT in mastocytosis patients. However, two fatalities have been described in two patients after stopping VIT respective 5 and 2.5 years (54). Therefore, the guidelines of the EAACI advise lifelong treatment for this group of patients [2] (8). However, it is presently unclear whether continuation of VIT will be able to prevent fatal anaphylactic reactions.

Taking into consideration all available data, we conclude, that VIT seems to reduce the amount of systemic reactions in patients with mastocytosis although the efficacy is less compared to the general IVA population

treated with VIT, especially in yellow jacket allergic patients [2].

Pretreatment and means of precautions

Pretreatment during the built-up phase of VIT in mastocytosis patients was described in two papers (45, 47). Engler et al. used prednisone, hydroxyzine, ranitidine and astemizole during the 5 days of rush therapy. A heparine lock and cardiovascular monitoring was applied (47). De Olano et al. considered VIT in mastocytosis patients as a risky procedure, therefore they used premedication (oral disodium cromoglicate) and intensive care unit or monitored setting with management for resuscitation in all patients. In subjects who did not tolerate the maintenance dose in addition antihistamines, prednisone and antileukotrienes were given (45). In this last group they also changed Pharmedin to Agnogen SQ – amine free extract (ALK, Denmark) allowing the continuation of the therapy without further side-effects in most patients (45). Concerning the maintenance phase of VIT, systemic reactions also have been reported. Therefore, pretreatment may also be considered in this phase of treatment (10, 26). Antihistamines blocking H1 receptor in high doses (i.e. 30 mg of cetirizine a day for adult patients) may be used in all patients (52, 55) [C], as steroids might be advised in patients with side-effects during treatment [2] (47, 52). Kontou Fili demonstrated that omalizumab decreased the incidence and severity of side-effects in mastocytosis patient during VIT (56). However, failures of pretreatment with omalizumab in prevention of recurrent anaphylaxis have also been reported (57), so the efficacy of omalizumab needs further evaluation.

Patients with mastocytosis, who have experienced systemic reactions, should carry two or more epinephrine self-injectors [B] (1–5, 51). This is also advised for all VIT-treated mastocytosis patients in spite of having reached maintenance dose, because of the persistent risk of a systemic reaction (10) and the possibility that systemic reactions may also occur after a sting of an insect whose venom was not used for VIT (27).

Unsolved problems

Golden et al. (41, 58) evaluated the risk of a systemic reaction in the general population taking into consideration asymptomatic sensitization and the occurrence of large local reaction and/or systemic reactions in the past. Similar studies have not been performed for mastocytosis patients so far, so it is difficult to assess the long term risk of a systemic reaction based on the response to previous stings. We consider that all mastocytosis patients with a systemic reaction (grade 1–4) to a *Hymenoptera* sting, might be eligible to preventive treatment. Venom immunotherapy lowers the response rate to the future stings,

but the long term efficacy of VIT in mastocytosis patients is less favorable compared to the general population of IVA patients. It is probable that higher doses of venom may increase the efficacy. As mastocytosis patients are regarded as highly vulnerable to insect sting anaphylaxis (6, 7, 9, 45), the question is whether patients with an allergy for one venom have an increased risk for systemic reactions to other venoms. If so, the question is whether prophylactic treatment with both honey bee and yellow jacket venom could be useful (24, 27).

Conclusions

In spite of the uncertainties listed above and the moderate [B] to very low quality [D] of data gathered so far, it seems that (1) mastocytosis patients have a high risk at severe sting reactions in particular to yellow jacket, (2) VIT could be suggested [2] in mastocytosis patients, (3)

probably should be done life long [2]. (4) VIT is able to reduce systemic reactions, but to a lesser extent compared with the general IVA population [2], so (5) increased dose of venom might be considered [2]. (6) VIT in mastocytosis is accompanied by a higher frequency of side-effects, especially in yellow jacket allergic patients, thus (7) special precautions such as premedication and prompt availability of the emergency treatment should be taken into account notably during the built up phase of the therapy [2] (8). Patients should be warned that the efficacy of the treatment may be less than optimal and they should continue carrying two adrenaline auto injectors [2].

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