

Physicians' experience and opinion on contraindications to allergen immunotherapy: The CONSIT survey

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ARTICLE INFO

Article history:

Received for publication December 3, 2016.

Accepted for publication February 13, 2017.

ABSTRACT

Background: Allergen immunotherapy (AIT) is the only disease-modifying treatment in allergy but several contraindications limit its use.

Objective: To collect the outcome of using AIT in theoretically contraindicated situations in real patients in the Contraindications to Specific ImmunoTherapy (CONSIT) survey.

Methods: The CONSIT is an electronic European Academy of Allergy and Clinical Immunology survey conducted to gather the safety outcomes of patients undergoing subcutaneous, sublingual, or venom AIT and the opinions of physicians on each of 17 selected conditions: children younger than 5 years; starting AIT during pregnancy; controlled severe asthma; arrhythmias; coronary disease; cancer; autoimmune disease; bone marrow and solid organ transplantation; human immunodeficiency virus and acquired immunodeficiency syndrome; previous anaphylaxis during AIT; use of β -blockers, angiotensin-converting inhibitors, cyclosporine, and methotrexate; and inability to communicate. Safety using AIT was reported in a 3-point scale: 1, "no problems"; 2, "minor problems" (requiring only dose modifications); and 3, "major problems" (AIT not tolerated). Each physician was asked about the degree of contraindication that each condition should have: no contraindication (score 1), relative contraindication (score 2), or absolute contraindication (score 3).

Results: Five hundred twenty physicians (75% Europeans, 89% allergists) reported on approximately 45,000 patients undergoing AIT with any of these conditions. Major problems were infrequent, occurring more frequently in patients with asthma (9.9%) and with previous anaphylaxis from AIT (9.5%). Regarding

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Disclosures: Dr Pfaar reports honoraria for consultancy and/or advisory board and/or lectures from ALK-Abelló, Allergopharma, Anergis, Allergy Therapeutics/Bencard, HAL-Allergy, LETI Pharma, Lofarma, and Stallergenes-Greer; and research grants from ALK-Abelló, Allergopharma, Allergy Therapeutics/Bencard, Circassia, HAL-Allergy, and Stallergenes-Greer. Dr Gawlik received honoraria for lectures from Astra-Zeneca, Allergopharma, and HAL-Allergy. Dr Larenas-Linnemann received honoraria for lectures from MSD, Pfizer, UCB, Astra-Zeneca, and Boehringer Ingelheim; received support for asthma guideline from GSK, Novartis, TEVA,

Astra-Zeneca, and Boehringer Ingelheim; serves as the Chair Immunotherapy for the Colegio Mexicano de Inmunología Clínica y Alergia; and is a member of the World Allergy Organization. Dr Demoly reported lecturing and serving on the board for Stallergenes-Greer and ALK; lecturing for Allergopharma; and serving as an investigator for Stallergenes-Greer and Circassia. Dr Calderon reported honoraria for lectures from ALK, Merck, Stallergenes-Greer, Allergopharma and HAL-Allergy, and honoraria as Advisor from ALK, Stallergenes-Greer and HAL-Allergy. Drs Rodríguez del Río, Pitsios, Tsoumani, Paraskevopoulos and Valovirta have no relevant financial interests to disclose.

Funding Sources: Grants from the European Academy of Allergy and Clinical Immunology.

opinions, experienced physicians scored a significantly lower mean for all conditions than non-experienced physicians for all routes.

Conclusion: Major problems were infrequent and experienced physicians were less likely to be restrictive in the use of AIT.

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Introduction

Allergen immunotherapy (AIT) is the hallmark in the treatment of respiratory and venom allergy.¹ AIT has been greatly advanced in standardization, dosage, understanding the underlying mechanisms for its clinical effects, improvement in administration routes, and widened indications² (food allergy^{3–6} and atopic dermatitis⁷). However, clinical contraindications for AIT remain diffuse; a general consensus has not been reached among physicians; and clinical contraindications to AIT are not usually discussed in detail in current guidelines.

Most current clinical contraindications lack a strong evidence base and are based on assumptions. These contraindications refer to (1) existing comorbidities, (2) possible pharmacologic negative effects of drugs taken by the patient, (3) possible interactions of those drugs with emergency treatment of adverse reactions, and (4) a theoretical negative interaction of AIT with the immunologic background of the patient's disease.

Within the framework of the European Academy of Allergy and Clinical Immunology (EAACI) Interest Groups for Immunotherapy and Venom Immunotherapy, a task force on contraindications to AIT was created. An extensive review of the literature and worldwide guidelines on AIT was performed to evaluate clinical contraindications, and an EAACI position paper was published.⁸ During this process, limited information on the day-to-day experience of practitioners performing AIT was identified. Therefore, it was decided to conduct an electronic survey among EAACI members to collect first-hand information on clinical situations considered contraindications to AIT.

The use of online tools to gather information from large medical groups has been successfully used in medicine^{9,10} and in clinical allergy,^{11,12} especially at the EAACI.^{13–15} Indeed, surveys on the number of adverse events during AIT in real life^{16–18} provided sensitive information on this topic and the evidence generated was seriously considered.

Therefore, an electronic survey was designed to assess the opinions of EAACI members performing AIT regarding clinical contraindications to subcutaneous immunotherapy (SCIT), sublingual immunotherapy (SLIT), and venom immunotherapy (VIT) in adults and children. The level of personal experience with prescribing AIT to patients with certain medical conditions and the actual experience of the number of patients treated with AIT and VIT having those clinical conditions were examined.

Methods

An open invitation to take part in this e-survey was e-mailed through the EAACI's mailing list to all EAACI members. No incentives were offered to the participants. The e-survey was first launched on January 23, 2013, and 2 reminders were sent out during the following 2 weeks.

The SurveyMonkey¹⁹ online survey instrument was used, and all data were stored and protected by an enhanced security system (secure sockets layer) in a centralized database. Users with the same internet protocol could not access the survey twice to avoid double entries. All data concerning medical physicians and patients were anonymous and not traceable; no ethical approval was needed.

The questionnaire was designed in accordance with the Checklist for Reporting Results of Internet E-Surveys (CHERRIES).²⁰ A skip logic pattern was used, allowing participants to avoid certain sections according to their responses to previous questions. The questions were presented in a fixed order and most were closed-ended and compulsory, with an “unknown” or “I don't know” option. Participants were allowed to review and change their answers before submission. The survey was beta tested by 10 physicians in 2 different countries. The detected programming errors were corrected and some minor proposed changes were made before releasing the final version.

Questionnaire Structure

The questionnaire used assessed the following information:

- Questions regarding the physician's profile: country of practice, specialty, years of experience in allergy and in the use of AIT, practice setting (public, private, and/or academic), geographic setting (urban or rural), approximate number of patients receiving AIT yearly, approximate percentage of SCIT, SLIT, or VIT prescriptions, and allergen doses given (low or high).
- Sets of 5 skip logic pattern questions (Fig 1) for each of the following 17 medical conditions:
 - Children younger than 5 years
 - Starting AIT during pregnancy
 - Controlled severe asthma
 - Arrhythmias
 - Coronary artery disease
 - Cancer (in remission)
 - Cancer (active, under oncologic treatment)
 - Autoimmune disease
 - Bone marrow transplantation
 - Solid organ transplantation
 - Infected with human immunodeficiency virus (HIV; without acquired immunodeficiency syndrome [AIDS])
 - AIDS
 - Patient with previous anaphylaxis from any modality of AIT
 - Use of β -blockers (any route)
 - Use of angiotensin-converting enzyme (ACE) inhibitors
 - Use of cyclosporine and/or methotrexate
 - Inability to communicate

Before the submission of each set of questions, physicians were invited to voluntarily provide any additional comment on each topic of the study in a free text box.

Assessment of Each Condition

The first question of each set of 5 questions (Fig 1) divided responders into those with experience and those who had never treated any patient with the condition (no experience).

The experienced group was asked to provide an estimated number of patients with any of the aforementioned conditions who had ever undergone SCIT, SLIT, and/or VIT under their surveillance. Then, participants evaluated the general safety of using AIT in these patients. Safety of treatment was classified on a 3-grade scale: “no problems,” indicating complete tolerability; “minor problems,” if the AIT dose needed to be lowered or postponed without other

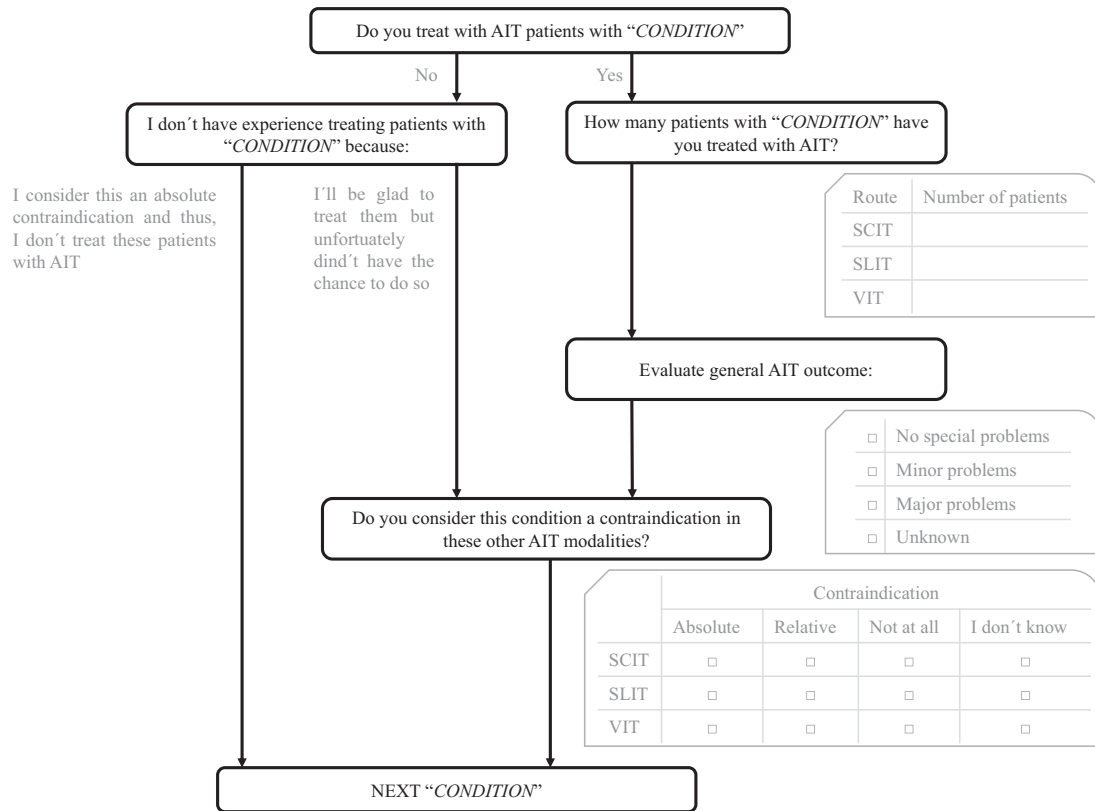


Figure 1. Question flow showing the logic skip pattern for each condition. Black text represents the heading of each question. Gray text represents the different options to each question. Arrows represent how questions were displayed according to the answers provided. AIT, allergen immunotherapy; SCIT, subcutaneous immunotherapy; SLIT, sublingual immunotherapy; VIT, venom immunotherapy.

complications; and “major problems,” if the AIT was not tolerated and/or perhaps systemic adverse events occurred.

Participants performing AIT who answered “no experience” to the initial question of each set were asked about their willingness to treat such patients if they had the chance. If physicians considered a condition an absolute contraindication, then that topic was concluded and the next condition was displayed. However, physicians without experience but willing to treat such patients and experienced physicians were asked in theoretical terms about their opinion on the grade of contraindication that should be established for that condition (“no contraindication,” “relative contraindication,” or “absolute contraindication”) for each AIT modality.

Scoring Methods

To analyze the outcome of experienced physicians of real-life patients with any of the conditions assessed, “no problems” was scored as 1, “minor problems” was scored as 2, and “major problems” was scored as 3. Each outcome was weighted with the number of patients treated by each physician using a weighted mean.²¹

To analyze the data obtained from every physician providing an opinion, a 3-point scale was used, “no contraindication at all” was scored as 1, “relative contraindication” was scored as 2, and “absolute contraindication” was scored as 3. The simple mean for each route, condition, and group (experienced vs non-experienced physicians) was calculated.

Correlation Between Opinions on Contraindication for Each Route

To assess differences in the opinion on the degree of contraindication for each condition and route, the correlation (strength of the linear relation) and the absolute difference of the average

simple mean for the pairs SCIT vs SLIT, SCIT vs VIT, and SLIT vs VIT in experienced and non-experienced physicians were calculated.

Statistical Analysis

For the description of normally distributed quantitative variables, the mean, SD, and range were calculated. Pearson χ^2 test was used for comparison in contingency tables of demographic variables. For the analysis of differences of the weighted mean, paired t test and Pearson correlation were used. A P value equal to .05 was fixed for the level of significance of the tests. Analyses were performed using SPSS 22 (SPSS Inc, Chicago, Illinois).

Results

Of 7,124 members approached (eFig 1), 631 (8.7%) responded at least to the first question; of these, 522 (7.33%) completed the questionnaire (clicked the “submit” button), leading to a “completion rate” of 82.7%. However, 2 physicians requested to be excluded from analysis. A final dataset of 520 questionnaires (7.3%) was used in the analysis.

Characteristics of Participants

The participants were medical physicians from all continents and 49 different countries; 394 (75.8%) were Europeans, 97 (18.7%) were non-Europeans, and 29 (5.5%) did not provide their nationality. The 3 countries with the most corresponding physicians were Spain, Italy, and Greece ($n = 51, 49$, and 27 , respectively).

Regarding medical specialties, 464 (89.2%) were allergists, 118 (22.7%) were pediatricians, 116 (22.3%) were immunologists, 75 (14.4%) were pulmonologists, 26 (5%) were ear, nose, and throat physicians, 18 (3.5%) were dermatologists, and 40 (7.7%) were

Table 1Report of Safety Outcome of AIT in Real Patients With Each Condition From Physicians With Experience in Each Condition^a

Condition	Physicians with experience, n (%)	Estimated number of patients				Overall outcome for any route (for physicians with experience)					
		SCIT	SLIT	VIT	Total	Unknown, %	No problems, %	Minor problems, %	Major problems, %	Weighted mean	Weighted SD
AIDS	11 (2.1)	108	117	1	226	0	81.8	9.1	9.1	1.02	0.19
HIV (no AIDS)	52 (10)	232	132	9	373	1.9	75	21.2	1.9	1.1	0.33
Cancer active	17 (3.3)	37	0	8	45	5.9	52.9	35.3	5.9	1.17	0.44
Cancer in remission	119 (22.9)	620	168	287	1075	0	84.9	14.3	0.8	1.21	0.47
Autoimmune disease	153 (29.4)	996	486	313	1795	1.3	76.4	19	3.3	1.24	0.50
Inability to communicate	71 (13.6)	379	79	52	510	2.8	70.4	22.5	4.3	1.27	0.45
Arrhythmias	122 (23.5)	1106	455	583	2144	2.5	75.4	20.5	1.6	1.28	0.49
Solid organ transplantation	6 (1.2)	12	5	0	17	16.7	66.6	16.7	0	1.29	0.46
Use of ACE inhibitors	246 (47.3)	3354	1631	1546	6531	1.7	76.8	21.1	0.4	1.31	0.46
Bone marrow transplantation	7 (1.3)	7	0	1	8	0	71.4	28.6	0	1.37	0.51
Coronary disease	163 (31.3)	811	528	1158	2497	1.8	68.1	29.4	0.7	1.43	0.49
Use of β -blockers	193 (37.1)	2463	1043	1174	4680	1	67.9	29.5	1.6	1.52	0.56
Start AIT during pregnancy	14 (0.03)	218	187	24	429	0	71.4	28.6	0	1.58	0.49
Use of cyclosporine or methotrexate	33 (6.34)	251	195	45	491	0	72.7	27.3	0	1.64	0.47
Children <5 y old	158 (30.4)	4532	3763	215	8510	0.6	56.3	42.5	0.6	1.66	0.49
Previous anaphylaxis in AIT	347 (66.7)	2666	1350	5279	9295	1.4	23.4	65.7	9.5	1.84	0.49
Severe asthma	214 (41.2)	4215	1730	433	6378	0.9	23.8	65.4	9.9	1.90	0.53

Abbreviations: ACE, angiotensin-converting enzyme; AIDS, autoimmune deficiency syndrome; AIT, allergen immunotherapy; HIV, human immunodeficiency virus; SCIT, subcutaneous immunotherapy; SLIT, sublingual immunotherapy; VIT, venom immunotherapy.

^aConditions are sorted from less to more troublesome. For weighted mean calculation, physicians responding “unknown” were excluded from analysis. Data are displayed starting from the lowest to the highest score of the weighted mean. Scale for weighted mean calculation is 1 (no problems), 2 (minor problems), and 3 (major problems). The closer the weighted mean calculation is to 1, the closer the final tolerability was to no problems, whereas if the mean is close to 3, then major problems occurred most of the time.

registered with other specialties. Mean experience in allergy and performing AIT expressed in years were 17.2 (SD 10.7) and 15.4 (SD 10.6), respectively.

For the setting (>1 could be selected), 302 (58.1%), 273 (52.5%), and 208 (40%) physicians worked in the public, private, and academic setting, respectively. The vast majority of the sample (381, 73.3%) worked in an urban area, only 11 (2.1%) worked solely in rural areas, and 128 (24.6%) worked in urban and rural locations.

The estimation of the total sum of patients being treated with AIT per year by the entire cohort of physicians was 94,117, and the mean per physician was 180 (SD 311), of which approximately 57.4% (SD 34)

were treated with SCIT, 31.5% (SD 33.6) were treated with SLIT, and 11.1% (SD 19.1) were treated with VIT. High-dose AIT was used by 405 physicians (77.9%) and low-dose AIT was used by 115 (22.1%).

After assessing homogeneity for the aforementioned variables, the following remarkable differences were found: 69.1% of non-Europeans vs 48.5% of Europeans ($P < .0001$) worked in private practice; 83.8% of Europeans vs 55.7% of non-Europeans ($P < .0001$) used high-dose extracts ($P < .0001$); VIT was prescribed by 65.3% of allergists and only 35.7% of non-allergists ($P < .0001$); and the SLIT route was used by 88.8% of Europeans and only 60.8% of non-Europeans ($P < .0001$).

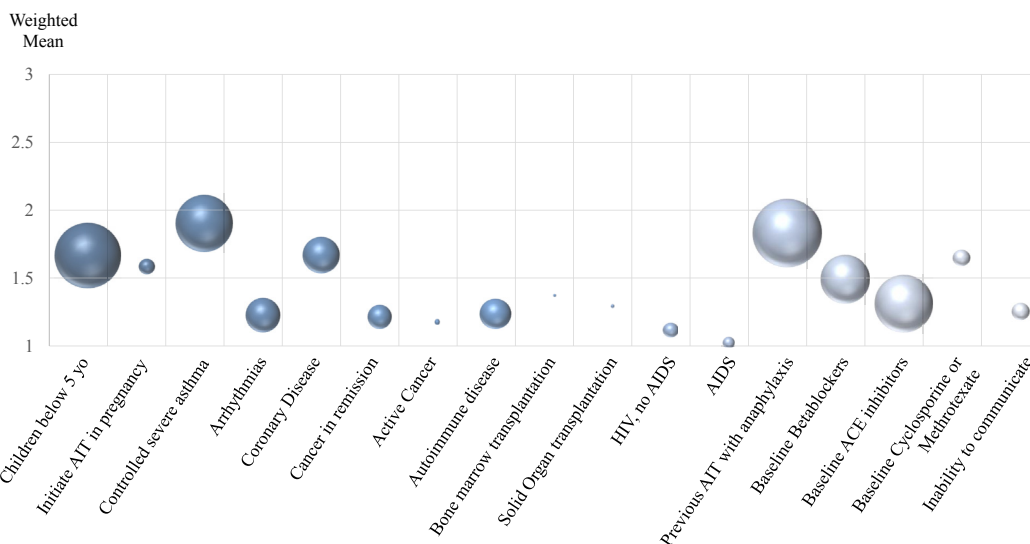


Figure 2. Experience in the safety of AIT (subcutaneous, sublingual, and venom immunotherapies) in real-life patients with each specific condition. Balloon size represents the number of patients treated with the condition with AIT (any route); that is, the largest balloon represents previous anaphylaxis ($n = 9,295$ patients) and the smallest balloon represents bone marrow transplantation ($n = 8$ patients). Balloon position represents the value of the weighted mean for each condition, where 1 was no problems, 2 was minor problems, and 3 was major problems. ACE, angiotensin-converting enzyme; AIDS, acquired immunodeficiency syndrome; AIT, allergen immunotherapy; HIV, human immunodeficiency virus.

Background Differences Between Experienced and Non-Experienced Physicians

Percentages of experienced and non-experienced physicians stratified according to their baseline characteristics were calculated to assess which of such baseline attributes were more frequent and more discriminative of the experienced physicians. Questions 1 to 5 and 8 from the questionnaire were considered. The geographic area (urban or rural) did not influence whether the physician was experienced with the conditions. Being an allergist, with many years of experience in AIT, prescribing high-dose AIT, working outside Europe, and working in a private setting composed the profile of an experienced physician treating the conditions surveyed. The less relevant characteristic when differentiating experienced from non-experienced physicians was the geographic area (urban or rural), and the most relevant difference was having more years of experience in AIT (eTable 1).

Safety Outcome in Real-Life Patients With Each Condition Undergoing AIT

The estimated number of patients with any condition treated throughout the entire professional life of experienced physicians was 45,004 (Table 1 and Fig 2). According to the route, 22,007 (48.9%) received SCIT, 11,869 (26.4%) received SLIT, and

11,128 (24.7%) received VIT. Previous anaphylaxis in the course of AIT ($n = 9,295$, 20.7%) and bone marrow transplantation ($n = 8$, 0.02%) were the conditions with the largest and smallest number of patients, respectively. Overall, major problems were infrequent, with the most common being severe controlled asthma (9.9%), and the lowest prevalence of major problems occurred for bone marrow transplantation (0%). The weighted mean ranged from 1.02 for AIDS (almost 1, representing “no problems”) to 1.90 in severe controlled asthma (almost 2, representing “minor problems”).

Opinion of Physicians for Each Contraindication

Experienced physicians scored a statistically lower simple mean for all conditions than non-experienced physicians (Table 2 and Fig 3).

Their averages of the simple mean for all conditions using SCIT, SLIT, and VIT were 1.72, 1.58, and 1.63, respectively, reflecting a situation between no contraindication (score 1) and relative contraindication (score 2). The simple mean varied from 1.3 for the use of SLIT in children younger 5 years to 2.08 for starting VIT in pregnant women. The percentage of experienced physicians considering any of the conditions an absolute contraindication ranged from 0% for initiating SLIT during pregnancy to 25% in active cancer. There was a statistically significant but moderate correlation on the degree of contraindication for SCIT vs SLIT and

Table 2
Opinion of Physicians if Each Condition Represents an Absolute Contraindication or Not^a

Condition	E and NE physicians, n	Unknown, %			Not a contraindication, %			Relative contraindication, %			Absolute contraindication, %			Simple mean of use of AIT in each condition		
		SCIT	SLIT	VIT	SCIT	SLIT	VIT	SCIT	SLIT	VIT	SCIT	SLIT	VIT	SCIT	SLIT	VIT
Children <5 y old	E, 158 NE, 362	5.1 4.7	12.0 5.5	20.9 9.1	50 19.1	62.7 30.7	46.8 21	39.2 23.5	23.4 11.9	27.2 15.2	5.7 52.7	1.9 51.9	5.1 54.7	1.53 2.35	1.30 2.22	1.47 2.37
HIV (no AIDS)	E, 52 NE, 468	7.7 4.7	9.6 5.1	15.4 5.4	44.2 10	48.1 11.1	44.2 11.5	46.2 18.4	40.4 16.9	38.5 15.8	1.9 66.9	1.9 66.9	1.9 67.3	1.54 2.59	1.48 2.58	1.5 2.58
Cancer in remission	E, 119 NE, 401	2.5 8.7	10.1 9.2	6.7 9.2	42.9 12.2	45.4 14	53.8 16.2	53.8 20.2	43.7 18.2	39.5 16.5	0.8 58.9	0.8 58.6	0 58.1	1.56 2.51	1.50 2.49	1.42 2.46
Bone marrow transplantation	E, 7 NE, 513	0 7.2	28.6 7	28.6 6.4	42.8 4.7	28.6 5.8	57.2 9	42.8 17.7	42.8 17.2	0 15	0 70.4	0 70	0 69.6	1.57 2.70	1.60 2.69	1.6 2.64
Use of ACE inhibitors	E, 246 NE, 274	2.4 6.9	7.3 9.5	7.7 10.2	41.5 15	50.5 19.7	43.2 15.3	54.1 33.9	40.2 27.7	46.7 31.1	2 44.2	2 43.1	2.4 43.4	1.59 2.31	1.47 2.25	1.55 2.31
Solid organ transplantation	E, 6 NE, 514	16.7 6	33.3 6.2	33.3 5.1	33.3 2.6	50 2.8	16.7 5.8	50 16.9	16.7 16.7	50 14.8	0 74.5	0 74.3	0 74.3	1.6 2.7	1.25 2.76	1.75 2.72
Cyclosporine and methotrexate treatment	E, 33 NE, 487	6.1 8.2	15.2 8.6	6.1 8	33.3 5.7	27.3 7	39.4 7	60.6 15.3	57.5 15.3	54.5 14.6	0 70.8	0 70.4	0 70.4	1.64 2.70	1.67 2.70	1.58 2.68
Controlled severe asthma	E, 214 NE, 306	0.4 0	10.3 0	15.9 1.6	30.4 2.3	37.9 6.9	34.6 4.6	65.9 12.4	48.5 8.2	43 7.2	3.3 85.3	3.3 84.9	6.5 86.6	1.72 2.83	1.61 2.78	1.66 2.83
Arrhythmias	E, 122 NE, 398	1.6 5.5	5.7 6.5	7.4 9.1	28.7 7.8	47.5 16.3	45.9 10.6	63.9 25.4	45.1 16.3	41 17.6	5.8 61.3	1.7 60.9	5.7 62.7	1.76 2.56	1.5 2.47	1.56 2.57
Cancer active	E, 17 NE, 503	0 2.8	5.8 2.8	5.8 3.4	41.2 2.2	35.4 2.2	47.1 2.2	41.2 4.8	41.2 5	47.1 4.8	17.6 90.2	17.6 90	0 89.6	1.76 2.91	1.81 2.91	1.5 2.91
Inability to communicate	E, 71 NE, 449	4.2 3.6	11.3 4.5	12.7 6	32.4 9.4	23.9 8.7	29.6 10.2	52.1 17.8	50.7 16.7	50.7 15.1	11.3 69.2	7 70.1	7 68.7	1.77 2.62	1.80 2.64	1.74 2.62
Previous anaphylaxis during AIT	E, 347 NE, 173	2.6 1.7	8.4 4.1	5.5 5.2	29.4 10.4	37.8 16.7	50.4 15.6	59.3 27.8	47.2 19.1	40.9 19.1	8.7 60.1	6.6 60.1	3.2 60.1	1.78 2.50	1.66 2.45	1.5 2.46
AIDS	E, 11 NE, 509	9.1 4.5	0 5.1	9.1 5.1	18.2 3.1	36.4 3.5	18.2 4.7	72.7 10.4	63.6 9.4	72.7 8.6	0 82	0 82	0 81.6	1.8 2.82	1.63 2.82	1.8 2.80
Autoimmune disease	E, 153 NE, 366	3.9 3.5	1.3 3.3	2 3.5	24.2 4.4	27.5 5.7	35.9 6	69.3 11.2	62.7 10.4	53 9	2.6 80.9	8.5 80.6	9.2 81.5	1.81 2.80	1.58 2.78	1.50 2.79
Coronary disease	E, 163 NE, 357	3.1 6.2	6.8 6.7	7.4 8.7	23.3 6.2	41.1 12	35.6 10.4	62.6 21.8	46 16.6	54.5 16	11 65.8	6.1 64.7	2.5 64.9	1.87 2.63	1.62 2.56	1.64 2.59
Initiate AIT during pregnancy	E, 14 NE, 506	0 2.5	0 3.2	14.3 3.6	14.3 3	42.9 4.3	14.3 1	71.4 8.1	57.1 7.1	50 8.5	14.3 86.4	0 85.4	21.4 86.9	2.0 2.83	1.57 2.83	2.08 2.89
Use of β -blockers	E(193) NE, 327	1.6 3.1	6.7 3.4	6.7 5.2	13 4	26.9 6.7	20.2 5.5	66.8 14.7	56.6 14.4	67.4 13.1	18.6 78.2	9.8 75.5	5.7 76.2	2.02 2.76	1.81 2.71	1.82 2.74

Abbreviations: ACE, angiotensin-converting enzyme; AIDS, autoimmune deficiency syndrome; AIT, allergen immunotherapy; E, experienced (these physicians have patients with this condition undergoing allergen immunotherapy); HIV, human immunodeficiency virus; NE, not experienced (these physicians do not have patients with this condition undergoing allergen immunotherapy; this group includes physicians who for the first question answered “absolute contraindication” and physicians who would treat if they came across with such patients); SCIT, subcutaneous immunotherapy; SLIT, sublingual immunotherapy; VIT, venom immunotherapy.

^aConditions are sorted from a less to a more restrictive contraindication; the SCIT score in experienced physicians was used for ranking.

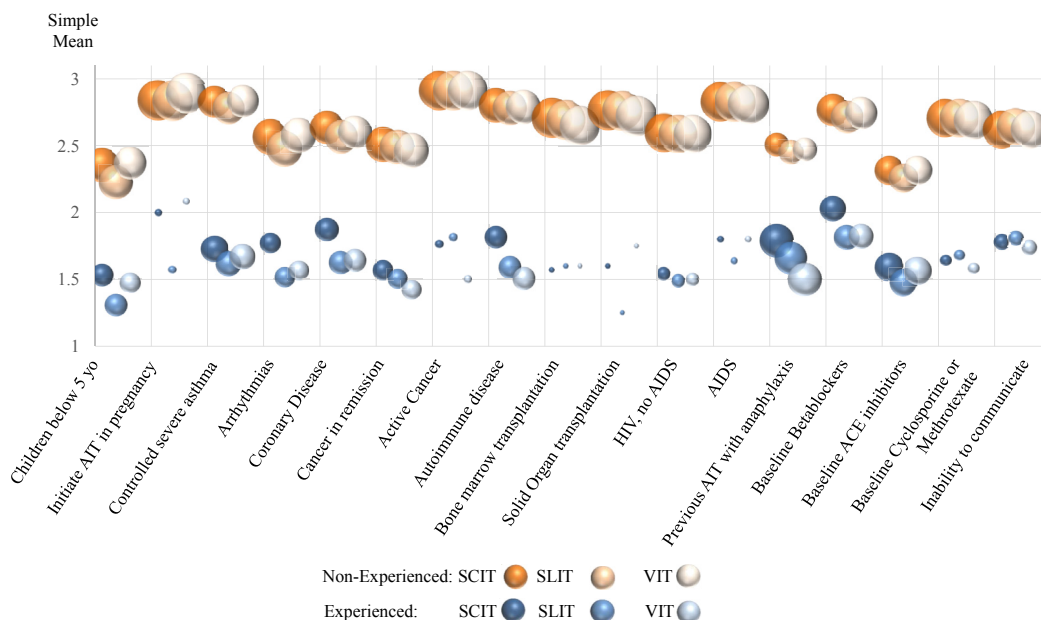


Figure 3. Opinion of every participating physician on the degree of contraindication that each condition should have, stratified according to AIT route (SCIT, SLIT and VIT) and experience. *Striped and plain balloons* represent the opinions of non-experienced and experienced physicians, respectively. Balloon size represents the number of physicians supporting the final mean. The larger balloon represents 496 non-experienced physicians (initiate SCIT during pregnancy), and the smallest balloon represents 4 experienced physicians (SCIT and SLIT for solid organ transplantation). Balloon position represents the value of the simple mean for each condition (1, no contraindications; 2, relative contraindication; 3, absolute contraindication). ACE, angiotensin-converting enzyme; AIDS, acquired immunodeficiency syndrome; AIT, allergen immunotherapy; HIV, human immunodeficiency virus; SCIT, subcutaneous immunotherapy; SLIT, sublingual immunotherapy; VIT, venom immunotherapy.

SCIT vs VIT (0.59 and 0.65; Table 3). No correlation was found for SLIT vs VIT. For the difference among absolute values of the simple mean in each, only SCIT vs SLIT and SCIT vs VIT showed significant differences toward a higher degree of contraindication for SCIT than for either of the other 2 modalities.

The averages of the simple mean for non-experienced physicians for all conditions were 2.64, 2.61, and 2.63 for SCIT, SLIT, and VIT, reflecting an overall position closer to an absolute contraindication (score 3) than a relative contraindication (score 2). The simple mean varied from 2.25 to 2.91 for SLIT use in patients using ACE inhibitors and patients with active cancer, respectively. Physicians in this group who considered the conditions an absolute contraindication varied from 43% for ACE inhibitors with any AIT

modality to 90% for pregnancy. The correlation (Table 3) for the opinion for all routes was high (close to 1) and significant ($P < .0001$). Statistically significant differences on the value of the simple mean were found when SCIT vs SLIT recommendations were compared, being slightly closer to an absolute contraindication for SCIT.

Additional Comments

According to the content of the last optional free-text question of the survey, 8 different categories were created (answers could be included in >1 group). Only 112 physicians (21.5%) provided additional comments; 17.9% highlighted the need for individual assessment of the risk-benefit ratio, 13.4% supported specific contraindications, 12.5% stated disagreement with certain aspects of this survey's methodology, 12.5% suggested other contraindications, 7.1% proposed the abolition of at least 1 additional contraindication, 7.1% commented on dosage matters, 6.3% supported this survey, and 28.6% commented on topics other than contraindications.

Discussion

Allergen immunotherapy has proved its efficacy in treating allergic rhinitis^{22,23} conjunctivitis²⁴ asthma,^{3,25–28} and venom allergy.²⁹ However, one of its major drawbacks, particularly SCIT, is its safety profile.^{16,17,30} To hinder its use in certain patients and conditions, many contraindications were established with no solid evidence based. The intention of this survey was to collect information on the experience of physicians performing AIT for patients who might have any of those clinical conditions considered “contraindications.”

To the best of our knowledge, the CONSIT is the first survey on contraindications to AIT, although other initiatives have been presented in scientific meetings.^{31,32} Conclusions elicited by this survey should be interpreted cautiously because most data provided by physicians were only estimations, but still represent a valuable starting point for future initiatives.

Table 3
Degree of Contraindication Between Modalities in Experienced vs Non-experienced Physicians^a

Modality	Correlation	P value	Average difference $\pm$ SD	P value
Experienced physicians				
SCIT vs SLIT	0.596	.012 ^b	+0.143 $\pm$ 0.14	.001 ^b
SCIT vs VIT	0.655	.004 ^b	+0.098 $\pm$ 0.13	.007 ^b
SLIT vs VIT	0.175	.5	−0.044 $\pm$ 0.2	.391
Non-experienced physicians				
SCIT vs SLIT	0.986	<.0001 ^b	+0.032 $\pm$ 0.04	.004 ^b
SCIT vs VIT	0.987	<.0001 ^b	+0.014 $\pm$ 0.03	.059
SLIT vs VIT	0.987	<.0001 ^b	−0.019 $\pm$ 0.05	.156

Abbreviations: SCIT, subcutaneous immunotherapy; SLIT, sublingual immunotherapy; VIT, venom immunotherapy.

^aThe contraindication recommended for each condition in every modality is compared for the 2 groups of physicians. Correlation represents how the degree of contraindication runs in parallel or not for each pair of modalities. The closer the ratio is to 1, the more similar the trends are for the 2 routes, regardless of the value. Average difference reflects the mean quantitative difference accumulated for each condition. Positive and negative values indicate the direction of the difference; a positive value favors the first modality of the comparison, whereas a negative value favors the second item.

^bStatistically significant differences for $P < .05$.

As expected, most participants were from Europe (75.8%), but a relevant proportion of non-Europeans (24.2%) addressed significant differences between these different origins and showed that non-Europeans were more prone to prescribe AIT to patients with any condition. In addition, high-dose prescribers and physicians with more years of experience with AIT treated more patients with any condition than physicians without these characteristics, which could be due to their higher level of expertise, knowledge, and reliability in the safety profile of AIT.

The experience reported for conditions with the larger number of patients (previous anaphylaxis during AIT, children <5 years old, controlled severe asthma, and use of ACE inhibitors or β -blockers), accounting for more than 35,000 patients, should definitely be taken into consideration and suggests that such conditions probably should not be regarded as absolute contraindications because no problems or only minor problems were reported. In agreement with this, in the recent position paper on AIT contraindications, those conditions are proposed to be considered only relative contraindications rather than absolute, as historically regarded.⁸ Results in conditions with smaller numbers of patients supporting the outcome should be interpreted with caution because experience in such cases is very limited. However, in this last position paper,⁸ other conditions with fewer patients gathered in this survey, such as autoimmune diseases in remission, cancer in remission, chronic cardiovascular diseases, inability of patient to communicate, and HIV-positive patients, are considered relative contraindications; this is in accordance with the results of this survey.

One of the strengths of the survey was collecting information for each route and modality of AIT because the characteristics of each modality could influence the degree of contraindication. Physicians with experience prescribing AIT to patients with certain conditions supported that SCIT, compared with SLIT and VIT, should have a significant higher degree of contraindications (Table 3). This might be due to the higher safety profile of SLIT vs SCIT^{1,33} and to the better risk-benefit ratio for VIT compared with aeroallergen SCIT because VIT is the treatment for a life-threatening condition. All these subtle but significant differences stated by experienced physicians might point to the need for specific guidelines with specific contraindications for each AIT modality. Interestingly, non-experienced physicians showed a very high level of correlation for the recommendations in all routes and only slightly significant differences for the degree of recommendation for SCIT vs SLIT. This situation is likely due to their lack of experience with the conditions, probably leading them to show a lower level of discrimination among different modalities and to strictly follow guidelines without questioning them.

It also is remarkable that experienced physicians provided a significantly lower simple mean of their opinion in the degree of contraindication for every condition compared with the non-experienced physicians. Their lower mean of opinion might only be the result of them using AIT in those conditions, but it is more likely that it is the good safety outcome in those patients that encourages them to decrease the degree of contraindication because it could be expected that real-life adverse results would make them advocate for a stronger restriction even more than non-experienced physicians.

As in every retrospective survey, the recall bias hampers the truth of the figures extracted. A specific weakness of the CONSIT was the low response ratio, with only 7.3% of responders, although other EAACI surveys had a similar ratio (7.7%).¹³ This might be due to several factors, such as the questionnaire being long and time consuming; however, this would explain only the unfinished questionnaires and these represented only 1.4% of all responses. A critical circumstance was the inability to select the eligible targets among all members of the EAACI. Ideally, only AIT prescribers were eligible, but because this information is not included in EAACI's

database, all members were contacted. Another factor explaining this low response ratio could be the overwhelming number of e-mails that health professionals currently receive, which might have driven 68.4% of contacted members to keep the survey's e-mail unopened. Despite this drawback, the lack of previous surveys, the relevance of the topic, and the large number of physicians and patients accumulated make this report on real experience and opinion on contraindications an interesting exploration of the sensitive issue represented by the contraindications for AIT.

This is the first approach to collect real-life data of patients in Europe dealing with established contraindications but still receiving AIT. The results of this survey should encourage future projects to gather prospective data from a larger number of patients to construct evidence to base future recommendations on this topic.

Acknowledgments

We thank all participants for their anonymous contribution to this survey by disclosing their experience and opinion. We thank Stalergenes for supporting the advice of a medical writer. We also express our gratitude to Prof David Bernstein who generously shared with the group information concerning this survey. We thank the EAACI for its support with a grant for this project.

Supplementary Data

Supplementary data related to this article can be found at <http://dx.doi.org/10.1016/j.jana.2017.02.012>

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eTable 1

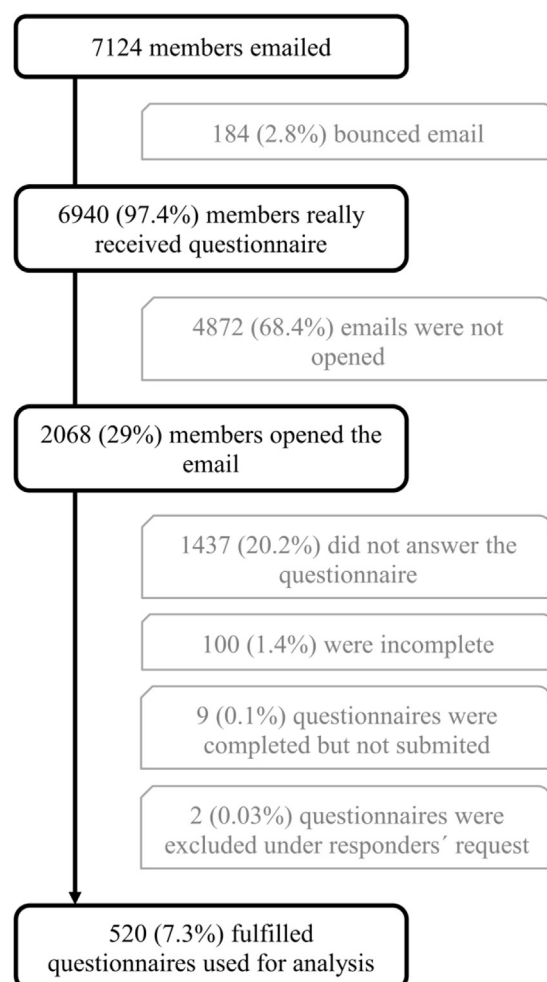
Experienced Physicians' Baseline Differences

Condition	Allergist, no/yes, %	Years of experience with AIT, <8/8–23/>24, %	AIT dose prescriber, high/low, %	Origin, Europe/not Europe, %	Practice setting, public/private, %	Total experienced physicians, % (n)
Children <5 y old	39.3/29.3	24.6/31.7/35.9	30.1/31.3	27.7/41.2 ^a	31.1/37 ^a	30.4 (158)
Starting AIT during pregnancy	0/3	0/3.2/5.5 ^a	2.7/2.6	1.8/6.2 ^a	3/4	2.7 (14)
Controlled severe asthma	42.9/40.9	38.6/42.1/43	40.7/42.6	37.1/55.7 ^a	39.7/47.3 ^a	41.2 (214)
Arrhythmias	14.3/24.6	15.8/22.6/35.2 ^a	25.9 ^a /14.8	23.9/23.7	23.8/22.7	23.5 (122)
Coronary artery disease	23.2/32.3	21.6/34.4/39.1 ^a	34.8 ^a /19.1	32.2/25.8	34.8/30	31.3 (163)
Cancer in remission	14.3/23.9	1.9/29/29.7 ^a	26.2 ^a /11.3	23.4/20.6	23.2/22.3	22.9 (119)
Cancer active	5.4/3	0.6/3.2/7 ^a	3.7/1.7	2.3/7.2 ^a	1.7/4.4	3.3 (17)
Autoimmune disease	19.6/30.6	22.8/34.4 ^a /29.7	32.8 ^a /17.4	29.9/28.9	30.5/25.6	29.4 (153)
Bone marrow transplantation	0/1.5	1.8/0.9/1.6	1.7/0	1.3/2.1	1/1.8	1.3 (7)
Solid organ transplantation	0/1.3	0/0.5/3.9 ^a	1/1.7	0.5/4.1 ^a	1/1.1	1.2 (6)
Infected with HIV (no AIDS)	5.4/10.6	5.8/10.9/14.1 ^a	9.9/10.4	7.6/19.6 ^a	10.3/11.7	10 (52)
AIDS	0/2.4	0.6/2.3/3.9	2.2/1.7	1.8/4.1	2/2.6	2.0 (11)
Previous anaphylaxis due to any modality of AIT	51.8/68.5 ^a	56.1/71/73.4 ^a	71.6 ^a /49.6	68/58.8	70.2 ^a /64.1	66.7 (347)
Use of β -blockers	19.6/39.2 ^a	24.6/41.2/46.9 ^a	38.8/31.3	37.6/37.1	41.1 ^a /35.2	37.1 (193)
Use of ACE inhibitors	16.6/50.6 ^a	33.9/52/57 ^a	49.1/40.9	48.7/43.3	50/47.3	47.3 (246)
Use of cyclosporine and methotrexate	1.8/6.9	36/29.3/22.6	6.7/5.2	4.1/15.5 ^a	4.6/7.3	6.3 (146)
Inability to communicate	8.9/14.2	9.4/17.2/13.3	13.6/13.9	11.7/23.7	10.9/15	13.7 (71)

Abbreviations: ACE, angiotensin-converting enzyme; AIDS, autoimmune deficiency syndrome; AIT, allergen immunotherapy; HIV, human immunodeficiency virus; SCIT, subcutaneous immunotherapy; SLIT, sublingual immunotherapy; VIT, venom immunotherapy.

According to the experienced physician's baseline profile, eTable 1 shows the conditions where any of the profiles prescribe significantly more than the others. The geographical area (urban/rural) did not influence whether the physician is experienced or not in any of the conditions; thus, this data is not shown.

^aStatistically significant differences are marked with ^a for $P < .05$.

**eFigure 1.** Response ratio flowchart.