

CHARACTERISTICS OF PATIENTS WITH RESPIRATORY ALLERGY IN FRANCE AND FACTORS INFLUENCING IMMUNOTHERAPY PRESCRIPTION: A PROSPECTIVE OBSERVATIONAL STUDY (REALIS)

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To describe the sensitization profile of respiratory allergies in France, identifying factors influencing the prescription of allergen immunotherapy (AIT) [Transversal phase (T)], and assess treatment efficacy, tolerability, compliance and satisfaction [Longitudinal phase (L)]. French allergists (600) and pneumo-allergists (600) were offered participation and asked to recruit the first 20 new patients with allergic rhinitis (AR) and/or asthma, consulting for a first time allergy check-up with skin prick-test (T), and 5 patients sensitized to pollens (skin test and/or specific IgE) for whom SLIT with pollens was prescribed (L). In the T phase, 2,714 patients were recruited by 169 specialists, mostly allergists (76.5%). The majority (98%) suffered from AR, alone (57.7%) or with asthma (40.3%) and 80.3% suffered from moderate-to-severe rhinitis, mostly persistent (65.8%). Asthma, when present, was mostly intermittent (63.7%) or mild persistent (20.1%). Sensitization to house dust mites was the most common (64.5%), followed by grass pollens (61.5%), tree pollens (41.6%) and cat danders (30.5%). Poly-sensitization was seen in 73.6% of patients. AIT, mostly sublingual, was recommended in 55.6% of the patients, mostly (78.1%) because of insufficient control with symptomatic treatments. The overall impact of symptoms on QOL, positive skin test to grass pollens, ocular pruritus and/or nasal obstruction and moderate-to-severe rhinitis were significant predictors of SLIT prescription. Poly-sensitization or concomitant asthma were not seen as deterrents. Most patients consulting a specialist for allergy testing suffer from moderate-to-severe rhinitis. Treatment in current practice includes immunotherapy in half of the patients, and follows ARIA recommendations.

Allergic rhinitis (AR) represents a global health, problem affecting 10% to 20% of the population (1). In Western Europe it is estimated that around 20% of the general population suffer from allergic rhinitis

(2-3). Many patients with rhinitis also suffer from asthma (4-5).

Exposure to inhaled allergens and genetic predisposition have been recognized as important

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risk factors for allergic rhinitis and asthma (6). Sensitization to multiple allergens is common (6-7).

Management of patients with allergic rhinitis begins with allergen avoidance, wherever possible, and symptomatic treatments with anti-histamines and local (nasal or inhaled) steroids. Allergen immunotherapy (AIT), the only treatment with the capacity to alter the natural course of the disease (8) is recognized as an additional option in some patients (9).

Clinical trials in allergic rhinitis have shown that allergen immunotherapy, whether subcutaneous or sublingual, was effective at alleviating symptoms and decreasing the use of anti-allergy medications (8, 10-11).

At the time of planning this study, information regarding the prescription of AIT in allergic rhinitis patients under real-world current practice was lacking, particularly with regards to the impact of sensitization status (mono- vs poly-sensitized) and the presence of concurrent asthma.

This prospective observational multicentre study (REALIS survey) was therefore conducted to establish, in a first step [Transversal phase (T)], the clinical and sensitization profiles of a large group of French patients with respiratory allergy referred to a specialist for a first time skin prick testing (SPT) and identify the factors predictive of prescription of AIT in these patients and, in a second step [Longitudinal phase (L)] the efficacy and tolerability of sublingual immunotherapy (SLIT) with pollens as well as patient compliance and satisfaction in real-world setting.

MATERIALS AND METHODS

Study design and patients

This is a multicenter, observational study conducted in France, entailing prospective data collected from a representative sample of allergy specialists. The study consisted of two phases:

- a T phase during which the main objective was to describe the clinical and sensitization profiles of patients with respiratory allergies in France and, as a secondary objective, to identify the factors influencing the prescription of AIT in these patients,
- an L phase during which the efficacy and tolerability of SLIT with pollens were evaluated (secondary objective).

Specialists

Based on demographic data published in January 2005 by the Direction de la Recherche des Etudes de l'Evaluation et des Statistiques (DREES) (12), there were 708 allergists in France, 600 of whom had an independent practice. In the absence of data in relation to pneumo-allergists, an estimate of 1000 was retained. To achieve good representation of all regions, participation in the study was offered to all allergists with an independent practice and 600 randomly selected pneumo-allergists. Recruitment target was 200 specialists, preferably 100 allergists and 100 pneumo-allergists. To avoid bias, each participating specialist was to recruit the first 20 new patients for whom an allergy check-up with SPT was planned (T) and five patients for whom SLIT with pollens was prescribed (L). To improve the feasibility of the study, patients included in the L phase of the study could be derived from those participating in the T phase, as long as they complied with eligibility criteria for the L phase, and agreed to participate in it (separate consent required).

Patient selection

For the T phase, the study population consisted of patients over than five years of age, with allergic rhinitis and/or asthma, consulting a specialist for an allergy check-up (SPT) for the first time. For inclusion in the L phase, patients had to have an allergy check with evidence of sensitization to pollens (positive skin test, and/or specific IgE > 0.1 kU/L) and be prescribed SLIT with pollens.

Data collection

For each patient in the T phase, the doctor completed a case report form including demographic information, clinical data including pathology, rhinitis type and severity [defining rhinitis as persistent when symptoms are present for ≥ 4 days/week and ≥ 4 weeks/year, and moderate or severe when one or more of disturbed sleep, impact on social activities or leisure, impact on school or professional activities, and/or bothersome symptoms are present (9)], asthma severity defined on the basis of the 2004 GINA (3) classification (i.e. considering symptoms, airflow limitation and lung function variability rather than asthma control for classification), current symptoms, skin test results, specific IgE results (if conducted), therapeutic intent (including pharmacotherapy) and reason for the choice.

For the L phase, data was collected at the two visits corresponding to the beginning and end of the first treatment season. Being an observational study, no specific visits or testing were imposed outside of normal patient management. Information in relation to demographic characteristics, clinical data including

pathology, rhinitis severity (9), asthma severity (3), current symptoms and the proposed SLIT protocol (pollen type, initiation regimen and dose, maintenance regimen and dose) was collected at baseline. At the follow-up visit, data in relation to evolution of symptoms, compliance, tolerability and satisfaction as perceived by the doctor was collected.

Skin prick tests

Allergen sensitization profiles were determined by SPTs in accordance with the current allergy practice. A positive reaction was defined as a wheal diameter >3 mm or $\geq 50\%$ of the positive control.

Statistical analysis

The statistical analysis was conducted using SAS® V8.2. Comparisons between groups (mono- vs poly-sensitized, rhinitis only vs rhinitis + asthma) were conducted using the χ^2 test or Fisher exact test for categorical variables, and Student *t*-test or Mann-Whitney-Wilcoxon 2-sample test for continuous variables. Statistical significance was set at the 5% level.

Descriptive statistics are presented as mean ($\pm$ SD) in the text that follows.

Sample size

The sample size was calculated on the basis of the primary objective, i.e. the description of the sensitization profile of patients with respiratory allergy, and based on the precision of the estimates expected from the study. Patient profiles were categorized according to sensitization status (mono- or poly-sensitized) and pathology (rhinitis alone,

rhinitis + asthma and asthma alone). It was assumed that more than 75% of patients with asthma also suffered from rhinitis (13), that 20 to 25% of patients with rhinitis suffered from asthma (14-16), and that 36% of the patients were mono-sensitized (17). It was calculated that 683 patients would be required to estimate a proportion of 20% of mono-sensitized patients in each subgroup with a relative precision included between 10 and 20%, and a risk of first kind of 5%. Considering the least represented group was approximately 20% of the population, a sample of 3,415 patients was required. Taking into account 15% of non-evaluable case report forms, it was planned to collect information from 4,000 patients, or 20 patients per specialist. For the L phase, assuming 25% of the patients were prescribed SLIT with pollens, it was estimated that each specialist should recruit five patients.

The study was conducted in accordance with the protocol, the declaration of Helsinki (2004), the "Bonnes Pratiques en Épidémiologie" edited by the Association Des Épidémiologistes de Langue Française (ADELF), the guidelines of Good Pharmaco-epidemiology edited by the International Society for Pharmaco-Epidemiology (ISPE), and the local regulations. Written informed consent was obtained for all patients. For children under 18 years of age, consent was obtained from a parent or legal guardian.

RESULTS

Specialists were recruited between September and November 2007, for both phases. In total, 236 specialists agreed to participate in the study within

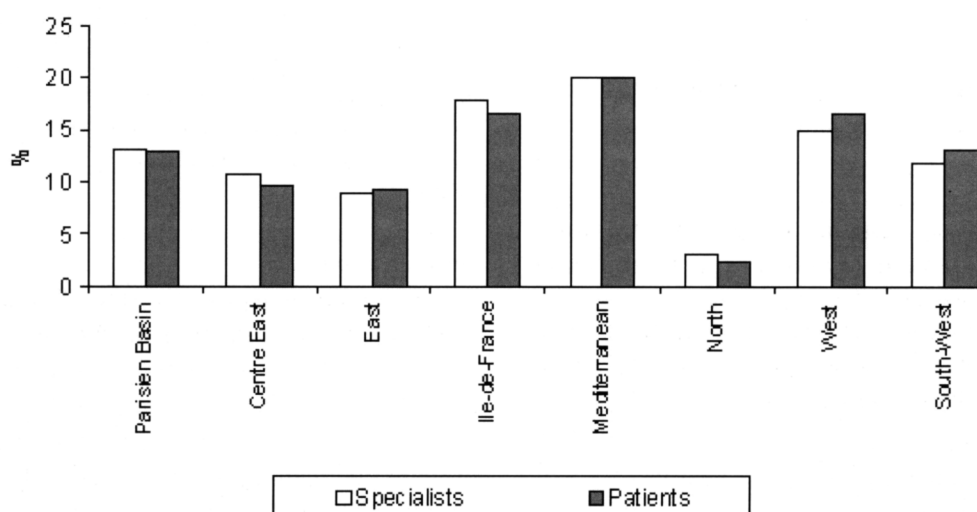


Fig. 1. Distribution of active specialists and patients across France (IRDES regions) – T phase.

the timelines: 169 were active participants (i.e. contributed at least one patient) in the T phase, and 156 in the L phase. Most (78.2%) of the L phase active participants had also contributed to the T phase.

The majority (76.5%) of the T phase active participants were allergists; the remaining 21.7% were pneumo-allergists. All French regions were represented (Fig. 1).

The distribution and characteristics of the L phase active participants were essentially similar to that described for the T phase.

Transversal Phase

Patients

A total of 2,780 patients were enrolled in the T phase between 4 September, 2007 and 28 March, 2008. Sixty patients did not have a positive skin test, and six patients had no skin test results available. Forty of these patients suffered from rhinitis only, 22 had rhinitis + asthma, and four suffered from asthma only. As one of the objectives of the study was to identify therapeutic intent in sensitized patients, these 66 patients were not included in the analyses. The analysis population therefore consisted of 2,714 patients (97.6%). Patient distribution across France is shown in Fig. 1.

Mean age of the study population was 26.2 (± 15.2) years, ranging from 5 to 77 years, including more adults (≥ 18 years) than children (63.7% vs 36.3%) and slightly more female than males (51.8% vs 48.2%). Among children, both the under eleven and under seventeen age groups were represented (20.3% and 16%). Few patients smoked (9.4%) and few lived in a passive smoking environment (5.8%). One in two patients (46.1%) owned a pet.

Clinical profile

The majority of patients (98%) suffered from rhinitis (Table I), alone (57.7%), or in combination with asthma (40.3%). The majority of the 1,148 patients with asthma (95.2%) also suffered from rhinitis: only 2% of the patients suffered from asthma alone. For patients with rhinitis (with or without asthma), mean disease duration was 4.56 years (± 7.32), with a duration of < 1 year in 45.3% of the subjects. Mean disease duration was significantly longer in patients suffering from rhinitis + asthma

compared with patients suffering from rhinitis alone (5.84 years, 95% CI: [5.33, 6.34] vs 3.67 years, 95% CI: [3.36, 3.98], p [Wilcoxon] < 0.001), as well as in poly-sensitized patients (4.93 years [95% CI: 3.04, 3.95] vs 3.49 years [95% CI: 4.59, 5.27], p [Wilcoxon] < 0.001). Based on the ARIA classification (9), most patients suffered from moderate or severe rhinitis (80.3%), mostly persistent (65.8%). Whether intermittent or persistent, at least two ARIA items affected the majority (1,657/2,131: 77.8%) of these moderate or severe patients, and at least three items in 49.7% (1,059/2,131). The majority (1,771/2,131: 80.3%) of patients with moderate or severe AR reported bothersome symptoms. Sleep, daily activities and/or school or work life were affected in more than 50% of these patients (53.8%, 61.8%, and 52.9%, respectively).

For patients with asthma, with or without rhinitis, mean disease duration was 5.60 years (± 8.46). Based on the GINA classification of 2004 (3), chosen at the time of the study design, and which considers symptoms, airflow limitation and lung function variability rather than asthma control as per the 2006 update, the majority of the patients (63.7%) suffered from intermittent asthma, followed by mild persistent asthma (20.1%).

Symptoms

Symptoms of rhinitis and conjunctivitis were observed in the majority of the patients (Table I). Rhinorrhea and sneezing were mostly diurnal (rhinorrhea: 53.1% diurnal vs 3.2% nocturnal and 43.7% no predominance; sneezing: 59% diurnal vs 3.4% nocturnal and 37.6% no predominance). The overall impact of these symptoms on the patient's quality of life (QOL) was perceived by the doctor as very important or important in 65.7% of the cases (Table I).

Primary objective

The main objective of the T phase was to establish the sensitization profile of patients with respiratory allergy consulting a specialist for a first time check of their allergy status on the basis of SPT. Total IgE results were available before consultation or were obtained at the time of consultation in only 6% (161/2290) of the patients. As a result, these data results are not presented.

Table I. Clinical profile of patients in Transversal and/or Longitudinal phase.

	Transversal phase		Longitudinal phase	
	N=2714		N=675	
Pathology of respiratory allergy				
Rhinitis alone	1566/2714	57.7%	435	64.4%
Rhinitis + asthma	1093/2714	40.3%	238	35.3%
Asthma alone	55/2714	2.0%	2	0.5%
Allergic rhinitis (with or without asthma)	2659	98.0%	673	99.7%
Disease duration (years)				
n	2633		671	
Mean (SD)	4.56 (7.32)		5.76 (7.79)	
Severity (ARIA) ^[a]				
Mild intermittent	225/2655	8.5%	18/673	2.7%
Moderate or severe intermittent	384/2655	14.5%	87/673	12.9%
Mild persistent	299/2655	11.3%	36/673	5.3%
Moderate or severe persistent	1747/2655	65.8%	532/673	79.0%
Allergic asthma (without or without rhinitis)	1148	42.3%	240	35.5%
Disease duration (years)				
n	1132		239	
Mean (SD)	5.60 (8.46)		6.00 (7.87)	
Severity (GINA 2004) ^[b]				
Intermittent	731/1147	63.7%	177/239	74.1%
Mild persistent	230/1147	20.1%	33/239	13.8%
Moderate persistent	169/1147	14.7%	29/239	12.1%
Severe persistent	17/1147	1.5%	-	-
Symptoms				
<i>Rhinitis and conjunctivitis (in patients with or without asthma)</i>				
Rhinorrhea	2365/2624	90.1%	606/662	91.5%
Sneezing	2294/2626	87.4%	606/663	91.4%
Nasal obstruction	2135/2627	81.3%	558/663	84.0%
Nasal pruritus	1789/2622	68.2%	551/660	77.4%
Anosmia	421/2610	16.1%	119/658	18.1%
Ocular pruritus	1551/2618	59.2%	503/664	75.8%
Teary eyes	1401/2622	53.7%	459/658	69.8%
<i>Asthma (in patients with or without rhinitis)</i>				
Cough	872/1084	80.4%	184/227	81.1%
Wheezing	745/1083	68.8%	158/227	69.6%
Difficult breathing	588/1082	54.3%	134/226	59.3%
Chest tightness	465/1084	42.9%	102/227	44.9%
Impact of symptoms on QOL (as perceived by the doctor) ^[a]				
Very important	316/2697	11.7%	-	
Important	1457/2697	54.0%	-	
Negligible	819/2697	30.4%	-	
No impact	105/2697	3.9%	-	

Categorical variables are presented as number and percentage of patients relative to total population with non-missing data. Population with data available shown in denominator. [a] not recorded for patients included in L phase.

Sensitization to HDM was the most common (Fig. 2), with 64.5% of the patients exhibiting a positive skin test to *D. pteronyssinus* and/or *D. farinae*, closely followed by five-grass pollens (61.5%), which was tested in 96.2% of the patients. Sensitization to tree pollens was also relatively common, with 41.6% of the patients presenting a positive skin test to at least one of birch, ash, olive tree, *cupressaceae* and/or plane tree pollens. Of these, the most common allergen was birch pollen (28.4%). Sensitization to cats and dogs, tested in 88.2% and 88.9% of the patients, respectively, was found in 30.5% and 17% of the patients. Less than 60% of the patients were tested for allergy to German cockroaches, latex, arachnid and various other allergens.

The majority (73.6%) of the patients were poly-sensitized. Compared with patients suffering from rhinitis alone, slightly more patients suffering from rhinitis + asthma were poly-sensitized (79.5% vs 69.8%).

Secondary objectives

The secondary objective of the study is to establish the therapeutic intent in this patient population, including its reason, as well as the factors influencing the decision for immunotherapy.

Treatment with oral and/or local anti-histamines was renewed or prescribed at the time of consultation in the majority of the patients (76.9%). Treatment with these compounds in combination with local steroids was renewed or prescribed in 51% of the patients, particularly those suffering from rhinitis + asthma (59.7%). The use of oral steroids was not common (4.6% of the patients). Immunotherapy was recommended in 55.6% of the patients overall, whether they suffered from rhinitis alone or from rhinitis + asthma. Immunotherapy was not usually recommended in patients with asthma only (Table II).

When immunotherapy was prescribed, SLIT was chosen in the majority of the cases (91.7%). The most frequent reason for prescribing AIT was insufficient control of the symptoms with pharmacological treatment (78.1% of the cases).

Factor influencing prescription of specific immunotherapy

The overall impact of symptoms on QoL as perceived by the doctor, positive skin test to grass pollens, the presence of ocular pruritus and/or nasal obstruction, the presence of moderate or severe rhinitis (whether intermittent or persistent) were significant predictors ($p < 0.0001$) of the prescription

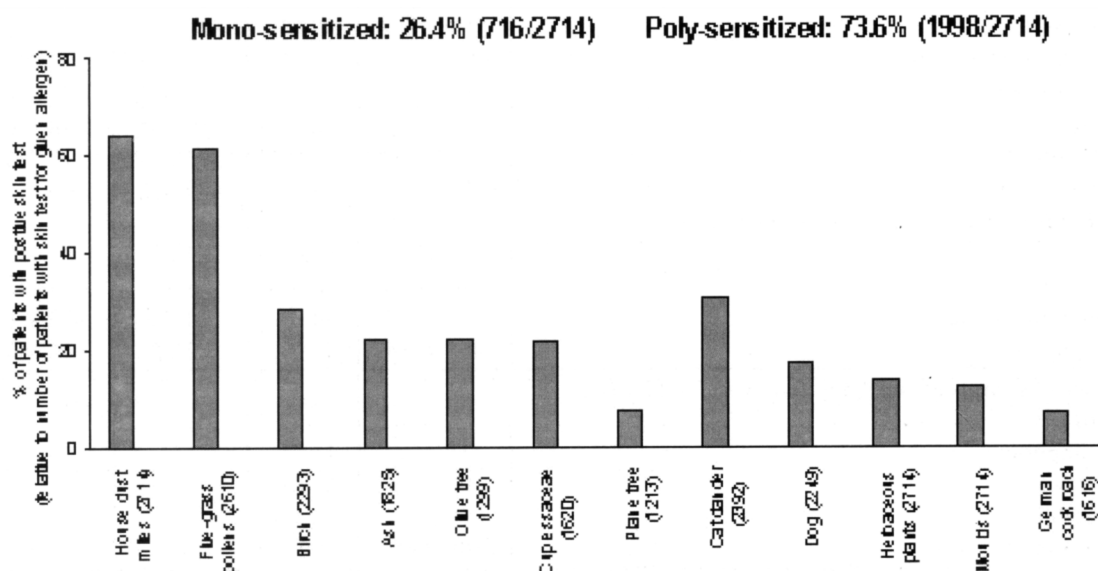


Fig. 2. Allergen sensitization. Numbers in bracket indicate number of patient with skin test for corresponding allergen. More than one positive test was possible per patient.

Table II. *Proposed therapeutic management.*

	Rhinitis only N=1566		Rhinitis + asthma N=1093		Asthma only N=55		Overall N=2714	
	n	%	n	%	n	%	n	%
Oral or local anti-histamines	1208	77.1%	854	78.1%	25	45.4%	2087	76.9%
Oral or local anti-histamines in combination with local steroids ^[a]	719	45.9%	652	59.7%	13	23.6%	1384	51.0%
Oral steroids	68	4.3%	55	5.0%	3	5.5%	126	4.6%
Immunotherapy	861	55.0%	641	58.6%	8	14.5%	1510	55.6%
If prescribed, type of immunotherapy								
Missing data	2		1		0		3	
Subcutaneous	66	7.7%	54	8.4%	0	0%	120	8.0%
Sublingual	791	92.1%	583	91.1%	8	100%	1382	91.7%
Subcutaneous + sublingual	2	0.2%	3	0.5%	0	0%	5	0.3%
Reasons for prescribing specific immunotherapy								
Patient not sufficiently controlled with pharmacological treatment	670	77.8%	504	78.6%	5	62.5%	1179	78.1%
Patient not wishing to take pharmacological treatment	192	22.3%	111	17.3%	2	25.0%	305	20.2%
Patient with side effects associated with pharmacological treatment	32	3.7%	19	3.0%	0	0%	51	3.4%
Other reasons	142	16.5%	135	21.1%	3	37.5%	280	18.5%

Number of patients (n) and % relative to total population in each group, or relative to number of patients with non-missing data where applicable [a] local steroids are defined as both nasal and inhaled steroids.

Table III. *Multivariate analysis of factor influencing decision to prescribe immunotherapy in patients with rhinitis (with or without asthma.)*

Factor	OR	95% CI	p value
Overall impact of symptoms on QOL (very important/important vs negligible/no impact)	2.049	[1.69, 2.49]	<0.0001
Skin test to grass pollens (positive vs negative or not done):	1.998	[1.68, 2.37]	<0.0001
Rhinitis severity (moderate or severe vs mild)	1.822	[1.44, 2.31]	<0.0001
Ocular pruritus (presence vs absence)	1.719	[1.45, 20.4]	<0.0001
Nasal obstruction (presence vs absence)	1.581	[1.27, 2.31]	<0.0001
Skin test to cat dander (positive vs negative or not done)	0.595	[0.49, 0.72]	<0.0001

of immunotherapy in patients suffering from rhinitis (with or without asthma). A positive skin test to cat dander had a significantly negative predictive value (Table III).

Poly-sensitization did not appear to be a deterrent, with 57.4% of the patients prescribed immunotherapy, compared with 50.8% among mono-sensitized patient.

Longitudinal Phase

Patients

A total of 684 patients were recruited into the L phase between 4 September, 2007 and 4 April, 2008. The end of the first treatment season follow-up visit took place on 15 September, 2008. 53.7% (367/684) of the patients included in the L phase had participated in the T phase.

Nine subjects were excluded from the analysis population: five because Part 1 of the CRF (initiation visit) was missing, three because they did not have a positive skin test to pollens, and one because the initiation visit was outside the above window. The analysis population therefore consisted of 675 patients (98.7%). Patient distribution across regions was essentially similar to that described for the T phase.

The mean age of the study population was 28.5 (± 14.4) years, ranging from 5 to 76 years. The majority of the patients prescribed SLIT with grass pollens who agreed to participate in the L phase were adult ≥ 18 years (71.7%), and male (53.8%). Among children, both the under eleven and under seventeen age groups were represented (12% and 16.3%, respectively). In keeping with the characteristics of the population included in the T phase, few patients smoked (8.7%) and few lived in a passive smoking environment (3.9%). One in two patients (42.8%)

owned a pet.

Clinical profile

The majority of the patients (99.7%) suffered from rhinitis, alone (64.4%), or in combination with asthma (35.3%). Less than 0.5% of the patients suffered from asthma alone (Table I).

For patients with rhinitis (with or without asthma), mean disease duration was 5.76 years (± 7.79). In accordance with the results of the T phase, which showed that rhinitis severity was a significant predictor of prescription for immunotherapy, the majority of the patients prescribed SLIT with pollens in the L phase suffered from moderate or severe AR (92%), mostly persistent (79%). Whether intermittent or persistent, at least two ARIA items were impacted in 81.2% (503/619) of these patients, and at least three in 58.3% (363/619) of the patients.

For patients with asthma, with or without rhinitis, mean disease duration was 6.00 years (± 7.87). The majority of patients (74.1%) suffered from intermittent asthma. No patient prescribed SLIT suffered from severe asthma.

Symptoms

Symptoms of rhinitis and conjunctivitis were observed in the majority of the patients (Table I). Sneezing was mostly diurnal (59.6% diurnal vs 1.9%

Table IV. Sublingual immunotherapy: type of allergen and regimens.

	Analysis population N=675	
	n	%
Type of allergen		
Grass pollens	559/675	82.8%
Grass pollens only	457/672	68.0%
Associated with other pollens	102/672	15.2%
Grass pollens + tree pollens	77/672	11.5%
Grass pollens + herbaceous pollens	17/672	2.5%
Grass pollens + tree pollens + herbaceous pollens	8/672	1.2%
Tree pollens only	100/672	14.9%
Herbaceous pollens only	8/672	1.2%
Tree pollens + herbaceous pollens	5/672	0.7%

Categorical variables are presented as number and percentage of patients relative to total population with non-missing data. Population with data available shown in denominator.

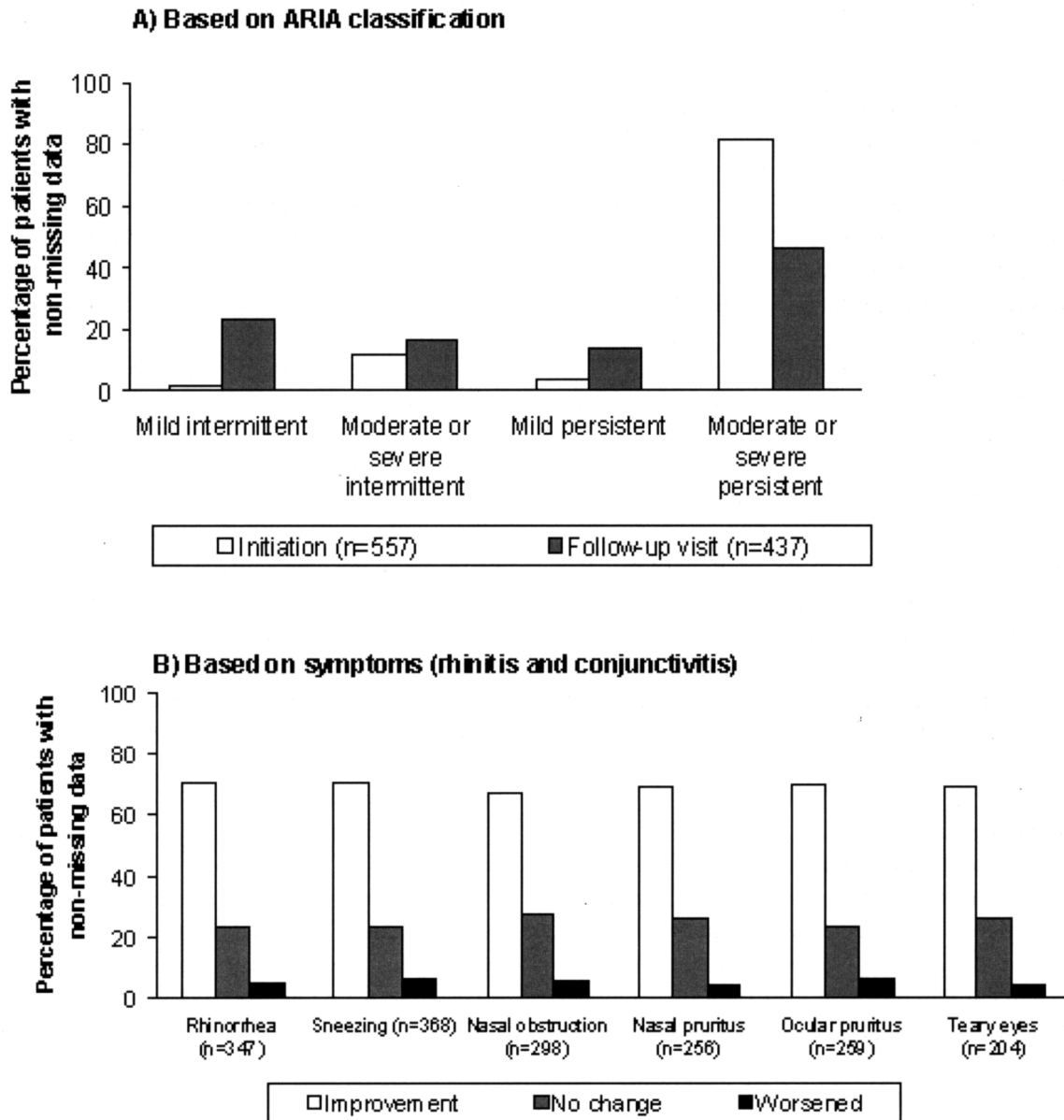


Fig. 3. Change in rhinitis following SLIT with grass pollens. Numbers in brackets indicate number of patients experiencing symptoms at initiation and with non-missing data.

nocturnal and 38.5% no predominance). Rhinorrhea was diurnal in 49.9% of the cases, but showed no predominance in 48.2% of the cases. In patients with asthma (with or without rhinitis), coughing and wheezing were the most common symptoms (69% or more of the patients). This profile was essentially similar to that observed in the T phase.

Reasons for prescribing immunotherapy

Immunotherapy could be prescribed for more than one reason. It was prescribed because the patients were insufficiently controlled by pharmacotherapy in 45.5% (307/675) of the cases; 7.6% (51/675) of the patients did not wish to take pharmacological treatment, 1.5% (10/675) could not take such treatment because of side effects, and other reasons for prescription were noted in 7.7% (52/675) of the

cases. In 46.6% (315/675) of the cases, no reason was specified by the doctor concerning their decision.

Secondary Objective of Longitudinal Phase

Sublingual immunotherapy: allergen types and treatment regimen

Sublingual immunotherapy with grass pollens was most often prescribed (82.8%), alone (68%) or associated with other pollens (15.2%, Table IV).

Concomitant immunotherapy was prescribed in 10.1% (68/672) of the patients, mostly with allergen extracts of *Dermatophagoides pteronyssinus* (50/68: 73.5%) and/or *Dermatophagoides farinae* (45/68: 66.2%).

Proposed treatment schedule was predominantly daily dosing (657/671: 98.1%), with a target weekly maintenance dose of 1111 IR (± 503), ranging from 120 to 2250 IR. The IR (Index of Reactivity) is a Company-specific unit of standardization: a 100 IR extract is defined by its capacity to induce a mean wheal diameter of 7 mm in skin prick tests in a panel of 30 patients sensitized to the allergen considered. Time to reach this target averaged 2.49 weeks (± 2.12), with a median of 2 weeks.

Maintenance phase

Based on data collected at the follow-up visit at the end of the first treatment season, which was attended by 532 patients, mean treatment duration was 4.52 months (± 1.49), ranging from less than one to 10 months after initiation, with a median of 5 months. In patients prescribed SLIT with grass pollens (alone or in combination with other pollens), treatment was mostly pre- and co-seasonal: it was initiated before the beginning of the pollen season in 99.8% (521/522) of the cases, lasting for 3.3 months (± 1.04) months on average; it was continued during the pollen season in 66.5% (372/559) of the patients, with a mean duration of 1.1 month (± 0.75) during the pollen season.

In most cases (521/525: 99.2% of the patients), the 300 IR dosage form was used during the maintenance phase. The weekly maintenance dose was 1101 IR (± 438), ranging from 270 and 2250 IR. The cumulative dose of the maintenance phase averaged 24395 IR (± 13094).

Few patients (62/526: 11.8%) encountered difficulties with the treatment, usually with regard to administration planning (29/62: 46.8%). Based

on the doctor's perception, overall compliance was considered good in the majority of the patients (464/526: 88.2%).

Efficacy of SLIT with grass pollens (alone or in combination with other pollens)

At the follow-up visit, the doctor considered that the allergic condition of the patient receiving SLIT with grass pollens who attended the visit (437/559) was stable in 77.8% (330/424) of the cases, and in acute stage in 22.2% (94/424).

The proportion of patients suffering from moderate or severe rhinitis changed from 81.7% at the initiation visit to 46.8% at the follow-up visit (Fig. 3A). Based on the change in rhinitis severity (as per ARIA classification) from the initiation visit to the follow-up visit for each patient (e.g. from «moderate or severe» to «mild» and/or from «persistent» to «intermittent»), it was found that rhinitis had improved in 44.3% (193/436) of the patients, had not changed in 47.7% (208/436), and had worsened in 8.0% (35/436).

Rhinitis symptoms improved in the majority of the patients (66.8% to 70.9%) following treatment with SLIT with grass pollens (Fig. 3B). Symptoms of conjunctivitis had also improved in 70% of these patients.

In patients with asthma, on the other hand, the representation of the different GINA categories remained more or less the same on an overall basis (Fig. 4A). On a per patient basis, asthma was considered stable in 73.6% (89/121) of the cases, had improved in 15.7% (19/121) of the cases, and worsened in 10.7% (13/121) of the cases.

The symptoms of asthma were considered to have improved in the majority of the patients (73.4% to 83.1%) following treatment (Fig. 4B).

Overall patient satisfaction as perceived by the doctor

Based on the doctor's perception, patient satisfaction following SLIT with grass pollens was good or very good in 86.4% of the cases (very good: 26.7%; good: 59.7%). Very poor satisfaction was encountered in very few patients (1.6%).

Tolerability

Specific reactions were reported by 30.4% (160/

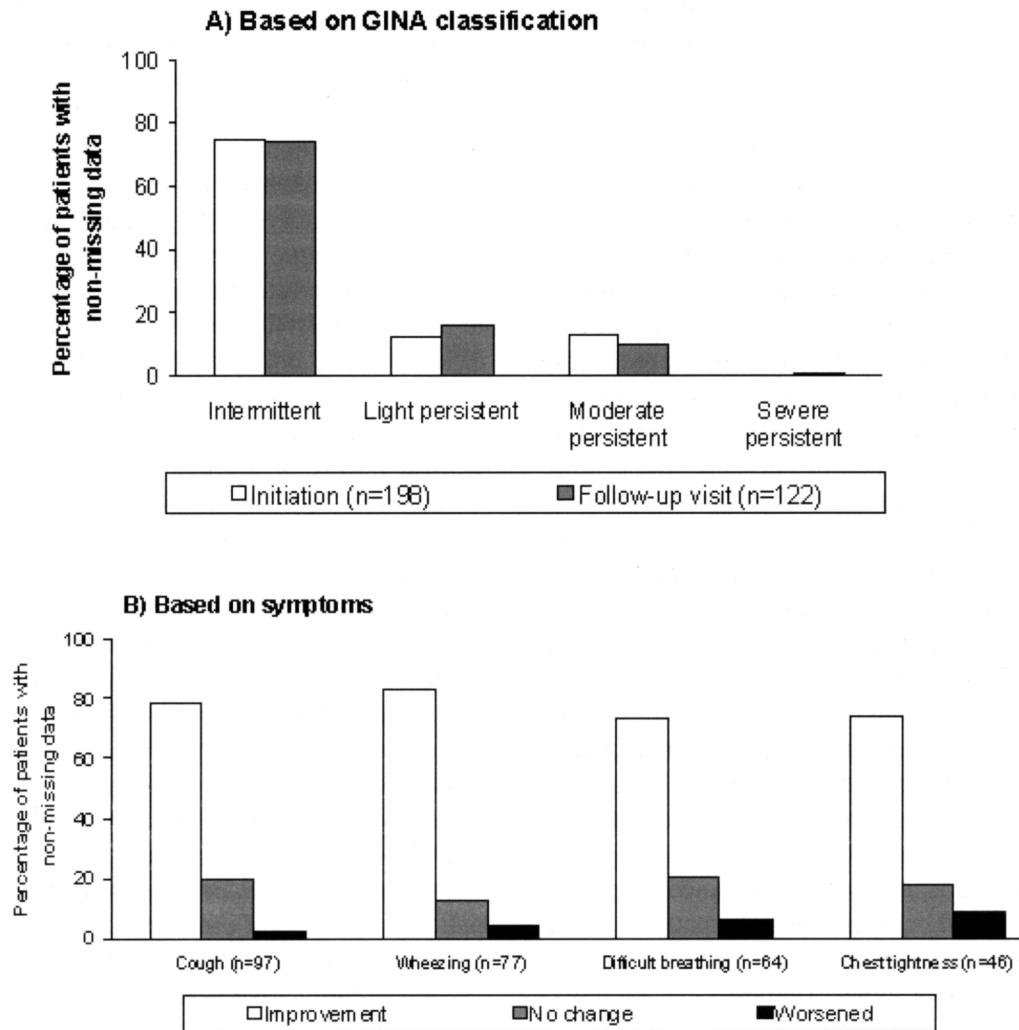


Fig. 4. Change in asthma following SLIT with grass pollens. Numbers in brackets indicate number of patients experiencing symptoms at initiation and with non-missing data.

527) of the patients at the follow-up visit at the end of the first season of treatment. In 93.1% (149/160) of the cases, these reactions consisted of local reactions, the most common of which were discomfort under the tongue (40/149: 26.8%), pruritus (35/140: 23.5%), local edema (21/140: 14.1%), sublingual edema (13/140: 8.7%), and/or sublingual pruritus (8/140: 5.4%). Systemic reactions were reported by 15.6% (25/160) of the patients and mostly consisted of rhinitis (13/25: 52%), breathing discomfort (4/25: 16%), eczema (3/25: 12%), and/or rhinoconjunctivitis (2/25: 8%). Incapacity to tolerate the treatment was recorded in the case of two patients. Of the nine patients not

included in the analyses as described above, eight attended the follow-up visit, two of whom reported a local reaction (one discomfort under the tongue and one sublingual edema).

DISCUSSION

This study included a large number of relatively young patients consulting a specialist for a first-time, skin-prick test, allergy status check-up. Less than 10% of the patients were current smokers, which is low compared with the latest available data showing that 28.2% men and 25% women aged 12 and older

are current daily smokers (18), suggesting that patients suffering from AR, with or without asthma, are aware of the detrimental effect of smoking on their condition.

Based on the ARIA definition of allergic rhinitis (9), the results show that the majority of these patients suffered from moderate to severe allergic rhinitis, mostly persistent, suggesting that when patients consult a specialist for a formal allergy check-up, quality of life is already affected. This concept is supported by the finding that based on the specialists' perception, the impact of the symptoms on the patient's quality of life was very important or important in more than 60% of the cases. More than eight in ten patients suffering from rhinitis with or without asthma experienced rhinorrhea and/or sneezing, mostly diurnal, and/or nasal obstruction. Three-quarters of the patients also suffered from ocular symptoms, indicating the condition should in fact be described as rhinoconjunctivitis.

The rhinitis:asthma ratio observed in the present study (2.3) is higher than that reported in most epidemiological studies (19). Considering that patients with moderate to severe rhinitis are more likely to have concomitant asthma (20), this observation is not surprising since the study population mostly consisted of patients with moderate to severe rhinitis.

In keeping with other studies (7, 21), poly-sensitization was frequent (73.6%), particularly in patients suffering from rhinitis and asthma as opposed to rhinitis alone (21, 22). Sensitization to HDM was most frequent, followed by sensitization to grass pollens, tree pollens (mostly birch) and cat danders (23). In addition, our results indicate that rhinitis duration was longer in patients with concomitant asthma as well as in poly-sensitized patients.

Immunotherapy, mostly SLIT, was recommended in more than one in two (55.6%) patients, primarily because of insufficient control with symptomatic treatments. The overall impact of symptoms on QoL, positive skin test to five-grass pollens, the presence of ocular pruritus and/or nasal obstruction and the presence of moderate to severe rhinitis, whether intermittent or persistent, were significant predictors of AIT prescription. In this regard, the results indicate that SLIT prescription within the real-world

setting follows the ARIA recommendation. As observed in recent studies (23-24) poly-sensitization did not appear to be seen as a deterrent. The presence of asthma which, within the study population, was mostly intermittent or mild persistent, also did not appear to be seen as a deterrent. A positive skin test to cat danders had a negative predictive AIT prescription value. Considering that sensitization to cat dander is pertinent in terms of being symptomatic, it was probably felt that it would compromise the efficacy of any pollen desensitization program.

The Longitudinal phase of the study focused on patients prescribed SLIT with pollens. The clinical profile of the 675 patients included in the Longitudinal phase of the study was essentially similar to that of the Transversal population, except that no patients suffered from severe asthma, once again showing that real-world current practice follows not only the ARIA recommendations, but also the GINA guidelines. Not surprisingly, considering the allergen sensitization profile of these patients, as reported in other studies and as described in the Transversal phase of this study, SLIT with grass pollens was most often prescribed (82.8% of the cases), usually alone. Association with other pollens was not common (15.2% of the patients). SLIT took a median of two weeks to reach target dose, with a weekly maintenance dose of 1101 IR and a cumulative dose of 24395 IR, according to a preseasonal regimen starting on average three months before the pollen season and continuing on average for one month during the pollen season. Only one in ten patients encountered difficulties with the treatment, usually related to administration planning. Concomitant immunotherapy, usually involving HDM extracts, was not frequent, being prescribed in one in ten patients. A snapshot of efficacy at the end of the first season of treatment shows that all symptoms (rhinitis, conjunctivitis as well as asthma) had improved in the majority of the patients, with a shift from moderate-to-severe rhinitis to mild rhinitis in 44.3% of the patients, confirming in real-world setting the findings of earlier SLIT studies (10). Based on the doctor's perception, patient compliance was good in the majority of the cases (88.2%), and satisfaction with SLIT was very good or good in more than 85% of the cases. One in three patients experienced specific reactions, usually

local reactions, mostly consisting of discomfort under the tongue, local and/or sublingual edema and/or pruritus, as expected from this kind of therapy.

These results support the findings of earlier clinical trials, in a broader patient population within a real-world practice setting, and show that SLIT is well accepted by the patients.

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