

American Academy of Asthma, Allergy & Immunology membership experience with venom immunotherapy in chronic medical conditions and pregnancy, and in young children

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ABSTRACT

Background: Few data exist regarding the use of venom immunotherapy (VIT) in specific high-risk chronic medical conditions and pregnancy, and in young children.

Methods: A Web-based survey was sent to American Academy of Asthma Allergy & Immunology members to explore their VIT experience in potential high-risk medical conditions and pregnancy, and in young children. Major problems were defined as “activation of underlying disease and/or VIT not well tolerated (systemic adverse events) and/or VIT discontinued for medical reasons.” Results were expressed descriptively.

Results: A total of 697 of 5123 surveys (14%) were completed: 87% of the respondents were based in the United States, and 28% worked in an academic setting. Most respondents (71%) believed that pregnancy was a contraindication for starting VIT. Most were comfortable continuing VIT (51%) if the woman became pregnant after starting therapy. Of the allergists who treated children, many would give VIT down to age 5 years (42%) or younger, ages 1–4 years (35%). The following list is of the specific medical condition, the number of allergists who used VIT in patients with this condition, and the percentage who reported major problems: severe asthma, 212 (4.2%); hypertension, 287 (1.1%); coronary artery disease, 222 (3.6%); arrhythmias, 136 (3.4%); cerebrovascular disease, 104 (5.1%); cancer in remission, 166 (0%); cancer stable but still under treatment, 44 (7.2%); a history of bone marrow transplantation, 15 (4.9%); a history of solid organ transplantation, 29 (3.6%); human immunodeficiency virus, 53 (1.4%); acquired immunodeficiency syndrome, 24 (6.2%); stable autoimmune disease, 164 (2.8%); mastocytosis, 66 (18.4%); elevated serum tryptase, 101 (10.8%); immunodeficiency 59 (2.5%).

Conclusion: Many allergists were comfortable using VIT in young children and continuing but not starting pregnant women on VIT. VIT was commonly used in patients with hypertension, coronary artery disease, arrhythmias, cancer in remission, and stable autoimmune disease. Major problems were most frequently reported in use with mastocytosis, elevated tryptase, and cancer still under treatment.

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Venom immunotherapy (VIT) is indicated for the treatment of Hymenoptera anaphylaxis. The updated stinging insect hypersensitivity practice parameter recommends initiating immunotherapy (IT) in all patients who experienced an anaphylactic reaction to an insect sting and who have specific immunoglobulin E (IgE) to venom allergens.¹ However,

the decision to initiate VIT is not always straightforward. Cutaneous-only systemic reactions are one example. Although VIT has generally been considered unnecessary in patients ≤16 years of age who experienced a cutaneous-only systemic reaction, the updated VIT practice parameter extends this recommendation for patients >16 years of age (personal written communication, David Golden, September 5, 2016). In addition, there are several potential patient risk factors that need to be considered when making the decision whether to initiate VIT. These potential risk factors may include pregnancy, extremes of age (young children, the elderly), and the presence of comorbid medical conditions, such as cardiovascular disease (hypertension, coronary artery disease (CAD), cerebrovascular disease, arrhythmias), symptomatic or severe asthma,² immunodeficiency (such as human immunodeficiency virus [HIV]), au-

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toimmune disease, cancer, and elevated tryptase and/or mastocytosis.³⁻⁷

The recommendations on the use of VIT in the presence of these higher-risk clinical situations has primarily been based on expert opinion, anecdotal experience, and extrapolation from small case reports. Therefore, we decided to initiate the current investigation to gain the collective experiences of expert physicians from the American Academy of Asthma Allergy & Immunology (AAAAI) membership in managing these clinical scenarios. This study presents the high-risk medical conditions in which allergists may still initiate VIT and also in which they have experienced a higher frequency of major problems. This investigation also details the various types of concomitant cancers, autoimmune disease, and immunodeficiencies in patients being treated with VIT.

METHODS

The methods of the development and implementation of this survey were presented in a previous publication.⁸ The final survey draft was transferred to a Web-based survey format (SurveyMonkey, Palo Alto, CA), which included 9 basic questions with 32 additional questions for those responders who agreed to offer more time (Supplemental data). In August 2012, an invitation to participate was sent by e-mail to a list of the AAAAI membership, followed by two reminders to nonrespondents. All the replies were captured anonymously in Excel files (Microsoft Corporation, Redmond, WA). In particular, the survey inquired about VIT dosing, the use of premedication, use in pregnant women and young children, and use in specific chronic medical conditions. Specific chronic medical conditions included in the survey were severe asthma, CAD, arrhythmias, cerebrovascular disease, cancer in remission, cancer stable but under treatment, patients with a history of solid organ transplantation, patients with a history of a bone marrow transplantation, patients infected with HIV but not yet acquired immunodeficiency syndrome (AIDS), autoimmune disease, mastocytosis, elevated serum tryptase, and immunodeficiency. The diagnosis of the specific medical conditions relied on the recall and clinical diagnoses made by the responding providers. The safety of giving VIT in these specific medical conditions was categorized as having major or minor problems with VIT.

A major problem was defined as "activation of underlying disease and/or VIT not well tolerated (systemic adverse events) and/or VIT discontinued for medical reasons." A minor problem was defined as "some dose reduction or doses postponed but no major problems." We only counted major or minor problems if the responder had mentioned in a previous question

that he or she had experience with some patients having the condition. For the calculation of the total number of subjects with a certain condition treated by the responders with VIT, we took the lower numbers of the intervals, *e.g.*, if the responder indicated that he or she had treated one to five patients, we only counted one patient. As such, the numbers in Fig. 1 are the lower estimate of patients with each condition who were treated. The results were tabulated in an Excel spreadsheet and are expressed descriptively. Approval for the study was obtained from the needs assessment committee of the AAAAI.

RESULTS

Survey Response Rate and Respondent Characteristics

A total of 697 of 5123 surveys (14%) were completed. The demographics of the survey respondents are presented in Table 1. Most respondents had fewer than 10 patients (43%) or 10–50 patients (41%) on VIT, whereas 5.8% did not prescribe VIT. Thirty-eight percent of the respondents prescribed imported fire ant IT.

VIT Dosing and Premedication

For winged Hymenoptera, a maintenance dose of 100 μ g (300 μ g for mixed Vespidae) was used by 92.5% of the respondents. For imported fire ant, all respondents used a maintenance dose of 0.5 mL. Most respondents (63%) used a 1:100 wt/vol vial as their maintenance concentration (1:1 vol/vol), some (28%) used a 1:10 wt/vol vial as their maintenance concentration (1:1 vol/vol), and a few respondents (9%) used 1:200 wt/vol vial as their maintenance concentration (1:1 vol/vol). Regarding premedication, 24% routinely premedicated, 10% only premedicated for accelerated schedules, and 62% did not routinely premedicate, whereas the remaining 4% reported variable responses ("Other"), with the most common (1.7% overall) being premedication "only if the patient had prior reactions." Regarding the question pertaining to which premedication regimens are used, 50.1% reported they did not premedicate, 46% used H₁ antihistamines, 6.4% used H₂ antihistamines, 9.3% used leukotriene receptor antagonists, and 6.4% reported variable ("Other") write-in responses, with the most commonly used being prednisone for rush protocols only ($n = 13$), prednisone plus H₁/H₂ antagonists for rush protocols only ($n = 4$), premedication for large local reactions only ($n = 7$), and premedication "on a case by case basis" ($n = 5$).

VIT Use in Pediatric Patients

Of the allergists who treat children, many would give VIT down to as young as age 5 years (42%), whereas some would give VIT down to 1 (8%), 2 (11%),

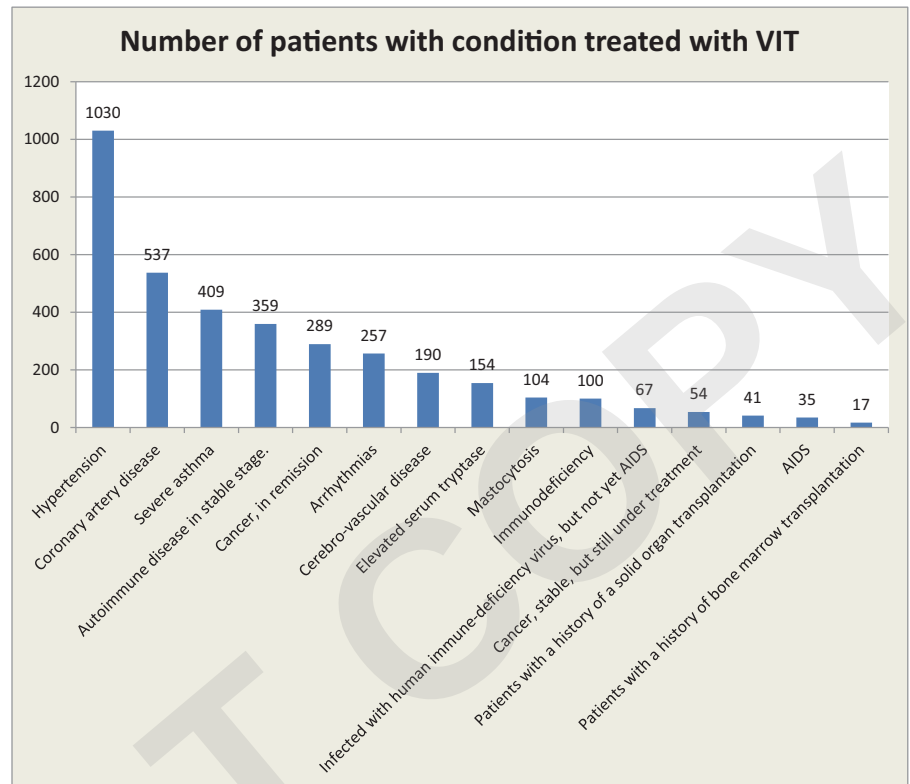


Figure 1. These are the numbers of patients with additional chronic medical conditions who were treated with venom immunotherapy (VIT). This is the low-end estimate of the number of patients treated.

Table 1 Survey respondent characteristics

Characteristic	No. surveyed, 5,123 members	No. respondents, 697 members (%)
Location of practice (N = 681)	Urban	279 (41)
	Suburban	366 (53.7)
	Rural	36 (5.3)
Type of practice (N = 679)	Academic	190 (28)
	Nonacademic	489 (72)
Size of practice (no. patients on VIT) (N = 676)	No. venom patients	39 (5.8)
	Small (≤ 10)	291 (43)
	Medium (10–50)	280 (41)
	Large (> 50)	66 (10)
Years in practice (N = 681)	< 5 y	116 (17)
	6–10 y	87 (13)
	11–15 y	55 (8.1)
	> 15 y	423 (62)
National and international replies (N = 683)	U.S.	596 (87)
	Non-U.S.	87 (13)

VIT = Venom immunotherapy.

3 (8%), or 4 (8%) years old. There were variable “Other” write-in responses as well: the most common included “they have no minimum age and based decision on medical history” (3.2%), “depends on the ma-

turity of the child” (0.8%), and down to age 6 years (2.6%).

VIT Use in Pregnancy

Most respondents (71%) believed that pregnancy was a contraindication for starting VIT. Of those who reported starting VIT in pregnant women, most had one to four patients on VIT and had experienced no problems (70%), whereas some had experienced minor (22%) or major (8%) problems. More respondents (51%) would continue VIT if the woman became pregnant after starting therapy. In this scenario, most allergists reported no problems (66%) or minor problems (18%), with very few major problems (1.2%).

VIT Use in Specific Chronic Medical Conditions

The cumulative number of patients with each chronic medical condition treated with VIT by the allergists who responded is shown in Fig. 1. This was the low estimate for the number of patients treated with VIT because the survey asked respondents to report in ranges of 1–4, 5–10, or > 10 . Therefore, we took the low end of this range for each response (1 for 1–4, 5 for 5–10, and 11 for > 10 patients) and summarized the total number of patients treated by all the respondents with each condition. VIT was most commonly used in patients with hypertension (1030), CAD (537), severe asthma (409), stable autoimmune disease (359), cancer in remission (289), and arrhyth-

Have you had patients on VIT with the following medical conditions?

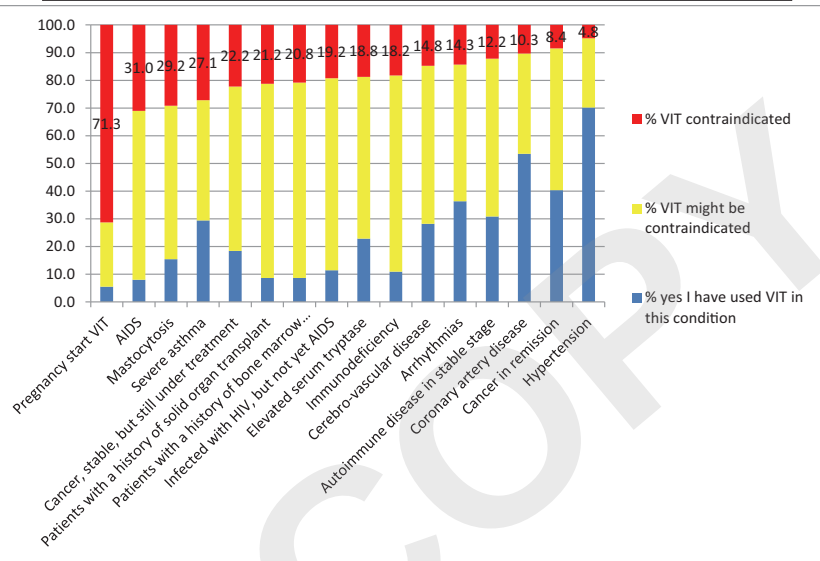


Figure 2. Of all the allergists (N = 628) who answered this question, the percentage who would use venom immunotherapy (VIT), might use VIT but have not to this point, and who believed that VIT is contraindicated in each of these chronic medical conditions.

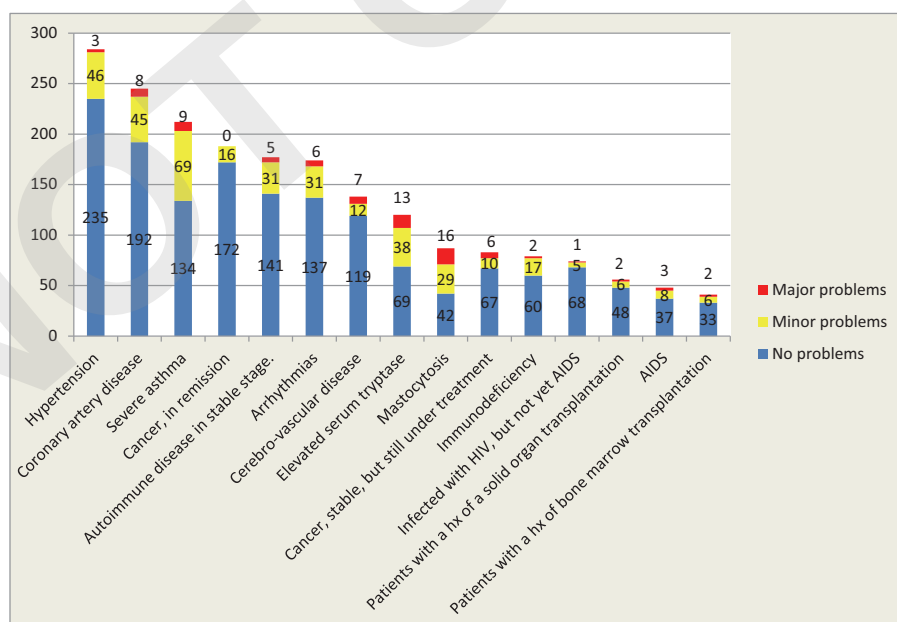


Figure 3. Of 697 allergists who responded to the survey, reports the number of allergists who used venom immunotherapy (VIT) in patients with these specific medical conditions and the number that reported major problems, minor problems, or no problems.

mias (257). Cumulatively across all the survey respondents, >100 patients were reported having received VIT with concomitant cerebrovascular disease (194), elevated serum tryptase levels (154), mastocytosis (104), and immunodeficiency (100). The medical conditions in which our respondents had the least experience with VIT were patients with HIV infection but not AIDS (67), cancer under treatment (54), a history of a bone marrow (17) or solid organ (41) transplantation, and AIDS (35).

The percentage of responding allergists who treated, would treat (have not treated yet), or believed that VIT is contraindicated in patients with the specific condition is shown in Fig. 2. Conditions in which VIT is most

frequently thought to be contraindicated by the respondents included AIDS, mastocytosis, severe asthma, or cancer undergoing treatment, or patients with a history of solid organ or bone marrow transplantation. The number of allergists who reported using VIT in the following conditions and the percentage that reported major problems are shown in Fig. 3 and Table 2: major problems were most frequently reported in patients with mastocytosis (18.4%), elevated serum tryptase levels (10.8%), and cancer still under treatment (7.2%), and when initiating VIT in pregnancy (8%); major problems were least frequently reported in cancer in remission, hypertension, HIV, and stable autoimmune disease (all <3% each).

Table 2 The percentage of the allergists who reported major problems when using VIT in patients with specific concomitant chronic medical conditions

Disease	Respondents, no.	Major Problems, %
Mastocytosis	87	18.4
Elevated serum tryptase	120	10.8
Cancer, stable but still under treatment	83	7.2
AIDS	48	6.3
Cerebrovascular disease	138	5.1
Patients with a history of bone marrow transplantation	41	4.9
Severe asthma	212	4.2
Patients with a history of solid organ transplantation	56	3.6
Arrhythmias	174	3.4
Coronary artery disease	245	3.3
Autoimmune disease in stable stage	177	2.8
Immunodeficiency	79	2.5
Infected with HIV	74	1.4
Hypertension	284	1.1
Cancer in remission	188	0.0

VIT = Venom immunotherapy; AIDS = acquired immunodeficiency syndrome; HIV = human immunodeficiency virus.

The number of respondents who administered VIT to patients with various types of cancer subdivided into cancer in remission and cancer currently still undergoing treatment is shown in Table 3. The most common cancers reported in patients on VIT were breast, prostate, colon, and lymphomas. The number of respondents who administered VIT to patients with various autoimmune diseases is shown in Table 4. The most common autoimmune diseases in patients on VIT included rheumatoid arthritis, systemic lupus erythematosus, thyroiditis, and Sjögren syndrome. Also, the number of respondents who administered VIT to patients with various immunodeficiencies is shown in Table 5. The most common immunodeficiencies in patients on VIT included common variable immunodeficiency, IgA deficiency, and specific antibody deficiency.

VIT Use in Asthma

Respondents ($n = 278$) reported on the forced expiratory volume in one second (FEV_1) of expiration below which they would not start VIT: <90% (0.7%),

Table 3 The allergists who administered VIT to patients with various types of cancer

Malignancy	No. Respondents Administered VIT to Patients	
	Cancer in Remission	Cancer Currently under Treatment
Breast	72	25
Prostate	29	7
Colon	12	2
Lymphoma or NHL	8	3
Skin	7	2
Ovarian	6	0
ALL or AML	3	3
Lung	2	2
Brain	2	0
Thyroid	3	0
Uterine	3	0
Head and neck	2	0
Cervical	2	0

VIT = Venom immunotherapy; NHL = non-Hodgkin's lymphoma; ALL = acute lymphocytic leukemia; AML = acute myeloid leukemia.

<80% (13.3%), <70% (55.4%), <60% (81.6%), and <50% (100%).

DISCUSSION

To our knowledge, this was the first comprehensive study that evaluated allergists' opinions and use of VIT in pregnant women and children, and in specific medical conditions. This study found a low frequency of major problems (all <3%) when using VIT in patients with comorbid hypertension, HIV infection, immunodeficiency, cancer in remission, and stable autoimmune disease. Analysis of this survey data indicated that VIT can be considered in these clinical situations and that these conditions should not automatically be regarded as a contraindication. There have been theoretical risks regarding the use of IT in patients with autoimmune disorders and immunodeficiency²; one theory is that, by altering the immune system, IT may worsen the autoimmune process; another theory is that, due to the immunodeficiency (T cells in particular), the body may not respond to the VIT adequately and VIT will be ineffective. To our knowledge, there are no controlled studies about the effectiveness or risk in patients with these conditions. There was a review article and other case reports on the treatment of patients with HIV for inhalant IT,⁹⁻¹¹ but no studies on assessing VIT. There are no previous studies that looked at the use of aeroallergen IT or VIT in other immunodeficiencies (such as common variable immu-

Table 4 The allergists who administered VIT to patients with various concomitant autoimmune conditions

Autoimmune Disease	No. Times Treated
Rheumatoid arthritis	51
Systemic lupus erythematosus	48
Thyroiditis	23
Sjögren syndrome	15
Psoriasis	5
Crohn disease	5
Mixed connective tissue disease	5
Multiple sclerosis	4
Ulcerative colitis	4
Scleroderma	3
Juvenile rheumatoid arthritis	2
Dermatomyositis	2
Diabetes mellitus	2
Polyarteritis nodosa	1
Wegener granulomatosis	1
Churg-Strauss syndrome	1
Pernicious anemia	1
Vitiligo	1

VIT = Venom immunotherapy.

Table 5 The allergists who reported using VIT in patients who also had immunodeficiencies

Immunodeficiency	No. Reports
CVID	26
IgA deficiency	13
Specific antibody deficiency	7
IgG subclass deficiency	6
IgM deficiency	2
Complement deficiency	1
Mannose binding lectin deficiency	1

VIT = Venom immunotherapy; CVID = common variable immunodeficiency; IgA = immunoglobulin A.

nodeficiency). The current study reported on dozens of patients with concomitant common variable immunodeficiency, IgA deficiency, specific antibody deficiency, or IgG subclass deficiency who received VIT with few major problems.

Regarding autoimmune diseases, a recent Danish registry-based observational study showed that receiving subcutaneous immunotherapy (SCIT) was associated with a lower risk of developing autoimmune disease or acute myocardial infarction, and decreased all-cause mortality; however, these patients did not have autoimmune disease at the inception of the aeroallergen IT.¹² The current study reported on the use of VIT in many patients with rheumatoid arthritis, systemic lu-

pus erythematosus, Sjögren syndrome, and thyroiditis, and reported low rates of major problems overall (2.8%). Therefore, results of this study indicated that one may consider VIT in patients with various autoimmune diseases, immunodeficiencies, and cancer, provided the concomitant disease is well controlled and stable. Conversely, this study found higher rates of major problems in its use with mastocytosis, an elevated serum tryptase level, cancer still undergoing treatment, severe asthma, and AIDS. In addition, conditions most frequently thought to be contraindications for VIT by respondents included AIDS, mastocytosis, severe asthma, cancer under treatment, or patients with a history of solid organ or bone marrow transplantation.

There has been substantial data in recent years regarding the high-risk nature of patients with elevated tryptase levels. Increased tryptase levels have been associated with more-frequent and more-severe anaphylactic reactions to stings as well as greater failure rates with VIT and greater relapse rates after stopping VIT.^{1,3-7} It is now recommended to measure a baseline tryptase level in patients with moderate or severe anaphylactic reactions to sting because of the aforementioned factors and because it is also an indicator for a possible clonal mast cell disorder. This study provided further evidence of the increased risk of VIT in the presence of an elevated tryptase level (10.8% major problems) or suspected or confirmed mastocytosis (18.4% major problems).

This study reported on many patients with asthma ($n = 409$) and patients with CAD ($n = 537$) who received VIT. These medical conditions may reduce the patient's ability to survive the systemic allergic reaction to an injection and thus are relative contraindications.² Regarding the use of VIT in severe asthma, the IT practice parameter recommends IT not be initiated in patients with asthma unless the asthma is stable.² Multiple surveys demonstrated that fatal and near-fatal reactions from IT injections were more common in patients with symptomatic, severe, or labile asthma.¹³⁻¹⁷ This study confirmed moderate rates of major problems in patients with severe asthma who received VIT (4.2% of 212 respondents). Allergists frequently reported this to be a contraindication, and many would not even start VIT in such a clinical scenario. In particular, most allergists would not start VIT with an FEV₁ of <70%, and very few would start when the FEV₁ was <60%. However, the rate of major problems was in the moderate range for the conditions evaluated, so VIT in patients with severe asthma should still only be considered a relative contraindication, and the decision to initiate should be individualized according to the patient's sting risk.

With regard to CAD, it was noteworthy that many patients with CAD were reported to receive VIT (at least 537), many allergists had used VIT in patients

with CAD (53.5%), and only a minority of allergists believed that CAD was an absolute contraindication (10.3%). In addition, of 245 allergists reported who used VIT in CAD, only 3.3% reported major problems. Given the potential lifesaving nature of VIT and the results of this survey, CAD should probably not be considered an absolute contraindication for VIT and the risk-benefit ratio of its use individualized. Further studies on the use of VIT in various cardiovascular disorders and in conjunction with various antihypertensive medications are needed. For example, we are currently investigating allergists' use of beta blockers and angiotensin-converting-enzyme inhibitors (ACEI) on VIT. Although beta blockers have not been found to increase the frequency of systemic reactions in inhalant or VIT,^{18–20} they theoretically may increase the severity of a VIT systemic reaction should one occur.^{21–25} The use of beta blockers may also make epinephrine less efficacious. Therefore, if an alternate medication is available for the patient, then it should be substituted. However, in the setting of a life-threatening Hymenoptera allergy (compared with inhalant IT, which is not life threatening), the benefits of initiating VIT in the setting of beta blocker use still generally outweigh this risk.²

ACEIs have been associated with an increased risk for more-severe reactions from Hymenoptera field stings but not systemic reactions from VIT.³ A large multicenter study of patients allergic to Hymenoptera found that ACEI exposure was associated with an increased risk for more-severe anaphylaxis to a field sting.³ However, risk factors for severe field sting reactions such as ACEI may not necessarily translate to increased risk during VIT. Although there are two case reports of severe systemic reactions to VIT while the patients were taking ACEI,^{2,26,27} two prospective studies found no increased risk with ACEI during VIT buildup.^{5–28} In addition, two retrospective cohort studies did not find an association between ACEI and systemic reactions to either inhalant or VIT.^{18,29} Therefore, in patients with a history of anaphylaxis to Hymenoptera venom (who are not receiving VIT), it is prudent to consider ACEI discontinuation. However, if these patients with venom allergy start VIT, then the decision to continue ACEI should be individualized because the risk of using ACEI during VIT seems similar to the baseline systemic reaction risk in four different studies.^{5,18,28,29}

Regarding pediatric patients, there are very few data on the use of VIT in very young children. The practice parameter states that IT can be initiated in young children.² Although there has been some disagreement about the role of VIT in children <5 years old, there have been reports of effectiveness in this age group.^{30,31} For patients with a history of anaphylaxis to stinging insects, the benefits of VIT might outweigh the

risks, given that it is lifesaving therapy, as demonstrated by a small case series of 3 young children (all <36 months old) who underwent a 1-day rush imported fire ant protocol.³² Two recent pediatric studies demonstrated that children treated with a 50- μ g dose had a frequency of systemic reactions to stings similar to the 100- μ g dose; smaller maintenance doses, of 50 μ g, would equate to smaller injection volumes and could be considered in individual cases.^{33,34} The current study demonstrated that allergists would give VIT down to age 5 years (42%) and younger (cumulative, 35% of the respondents would give to age 1–4 year olds) and many have no minimum age. It seems reasonable that there should be no minimum age in which life-saving VIT should be contraindicated in a child who has experienced Hymenoptera-induced anaphylaxis.

With concern for the use of VIT in pregnancy, a survey published in 1989 by the committee on insects of the AAAAI reported on 26 women with 43 pregnancies and did not see an increased risk of congenital malformations during pregnancy.³⁵ A similar study regarding the use of inhalant IT in pregnancy found the incidence of prematurity, toxemia, abortion, neonatal death, and congenital malformation was no greater than that of the general population.³⁶ To our knowledge no recent studies have investigated allergists' experience and opinion of using VIT in pregnancy. The current survey found that, although 51% of allergists would continue VIT in pregnancy, 71% of allergists believed that it was contraindicated to start VIT in pregnancy. Of those who reported starting VIT in pregnancy, most had one to four patients, and 8% had reported major problems. Of those who continued VIT in pregnancy, only 1.2% had reported major problems. There have been no large prospective studies that evaluated the safety of pregnancy on VIT; one may consider initiating VIT in pregnant patients with high-exposure risk and/or during peak sting season. Thus, the survey demonstrated that continuing but not starting VIT was the most common practice pattern and those who continued VIT during pregnancy had few major problems.

The strengths of the current study included it being the first study, that investigated the use of VIT in many chronic medical conditions. Data were gathered from >600 allergists and hundreds of patients on VIT with additional serious medical conditions. The limitations of the current study included recall bias and the retrospective design, and, although it described patterns of practice, this did not necessarily imply best practice or optimal outcomes. Major problems with VIT could not be further elucidated based on the nature of the information gathered. In addition, one cannot assess whether some patients reported had more than one of the aforementioned chronic medical conditions.

This study had many clinical implications. Allergists can use the current information and arm themselves with the knowledge that other allergists are using VIT in many of these medical conditions. Especially for the conditions with few major problems reported, one must scrutinize whether these are contraindications at all. Conversely, the higher percentage of major problems in some medical conditions indicated that they should be relative (and perhaps absolute) contraindications for VIT. Mast cell disorders might form an exception because the risk-benefit balance probably favors VIT administration because of the elevated risk of severe reactions with field stings. In addition, clinicians have information readily available about the different types of cancers, immunodeficiencies, and autoimmune diseases that allergists have seen in their patient on VIT. These patients on VIT have low rates of major problems as long as their concomitant diseases are stable. Future studies in this area that are ongoing include surveys on the use of VIT with antihypertensive and immunomodulatory medications. In addition, getting other member organizations' input (World Allergy Organization, American College of Allergy, Asthma and Immunology) would add to the wealth of data. The formation of a prospective clinical registry would complement the qualified clinical data registry and aeroallergen IT prospective surveillance safety studies.^{37–41} It is hoped that the current investigation can be a springboard toward these future endeavors.

CONCLUSION

This study demonstrated that VIT was commonly used in hypertension, CAD, arrhythmias, cancer in remission, and stable autoimmune disease, with few major problems reported and that these conditions need to be reconsidered as contraindications. In contrast, it showed that major problems were most frequently reported with the use of VIT with mastocytosis, elevated serum tryptase, and cancer still under treatment, which strengthened the argument that VIT be used with caution in these conditions.

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