Survey on practice of venom immunotherapy in France

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Abstract

Introduction: Venom immunotherapy (VIT) is the only efficient prevention for sting-induced anaphylaxis, but its application is not without risks and needs precautions and standardization. European guidelines were proposed in 2005, but recent practice surveys and more recent knowledge raise the need for an update. The aim of this study was to analyze VIT practices in France, based on previous surveys in Europe but also extended to outcome event management.
Material and methods: A paper questionnaire was sent widely to persons involved in venom treatment.
Results: Eighty-six responses could be included from physicians actively involved in VIT induction evenly distributed in France. The survey shows that VIT was engaged from grade III down to grade I reactions, starting preferentially with the ultra-rush protocol. Premedication was used by 42% only and risks induced by co-treatment with β-blockers were well known but not with angiotensin-converting enzyme inhibitors. However, side effects were very variably managed from arrest to enhancement in doses, time-delay or duration. Similarly, we observed a large discrepancy in treatment evaluation (skin tests, biology, timing and interpretation), decision making for treatment termination (when and how long to be prolonged) and post-treatment follow-up (adrenaline kit, event record) as well as procedures in case of late relapse (new induction, different doses).
Conclusions: Our study shows that most recommendations were fully or partially followed and may need reminding, but many points need to be completed or updated with new tools and knowledge acquired during the last 10 years.

Key words: immunotherapy, venom allergy, practice survey.

Introduction

Systemic reactions to hymenoptera sting can concern up to 8.9% of the population in Europe [1]. Approximately 40% are life-threatening and gravity factors include age, cardiovascular or respiratory diseases and most of all mastocytosis. Angiotensin-converting enzyme can increase the risks of severe allergy while β-blockers can reduce its adrenaline

treatment efficacy [2, 3]. Venom immunotherapy (VIT) is the only preventive treatment with 80% to 95% efficiency in terms of mortality and morbidity provided the specific venom responsible was clearly identified [1, 4]. It consists in injections of rapidly increased doses of rapidly increasing doses (induction phase) followed by periodic injections of high doses for classically 5 years and possibly longer (maintenance phase). A few protocols have been proposed for the induction phase in 15 days (classical), 3 days (rush) or even 3:30 hours (ultra-rush) [4–6]. The target dose for continuous injection should classically reach 100 µg, which represents approximately 2 natural doses of sting. However, medical injection of venom in allergic patients also includes some risks and requires precautions, especially in high risk patients who are also the most in need of VIT [4]. In France, VIT is usually performed by a reduced number of experts, and European guidelines were published several years ago by the EAACI working group [7]. After 10 years, it is time to evaluate the applicability of the guidelines and the needs for updating regarding recent developments since their publication. Indeed previous surveys have shown that recommendations were not always applied regarding the local health organization and daily practice constraints [8, 9].

The aim of this work was to evaluate the practice in France, compared to the 2 previous studies, and identify the needs for updating of the recommendations. This is the first extensive survey performed in France on VIT.

Material and methods

The questionnaire was based on the previously published surveys in the UK and Poland [10, 11]. The Diwakar questionnaire asked questions on skin test procedures (order, dosages, venom tested), IgE dosages, basal tryptase, VIT procedures (type, doses, duration frequency, evaluation and premedication), decision making in case of discordance or side effects, and efficiency evaluation. We have added questions on IgE specificities tested including cross reactive carbohydrate determinants (CCD) and components, decision making in case of double sensitization, and late follow-up. Physicians involved in venom therapy are frequently practicing in different places and some of them only do maintenance treatment but not diagnosis or VIT decision making. In order to reach most of the concerned physicians, we sent a great excess of questionnaires (300) to any correspondents directly or indirectly involved in venom injections in 2010. The questionnaire was completed with questions on the diagnostic process that have been analyzed previously (Charles Dzviga submitted). Only responses from the physicians involved in the decision making and induction of the treatment were considered. The number of experts involved in VIT was estimated at 100–120 in France.

Statistical analysis

Data collected were analyzed using an Excel data sheet and statistical tools. Results are expressed in frequency or item chosen related to the number of responders or mean values and one standard deviation and compared using Student's or χ^2 tests.

Results

Among 88 responses, 86 were provided by practitioners effectively involved in decision making and inducing VIT (Table I). Among them, 35 (41%) were exclusive allergists while 39 (46%) were pneumologists and 4 (5%) dermatologists and 7 (8%) pediatricians. The majority were treating from 6 to 30 new patients a year.

Our study reveals that 40% of practitioners indicated VIT at grade II or 21% even at grade I, with 39% of them taking into account the associated medical conditions that increase the risk for anaphylaxis by starting VIT at an even lower grade.

All but one practitioner executed the induction phase in a hospital environment. The ultra-rush protocol was preferentially used (60%) except by pediatricians (30%; Table II). Other protocols used were rush (23%) and rarely the classical method. The rush duration protocol could vary between 2 and 3 days.

Premedication was used systematically by 42% of practitioners. It was occasionally used by 30% more in case of severe (5%) or even local (12.5%) reaction in previous VIT injections. It always con-

Table I. Survey on practice of venom immunotherapy in France from 86 practitioners effectively involved in decision making and practice of VIT (% of responses) treatment induction

	N (%)
Your practice?	
Allergology exclusively	35 (41)
Pulmonology	39 (46)
Dermatology	4 (5)
Pediatrics	7 (8)
From what stage do you usually indicate VIT?	
Grade III	17 (27)
Grade II	25 (40)
Grade I	13 (21)
Regional	7 (11)
Do you indicate more VIT in case of	
Medical risks	24 (39)

sisted of an anti-histamine drug, rarely associated with corticosteroids (1 case), anti-leukotriene (1 case) or other (3 cases).

Sixty-eight (92%) practitioners knew the added risks of β-blocker treatment and considered that it should be absolutely (46%) or only when possible (46%) stopped during VIT induction, 47 of them (74%) referring to the prescriber of the treatment. On the other hand, possible added risks induced by angiotensin-converting enzyme were either ignored (8%) or neglected (61%) by practitioners.

In the event that a systemic reaction appeared during the induction phase, 50% of practitioners reported changing the protocol, 19%, 14% and 17% in case of reaction of grade 1, 2 or 3 respectively. They thus either introduced premedication as mentioned, or used smaller dose escalation in each step (71%) or increased the delay between the steps (9.3%). On the other hand, 6 (7%) practitioners declared that they just stopped the VIT.

The maintenance phase (Table III) was in a great part practiced outside of hospital facilities, sometimes referring to another allergist (18%) or local medical practitioner including a GP or nurse (37%). The target dose was 100 µg for 99% of practitioners for wasp venom and 96.5% for honey bee venom, unless the patient was at high risk, when target doses were raised to 150 (5% for wasp and 10% for honey bee) or 200 µg in 8.5% and 15% respectively. The time delay between injections was more than 4 weeks in 34% of practitioners and was extended to 6 weeks (77% of practitioners) after 1 year (33%), 2 years (24.4%) or even 3 years (31.1%).

In case of systemic reaction during the maintenance phase, 12.5% or practitioners stopped VIT, 46.6% reduced it, while 11% increased the dose and 27.4% reduced the time delay between injections (Table IV). Furthermore, 48% introduced anti-histamine premedication before injections and 27.5% considered that VIT was not efficient enough and an induction should be repeated. The strategy was reconsidered if reactions were of grade I (31%), II (17%) or higher than II (43%).

The VIT was planned for a fixed duration of 5 years for 50% or 3 years for 9.3% of practitioners or for a variable duration, 13.3% between 3 and 5 years, 8.3% between 5 and 10 years, and 7.2% for more than 10 years (Table V). Practitioners felt the treatment was well followed by patients and 54% estimated that less than 5% stopped earlier

Table II. Practice of VIT induction

The inducing protocol you generally use:	
Ultra-rush	47 (60%)
Rush	18 (23%)
Classical	6 (8%)
Do you use premedication?	
Always	35 (42%)
Occasionally	25 (30%)
How do you consider drug induced added risk?	
B-blockers:	
Stop if possible bb	34 (46%)
Absolutely stop bb	34 (46%)
No change	8 (11%)
ACE Inhibitor:	
Stop	24 (32%)
Don't know	6 (8%)
No change	46 (61%)
Do you change the protocol in case of systemic reaction during induction phase?	
Yes	43 (62%)
From grade I	16 (23%)
From grade II	12 (17%)
From grade III	15 (22%)
What change do you choose?	
Stop VIT	6 (7%)
Smaller steps	61 (71%)
Longer time delay	8 (9.3%)
Premedication	23 (48%)

Table III. Practice of VIT maintenance phase (% of responses)

Maintenance phase	
Usual target dose:	
Wasp venom 100 µg	83 (99%)
Honey bee venom 100 µg	82 (96.5%)
Adjusted in patients at risk:	
Wasp venom 150 µg	4 (5%)
200 µg	7 (9%)
Honey bee venom 150 µg	8 (10%)
200 µg	12 (15%)
Initial time delay:	
4 weeks fixed	46 (58.2%)
4–5 weeks	7 (8.9%)
4–6 weeks	18 (22.8%)
Increased delay after:	
1 year	15 (33%)
2 years	11 (24.4%)
3 years	14 (31.1%)
> 3 years	5 (11.1%)

than planned, most of the time due to slackness (40%) more than because of side effects (20%).

The treatment efficacy was evaluated through the local effect of injection by 25.6% or periodic skin tests (66.3%), after 1 (64%), 2 (15%) or 3 (15%) years. Biological tests were used by 65.1% of practitioners but mostly specific IgE and rarely IgG4 (5%) or cellular tests (2%). If efficacy was not satisfactory, VIT prolongation was frequently proposed for 1 year (46%), 2 years (23%) or more (26%).

Follow-up after the termination of treatment was proposed by 60.7% of practitioners, every 1 year for 54.3% of them or 2 years for 39.1%, although they estimated that this was respected by less than one third of the patients. The follow-up included skin testing (60%) and biological tests (53%). No procedure was proposed for long-term follow-up and systemic reaction relapses were estimated at less than 10% of the patients in the first 5 years for half of the practitioners. A new VIT could then be considered by 91.5% of the practitioners according to the clinical risk and/or after a new diagnosis test.

Discussion

Our study shows that VIT practice in France is close to the EAACI guidelines [7] as reported from Poland [9] but unlike in the UK [8]. Differences may be linked to the respective health care organizations, and indeed the British Society for Allergy and Clinical Immunology (BSACI) has recently published new guidelines that do not always comply further with the EAACI guidelines [12]. In France, allergology can be performed either exclusively or as part of another specialty, mainly dermatology, pneumology or pediatrics, which show small differences in VIT practices. Our results reflect the reality and the view of the French working group on allergy to insect sting, although it was an opinion survey and responses came from 86 out of an estimated 100–120 practitioners in France, which is similar in proportion to the two other studies.

Our survey shows that a few recommendations from the EAACI guidelines [7] need a reminder: The VIT indication should be limited to patients who experienced grade III or IV reaction unless grade II was worsened by gastro-intestinal or angioedema symptoms. Since these recommendations, more risk factors have been identified, especially mastocytosis [13–15] but also cardiovascular pathology such as uncontrolled hypertension, coronaropathy or arrhythmia, or respiratory instability as in severe chronic asthma or respiratory insufficiency [7]. Anxiety and quality of life degradation due to the risk of anaphylaxis must also be considered [7].

It was reported that β-blockers could eventually reduce the efficiency of adrenalin in case of sys-

Table IV. Management of VIT side effects (% of responses)

What to do if late systemic reaction:	
Stop VIT	9 (12.5%)
Reduced dose	34 (46.6%)
Increased dose	8 (11%)
Reduced time delay	20 (27.4%)
Anti-histamine	36 (48%)
New induction	22 (27.5%)
From which grade consider change:	
From grade I	11 (31%)
From grade II	6 (17%)
From grade III	15 (43%)

Table V. VIT termination and efficacy evaluation (% of responses)

Duration of maintenance:	
5 years	42 (50%)
3 years	8 (9.3%)
Between 3 and 5 years	11 (13.3%)
Between 5 and 10 years	7 (8.3%)
More than 10 years	6 (7.2%)
VIT efficiency evaluation:	
Effect of injection	22 (25.6%)
Periodic skin tests:	57 (66.3%)
After 1 year	28 (63.6%)
After 2 years	11 (15.9%)
After 3 years	11 (15.9%)
sIgE dosages	56 (65.1%)
sIgG4	4 (5%)
Cellular tests	1 (2%)
Prolongation if not efficient:	
1 year	16 (46%)
2 years	8 (23%)
> 2 years (26%)	9 (26%)
Post termination of VIT	
Follow-up after termination:	
Yes	51 (60.7%)
Every 1 year	25 (54.3%)
Every 2 years	18 (39.1%)
Every 3 years	2 (4%)

temic reaction due to VIT, and it was proposed to stop the treatment before injections [2, 16]. Risk of treatment arrest (for 1 or 2 days before injections and until at least 3 maintenance injections) may exceed the added risk for VIT. Our study revealed that when it is not reasonable to stop a β-blocker, practitioners preferred proceeding VIT under β-blocker: the risk of this treatment seems lower than an sting in the country without protection. The added risk of converting enzyme inhibitors is even less clear. The drug has been suspected to increase the systemic reaction for pharmacological mechanisms, but interaction with VIT efficiency has not been evaluated [3, 10, 17].

The induction protocol to be used was not restricted by the guidelines [7], as studies have mostly shown that they were equivalently efficient [5] and respective indications depend on the practical conditions. Indeed our data show that ultra-rush was preferred in France, for wasp VIT and in adults, while rush or even the classical protocol was more frequently used for honey bee VIT in children as it is also generally preferred in the UK [8].

Anti-histamine premedication is a good treatment of immediate hypersensitivity symptoms and reduces the symptoms of VIT side effects. Our study shows that its use should be encouraged, at least during the induction phase, since this widely used treatment has very low side effects and could even increase the VIT efficacy [11], even if the mechanism is not clarified yet.

The maintenance procedure used appeared to agree quite well with the guidelines, although the time laps between injections could be increased earlier and more progressively over the 5-year schedule. The conventional target dose for VIT maintenance (100 µg) was the most frequently used in our survey. It was also admitted or acknowledged that the dose should be raised in high-risk cases, but we observed that the new dose was frequently at an intermediate level (150 µg), while few studies have shown that VIT efficiency was improved with a double dose [18].

We observed a wide discrepancy in the management of possible side effects. While intuitively the approach consists in rapidly stopping the protocol, this left the patient facing a high risk for anaphylaxis without any assistance. This should be considered as a lack of efficiency and VIT intensification is then needed to significantly improve the treatment efficacy and patient safety [18]. There is no procedure proposed yet for the dose escalation. Similarly, the duration of the treatment and the risk assessment when it is finished were very heterogeneous. In case of insufficient efficiency or high risk, VIT prolongation has proven its efficiency [19, 20], but the conditions for this decision and schedule need homogenization. The evaluation of VIT efficiency is even more difficult and needs clarification. The risk assessment should now include mastocytosis even at the infraclinical stage [21, 22].

Post-treatment procedures: Monitoring of VIT efficiency is not clarified. Skin reactivity and specific IgE levels frequently decline but most of the time are not completely abrogated [23, 24]. The role of *ex vivo* basophile activation needs to be confirmed [23, 25]. Similarly, precautions to be applied after the treatment is stopped including any drug use (anti-histaminic; adrenaline self-injection kit) are very diverse and making a late event report (new sting, any reaction, etc.) would certainly be very helpful in managing long-term efficiency.

Since this study was started, a new therapeutic tool, anti-IgE monoclonal antibody (omalizumab), has been developed, which may help in VIT tolerance and possibly efficiency [26], and its possible use should also be included in new guidelines.

In conclusion, the role of VIT should be defined in some special medical conditions such as pregnancy, chronic inflammatory diseases, auto-immunity, cancer and immunotherapy or biotherapy.

Conflict of interest

All authors are members of an academic institution and have no financial engagement in conflict with the study.

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