

MEDICAL MANAGEMENT AND SUBLINGUAL IMMUNOTHERAPY PRACTICES IN PATIENTS WITH HOUSE DUST MITE-INDUCED RESPIRATORY ALLERGY: A RETROSPECTIVE, OBSERVATIONAL STUDY

F. TREBUCHON¹, M. DAVID² and P. DEMOLY³

¹Private office, Montferrier sur Lez, France; ²Stallergenes S.A., Antony, France; ³Allergy Division, Pneumology Department, INSERM U657, Hôpital Arnaud de Villeneuve, University Hospital of Montpellier, Montpellier, France

Received November 4, 2011 – Accepted January 26, 2012

The primary objective of this study is to retrospectively describe the treatment regimens (initiation, maintenance, dosage and duration) in sublingual immunotherapy (SLIT) with house dust mite (HDM) extracts in routine practice in France. The secondary objectives include a description of the respiratory allergies that led to treatment and an evaluation of the treatment's efficacy and safety, patient satisfaction and compliance (as assessed by the physician) and patient management practices. Randomly-selected allergy specialists each included ten patients over the age of five with a respiratory allergy and proven sensitization to HDM (positive skin test and/or specific IgE >0.7 kUI) and in whom SLIT had been initiated in 2002 or 2005. The participants were monitored for at least two years. A total of 139 physicians participated in the study and contributed data from 1,289 patients (57% of whom were under the age of 18). More than 70% of the patients suffered from moderate-to-severe allergic rhinitis and 50% also suffered from asthma. More than 60% of the patients were polysensitized. A shift to shorter SLIT protocols was observed over time. Longer protocols tended to be used in children. Compliance was deemed good or very good in 84% of the patients. Treatment was deemed effective or very effective in 82% of the patients. Symptoms of rhinitis and/or asthma improved in 66% and 63% of the patients respectively, with a concomitant reduction in symptomatic medication intake. The majority of the patients were satisfied with their treatment, which was well tolerated. The results of this large, retrospective, observational study confirm the efficacy and tolerability of HDM SLIT in routine French practice in a "real-world" setting.

Allergen immunotherapy (AIT) with curative intent is currently the only treatment likely to impact the aetiology of atopy. According to the Allergic Rhinitis and its Impact on Asthma (ARIA) initiative, AIT is indicated in allergic patients in whom conventional pharmacological agents are relatively ineffective, unwanted or contraindicated (1, 2). Sublingual AIT immunotherapy (SLIT) has been

validated by the World Health Organization (WHO) (3) as an alternative to the subcutaneous route for the treatment of respiratory allergies.

The efficacy of SLIT in allergic rhinitis (AR) and allergic asthma induced by house dust mite (HDM) sensitization has been demonstrated by a meta-analysis of 12 randomized controlled trials (4). Several regimens have been suggested, particularly

Key words: observational study, respiratory allergy, house dust mites, medical management, sublingual immunotherapy

Mailing address:

Dr Florence Trebuchon,
3 chemin du Fescau,
F-34980 Montferrier-sur-Lez, France
Tel: +33 467 594 059
Fax: +33 155 592 129
e-mail: ftrebuchon@free.fr

with regard to the following parameters:

- Treatment initiation (i.e. the titration schedule or build-up phase)
- Daily and/or cumulative dose
- Treatment duration and protocol (year-round or discontinuous).

The main objective of the present study is to collect information on the treatment regimens actually used in real-world routine allergy practices in France over the past few years.

In order to better understand how respiratory allergies are managed, we collected information on the care received by these patients, their clinical and diagnostic characteristics and their treatments. These data were examined with respect to efficacy, safety, tolerability, satisfaction and compliance as perceived by the physician.

MATERIALS AND METHODS

Study design and patients

This is a multicentre, observational study conducted in 2008 in France. Data were collected retrospectively from medical files held by a representative sample of randomly-selected allergy specialists.

To limit patient selection bias, participating physicians were required to collect information on a total of ten consecutive patients started on HDM SLIT (preferably five patients initiated in 2002 and five patients initiated in 2005) and monitored during their treatment. For each patient, the physician completed a case report form (CRF) based on the patient's medical notes. We collected information on the patient's clinical characteristics and sensitization profile (to the most common allergens, as per usual practice) at the time of SLIT initiation, the SLIT regimen (including the initiation protocol, the dose and the treatment duration), concomitant symptomatic medications, the number of visits between the start and the end of the treatment period (or the last visit during treatment), any changes to the treatment (dose changes, early termination, etc.), symptom progression, any adverse events (and the latter's date of occurrence) and, as perceived by the physician, the treatment efficacy, the patient's compliance and patient satisfaction (overall and during the follow-up). Each form was then returned to a clinical research organization (REGISTRAT-MAPI, Lyon, France) in a pre-paid envelope. We did not collect any information that could identify the patient. In view of its retrospective nature, the study did not affect patient management in any way.

The study population consisted of patients (i) over

the age of five, (ii) with a respiratory allergy and proven sensitization to HDM (a positive skin test according to the allergist's usual practice and/or specific IgE >0.7 kUI), (iii) having started on SLIT in 2002 or 2005, (iv) with at least two years of follow-up and (v) with detailed medical files enabling consistent, reliable data collection. The study's primary objective is to describe the HDM SLIT regimens used in "real-world" settings (i.e. allergy practices) in France. The secondary objective is to evaluate the treatment duration and reasons for treatment discontinuation.

Treatments

The HDM SLIT generally administered in this observational study, consisted of a standardized mixture of equal proportions of *D.pteronyssinus*/*D.farinae* extract in several concentrations (for example 1, 10, 100 and 300 index of reactivity (IR)/ml). The IR is a measure of biological potency (skin reactivity) used to describe the allergenic content of an extract. In most cases, the study medication was incrementally titrated up to the daily maintenance dose of 300 IR over one or two weeks.

Statistical analysis

Statistical analyses were performed using SAS® software (version 8.2, SAS Institute Inc., Cary, NC, USA) and AdClin® software (version 3.1.1., AdClin Paris, France). For categorical variables, comparisons between subgroups were performed using a χ^2 test or Fisher's exact test. For continuous variables, Student's *t*-test or non-parametric tests (such as Mann-Whitney (for two subgroups) or a Kruskal-Wallis test or an analysis of variance (for >2 subgroups)) were used.

A multivariate logistic regression analysis of patient satisfaction included variables that were significant at $p < 0.2$ in a univariate model. The final covariates were selected stepwise, with an entry level of $p < 0.1$ and an exit level of $p < 0.05$. The outputs of the final model are presented as odds ratio (ORs) with their corresponding 95% confidence intervals (CIs) and *p* values. The threshold for statistical significance was set to $p < 0.05$.

Descriptive statistics are presented below as the mean $\pm$ SD.

Sample size

The sample size was calculated on the basis of the primary objective (i.e. the description of the SLIT regimens used) and the precision of the expected estimates. Considering that there were no literature data on the distribution of the different types of SLIT regimens (treatment initiation (titration schedule or build-up phase)/daily or cumulative dose/treatment duration and protocol used (year-round or discontinuous), we hypothesized

that each therapeutical subgroup would contain 30% of the patients. It was estimated that 400 patients would be required to estimate a proportion of 30% with a relative precision of between 10 and 20% and a first-order risk of 5%. We expected 20% of the CRFs to be non-evaluable and thus planned to collect information on 500 patients.

The study was conducted in compliance with the protocol, the Declaration of Helsinki (2004), the good epidemiological practice guidelines issued by the Association of French-Speaking Epidemiologists (ADELF), the good pharmacoepidemiological practice guidelines issued edited by the International Society for Pharmacoepidemiology (ISPE) and local regulations.

RESULTS

Specialists

In total, 175 specialists agreed to participate into the study: 139 participated actively and contributed at least one patient. The majority (73%) of the active participants were allergists and 34% were pneumo-allergists. Few (2.1%) were dermatologists, ENT specialists or paediatricians. Most were working in private practice (57.7%) or mixed private practice/hospital (40.1%) settings. With the exception of the Franche-Comte region, all regions of France were represented.

Patients

Actively participating physicians collected data on a total of 1,314 patients between September 8, 2008, and November 21, 2008. Twenty-five of these patients were not included in the analyses as they did not comply with one or more of the entry criteria - mostly with regard to a SLIT initiation date outside the required window (2002 or 2005) or missing (16 patients) or lack of sensitization to HDM or missing information on sensitization (11 patients). The final analysis therefore covered a total of 1,289 patients. SLIT was initiated in 567 patients (44%) in 2002 and 722 (56%) in 2005.

The patients in whom HDM SLIT was initiated in 2002 or in 2005 did not differ significantly in terms of demographic and clinical characteristics (Table I). The mean age of the study population was 20.5 ± 14.3 years. The study population comprised slightly more children (57.2%) than adults (particularly in the group with initiation in 2002 (61.5%)) and slightly more males than females (54%).

Clinical profile

Most of the patients suffered from AR (Table I) with or without asthma. Few patients suffered from allergic asthma alone. Patients had suffered from AR (with or without asthma) for 5.86 years on average. The AR was generally moderate or severe and persistent (64.9%). Two ARIA items of quality of life (QoL) were impacted in 57.0% (520 out of 913) of these moderate or severe AR patients (whether intermittent or persistent) and three items were impacted in 31.9% of cases (291 out of 913). Bothering symptoms were the most common item reported (772 out of 913: 84.6%). Sleep, daily activities and/or school or work life were impacted in less than 40% of the patients (38.2%, 37.0%, and 36.8%, respectively).

Patients with asthma (with or without AR) had suffered from the condition for 5.40 years, on average. Most suffered from intermittent asthma or mild persistent asthma.

Symptoms

As shown in Table I, the most common nasal symptoms were rhinorrhoea, sneezing and nasal obstruction. Rhinorrhoea and sneezing were mostly diurnal (41.8% and 45% of the cases, respectively). Anosmia was rare. The most common respiratory symptoms were coughing and wheezing. Although a few patients experienced ocular symptoms (Table I), the latter (most frequently teary/watery eyes and ocular pruritus) were mostly diurnal.

Sensitization profile

Overall, 1,073 patients (83.2%) had undergone least one skin test in the 24 months preceding treatment initiation (within between one and six months for 50% of the patients). Of these, 99% had a positive test to at least one HDM allergen (eleven patients with a negative skin test had a specific IgE level >0.70 kUI/l). Sensitization to grass pollens, tree pollens and/or cat dander each concerned at least one in five of the patients. Based on the available skin test data, 402 patients (37.5%) were monosensitized to HDM and 671 patients (62.5%) were polysensitized to HDM and at least one other allergen. This profile was similar for patients initiated in 2002 or in 2005.

Table I. Demographic and clinical characteristics at treatment initiation.

	2002 N=567		2005 N=722		Total N=1289	
Gender						
Male	290	51.2%	404	56.0%	694	53.9%
Female	276	48.8%	318	44.0%	594	46.1%
Age (years)						
Mean (SD)	19.25 (14.21)		21.49 (14.38)		20.50 (14.34)	
Min-max	5 - 72		5 - 72		5 - 72	
Children	348	61.5%	388	53.8%	736	57.2%
Adults ^[a]	218	38.5%	333	46.2%	551	42.8%
Pathology of respiratory allergy						
Rhinitis alone	252	44.4%	337	46.7%	589	45.7%
Rhinitis + asthma	299	52.7%	357	49.5%	656	50.9%
Asthma alone	16	2.8%	27	3.7%	43	3.3%
Allergic rhinitis (with or without asthma)	551	97.2%	695	96.3%	1246	96.7%
Disease duration (years)						
n	521		651		1172	
Mean (SD)	5.51 (6.06)		6.15 (6.03)		5.86 (6.05)	
Severity (ARIA)						
Mild intermittent	39	7.1%	54	7.8%	93	7.5%
Moderate or severe intermittent	47	8.5%	60	8.7%	107	8.6%
Mild persistent	125	22.7%	110	15.9%	235	18.9%
Moderate or severe persistent	339	61.9%	467	67.6%	806	64.9%
Allergic asthma (with or without rhinitis)	315	55.6%	384	53.3%	699	54.3%
Disease duration (years)						
n	303		366		669	
Mean (SD)	4.70 (5.15)		5.98 (6.19)		5.40 (5.77)	
Severity (GINA 2004)						
Intermittent	145	46.3%	169	44.4%	314	45.2%
Mild persistent	104	33.2%	130	34.1%	234	33.7%
Moderate persistent	59	18.8%	74	19.4%	133	19.2%
Severe persistent	5	1.6%	8	2.1%	13	1.9%
Symptoms						
<i>Rhinitis (with or without asthma)</i>						
Rhinorrhoea	493	89.8%	613	88.7%	1106	89.2%
Sneezing	470	85.6%	556	80.7%	1026	82.9%
Nasal obstruction	446	81.4%	561	81.2%	1007	81.3%
Nasal pruritus	359	65.9%	428	62.1%	787	63.8%
Anosmia	22	4.1%	30	4.4%	52	4.2%
<i>Asthma (with or without rhinitis)</i>						
Cough	212	67.5%	233	60.8%	445	63.8%
Wheezing	164	52.1%	204	53.3%	368	52.7%
Difficult breathing	113	36.0%	152	40.0%	265	38.2%
Chest tightness	79	25.2%	99	26.1%	178	25.7%
<i>Rhinitis and/or asthma</i>						
Ocular pruritus	168	29.7%	205	28.6%	373	29.1%
Teary eyes	128	22.7%	156	21.7%	284	22.1%
Others	51	9.2%	86	12.2%	137	10.9%

Categorical variables are presented as number and percentage of patients relative to total population with non-missing data. [a] ≥ 18 years.

Table II. Initiation phase.

	2002 N=567		2005 N=722		Total N=1289	
	n	%	n	%	n	%
4-month period during which SLIT was initiated						
January – April	158	28.0%	300	41.7%	458	35.6%
May – August	118	20.9%	122	16.9%	240	18.7%
September – December	289	51.2%	298	41.4%	587	45.7%
Treatment units						
IR	473	85.1%	701	98.2%	1174	92.4%
AU	83	14.9%	13	1.8%	96	7.6%
Protocol for treatments in IR						
10/100/300 IR/ml	204	43.1%	191	27.2%	395	33.6%
10/300 IR/ml	91	19.2%	318	45.4%	409	34.8%
1/10/100/300 IR/ml	130	27.5%	100	14.3%	230	19.6%
Other ^[a]	48	10.1%	92	13.1%	140	11.9%
Protocol for treatments in AU						
5/50/500/1000 AU/ml	62	74.7%	11	84.6%	73	76.0%
Other	21	24.3%	2	15.4%	23	24.0%
Dosing frequency for treatments in IR						
Daily	447	94.7%	670	96.0%	1117	95.5%
Other	25	5.3%	28	4.0%	53	4.5%
Target maintenance dose (IR/week)						
n	373		577		950	
Mean (SD)	1013 (399.8)		1050 (426.2)		1035 (416.2)	
95% CI	972.3, 1053.7		1014.7, 1084.5		1008.7, 1061.7	
Time to reach target maintenance dose (weeks)						
n	466		697		1163	
Mean (SD)	4.04 (5.11)		3.28 (4.03)		3.58 (4.51)	
95% CI	3.57, 4.50		2.98, 3.58		3.32, 3.84	

Categorical variables are presented as the number of patients (n) and a percentage, calculated relative to population with non-missing data. [a] The other most frequent protocols were 100/300 IR/ml and 0.1/1/10/100/300 IR/ml, with 2.3% and 3.6% of the total number of patients, respectively.

Symptomatic treatments at the time of initiation and concomitant immunotherapy

Overall, oral antihistamines were renewed (58.4%) or newly prescribed (27.2%) for the symptomatic treatment of rhinitis in the majority of the patients. Nasal steroids were used by 46.5% of the patients, with prescription renewals in 26.5% of the cases and new prescriptions in 19.9% of the cases. Local antihistamines were renewed or prescribed in 12.6% of the patients. Treatment of rhinitis with other medications (such as oral corticoids, cromones and/or antileukotrienes) was not common (<5% of

the patients).

In the majority of asthmatic patients, oral antihistamines had been renewed (60.1%) or newly prescribed (24.5%). Inhaled steroids were used by 63.8% of these patients (prescription renewals in 47.4% of the cases and new prescriptions in 16.4% of the cases). Inhaled long-acting and short-acting beta-agonists (LABAs and SABAs) were used in 40.9% and 44.6% of the patients (mostly as renewed prescriptions, with 28.2% and 35.8%, respectively). Treatment of asthma with oral steroids, oral LABAs, theophylline and/or cromones was not common

(<5% of the patients). Fewer than 15% of the patients were prescribed or given renewed prescriptions for antileukotrienes. The treatment profile did not differ significantly according to whether patients were started on SLIT in 2002 or in 2005.

One in five of the patients (283 out of 1284: 22%) received a concomitant AIT in addition to HDM SLIT; this was mostly for grass pollens (169 out of 280: 60.4%), birch tree pollen (27 out of 280: 9.6%) and animal dander (24 out of 280: 8.6%). Again, this profile did not differ significantly according to whether patients were started on SLIT in 2002 or in 2005. Concomitant immunotherapy was slightly less frequent in children than in adults (20.4% vs 24.3%, respectively).

Treatment regimens

The initiation phase. More treatments were initiated at the beginning of the year (January to March) in 2005 than in 2002. Treatment was not usually initiated during the May–August period (18.7% of the cases). This was the case for treatments initiated in 2002 and those initiated in 2005 (Table

II). Patients sensitized to HDM and at least one other allergen were more likely to be initiated between September and December than patients sensitized to HDM only (49% vs 41%, respectively).

The treatment regimen was usually based on IR/ml (92.4%) - particularly in 2005 (98.2% vs 85.1% in 2002). The most frequent initiation protocols were 10/100/300 IR/ml in 2002 and 10/300 IR/ml in 2005. Few patients were initiated on 1/10/100/300 IR/ml, particularly in 2005 (14.3% vs 27.5% in 2002). This profile did not appear to depend on the patient's sensitization status or age, except that children were less likely to follow a 10/300 IR/ml protocol than adults (30.6% vs 40.4%, respectively) but were more likely to follow the 1/10/100/300 IR/ml protocol (21.3% vs 17.4%, respectively).

The dosing frequency of IR regimen during the initiation phase was mostly daily (95.5% of the cases), irrespective of whether initiation occurred in 2002 or 2005. The mean target maintenance dose was close to 1035 IR/week and was essentially the same in 2002 and 2005. The time to reach the target maintenance dose was shorter in 2005 than in 2002,

Table III. *Maintenance phase.*

	2002 N=567		2005 N=722		Total N=1289	
	n	%	n	%	n	%
Prescribed treatment duration (years)						
3	238	42.2%	296	41.5%	534	41.8%
4	150	26.6%	184	25.8%	334	26.2%
5	167	29.6%	226	31.7%	393	30.8%
Prescribed number of months of treatment per year						
12	511	92.4%	655	92.0%	1166	92.2%
7-11	37	6.7%	47	6.6%	84	6.6%
6 or less	5	0.9%	10	1.4%	15	1.2%
Suggested time to first follow-up visit after the end of the initiation phase (months)						
n	561		718		1279	
Mean (SD)	2.68 (1.92)		2.89 (2.11)		2.80 (2.03)	
Median	2.00		2.00		2.00	
Suggested number of follow-up visits/year						
2	243	43.6%	294	41.7%	537	42.6%
3	135	24.2%	148	21.0%	283	22.4%
4	117	21.0%	154	21.8%	271	21.5%

Categorical variables are presented as number of patients (n) and a percentage, calculated relative to the population with non-missing data..

with mean values of 3.3 and 4 weeks, respectively. Dosing frequency and target dose did not differ significantly according to age. Time to reach the target dose was, however, slightly longer in children than in adults (3.9 ± 5.1 weeks vs 3.2 ± 3.6 weeks, respectively). Given the small sample size (see Table II), data related to regimens based on allergen units (AU) were not analysed.

The maintenance phase. The prescribed treatment duration was usually three (41.8% of the cases) to five years (30.8%). Year-round regimens were prescribed in the great majority of the cases (92.2%). The median time to first follow-up visit was 2 months, with two follow-up visits per year in 42.6% of the cases. This profile did not depend significantly on whether patients were started on SLIT in 2002 or in 2005 (Table III).

Treatment duration

The follow-up period. At the time of data collection in 2008, 92.5% of the patients initiated in 2002 and 33.1% of the patients initiated in 2005 had discontinued their treatment. The mean treatment duration in these patients was 3.46 ± 1.24 and 2.40 ± 0.78 years, respectively.

In approximately 50% of the discontinuations, the regimen had been completed. Unsurprisingly, a greater proportion of the patients initiated in 2002 had completed their treatment by the time the data were collected (56.5% vs 37.7% in 2005). Treatment had been discontinued prematurely in 26.7% of the cases, with a slightly greater frequency for treatments initiated in 2005 than in 2002 (36.9% vs 22%). The most common reasons for premature discontinuation were poor compliance (32.2%) and poor efficacy (25.1%). Overall, only 8% of the patients discontinued prematurely because of poor safety. This profile did not appear to depend on the year of treatment initiation.

The mean treatment duration in patients who had stopped their treatment (irrespective of the reason) was similar in children and adults (3.20 ± 1.23 years and 3.02 ± 1.23 years, respectively) and when comparing monosensitized and polysensitized patients (3.22 ± 1.30 years and 3.10 ± 1.18 years, respectively).

The proportion of children having discontinued

their treatment prematurely was lower than that of adults (23.8% vs 31%, respectively) and discontinuation was more likely to be due to poor compliance (38.1% vs 25.5%, respectively). Treatment status was similar in monosensitized and polysensitized patients, particularly with regard to premature discontinuation (28.1% and 27.9% of the cases, respectively). However, polysensitized patients were more likely to discontinue prematurely as a result of poor compliance (40.4% vs 21.5%).

Data was available up to the seventh follow-up visit for 47.3% of the patients who had stopped their treatment (regardless of the reasons) and for 55% of the patients whose treatment was ongoing. The interval between treatment initiation and the last available follow-up visit ranged from 2 to 75 months, with a mean value of 31.3 ± 12.5 months in both groups (irrespective of treatment status at the time of data collection).

For patients following treatment regimens in IR, the total cumulative dose during the maintenance phase for those who had stopped treatment (irrespective of the reason) ranged from 3137 to 549000 IR, with a mean value of 123968 ± 73399 IR. In patients whose treatment was ongoing, the total cumulative dose during the maintenance phase ranged from 16731 to 592920 IR, with a mean value of 145519 ± 86620 IR.

Difficulties encountered by the patients

Relatively few patients (191 out of 1285: 14.9%) experienced difficulties with the treatment regimen, whether initiated in 2002 (85 out of 564: 15.1%) or in 2005 (106 out of 721: 14.7%). The most common issue was related to administration planning (71 out of 191: 37.2%) and/or dose planning (29 out of 191: 15.2%).

Compliance

Compliance was deemed to be very good or good in 88% of the patients overall, in 84.1% of the patients who had stopped their treatment for any reason and in 95.6% of the patients whose treatment was ongoing at the time of data collection. Physicians had a perception of better compliance in patients whose treatment was ongoing at the time of data collection (Fig. 1).

Efficacy. The physician deemed the treatment to

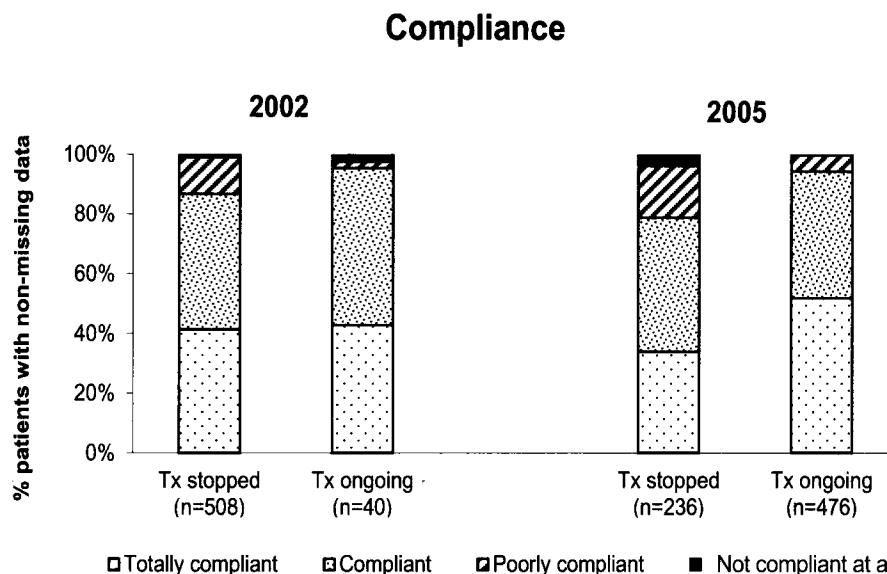


Fig. 1. Patient compliance, as perceived by the physician. *n* corresponds to the number of patients with at least one follow-up visit and no missing data.

be effective or very effective in the majority (82.5%) of patients, regardless of whether treatment had been discontinued for any reason or was ongoing at the time of data collection (Fig. 2A). Treatment was more likely to be deemed effective or very effective in patients whose treatment was ongoing, regardless of whether it was initiated in 2002 or in 2005.

The symptoms of rhinitis were considered to have improved in the majority (66%) of patients with or without asthma - particularly those initiated in 2005 and whose treatment was ongoing (Fig. 2B). Likewise, asthma was considered to have improved in the majority (63%) of patients with or without rhinitis - particularly those initiated in 2005 and whose treatment was ongoing (Fig. 2C).

Changes in symptomatic medication use during SLIT. Few patients were prescribed symptomatic medication (<2% for oral antihistamine and <3% for nasal steroids) for rhinitis after initiation of SLIT (Fig. 3A). Overall, 38.1% (396 out of 1039) of the patients having received a new or renewed prescription for oral antihistamines for rhinitis at SLIT initiation stopped using the medication prior

to their last visit. The corresponding figure for nasal steroids was 22.5% (244 out of 1084). This profile did not differ according to whether SLIT had been stopped (for any reason) or was ongoing at the time of data collection.

Similarly, few patients with asthma (with or without rhinitis) started to take symptomatic medications after the start of SLIT (Fig. 3B). Overall, 33.1% (195 out of 589) of the patients prescribed or re-prescribed oral antihistamines for asthma at SLIT initiation stopped using the medication before their last visit. The value was 26.3% (162 out of 616) for inhaled steroids. The use of LABAs and SABAs also decreased slightly, with respectively 15.2% (98 out of 644) and 8.0% (49 out of 613) of the patients discontinuing the use of these medications. This profile did not differ according to whether SLIT had been stopped (for any reason) or was ongoing at the time of data collection.

Overall patient satisfaction as perceived by the physician. Based on the physician's perception, 86% of the patients were satisfied or very satisfied with their treatment (78.4% of the patients who had

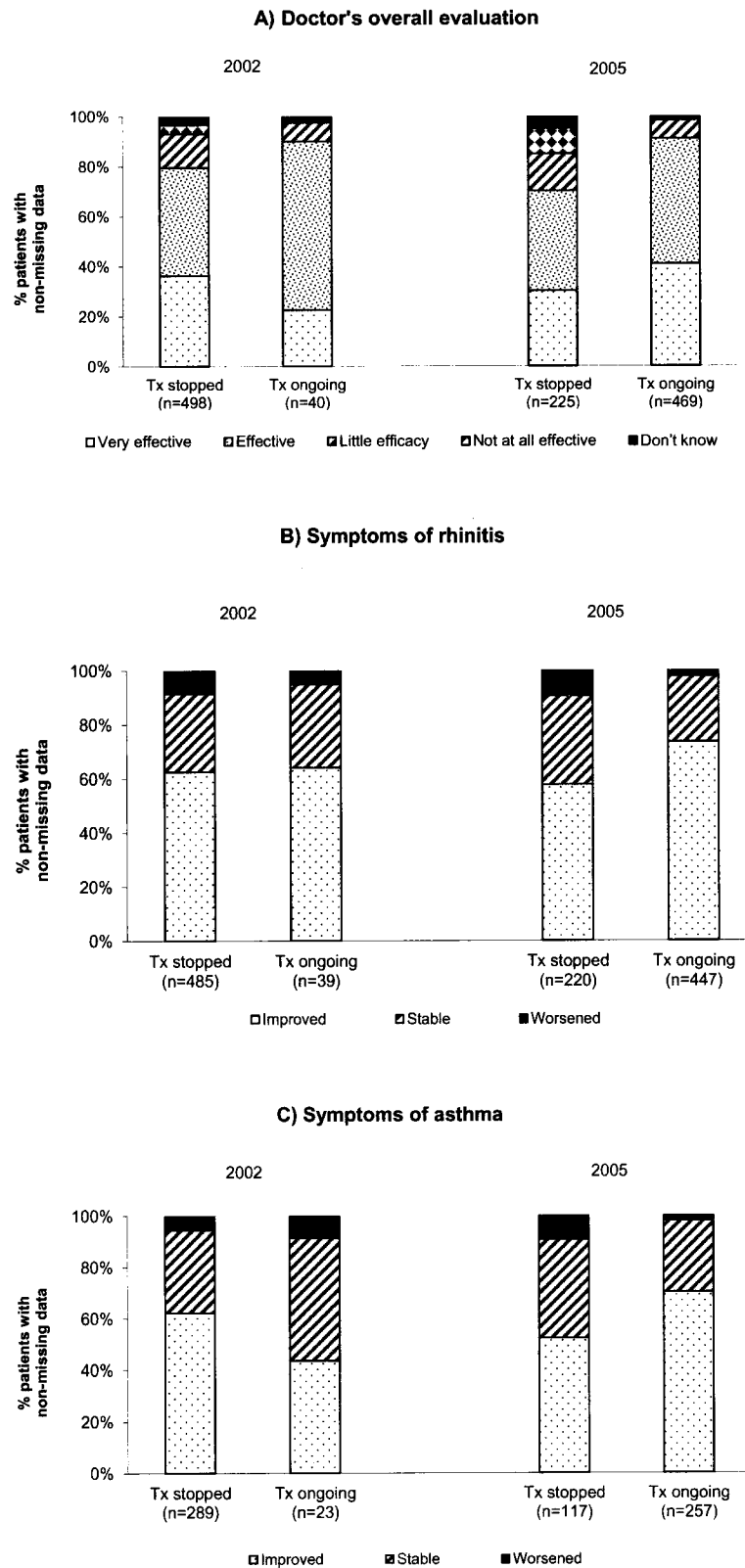


Fig. 2. Efficacy at the last recorded visit. *n* corresponds to the number of patients with at least one follow-up visit and no missing data.

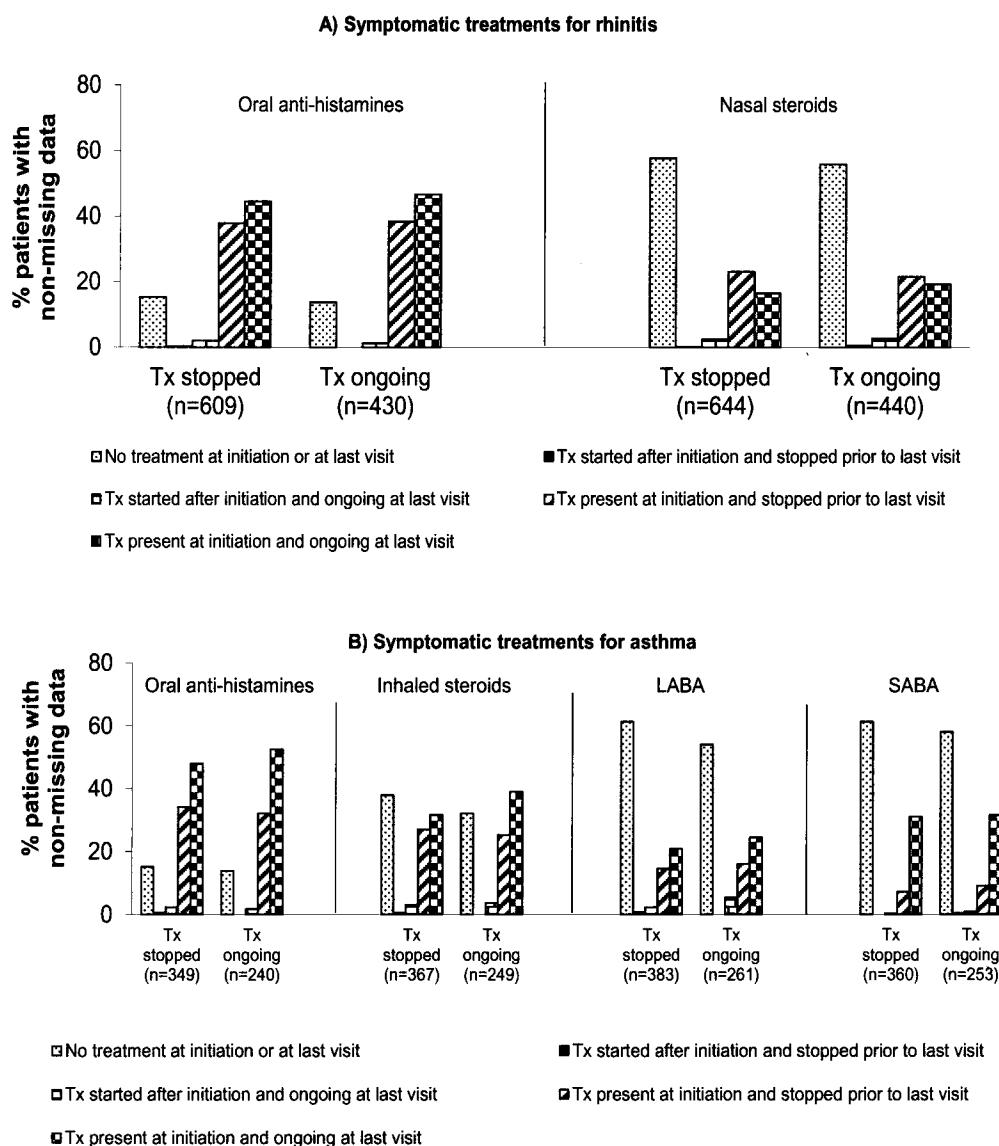


Fig. 3. Changes in symptomatic medication use at the last visit. *n* corresponds to the number of patients with at least one follow-up visit and no missing data.

stopped their treatment for any reason and 96.1% of the patients whose treatment was ongoing) (Fig. 4). Compared with patients having stopped treatment, patients whose treatment was ongoing at the time of data collection were more likely to be deemed satisfied or very satisfied with their treatment (regardless of whether it was initiated in 2002 or in 2005).

The results of a multivariate analysis of AR patients with rhinitis (with or without asthma), a

treatment regimen in IR and at least one positive skin test showed that good or very good compliance as perceived by the physician, a cumulative dose during the maintenance phase of ≥ 130000 IR, ongoing treatment and the presence of rhinorrhoea were all independent factors with a positive impact on overall patient satisfaction as perceived by the physician (Table IV).

Safety. Overall, treatment-emergent adverse events were reported by 17.6% (212 out of 1207)



Fig. 4. Patient satisfaction as perceived by the physician. *n* indicates number of patients with at least one follow-up visit and no missing data.

Table IV. Multivariate analysis of factors influencing patient satisfaction (as perceived by the physician) in patients with rhinitis (with or without asthma), whose treatment regimen was in IR and with at least one skin test.

Factor	OR	95% CI	p value
Overall compliance, as perceived by the physician: Completely compliant or compliant vs poorly or not compliant	7.024	[3.46, 14.26]	<0.0001
Cumulative dose (IR) during the maintenance phase: ≥130000 versus <90000	5.131	[2.27, 11.6]	<0.0001
Cumulative dose (IR) during maintenance phase: [90000-130000] vs <90000	2.068	[0.98, 4.37]	0.0570
SLIT treatment status: Ongoing treatment vs treatment stopped	3.973	[1.81, 8.74]	0.0006
Rhinorrhoea (at initiation): Presence vs absence	3.668	[1.48, 9.11]	0.0051

Table V. Safety profile for patients initiated with IR protocols.

Patients initiated in 2002				
Protocols	10/300 IR/ml (N=88)	10/100/300 IR/ml (N=194)	1/10/100/300 IR/ml (N=129)	Other IR protocols (N=47)
	n (%)	n (%)	n (%)	n (%)
Patients with at least one specific reaction	15/85 (18.8%)	33/183 (18.0%)	28/125 (22.4%)	7/45 (15.6%)
Patients initiated in 2005				
Protocols	10/300 IR/ml (N=312)	10/100/300 IR/ml (N=186)	1/10/100/300 IR/ml (N=97)	Other IR protocols (N=91)
	n (%)	n (%)	n (%)	n (%)
Patients with at least one specific reaction	45/298 (15.1%)	38/181 (21.0%)	23/93 (24.7%)	10/90 (11.1%)

N indicates number of patients in category with at least one follow-up visit; *n* indicates number of patients with at least one specific reaction; the percentage is expressed relative to the number of patients with non-missing data, which is shown as the denominator when different from *N*.

of the patients. This profile was similar for patients initiated in 2002 (93 out of 526: 17.7%) or in 2005 (119 out of 681: 17.5%). The safety profile did not appear to depend on the different IR protocols (Table V).

In more than 80% of the cases, the treatment-emergent adverse events were local and mild. Systemic reactions being reported by less than 4% of the patients overall (42 out of 1207) and did not appear to depend on the year of initiation or the treatment status at the time of data collection. Most reactions occurred early on in the treatment period. There were no anaphylactic reactions.

DISCUSSION

The present study included retrospective data on a large group of patients with HDM-induced respiratory allergy initiated to SLIT in a "real-world" setting in France. Over half the patients were children. The proportion of patients suffering from moderate or severe AR and/or asthma observed in the present study was higher than in the general population but similar to that for populations consulting physicians (5, 6), reflecting patient selection in accordance with the ARIA guidelines (1, 2). As observed in grass pollen-induced AR, more than 80% of the patients suffering from moderate or severe AR complained of bothersome symptoms. However, the symptoms seen in the two conditions differ: patients with HDM-induced AR mostly suffer from pulmonary and nasal symptoms, whereas QoL-impacting ocular symptoms are prominent in patients with grass pollen-induced AR (5, 7-9).

As observed in previous studies (5, 7, 10, 11), poly-sensitization (to grass pollens, tree pollens and cat as well as HDM) was common, irrespective of the main allergic disease (i.e. AR vs asthma). The proportion of HDM-monosensitized subjects in our study (37.5%) was very similar to that observed (37.7%) in 260 HDM-sensitized subjects attending an outpatient ear, nose and throat clinic in Belgium (12). In contrast, a lower value of 23.1% was observed in a 2005-2006 trial on 251 children being treated with HDM SLIT in general practice in the Netherlands (13). However, these disparities may reflect geographical differences and differences in the test panel of aeroallergens used.

Our results showed that both rhinitis and asthma symptoms improved as a result of HDM SLIT, thus confirming the results of clinical trials and meta-analyses (14) [particularly in children (4)] in a real-world setting in a broader group of patients.

Symptom relief was accompanied by a decrease in symptomatic medication use, again confirming the results of previous studies (3, 5) but in a broader setting.

The results for the study's primary objective (to describe HDM SLIT management in France) showed that treatment was not usually initiated in summer: patients and/or physicians may be on holiday or patients may not experience as many symptoms in summer, when HDM counts are usually lower (15). We also found that treatment initiation for polysensitized patients generally occurred between September and December: this is compatible with concomitant allergen immunotherapy with grass pollen two to four months before the pollen season, which usually starts around March. A shift to simpler protocols (from 1/10/100/300 to 10/300 IR/ml and with more rapid achievement of the maintenance dose) was observed over time; this probably reflected growing confidence in the efficacy and safety observed with rapid-initiation protocols for pollen immunotherapy as clinical trial data became available (10, 16).

Physician-rated compliance was generally deemed good or very good, as observed in other studies (17, 18). This also matches the conclusion of a systematic review of the published data on compliance with SLIT (and SCIT) in recent studies with a range of allergens (19), which was found to range between 75% and 97%. By way of an example, Passalacqua et al. investigated 71 children aged from 2 to 13 (including 57 with HDM allergy) and found that after 6 months of treatment, 84% of the patients had a compliance rate of over 75% (20).

Efficacy was rated over a mean duration of 31 months in patients with ongoing treatment and those who had completed their course of treatment during this time. The optimal and minimum duration of treatment in this field are subject to debate in the literature. In the 2009 World Allergy Organization Position Paper 2009 on SLIT in general, Canonica et al. commented that "at present only 30% of vaccinated patients complete at least 3 years of

treatment in accordance with the recommended guidelines for duration of therapy” (3). Very recently, Tabar et al. suggested that three years of HDM SCIT may be sufficient; in a prospective, controlled trial, the researchers compared a 3-year course of treatment and a 5-year course of treatment (21). Although the 3-year course produced significant symptom relief, the 5-year course did provide further benefits. However, Tabar et al.’s results were obtained with SCIT and not SLIT. Interestingly, our results show that the perception of compliance and efficacy tended to be more frequent in patients whose treatment was initiated in 2005. However, as the treatment was more likely to be ongoing, this may reflect recall bias by the physician (22).

Overall, 86% of the surveyed patients were satisfied or very satisfied with their treatment (as perceived by their physician). This compares well with the results of a recent study of HDM SLIT in which 88.1% of the patients (mean age: 16.3; age range: 5 to 71) were satisfied or fairly satisfied with their treatment (23). Satisfaction was associated with good compliance and appropriate dosage. Treatment status at the time of data collection was also a predictor of satisfaction. This is not surprising because some of the patients having discontinued treatment had done so because of poor compliance and thus suboptimal dosage.

The treatment was well tolerated; most reactions were local and occurred during the first few weeks of treatment. Few systemic reactions and no cases of anaphylaxis were observed. According to a recent large-scale trial and a comprehensive review, this reflects the safety profile observed for SLIT in general, with predominantly mild, local, transient events (3, 10, 24, 25).

In conclusion, this retrospective, observational study in France confirmed the “real-world” efficacy and tolerability of HDM SLIT in both children and adults.

ACKNOWLEDGEMENTS

The study was funded by a grant from Stallergenes.

Conflict of interest: Florence Trebuchon has no conflicts of interest to declare. Marie David is

an employee of Stallergenes. Pascal Demoly is a consultant and a speaker for Stallergenes, ALK and Therabel and was a speaker for Schering-Plough-MSD, Astra Zeneca and GlaxoSmithKline in 2009-2011.

The results from this observational study were presented in abstract/poster form at the 2011 CFA congress and at EAACI 2011.

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