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Congruence between international guidelines and mite specific immunotherapy prescribing practices

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Summary

Both rhinitis (ARIA) and asthma (GINA) guidelines recommend allergen-specific immunotherapy (SIT) tailored to the specific levels of severity of each disease. Real world studies evaluating congruence between these recommendations and prescribing practice in the single patient with comorbidity are lacking.

An observational polycentric study was carried out in 518 patients recruited from 34 allergy centers throughout Italy. A questionnaire was administered to each consecutive patient over a span of four months.

Taking into account guideline recommendations for both diseases, concomitant in the same patient, three subsets resulted: patients not eligible for SIT (11%); patients eligible for SIT for one disease only (60%); patients eligible for SIT for both diseases (29%). SIT was prescribed in 257 (49.6%) subjects. The level of SIT prescription was about 50% in all three groups. Consistent with the ARIA guidelines, a correlation between the prescription of SIT and the severity of rhinitis was documented ($r = 0.87$; $p = 0.001$). An association with asthma severity was found ($p = 0.02$), but the trend was inconsistent with the GINA recommendations. Young age was the most important factor for SIT prescription both in the eligible for one disease and in the eligible for both diseases subset. The tendency towards worsening of symptoms was a factor for SIT in the eligible for one disease subset.

In mite allergic patients with rhinitis and asthma comorbidity, the severity of rhinitis and the young age are the most important factors driving the SIT prescription. The congruence of SIT prescription was better for the ARIA than GINA guidelines.

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Introduction

Although a high level of comorbidity among allergic (and non-allergic) diseases of the upper and lower airways is widely acknowledged,^{1–3} the vast majority of available therapies are single disease-oriented. The international guidelines both for allergic rhinitis (ARIA) and for asthma (GINA) take this into account and prescribe therapies geared towards the severity of symptoms of each single disease.⁴

Montelukast, omalizumab and specific immunotherapy (SIT) are exceptions to this approach, as they are single therapies, which are beneficial for both diseases.

As consequences of their prevalent efficacy on asthma and of the elevated cost of omalizumab, the first two medications have been adopted by the Italian version of international guidelines for the asthma treatment only.

For SIT this is not the case, because recommendations tailored to the specific levels of severity of both rhinitis and asthma were produced, consistent with the results of the single disease related meta-analyses.^{5,6}

The Italian edition of the ARIA guidelines (2005) recommend SIT for intermittent moderate-severe rhinitis and both mild and moderate-severe persistent rhinitis,⁷ while the Italian edition of the GINA guidelines (2006) recommend its administration for mild persistent and moderate persistent asthma.⁸ The problem of the concomitance of both disease, with different levels of severity in the same patient, was not openly handled.

Few studies have investigated the congruence of SIT prescription with international guidelines in the real world and the quality of their results is poor.

One German study highlighted the differences between clinical practice and guideline recommendations,⁹ while another performed in asthmatics, assessed according to GINA guidelines, documented that the prescription of SIT fell as the severity of bronchial asthma increased.¹⁰ In yet another, done in a specialist setting, SIT was reported to have been prescribed for moderate-severe rhinitis (35%), rhinitis and asthma (34%) and bronchial asthma (31%) but did not provide further information.¹¹

While disease-centred guidelines underline the severity of the disease, the position papers focusing on SIT emphasize the importance of the patient-centred approach. In order to optimize the specificity and results of SIT, certain features (in particular, sensitization to a single allergen, the early commencement of SIT, the preventive effect of SIT on the progression from rhinitis to asthma) were focused on in the decision making process that eventually led to SIT prescription.^{12–14}

The three-fold aim of our study was: (1) to investigate the congruence of SIT prescription with the ARIA and GINA guideline recommendations in mite allergic patients with both rhinitis and asthma, (2) to evaluate the interplay between the recommendations provided by disease-oriented guidelines and SIT-oriented position papers and its influence on SIT prescription, and (3) to identify those factors which favour the prescription of subcutaneous immunotherapy (SCIT) over its sublingual alternative (SLIT) and vice versa in Italy, where both are commercially available.

Materials and methods

Study design

multicentre, observational, cross-sectional study, involving allergy and pneumology units throughout Italy was carried out.

The units were selected through emails enlisting their participation in the survey sent to 570 members of the AAITO (Italian Association of Territorial and Hospital Allergists and Immunologists). Forty-three centers joined the survey, nine subsequently dropped out for reasons unrelated to the study.

During their scheduled doctor's appointment, patients were invited by their doctors to enrol for the study and those consenting to do so signed an informed consent form and completed a self-administered questionnaire.

A two-share standard questionnaire was used.

The patient share of the questionnaire collected basic demographic details (age, sex, etc.) and clinical details (predominant symptoms). This share of the questionnaire was filled in by patients prior to being examined, without doctor supervision.

At the end of the appointment, the physician completed his/her share of the questionnaire, which was designed to gather specific clinical details and factors supporting the decision to prescribe SIT and divided into patient and non-patient related features.

The first domain listed the level of education, smoking habits, the mite allergic mono/polysensitisation, the concomitant disease, the physician's assessment of both the evolution of symptoms and efficacy of current therapy.

The second domain reported the physician's specialty, the stage of the doctor-patient relationship (first time or follow-up visit) and the cost of the treatment.

In Italy the reimbursement of SIT varies, depending on the Regional Health Service. SIT is either fully charged to the patient in some regions or is partially or completely subsidized by the Health Service in others.

Concerning the severity of rhinitis and asthma, the questionnaire was completed by physicians prior to the decision to or not to treat and was designed to collect guideline-orientated data. However, in order to maintain physician objectivity the severity index of both diseases remained undisclosed during completion of the questionnaire, thereby ensuring as far as possible that the decision was not solely based on the unequivocal evidence of disease severity.

The severity of the both diseases was later classified by a peer, applying the rhinitis and asthma-severity guidelines scale. All data were collected from September 1st 2007 to December 31st 2007.

The study was approved by the Ethics Committee of the Coordinating Unit.

Patients

All consecutive patients, aged 14 and older, attending a specialist unit, with a history of rhinitis and asthma comorbidity and evidence of house dust mite allergy, were eligible for the study.

Histories of rhinitis and asthma comorbidity were controlled for as part of the inclusion criteria.

A diagnosis of mite allergy was admitted, provided that at least the following two conditions were fulfilled: a history consistent with mite allergy (predominant symptoms, seasonality of symptoms and exacerbating factors) and a positive skin prick test for mite. Skin prick testing with a panel of the most prominent inhalant allergens in Italy was performed in all patients, with a positive and negative control. A mean wheal diameter ≥ 3 mm was considered positive. Patients were enrolled even if they were positive to more than one of aeroallergen skin tests.

Rhinitis and asthma severity assessment

Consistent with the ARIA guidelines,⁷ the severity of rhinitis was evaluated by combining the duration of symptoms and the disease's impact on patient quality of life and classified as follows: intermittent (<4 days/week or <4 weeks/year) and persistent (>4 days/week and >4 weeks/year). Rhinitis was diagnosed as moderate-severe in patients who replied "yes" to one or more of the following items: abnormal sleep; impairment of daily work or school; impairment of leisure activities; and presence of troublesome symptoms. Rhinitis was classified as mild in patients who replied "no" to all of the above listed items.

In accordance with the GINA classification algorithm (2006), the severity of asthma was ascertained using the grid sheet, describing the patient's level of symptoms and his/her level of treatment.⁸

Statistics

Statistical analysis of the data yielded by the questionnaire was done using SPSS 10.0 for Windows. The bivariate analyses done to compare the rates of prevalence among groups and the analysis of variance done to compare continuous variability among groups were conducted by chi-square test.

Logistic regression models designed to estimate the association among variables of effect and variables of exposure were used for the multivariate analyses while allowing for the independent effect of potential confounding factors. Statistical significance was set at <0.05 .

Results

General characteristics of the sample population

Five hundred and ninety-eight patients were enrolled, of which 42 were excluded as they did not fit the selection criteria. The most important demographic and clinical features of the patients referred to the specialist are presented in Table 1.

The sample was made up of young adults who were fairly evenly distributed throughout Italy.

The majority of patients were enrolled at a follow-up visit, while 35.8% of them were recruited on visit one. Allergology (81.1%) and pulmonology (18.7%) were the most predominant specialties of the prescribing doctors.

Table 1 Demographic characteristics and clinical data of the study participants.

Sample size	556 patients
Gender	
Male	59.1%
Female	40.9%
Age (years)	
Mean	33 years
Range	14–76 years
Median	32 years
Geographic area	
North	15 centers
Centre	8 centers
South	11 centers
Smoking status	
Never smoked	76.6%
Current	13.2%
Former	10.2%
Education	
None	0.4%
Elementary school	6.4%
Middle school	30%
High school	48.4%
University ordinary degree	3.5%
Honours degree	10%
Master/specialization	1.3%
Sensitization	
Mite mono-sensitized	31.6%
Mite plus other sensitizations	68.4%
Comorbidity	
Sinusitis	13.1%
Nasal polyps	4.0%
GERD	10.5%
Specialist's belief about the tendency of the disease	
No worsening	74.1%
Worsening	25.9%
Current drug therapy	
Yes	65.9%
No	34.1%

Comorbidities with a prevalence greater than 4% are tabulated.

House dust mite single allergic sensitization affected around a third of the cases. The majority of patients were receiving drug therapy and in a quarter of cases clinicians judged the symptomatology to be worsening.

The most common comorbidities were sinusitis and gastroesophageal reflux disease.

SIT prescription: the role of ARIA and GINA guideline recommendations

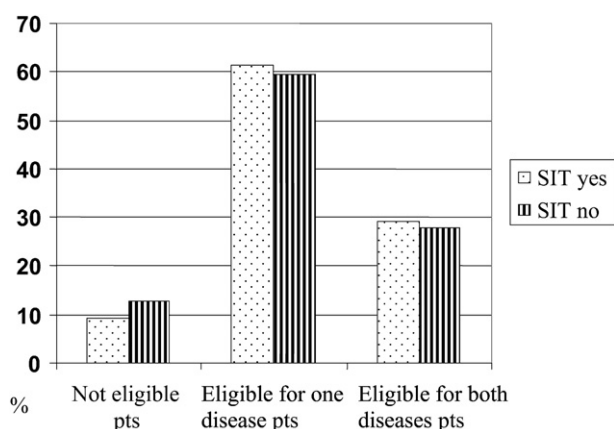
Though 556 patients met the selection criteria, only 513 questionnaires were completed correctly by patients and were valid for the study.

Table 2 Distribution of the severity of comorbidity and of the prevalence of SIT prescription in all study participants. The three subsets of the patient's eligibility for SIT are underlined.

Severity of the concomitant rhinitis and asthma in the same patient	Pts n°: 513 (%)	SIT n°: 257 (%)
Not eligible for SIT		
Mild intermittent rhinitis plus intermittent asthma	38 (7.4)	10 (3.9)
Mild intermittent rhinitis plus severe asthma	19 (3.7)	14 (5.4)
Eligible for one disease for SIT		
Mild intermittent rhinitis plus mild persistent asthma	13 (2.5)	5 (1.9)
Mild intermittent rhinitis plus moderate persistent asthma	11 (2.1)	1 (0.4)
Moderate-severe intermittent rhinitis plus intermittent asthma	13 (2.5)	6 (2.3)
Moderate-severe intermittent rhinitis plus severe persistent asthma	4 (0.8)	1 (0.4)
Mild persistent rhinitis plus intermittent asthma	70 (13.6)	35 (13.7)
Mild persistent rhinitis plus severe persistent asthma	33 (6.5)	18 (7)
Moderate-severe persistent rhinitis plus intermittent asthma	91 (17.7)	51 (19.8)
Moderate-severe persistent rhinitis plus severe persistent asthma	75 (14.6)	41 (16)
Eligible for both diseases for SIT		
Moderate-severe intermittent rhinitis plus mild persistent asthma	4 (0.8)	0
Moderate-severe intermittent rhinitis plus moderate persistent asthma	2 (0.4)	0
Mild persistent rhinitis plus mild persistent asthma	23 (4.5)	12 (4.7)
Mild persistent rhinitis plus moderate persistent asthma	30 (5.9)	11 (4.3)
Moderate-severe persistent rhinitis plus mild persistent asthma	33 (6.5)	26 (10.1)
Moderate-severe persistent rhinitis plus moderate persistent asthma	54 (10.5)	26 (10.1)

Consistent with the ARIA and GINA guideline recommendations, the majority of patients (89%) referred to a specialist was eligible for SIT, based on the severity of one disease only.

In order for the levels of severity of both diseases, concomitant in the same patient, to match the ARIA and GINA guideline recommendations, three subsets of patients had to be formed (Table 2). The first group included 57 patients (11%) non-eligible for SIT, because the severity of both diseases did not meet the ARIA and GINA criteria. The second group included 310 patients (60%), who were eligible for SIT because of the severity of one disease but not the other. The third group included 146 patients (29%) who met the recommendations for both diseases.

**Figure 1** Percentage of SIT prescription in the three subsets of eligibility, consistent with ARIA and GINA guidelines recommendations.

SIT was prescribed in 257 subjects (49.6%), this percentage was roughly similar in each subset (Fig. 1). The inappropriate prescription of SIT was limited (9.3% of the total number of SIT prescriptions).

A statistically significant correlation ($r = 0.87$; $\chi^2 p = 0.001$) between the prescription of SIT and the severity of rhinitis, consistent with ARIA recommendations, was documented. A statistically significant difference ($\chi^2 p = 0.02$) in the prescription of SIT according to the severity of asthma was recorded, though this trend was inconsistent with the GINA recommendations (Table 3).

Analysis of the subsets confirmed the leading role of rhinitis for SIT prescription (Table 2).

Table 3 Prevalence of SIT prescription in each level of disease severity consistent with ARIA and GINA guidelines.

	Prescription of SIT	
	Yes, n (%)	No, n (%)
Rhinitis severity (no. pts: 542)*		
• Mild intermittent	32 (38.1)	52 (61.9)
• Moderate severe intermittent	8 (32.0)	17 (68.0)
• Mild persistent	79 (47.0)	89 (53.0)
• Moderate severe persistent	154 (58.1)	111 (41.9)
Asthma severity (no. pts: 520)**		
• Intermittent	103 (48.4)	110 (51.6)
• Mild persistent	44 (58.7)	31 (41.3)
• Moderate persistent	38 (38.8)	60 (61.2)
• Severe persistent	76 (56.7)	58 (43.4)

* $\chi^2 p = 0.001$; ** $\chi^2 p = 0.02$.

In the eligible for one disease subset, where the recommendations for each concomitant disease were conflicting, patients with an ARIA positive and GINA negative profile (72.9% of patients) prevailed over those with an ARIA negative and GINA positive profile.

SIT was prescribed in 67.2% of patients who met the ARIA positive and GINA negative recommendations and in 25% of patients who met the ARIA negative and GINA positive recommendations ($\chi^2 p = 0.004$).

Moreover, the prescription of SIT correlated with the increase of the severity of rhinitis (7% of SIT prescriptions in mod-severe-intermittent, 26% in mild persistent and 69% in mod-severe persistent rhinitis) instead of the severity of coexisting asthma (60.5% in intermittent asthma and 39.5% in severe persistent asthma).

In the subset of eligible for both diseases patients, the prescription of SIT goes up 48.8% consistent with the increase of the severity of rhinitis instead of the severity of coexisting asthma, even though the statistical significance was not reached.

SIT prescription: the interplay between international guidelines and patient-tailored approach

In addition to the guideline recommendations, other factors potentially involved in decision to prescribe SIT were evaluated (Table 4).

A statistically significant association between the prescription of SIT and young age, mite monosensitisation, current drug therapy, and the medical opinion of worsening symptoms was documented.

Surprisingly, the reimbursement policies of the Regional Health Services had no effect.

To assess the interplay between the guidelines and the patient-tailored approach a bivariate analysis logistic regression model was carried out (Table 5).

Young age was the most important independent factor for SIT prescription in the two eligible patient subsets. In the eligible for one disease subset, the probability of SIT being prescribed was almost 6 times higher in teenagers, and almost 3 times higher in the 21–50 age group than it was in patients over 50 years.

In the eligible for both diseases patients once again the probability of SIT being prescribed was 4.5 times higher in the teenagers compared to the subsets of older patients.

In the eligible for one disease patient subset, the disease's tendency to worsen, as evaluated by the doctor, was another independent factor for SIT prescription [OR 2.5 (95% CI, 1.403–4.542)].

SIT prescription: the route of administration

SCIT was prescribed in 107 patients and SLIT in 150 patients. The prevalence of SLIT was greater in each subset of eligible patients ($\chi^2 p = 0.05$) (data not shown). This finding was consistent with the prevalent market share of SLIT in Italy. No specific factor determining the choice of the route of administration was documented.

Discussion

Three main findings, concerning the congruence of SIT prescription with guidelines recommendations, emerge from this nationwide survey on mite allergic patients with rhinitis and asthma comorbidity.

The referral and the prescription of SIT

The majority of patients (89%) referred to specialist were eligible for SIT, based on the severity of one disease, but the single disease-oriented guidelines produced conflicting recommendations for SIT, in the same patient, in more than 2/3 of cases.

Though not always openly admitted, the guidelines are written for primary care doctors, which usually do not prescribe SIT but refer the patient to the specialist.

Therefore, if the disease's severity is considered a marker for the specialist consultation our result confirms the utility of the guideline recommendations, but this is no longer the case if the guideline recommendations are considered a marker for SIT prescription.

Because SIT is a single therapy effective for the treatment of rhinitis and asthma, which often coexist in the same patient with different level of severity, our result underlines the quandary of the SIT prescription in the severity-oriented guidelines framework.

The specialist's basis for SIT prescription

The almost equal levels of SIT prescription in the two subsets of eligible for both diseases and eligible for one disease patients, suggests a discrepancy between the ARIA and GINA guidelines and the specialist's intention to treat.

Our study provides evidence that the severity of rhinitis and the age of the patient are the most important factors underlining the decision to prescribe SIT.

We speculate that the aim of interfering with the progression of the disease from the nose to the lower airways and the aim of reducing the impact of rhinitis on asthma are involved in this result. Indeed these are specific effects of SIT on comorbidity, underlined by the SIT position papers.^{12–14}

In the case of the former, the early commencement the SIT was judged to be the best approach of interrupting the allergic march, indeed in the bivariate logistic regression model, young age was the most important independent factor for SIT prescription, both in the eligible for one disease and eligible for both diseases patients.^{12–14}

Early intervention on the comorbidity is in line with this purpose, as well.

Indeed, the most common condition for SIT prescription (56%) in our survey was persistent rhinitis (both mild and moderate-severe) with coexisting intermittent asthma (Table 2).

Mite allergic rhinitis represents a major risk factor for asthma, even in the adult population¹⁵ and the ability of SIT to interfere with the progression of the comorbidity was shown.^{16,17}

In the latter case, it has been shown that the asthma control is more difficult to achieve when an uncontrolled

Table 4 Non-guidelines factors investigated in the prescription of SIT.

	Prescription of SIT	
	Yes, n° (%)	No, n° (%)
Gender (no. pts 546)		
• Male	124 (55.1)	101 (44.9)
• Female	152 (47.4)	169 (52.6)
Age ^{§§} (no. pts 547)		
• ≤20 yrs	52 (60.5)	34 (39.5)
• 21 < yrs ≤ 50	206 (51.1)	197 (48.9)
• >51	17 (29.3)	41 (70.7)
Comorbidity (no. pts 545)		
• Yes	56 (49.1)	58 (50.9)
• No	218 (50.6)	213 (49.4)
Appointment (no. pts 542)		
• First visit	100 (51.3)	95 (48.7)
• Follow-up	171 (49.3)	176 (50.7)
Sensitization* (no. pts 523)		
• Monosensitive	96 (57.5)	71 (42.5)
• Polysensitive	167 (46.9)	189 (53.1)
Smoking status (no. pts 541)		
• Never smoked	216 (52.2)	198 (47.8)
• Current	30 (42.3)	41 (57.7)
• Former	24 (42.9)	32 (57.1)
Drug therapy** (no. pts 543)		
• Yes	193 (53.9)	165 (46.1)
• No	78 (42.2)	107 (57.8)
Education (no. pts 541)		
• None	2 (100)	0
• Elementary school	13 (37.1)	22 (62.9)
• Middle school	85 (52.1)	78 (47.9)
• High school	126 (48.3)	135 (51.7)
• Ordinary degree	11 (57.9)	8 (42.1)
• Honours degree	31 (57.4)	23 (42.6)
• Master/specialization	6 (85.7)	1 (14.3)
Side effects to drug therapy (no. pts 424)		
• Yes	13 (44.8)	16 (55.2)
• No	200 (50.6)	195 (49.4)
Tendency of the disease ^{§§} (no. pts 524)		
• No worsening	167 (43.8)	214 (56.2)
• Worsening	93 (65)	50 (35)
Specialist (no. pts 515)		
• Allergist	228 (54.4)	191 (45.6)
• Pneumologist	42 (44.2)	53 (55.8)
• Other (internal medicine)	0	1 (100)
Payment (no. pts 489)		
• Charged to patient	144 (53.3)	126 (46.7)
• Partially charged to patient	59 (57.8)	43 (42.2)
• Not charged to patient	65 (55.6)	52 (44.4)

* $\chi^2 p = 0.024$; $\chi^2 p = 0.015$; ** $\chi^2 p = 0.009$; $\chi^2 p < 0.001$.

upper airway disease coexists¹⁸ as well as the treatment of rhinitis improves the asthma control.¹⁹

On the other hand, the available drug therapy for rhinitis is, not very effective for many patients,²⁰ insomuch as patients with moderate-severe persistent rhinitis, notwithstanding coexisting treatment, are the majority of patients referred to specialist setting.^{21,22}

Our results show that the prescription of SIT follows the increase in the severity of rhinitis instead of the severity of coexisting asthma in both subsets of eligible for one disease and eligible for both diseases patients (Table 2).

Moreover, in the subset of eligible for one disease patients, in which SIT was most prescribed for the upper airways share of comorbidity, the specialist's belief that the patient's respiratory symptoms are worsening doubles SIT prescription.

Taken together, these results suggest that the high efficacy of SIT in mite allergic rhinitis²³ is considered fulfilling this unmet need of the therapy of severe allergic rhinitis, particularly remarkable in the context of comorbidity.²⁴

This overriding concern for rhinitis undermines the congruence of SIT prescription with the GINA guidelines, as well.

SIT was prescribed in 47.6% of asthmatics eligible for both diseases for SIT, consistent with the GINA guidelines, but the SIT prescription, driven by rhinitis severity, groups asthmatics, whose asthma severity was outside the GINA recommendations. In the eligible for one disease subset, 92.5% of asthmatics was outside the GINA recommendations.

Therefore in the real world, the approach of the specialist to comorbidity partially fulfils the recommendations of the guidelines, in particular for asthma.

The route of administration of SIT

The prevalence of SLIT prescriptions mirrors the market share between the two routes of SIT administration in Italy. The absence of any specific factor, determining the choice of the route of administration is consistent with the absence of any route-oriented recommendations in Italian guidelines, to date. Equivalence or superiority trials comparing SLIT and SCIT in mite allergic patients are lacking; however the best evidence of efficacy is provided by SCIT both in mite allergic rhinitis and in mite allergic asthma.^{23,25–27}

The main limitation of the study is that the extent of the specialists' knowledge of the guidelines, is unknown. A recent French study documented ENT specialists' partial awareness of the ARIA guidelines, notwithstanding considerable efforts to disseminate them.²⁸ In Italy, a survey performed in the same setting studied in this survey (specialists belonging to AAITO) suggests good awareness of the guidelines.¹²

In conclusion, the findings of our survey highlight the discrepancy between the framework of disease-oriented guidelines and the prescribing practices in mite allergic patients, in the real world. Some distinctive feature of SIT, not involved in the severity stepwise approach, seem to be crucial points in the decision to prescribe SIT. Unfortunately, their level of evidence in mite allergic patients with rhinitis and asthma comorbidity is not yet totally satisfactory,^{16,17,29}

Table 5 Logistical regression model to characterize the SIT prescription adjusting for guideline-driven and not guideline-driven factor in the three subsets of the patient's eligibility for SIT.

Factors	OR	IC		p
		Inf.	Sup.	
Not eligible for SIT				
Monosensitive	1.899	0.299	12.060	Ns
Comorbidity	1.074	0.169	6.837	Ns
Tendency towards worsening	1.060	0.063	17.942	Ns
Payment (charged to patient)	7.764	0.702	85.866	Ns
Presently undergoing drug therapy	4.423	0.825	23.714	Ns
Gender	2.059	0.332	12.757	Ns
Age (≤ 20)	0.578	0.009	38.716	Ns
Age (>20 and ≤ 50)	3.580	0.355	36.079	Ns
Eligible for one disease for SIT				
Monosensitive	1.734	0.967	3.108	Ns
Comorbidity	0.268	1.426	0.761	Ns
Tendency towards worsening	2.524	1.403	4.542	0.002
Payment (charged to patient)	1.078	0.626	1.857	Ns
Presently undergoing drug therapy	1.668	0.919	3.025	Ns
Gender	1.480	0.852	2.573	Ns
Age (≤ 20)	6.140	1.995	18.895	0.002
Age (>20 and ≤ 50)	2.973	1.193	7.408	0.019
Eligible for both diseases for SIT				
Monosensitive	1.697	0.712	4.043	Ns
Comorbidity	0.991	0.381	2.577	Ns
Tendency towards worsening	1.636	0.648	4.131	Ns
Payment (charged to patient)	0.521	0.244	1.114	Ns
Presently undergoing drug therapy	1.318	0.489	3.551	Ns
Gender	1.247	0.578	2.689	Ns
Age (≤ 20)	4.532	1.029	19.959	0.046
Age (>20 and ≤ 50)	1.721	0.487	6.085	Ns

therefore our result underlines the need of studies specifically designed for the mite respiratory allergy.

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Conflict of Interest Statement

The authors have declared that they have no conflicts of interest.

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