



Dealing with absolute and relative contraindications to specific immunotherapy using Hymenoptera venoms

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Abstract

Background Acute infectious disorders, uncontrolled bronchial asthma, severe chronic inflammatory disorders, severe cardiovascular disorders, autoimmune or immunodeficiency disorders, active or progressive cancer, acquired immunodeficiency syndrome (AIDS), treatment initiation during pregnancy, as well as medication with β -blockers and angiotensin-converting enzyme (ACE) inhibitors, among others, are considered either absolute or relative contraindications to specific immunotherapy using Hymenoptera venom (HV-SIT). Some of the contraindications listed above, however, are potential risk factors in the event of anaphylaxis, such that one regularly needs to challenge these contraindications on a case-by-case basis so as not to withhold HV-SIT from patients at particularly high risk.

Methods Literature review.

Results and conclusion Study data on a risk-increasing effect are available for only some of the contraindications to HV-SIT listed in the product information or guidelines. Moreover, these data are partially conflicting. Nevertheless, acute infectious disorders, active autoimmune disorders during flare-ups, active or progressive malignant disease, uncontrolled bronchial asthma, AIDS, and treatment during pregnancy are considered absolute contraindications to the initia-

tion of HV-SIT. Some of these contraindications are, by their very nature, temporary. In other cases, therapy can be initiated once the underlying disease has been optimally treated. Relative contraindications to the initiation of HV-SIT include autoimmune disorders in remission, immune defects and immunosuppressive therapy, well-controlled chronic infectious diseases, category A and B HIV, partially controlled bronchial asthma, limited compliance, age below 5 years, cancer in remission, comedication with ACE inhibitors and β -blockers, as well as treatment (continuation) during pregnancy. In the case of relative as well as absolute contraindications, it is essential to conduct a risk/benefit analysis prior to initiating or continuing HV-SIT.

Keywords Insect venom · Anaphylaxis · Allergy · Specific immunotherapy · Contraindication

Abbreviations

ACE	Angiotensin-converting enzyme
AIDS	Acquired immunodeficiency syndrome
CI	Confidence interval
EAACI	European Academy of Allergy and Clinical Immunology
HAART	Highly active retroviral therapy
HV	Hymenoptera venom
HV-SIT	Specific immunotherapy using Hymenoptera venom
HIV	Human immunodeficiency virus
SIT	Specific immunotherapy
SLE	Systemic lupus erythematosus

Introduction

The indications to initiate highly effective specific immunotherapy using Hymenoptera venom (HV-SIT) are clearly defined [1, 3]. HV-SIT is well tolerated

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Table 1 Absolute and relative contraindications to specific immunotherapy using Hymenoptera venoms [6]

Disorders, comedication		Contraindication: absolute (A), relative (R)
AIDS		A
HIV category 1/2 on HAART with no detectable virus load, CD4+ cells >200/μl		R
Bronchial asthma	Uncontrolled	A
	Partially controlled	R
Autoimmune disorders	During flare-ups	A
	In remission	R
Chronic infections	Uncontrolled	A
	Controlled	R
Compliance		R
Immune defects		R
Immunosuppressive therapy		R
Children aged under 5 years		R
β-Blockers		R
ACE inhibitors		R
Malignant tumors	Active or progressive malignant disease	A
	Stable remission	R
Pregnancy	Initiation during pregnancy	A
	Continuation during pregnancy	R
ACE acquired immunodeficiency syndrome, HIV human immunodeficiency virus, HAART highly active retroviral therapy, ACE angiotensin-converting enzyme		

today: fewer than 10% of patients in a large case series developed systemic anaphylactic reactions upon initiation of HV-SIT, and the vast majority of these reactions were mild and did not require treatment [3, 4]. Since it is essential not to jeopardize the treatment's good tolerability and efficacy, it becomes particularly important to avoid potential risks and contraindications. General guidelines on SIT [5] as well as HV-SIT [1, 2] list several contraindications that largely tally with those found in the product information on therapeutic allergens for HV-SIT.

However, some of these contraindications are considered to be risk-increasing, for instance, in the case of insect sting anaphylaxis. In particularly high-risk patients, e. g., with severe cardiovascular or respiratory diseases, protection against insect sting anaphylaxis is especially important. There is much uncertainty in clinical routine about the extent to which treatment can be considered for this patient group, despite the contraindications listed in the product information or guidelines.

At present, these uncertainties cannot be dispelled by simply referring clinicians to conclusive data. If contraindications exist, it is essentially impossible to include affected patients in clinical studies on treatment efficacy. As such, these studies are unable to obtain evidence-based data on whether and to what

extent a postulated contraindication actually represents a risk in HV-SIT. Also, no large case numbers are known from observational studies, since only few patients with absolute or relative contraindications are treated in clinical routine. Therefore, there are virtually no data, apart from retrospective case series or case reports, on whether and, if so, to what extent HV-SIT poses a particular risk for patients with putative contraindications. Precisely due to the lack of data on safety, therapeutic allergens are not approved for the treatment of insect venom allergy in children under 5 years of age. This means in clinical routine that, in the case of relative contraindications, an individual risk/benefit analysis is required prior to initiating SIT using HV. Furthermore, even if an absolute contraindication is present, treatment can still be considered in individual cases.

This paper summarizes the evidence available on the role of contraindications based on the EAACI position paper “Clinical contraindications to allergen immunotherapy” (Table 1; [6]) and a systematic literature review.

Methods

The EAACI position paper on contraindications in allergen specific immunotherapy formed the basis of this paper and the consensus recommendations therein were considered [6]. The publications it included were re-evaluated and, in addition, a complementary systematic literature review was conducted on the possible influencing factors of relative and absolute contraindications on the efficacy and safety of SIT using Hymenoptera venoms. The search strategy used the following terms: [(insect OR wasp OR bee OR hymenopt*) AND (immunotherapy OR hyposensitization OR hyposensitisation OR VIT) AND (contraindic* OR asthma OR autoimmune disorders OR malignant neoplasias OR b-blockers OR beta-blockers OR ACE inhibitors OR monoamine oxidase inhibitors OR MAOIs OR cardiovascular diseases OR children OR pregnancy OR pregnant OR acquired immunodeficiencies OR HIV OR AIDS OR chronic infections OR congenital immunodeficiencies OR mental diseases OR chronic inflammatory disorders OR immunosuppressive drugs OR inability to communicate OR poor compliance) AND (“2014/07/01” [Date – Create]: “3000” [Date – Create])].

Results

AIDS and HIV

Thanks to highly active antiretroviral therapy (HAART), HIV-infected individuals that undergo prompt diagnosis and, where necessary, treatment now have a normal life expectancy. As a result, allergic disorders that were virtually irrelevant in the pre-HAART era now play a role for affected individuals. There are

no controlled studies on the efficacy and tolerability of SIT using Hymenoptera venoms in HIV infection or patients with manifest AIDS. Only data on efficacy and tolerability of SIT using pollen and house dust mites in HIV-infected patients have been published, whereby patients were category A or B on HAART, viral load was undetectable, and a CD4+ cell count of >200/ μ l was measured. No negative effect on the course of the underlying disease or on the efficacy and safety of SIT using pollen and house dust mites was seen [7–10].

Since SIT using Hymenoptera venom is also unlikely to affect HIV infection adversely, HIV-positive status is deemed a relative contraindication to HV-SIT. No data is available on patients with manifest AIDS; therefore, these patients should not be treated [6].

Bronchial asthma

The criteria used to assess asthma control include frequency of daytime asthma symptoms, asthma-related disruption to daily life, nighttime waking, and weekly emergency medication requirements.

There were no indications of a negative effect on the safety of HV-SIT in patients with controlled bronchial asthma. Multivariate logistic regression analysis in an EAACI multicenter study on HV-SIT side effects showed no increased risk for the development of systemic anaphylactic reactions in bronchial asthma patients compared with patients without bronchial asthma. When systemic reactions did occur in the HV-SIT setting, they were not more severe than in patients without bronchial asthma [3]. A negative effect on the efficacy of HV-SIT in bronchial asthma patients is not anticipated.

Partially controlled asthma is deemed a relative contraindication to HV-SIT. Once adequate treatment has been initiated and the disease followed-up, controlled asthma does not represent a contraindication to HV-SIT [6]. Uncontrolled asthma, on the other hand, is an absolute contraindication to HV-SIT.

Autoimmune disorders, immune defects, and immunosuppressive therapy

The guidelines and product information do not consider immune disorders in a differentiated manner, despite the fact that, from a practical perspective, there is a significant difference between an organ-specific, well-manageable autoimmune thyroid disorder and a systemic disorder associated with a considerable disease burden, such as systemic lupus erythematosus (SLE). Various guidelines and position papers describe autoimmune disorders as relative and absolute contraindications [1, 2, 6, 11, 12]. The hypothesis behind this is that, in patients with autoimmune disorders, immune defects, and drug immunosuppression, SIT could possibly provoke disease flare-ups on the one hand and, on the other, reduce treatment

efficacy depending on the immunosuppressants used and the clinical picture. There are no reliable data on this.

A number of case reports have been published on patients that received SIT for allergic rhinitis. The development of autoimmune disorders was observed in the first year of treatment in previously healthy patients [6]. One case of new-onset rheumatoid arthritis during HV-SIT has been published [13]. On the other hand, no worsening of disease activity was seen within 1 year following the start of wasp venom hyposensitization in a case of pre-existing SLE [14]. As such, there are no reliable data on the induction of autoimmune disorders or the provocation of flare-ups of existing autoimmune diseases under HV-SIT or SIT with aeroallergens. It is on the whole unlikely that SIT triggers autoimmune disorders, given that larger studies would have shown a medium-sized effect and no abnormalities of this kind have been observed.

In the case of limited autoimmune disorders restricted largely to one organ and well-controlled, there is virtually no need for serious concern about HV-SIT. Autoimmune disorders and immunosuppressive therapy are relative contraindications to SIT using HV; HV-SIT can be initiated during stable remission. Active autoimmune disorders during flare-ups are an absolute contraindication to SIT. Moreover, it is recommended that SIT be discontinued if a systemic autoimmune disorder associated with a significant disease burden develops during SIT [6].

It must be borne in mind that the efficacy of SIT is reduced under some forms of immunosuppressive therapy; no data on this are available.

Acute/chronic infections and chronic noninfectious inflammatory disorders

Severe acute infections represent a temporary absolute contraindication to starting SIT with HV. There is a very real risk here of poorer HV-SIT tolerability. SIT is not initiated or continued until symptoms have resolved. Well-controlled chronic infectious diseases, e.g., hepatitis B or C, are a relative contraindication to HV-SIT [6].

The case of a female patient with known sarcoidosis who developed subcutaneous sarcoidosis nodules at the injection site of aluminum-containing SIT to treat allergic bronchial asthma has been described [15]. Controlled studies are not available.

Poor compliance

Good compliance is essential to the success and side effects management of SIT. Compliance issues may be seen in patients with addictive or mental health disorders. Any feasible therapeutic and other measures aimed at improving cooperation and compliance should be pursued and close collaboration with

therapists and carers fostered prior to the initiation of treatment.

Under no circumstances should HV-SIT be dismissed out of hand in the mentally ill or mentally disabled. Some patients with mental disabilities may be at particular risk, since they are unable to adequately protect themselves from stings, nor are they able to administer themselves with drugs in the case of an emergency. Performing HV-SIT in anxiety disorders can also reduce insect-related panic attacks and restore much of the quality of life of those affected. SIT is particularly important in such cases [6].

Cardiovascular disorders

Anaphylactic sting reactions in patients with pre-existing relevant cardiovascular disorders more commonly result in severe systemic reactions and cause death [16–18]. The fact that mast cells accumulate in arteriosclerotic plaques explains the causal link to increased susceptibility to vascular occlusion in anaphylactic reactions among patients with coronary heart disease [19]. Since HV-SIT is usually well tolerated, the highly likely benefit conferred by achieving a protective effect outweighs the extremely low risk of severe anaphylaxis.

HV-SIT is not contraindicated in this patient group, in contrast to SIT in allergic rhinoconjunctivitis or allergic bronchial asthma, in which relevant pre-existing cardiovascular disorders represent a relative contraindication [6]. The underlying disease needs to be as well controlled as possible in close cooperation with the treating cardiologist; this is particularly important with regard to the required comedication, since here again restrictions need to be borne in mind.

Medication in cardiovascular disorders

There is only scant evidence that medication for cardiovascular disorders limits the efficacy of SIT. Safety aspects are the primary subject of discussion, since any pharmacological blood pressure reduction in the context of anaphylaxis must be unfavorable. A group of US authors [20] analyzed data from 251 patients treated for severe anaphylaxis in an emergency department. Logistic regression analysis adjusted for age, sex, triggering allergen, and lung disease revealed a significantly increased risk for multiorgan involvement (>three organs, odds ratio 2.8; 95% confidence interval [CI] 1.5–5.2; $p = 0.0008$) and the need for hospital admission (odds ratio 4.0; 95% CI 1.9–8.4; $p = 0.0001$) in patients on antihypertensive treatment. Nonadjusted regression analysis showed a significant association to multiorgan involvement and the need for hospitalization to manage anaphylaxis in patients on β -blockers, ACE inhibitors, and diuretics [20].

Data from the anaphylaxis registry for German-speaking countries for the period 2006–2014 was recently analyzed and the effect of β -blockers on

the severity of anaphylactic reactions in the patient history investigated. This revealed that the use of β -blockers and ACE inhibitors significantly increased the risk of severe anaphylactic reactions and that the use of both substances together compounded this risk [21]. The authors also investigated the role of β -blockers (metoprolol) and ACE inhibitors (ramipril) in an animal model and found the anaphylaxis-increasing effect of the two substances combined to be confirmed [21].

β -Blockers

β -Blockers are essential in the treatment of cardiac arrhythmia and significantly increase life expectancy in patients with heart failure, coronary heart disease, and following myocardial infarction [22–24]. In the context of anaphylaxis treatment, β -blockers can inhibit the efficacy of endogenous and therapeutically administered adrenaline on β -receptors in the heart and cause other undesired effects [25, 26]. This can make systemic anaphylactic reactions more difficult to manage [27–33]. β -Blockers in eye drops also have a systemic effect and, as such, are able to affect anaphylactic reactions [34].

An analysis of the anaphylaxis registry for German-speaking countries investigated the effect of β -blockers on the severity of anaphylactic reactions in the patient history. This was able to show that patients on β -blocker monotherapy had a moderately, yet significantly, increased risk, particularly for severe anaphylactic reactions [21]. Other investigations on insect venom-allergic patients failed to identify this link [4, 35, 36].

There is no evidence to suggest a higher rate of systemic anaphylactic reactions under β -blocker therapy during HV-SIT [18, 35, 37–40]. The reliability of some of the studies mentioned was limited due to their retrospective design, low case numbers, and the low rate of systemic reactions compared with the number of parameters investigated.

Based on the evidence available up to 2015, the latest position paper on contraindications makes the recommendation that β -blockers not be contraindicated during HV-SIT [6]. The potential hazard posed by β -blockers is primarily relevant in field stings in inadequately protected patients and not in HV-SIT, which is largely well-tolerated.

On the basis of the up to date available evidence, β -blocker therapy (if not absolutely medically indicated) should be modified in collaboration with the treating physicians prior to the initiation of SIT using HV, as has hitherto been the practice.

Angiotensin-converting enzyme inhibitors

Angiotensin-converting enzyme (ACE) inhibitors are often used in patients with complex cardiovascular disorders for the purpose of lowering blood pres-

sure, as well as for their nephroprotective effects [41]. The inhibition of ACE prevents the formation of angiotensin II from angiotensin I, causing vasodilation and subsequent hypotension which, in the case of anaphylaxis, may be more difficult to manage [42–44]. Moreover, the breakdown of bradykinin is inhibited [45], which results in protracted edema and bronchospasm, on the one hand, as well as reducing the mast cell activation threshold, on the other, thereby potentially promoting anaphylactic reactions [21, 46].

Up to now, data from a number of studies have pointed to a potentially unfavorable role for ACE inhibitors in insect venom-allergic individuals prior to and also during treatment, whereby the quality and results of these studies are inhomogeneous as well as partially contradictory. Data from a retrospective EAACI study on as yet untreated insect venom-allergic individuals on ACE inhibitors yielded a significantly increased risk of severe anaphylactic reactions in multiple regression analysis (odds ratio 2.26; CI 1.13–4.56) [4]. Current data in the German anaphylaxis registry likewise show an increased risk for severe anaphylactic reactions under ACE inhibitor therapy [21]. A monocentric study with a smaller number of cases saw no effect for ACE inhibitors on severe stinging reactions [36].

With regard to the data on ACE inhibitors and tolerability of SIT, the picture is inconsistent. Data from a prospective multicenter study recently published by the EAACI show no link between ACE inhibitors and the risk for anaphylaxis in the buildup phase of SIT [18]. A smaller monocentric study reached the same conclusion [47]. In contrast, Bernkopf et al. [40] in their 2016 retrospective data analysis showed a significant association between the use of ACE inhibitors and the incidence of systemic anaphylactic reactions in the SIT buildup phase (30.8% versus 9.3%, $p = 0.03$). It is a cause for concern that ACE inhibitors were significantly associated with reduced HV-SIT efficacy in a prospective multicenter [48] and a retrospective monocentric [49] study. It is possible that, in the case of stings, an ACE inhibitor-related reduction in the inactivation of bradykinin transforms stinging reactions from subclinical into clinical.

Even if the reliability of some of the studies mentioned above is limited for methodological reasons, ACE inhibitors should be substituted where possible for safety reasons. According to the recommendations in the EAACI position paper, ACE inhibitors are deemed a relative contraindication to HV-SIT [6].

Malignant tumors

Since immunomodulatory substances are also used in the treatment of malignant tumors, the same considerations apply as in the section on “Autoimmune disorders”. There are no data from controlled studies to suggest that one should anticipate insect venom hy-

posensitization to be less effective and less safe in the setting of underlying malignant disease or its treatment. By the same token, there is no evidence that HV-SIT could exacerbate underlying malignant disease [6]. However, only findings from small case series are available here. For example, four cancer patients that underwent wasp venom hyposensitization tolerated HV-SIT without complications of any kind [50].

Whereas malignant disease is an absolute contraindication to SIT using aeroallergens, this recommendation only applies to HV-SIT in active malignant disease [6]. On the other hand, the EAACI position paper classifies underlying malignant disease in remission as a relative contraindication to the initiation of HV-SIT [6].

Age below 5 years

There are no controlled studies on the efficacy and tolerability of SIT in the under 5-year age group. Therefore, the preparations with marketing authorization in Germany for the treatment of insect venom-allergic individuals are only approved for use in over 5-year-olds. According to the EAACI position paper, there is an absolute contraindication to HV-SIT in infants under 2 years and a relative contraindication in children aged between ≥ 2 and 5 years [6]. However, severe anaphylactic reactions are seen, albeit rarely, in young infants [51, 52]. In the case of high-risk children with a previous history of anaphylactic reactions (anaphylactic shock, the need for resuscitation), the absolute and relative contraindication to SIT cited in the EAACI position paper may require critical scrutiny. Here again, treatment may be possible in individual cases.

Pregnancy

A severe systemic anaphylactic reaction during pregnancy can cause placental hypoperfusion secondary to uterine contraction, resulting either from the reaction itself or from the required medication with adrenaline. Furthermore, maternal hypoxia can cause fetal damage. Subsequent abnormalities in the surviving fetus, premature contractions, and miscarriages have been described [53, 54]. A study on the safety of HV-SIT during pregnancy revealed no increased risk to mother and child [55]. However, higher rates of uterine contractions and premature birth have been reported in some cases [51, 56, 57].

Since SIT is able to prevent systemic anaphylactic reactions during pregnancy, thereby avoiding damage to mother and child, the EAACI guideline recommends that SIT, provided it was well tolerated in the maintenance phase, can be continued during pregnancy [6]. Initiating HV-SIT during pregnancy, on the other hand, is absolutely contraindicated [6, 58].

Legal aspects of performing HV-SIT despite contraindications

Although data on increased risk are lacking for virtually all the possible contraindications discussed here, for forensic reasons this risk cannot be simply brushed aside when dealing with patients. The warning under contraindications means that performing treatment nevertheless represents off-label use. In principle, treating a patient despite the presence of contraindications is not medical malpractice if there is valid justification. The requirements here include documented medical justification, a careful weighing up against alternative treatments, and patient information.

Thus, an individual risk/benefit analysis that takes the patient and, where appropriate, their treating physicians into consideration should be performed prior to initiating HV-SIT. It is advisable to contact other physicians treating the patient and obtain their prognosis of the underlying disease. In the case of a high risk for potential fatal and/or frequent sting reactions, e.g., in elevated basal mast cell tryptase or systemic mastocytosis, intense exposure, cardiovascular disease, and a history of severe anaphylactic reactions (anaphylactic shock, need for resuscitation), one generally decides in favor of SIT. The patient needs to be informed about possible interactions between HV-SIT and their underlying disease or the drugs they use. Information relating to off-label use needs to be documented and the patient's consent preferably obtained in writing.

Conflict of interest A. Bauer and F. Rüff declare that they have no competing interests.

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