Article

Predictors of Quality of Life Improvement in Allergic Rhinitis Patients After Sublingual Immunotherapy

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Abstract

Objectives: Sublingual immunotherapy (SLIT) has been described as a significant intervention in the treatment of allergic rhinitis (AR). However, factors that may predict treatment outcomes with respect to quality of life (QoL) results and mainly the role of olfactory function are still being underestimated. In this study, we investigated determinants that best predict treatment outcomes for QoL, exploring mainly the role of olfaction.

Methods: One hundred forty-five patients following SLIT, 45 placebo-controls, and 48 healthy subjects were studied. Olfactory function was objectively evaluated using "Sniffin' Sticks" test pre- and post-cessation of SLIT. Three categories of validated QoL questionnaires were filled out by all subjects: questionnaire specific for olfaction (Questionnaire of Olfactory Deficits), questionnaires for assessing psychology (Beck Depression Inventory, Zung Depression Scale, State & Trait Anxiety Inventory), general Short Form-36 health survey.

Results: Statistically significant improvement of olfactory function by 11.1% and of all QoL questionnaires results (all $P < .001$) was observed on final evaluation. Anosmia, asthma history, and the severity of symptoms—expressed by the Total Symptoms Score—were proven independent determinants of clinically significant improvement in patients' QoL.

Conclusions: Several factors were found that may predict QoL outcomes in AR patients following SLIT.

Keywords

allergic rhinitis, anosmia, asthma, sniffin' sticks, immunotherapy, quality of life

Introduction

Although allergic rhinitis (AR) does not represent a life-threatening condition, it is usually the cause of evident deterioration in patients' quality of life (QoL).[1-4] To date, it is recognized that in addition to symptom improvement, the patients' perceptions also play a significant role for an objective evaluation of the effects of medical treatment. Accordingly, assessment of QoL is assuming a more important place in the study of allergy.[4,5] Presently, although there are studies[5-13] reporting the positive effects of immunotherapy on AR patients' QoL, there are no data regarding demographic and clinical factors that may play essential role as predictors for better QoL outcomes after sublingual immunotherapy (SLIT). Moreover, olfactory dysfunction is often underestimated by patients and overlooked by doctors,[14,15] and its predictive value still remains a matter of future studies. The use of standardized olfactory tests and validated olfaction-specific QoL questionnaires may be proven useful for the evaluation of the role of olfaction as a possible determinant of QoL outcomes after SLIT.

This study aims to identify determinants that objectively predict treatment outcomes for QoL, focusing mainly on the role of the patients' olfactory status. Consequently, otolaryngologists may provide better counselling to their patients

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about the anticipated benefit for their QoL after SLIT, optimizing medical treatment.

Methods

Study Groups

This study is part of a prospective study for AR. Three groups of subjects participated. The first group included 145 patients with AR who received SLIT. Forty-five "blinded" patients served as a single-blinded randomized placebo control group. Finally, 48 healthy controls with no evidence of sinonasal diseases (lack of symptoms, negative skin prick tests [SPTs], normal olfactory function, and no findings on spirometry and nasal endoscopy) were used as controls to demonstrate the affected QoL of AR patients before treatment.

Diagnosis of AR was based on history, nasal endoscopy, sinus computed tomography scanning, SPT for atopy, test of pulmonary function, and olfactory testing. Subjects who had a clinical history of moderate to severe perennial AR[1]—resistant to other medical therapies and a positive SPT (mean diameter of wheal, ≥3 mm) were included in the patients' group. Criteria for exclusion were: (1) seasonal AR, (2) history of chronic rhinosinusitis or malignancy, (3) previous sinus surgery, (4) history of anaphylaxis or angioedema and dermographism, (5) immunotherapy treatment during the last 5 years, and (6) relative contraindications to immunotherapy. All patients fulfilled the criteria of AR according to the ARIA guidelines.[16] Moreover, none of the subjects used oral or nasal corticosteroids 4 weeks prior to inclusion and oral antihistamines 1 week prior to SPT. All subjects underwent a brief psychiatric interview to exclude those with preexisting major psychiatric disorder. The study protocol was approved by the local Institutional Review Board. All subjects signed informed consent. The study was performed in accordance with the Declaration of Helsinki/Hong Kong.

Symptoms Evaluation

Overall symptoms of AR were assessed using the Total 5 Symptoms Score (T5SS) that includes the symptoms of nasal discharge (rhinorrhea), nasal congestion, itchy nose, sneezing, and itchy eyes. All symptoms were graded from 0 (absent) to 3 (very troublesome), with total scores ranging from 0 to 15. SPTs were performed and evaluated as described by the European Academy of Allergy and Clinical Immunology.[17] The panel consisted of common aeroallergens and more specifically *Dermatophagoides pteronyssinus, Dermatophagoides farinae, Cat and Dog epithelium, Grass mix, Parietaria, Olive, Poplar, Alternaria alternatae, Cladosporium, Aspergillus, Cypress*, and *Pine*. Sensitivities and antigens used for SLIT are presented in Table 1. All patients were either mono- or polysensitized, and all of them were sensitized to dust mites that cause perennial AR. Sensitivities of the placebo-control group were similar to the AR patients' group. Olfactory function of patients and controls was assessed using "Sniffin' Sticks" test package[18] pre- and posttreatment. Olfactory function was expressed by Threshold-Discrimination-Identification (TDI) score. TDI score ranges from 0 to 48 (values of 15 or less represent anosmia, values between 16 and 34.5 represent hyposmia, and values over 34.5 represent normosmia for the mild climate conditions in Greece).[19]

Table 1. Sensitivities and Antigens Used for Sublingual Immunotherapy (SLIT) in Allergic Rhinitis Patients Group.

Antigens	No. of Patients (%)
Dernatophagoides mix (farinae,pteronyssinus)	58 (40.0)
Dernatophagoides mix, Grass mix	30 (20.7)
Dernatophagoides mix, alternaria alternata	18 (12.4)
Dernatophagoides mix, olive	10 (6.9)
Dernatophagoides mix, parietaria	8 (5.5)
Dernatophagoides mix, epithelium	4 (2.8)
Dernatophagoides mix, other antigens	17 (11.7)

QoL assessment was based on 5 validated, widely used questionnaires (Table 2), a specific olfaction-associated QoL (Questionnaire of Olfactory Deficits [QOD][20]), mental health assessments (Beck Depression Inventory [BDI],[21] Zung Depression Scale [ZDS],[22] State and Trait Anxiety Inventory [STAI][23]), and a general health survey (Short Form-36 [SF-36][24,25]), that all participants had to complete at the beginning of the study and immediately upon cessation of SLIT.

Treatment Protocol

SLIT duration ranged from 12 to 24 months according to treatment response (average 18 months). In detail, SLIT consisted of Staloral[26] (10 IR/ml and 300 IR/ml; Stallergenes, Antony, France; build-up phase 10 IR/ml for 1 week and then 300 IR/mL for 1 week gradually increasing every day and maintenance phase 300 IR/ml 8 applications 3 times a week) or Sublivac[26] (10 000 AUN/ml; HAL Allergy BV, the Netherlands; build-up up-dosing phase lasting 5 days gradually increasing every day and maintenance dosage of 5 drops every day). In polysensitized patients we used a mixture of no more than 2 antigens, according to SPT results, history, and clinical information. The dropout rates for the placebo-control group were as SLIT.

Statistical Analysis

Statistical analysis of the data was performed using the Statistical Package for the Social Sciences (SPSS), version 19.0 (IBM, Armonk, New York, USA). The normality of

Table 2. Characteristics of the Questionnaires' Used for Quality of Life (QoL) Assessment.

QoL Questionnaires	Intent	Number of Items	Score Range	Other important items
Questionnaire of Olfactory Deficits (QOD)[20]	Specific for olfaction-associated QoL	25 four-scale statements (17 "negative," 2 "positive," 6 "socially desired")	Maximum score of 57 points	High scores indicate a strong impairment of QoL
Beck Depression Inventory (BDI)[21]	Measures depression	21 self-reporting items	Graded from 0 to 3	Higher scores indicate higher level of depression
Zung Depression Scale (ZDS)[22]	Measures depression	20 items	Graded from 1 to 4	Higher scores indicate higher level of depression
State and Trait Anxiety Inventory (STAI)[23]	Measures anxiety	Includes 2 parts, 1 that refers to anxiety due to a specific condition (state) and another that refers to the general tendency of subjects to react anxiously (trait); each one of these parts has 20 questions	Graded from 1 to 4	Higher scores indicate higher level of anxiety
Short Form survey (SF-36)[24,25]	General health survey	Assesses QoL in 8 domains covering both physical and mental health	Scores range from 0 to 100	A higher score represents better functioning

quantitative variables was ascertained with Kolmogorov-Smirnov test. The chi-square test, analysis of variance (ANOVA), and Mann-Whitney U-test were used to assess differences of demographic and disease characteristics between patients and controls. The scores of olfactory function and all QoL questionnaires were expressed as the mean and standard deviation (SD). Differences in the scores of T5SS, olfactory function, and QoL questionnaires between (1) patients and controls and (2) pre- and posttreatment were assessed by Student *t* test for independent and related samples, respectively. When the distribution of a questionnaire was skewed, the statistical analysis was performed on the log-transformed scores. The chi-square test was used to evaluate any potential association between the incidence of clinically significant improvement for each QoL questionnaire with patients' demographics and clinical characteristics. Multivariate stepwise logistic regression analysis was constructed to explore the independent effect of patients' characteristics on clinically significant improvement. Odd ratios (OR) and 95% confidence intervals (CI) were estimated as the measure of association between clinically significant improvement and all potential predictors. All tests were 2-tailed, and statistical significance was considered for P values of less than .05.

Results

Demographics and disease characteristics of all study groups are presented in Table 3. All patients' pretreatment scores in all psychometric questionnaires were statistically significantly worse (all $P < .05$) compared to healthy controls, revealing the deteriorated QoL of AR patients. We found no statistically significant differences in placebo-control group between the pretreatment and follow-up scores, thus excluding any placebo effect to treatment outcomes (Table 4).

Analyzing the posttreatment outcomes of AR patients who received SLIT, a significant improvement was observed of total symptom score (T5SS) by −61.7% ($P < .001$), of all indices of olfactory function (Odor Threshold, Odor Discrimination, Odor Identification, and TDI score), and of the scores of all QoL questionnaires: (QOD, SF-36, BDI, ZDS, and STAI). Nevertheless, only posttreatment scores of QOD and its 3 dimensions remained significantly worse compared to healthy controls (all $P < .05$) (Table 4).

Furthermore, clinically significant improvement was defined for each QoL questionnaire as a change of ≥.5 SD of the pretreatment score.[27] Accordingly, improvement was defined as a decrease of 3.92 points for QOD, 2.46 for BDI, 3.06 for ZDS, and 4.20 for STAI and an increase of 6.64 points for SF-36. Among the entire cohort, clinically significant improvement was observed in 29 (20.0%) patients for QOD, 97 (66.9%) patients for SF-36, 57 (39.3%) patients for BDI, 89 (61.4%) patients for ZDS, and 85 (58.6%) patients for STAI. In univariate statistical analysis, it was found that a clinically significant improvement of (1) QOD was associated with younger age ($P < .001$), medium or low socioeconomic status ($P = .028$), smoking ($P < .001$), higher T5SS score ($P = .002$), asthma ($P = .005$), lower TDI score ($P < .001$), hyposmia and anosmia ($P < .001$), and shorter duration of olfactory dysfunction ($P = .079$); (2) SF-36 was associated with younger age ($P < .001$), medium or low socioeconomic status ($P = .014$), smoking ($P = .038$), higher T5SS score ($P < .001$), asthma ($P = .013$), lower TDI

Table 3. Demographics and Disease Characteristics of All Study Groups: (1) Healthy Controls (n = 48), (2) Patients of the Placebo-Control Group (n = 45), and (3) Patients Received Sublingual Immunotherapy (n = 145).[a]

	Control Group (n = 48)	Placebo-Control Group (n = 45)	Patients (n = 145)	*P* Value
Male gender, n (%)	25 (52.1)	29 (64.4)	92 (63.4)	.335
Age, mean, SD, y	40.15 (15.50)	38.25 (13.67)	36.17 (13.98)	.222
Socioeconomic status				<.001
Low, n (%)	1 (2.1)	3 (6.7)	8 (5.5)	
Medium, n (%)	21 (43.8)	6 (13.3)	17 (11.7)	
High, n (%)	26 (54.2)	36 (80.0)	120 (82.8)	
Smoking, n (%)	15 (31.3)	11 (24.4)	33 (22.8)	.497
Asthma presence, n (%)	—	7 (15.6)	21 (14.5)	.859
T5SS score	—	10.74 (2.41)	10.55 (2.10)	.610
TDI score, mean (SD)	38.88 (1.38)	33.50 (6.75)	34.20 (7.47)	<.001
Olfactory function				<.001
Normosmics, n (%)	48 (100.0)	31 (68.9)	98 (67.6)	
Hyposmics, n (%)	0 (0.0)	10 (22.2)	35 (24.1)	
Anosmics, n (%)	0 (0.0)	4 (8.9)	12 (8.3)	
Duration of olfactory dysfunction, y	—	3 (1.5-7)	3 (2-8)	.899

[a]Normally distributed quantitative variables were expressed as mean (standard deviation [SD]); non-normally distributed quantitative variables were expressed as median (interquartile range); qualitative variables were expressed as frequencies (%). TDI, Threshold-Discrimination-Identification; T5SS, Total 5 Symptoms Score.

score (P = .021), hyposmia and anosmia (P = .040), and shorter duration of olfactory dysfunction (P = .028); (3) BDI was associated with younger age (P < .001), smoking (P = .004), higher T5SS score (P < .001), asthma (P = .022), lower TDI score (P = .025), anosmia (P = .005), and shorter duration of olfactory dysfunction (P = .001); (4) ZDS was associated with medium or low socioeconomic status (P = .003), smoking (P = .006), higher T5SS score (P < .001), asthma (P = .013), lower TDI score (P = .004), and anosmia (P = .048); and (5) STAI was associated with female gender (P = .038), medium or low socioeconomic status (P = .005), smoking (P = .023), higher 5TSS score (P < .001), asthma (P = .025), lower TDI score (P = .004), anosmia (P = .044), and shorter duration of olfactory dysfunction (P = .028).

Multivariate logistic regression analysis revealed that the following independent predictors were significantly associated with higher likelihood of clinically significant improvement: anosmia, asthma, and T5SS score for all 5 questionnaires (all P < .05); hyposmia for QOD and SF-36 (all P < .05); and medium or low socioeconomic status only for ZDS (P < .05) (Table 5).

Discussion

The beneficial effects of SLIT to patients' QoL have already been extensively discussed in literature.[5-13] A specific goal of the present study was to measure the proportion of patients who experienced a clinically significant improvement of QoL after SLIT and consequently, the evaluation of the predictive role of various clinical factors for treatment outcomes with regards to QoL results, investigating especially the role of olfactory function.

We found that besides other common clinical symptoms that significantly improved after SLIT, olfactory function recovered as well, and this was expressed by a significant improvement in the TDI and all separate test scores. In addition to the AR patients with olfactory deficits who significantly improved their olfactory ability after treatment, the normosmic group (65%) of AR patients presented an increase of the absolute values of olfactory function after treatment. Moreover, patients' total symptom score who received SLIT was also significantly improved. All these resulted in patients' QoL improvement as well, as proven by the significant improvement of the results of all questionnaires used. Additionally, we observed that posttreatment outcomes in AR group approached the results of the healthy control group. It is important to mention that we found no placebo effect on our results, in agreement with previous studies[28,29] that showed no effect or even worsening in the SLIT placebo group. Our results agree with previous studies that reported positive effects of immunotherapy on patients' QoL.[5-13]

In our study, we explored clinically significant improvement for patients' QoL, as defined by Norman et al,[27] aiming to provide clinically important data and allowing to build predictive models about treatment outcomes. According to these, although we observed that all patients' QoL improved significantly after SLIT, a clinically significant improvement was found in 39.3 to 61.4 percent of patients according to questionnaires assessing mental health, in 66.9 percent of patients in general health survey SF-36, whereas the clinically significant improvement for the specific for olfaction QoL questionnaire was only 20.0%. This can be possibly attributed to the fact that QOD

Table 4. Scores of Olfactory Function, Total Symptoms Score and Quality of life (QoL) Questionnaires Results Pre- and Posttreatment in All Study Groups.[a]

		Olfactory and Psychometric Scores				
			Patients			
	Control Group		Pretreatment	Posttreatment	% Change	*P* Value
T5SS	—	SLIT	10.55 (2.05)	4.04 (1.11)	–61.7	<.001
		Placebo	10.88 (1.97)	10.25 (1.92)	–5.8	.318
Olfactory scores						
OT	8.10 (0.69)	SLIT	6.39 (1.59)[b]	7.66 (1.32)	19.9	<.001
		Placebo	6.08 (1.47)[b]	6.15 (1.51)[b]	1.2	.804
OD	15.61 (0.60)	SLIT	14.23 (3.02)[b]	15.47 (0.96)	8.7	<.001
		Placebo	14.02 (2.82)[b]	14.39 (0.91)[b]	2.6	.397
OI	15.17 (0.56)	SLIT	13.59 (3.10)[b]	14.80 (1.35)	8.9	<.001
		Placebo	13.41 (2.89)[b]	13.66 (2.31)[b]	1.9	.645
TDI	38.88 (1.38)	SLIT	34.20 (7.47)[b]	37.98 (3.46)	11.1	<.001
		Placebo	33.50 (6.75)[b]	34.20 (5.97)[b]	2.1	.714
Psychometric questionnaires						
QOD	6.25 (0.76)	SLIT	10.23 (7.85)[b]	6.82 (1.21)[b]	–33.3	<.001
		Placebo	9.78 (6.49)[b]	9.22 (3.75)[b]	–5.7	.475
QOD-NS	0.00 (0.00)	SLIT	3.17 (6.57)[b]	0.14 (0.48)[b]	–95.6	<.001
		Placebo	3.09 (5.51)[b]	2.73 (0.97)[b]	–11.7	.660
QOD-PS	6.00 (0.00)	SLIT	4.98 (1.10)[b]	5.67 (1.00)[b]	13.9	<.001
		Placebo	4.67 (1.27)[b]	4.72 (1.42)[b]	–1.1	.855
QOD-SD	0.25 (0.21)	SLIT	2.08 (1.71)[b]	1.01 (1.12)[b]	–51.4	<.001
		Placebo	2.02 (1.27)[b]	1.77 (1.17)[b]	–12.4	.234
SF-36	86.59 (10.73)	SLIT	79.62 (13.28)[b]	91.85 (5.08)	15.4	<.001
		Placebo	78.92 (12.98)[b]	80.62 (9.28)[b]	2.2	.571
BDI	4.98 (3.48)	SLIT	6.57 (4.92)	4.43 (2.91)	–32.6	<.001
		Placebo	6.75 (4.17)	6.47 (3.53)[b]	–4.2	.787
ZDS	28.12 (5.60)	SLIT	33.81 (6.13)[b]	29.63 (5.40)	–12.4	<.001
		Placebo	34.38 (7.01)[b]	33.23 (5.25)[b]	–3.3	.322
STAI	34.44 (7.90)	SLIT	38.21 (8.41)[b]	32.19 (6.62)	–15.8	<.001
		Placebo	37.21 (7.91)[b]	36.32 (6.07)[b]	–2.4	.441

[a]Data are expressed as mean values (SD). BDI, Beck Depression Inventory; OD, Odor Discrimination; OI, Odor Identification; OT, Odor Threshold; QOD, Questionnaire of Olfactory Deficits; QOD-NS, Questionnaire of Olfactory Deficits-Negative Statements; QOD-PS, Questionnaire of Olfactory Deficits-Positive Statements; QOD-SD, Questionnaire of Olfactory Deficits-Socially Desired Statements; SF-36, Short Form-36; SLIT, sublingual immunotherapy; STAI, State and Trait Anxiety Inventory; T5SS, Total 5 Symptoms Score; TDI, Threshold-Discrimination-Identification; ZDS, Zung Depression Scale.
[b]Indicates statistically significant worse scores compared to healthy control group; *P* values refer to comparison between pre- and posttreatment scores.

is an olfaction-specific scale, reflecting only the effects of olfactory changes on patients' QoL.

Then we explored the pretreatment clinical and demographic determinants that best predict outcomes for a clinically significant QoL recovery after SLIT. After univariate screening of all possible predictors we found that certain demographic and disease characteristics such as age, socioeconomic status, symptom score, asthma history, smoking habits, and olfactory loss were significant predictors of QoL outcomes. However, only baseline olfactory loss (anosmia), irrespective of its duration, asthma history, and the severity of clinical symptoms, as expressed by T5SS, appeared to be independent clinical predictors when multiple risk factors were accounted for in the predictive model.

Specifically, we found out that anosmic patients were 3.52 up to 7.54 times more likely to experience clinically significant improvement on QoL. Also patients with higher T5SS score were more possible to display clinically significant improvement. Asthmatics presented 2.63 up to 4-fold increase on QoL results on each occasion compared to non-asthmatics. A possible reason for the results could be that there is greater room for improvement in patients with anosmia, asthma, and higher T5SS score, as they are starting out with lower QoL results that we have already showed in a previous work.[30] Another possible explanation could be the significant beneficial effects of SLIT on asthma and olfactory dysfunction.[31] Other potential determinants that have been described in literature include asthma, birth during a

Table 5. Results of Multivariate Logistic Regression Analysis Between Predictor Variables and Clinically Significant Improvement of QOD, SF-36, BDI, ZDS, and STAI Questionnaires in Patients Suffering From AR Who Received SLIT.[a]

	aOR	95% CI	*P* Value
QOD			
Olfactory function			
Normosmia	Reference		
Hyposmia	4.95	1.95-12.60	<.001
Anosmia	7.54	1.12-26.90	<.001
T5SS score	1.22	1.01-1.49	.048
Asthma	2.90	1.06-7.90	.032
SF-36			
Olfactory function			
Normosmia	Reference		
Hyposmia	2.44	1.01-5.91	.045
Anosmia	4.53	1.02-21.19	.039
Asthma	3.88	1.09-13.78	.026
T5SS score	1.45	1.15-1.86	.002
Low socioeconomic status	2.72	0.97-7.68	.052
Smoking	2.17	0.87-5.42	.093
BDI			
Olfactory function			
Normosmia	Reference		
Hyposmia	1.07	0.49-2.34	.872
Anosmia	5.03	1.28-19.76	.012
T5SS score	1.43	1.18-1.72	<.001
Asthma	2.63	1.01-6.81	.042
Smoking	1.98	0.92-4.27	.078
ZDS			
Olfactory function			
Normosmia	Reference		
Hyposmia	1.14	0.52-2.48	.745
Anosmia	4.71	1.01-21.97	.033
T5SS score	1.31	1.09-1.56	.015
Asthma	4.01	1.29-12.50	.011
Low socioeconomic status	3.45	1.29-9.20	.010
STAI			
Olfactory function			
Normosmia	Reference		
Hyposmia	1.02	0.49-2.14	.957
Anosmia	3.52	1.00-13.03	.048
T5SS score	1.41	1.17-1.70	<.001
Asthma	3.97	1.28-12.35	.012
Low socioeconomic status	2.60	0.97-6.96	.051

[a]Expressed as adjusted odds ratios (aOR) with their 95% confidence intervals (CI). AR, allergic rhinitis; BDI, Beck Depression Inventory; QOD, Questionnaire of Olfactory Deficits; SF-36, Short Form-36; SLIT, sublingual immunotherapy; STAI, State and Trait Anxiety Inventory; T5SS, Total 5 Symptoms Score; ZDS, Zung Depression Scale.

pollen season, heavy maternal smoking during the first year of life, and high serum concentrations of IgE, raising interest for future studies.[1,7,32]

Conclusions

This study for the first time clearly defines proportions of patients who experienced clinically significant improvement on their daily lives after SLIT and explores certain demographic and disease characteristics such as age, socioeconomic status, clinical symptom score, asthma history, smoking habits, and olfactory loss as significant determinants for better QoL outcomes. Among these, only olfactory loss (anosmia), asthma history, and the severity of symptoms (expressed by T5SS score) were proven as independent clinical predictors associated with higher likelihood of

clinically significant improvement on patients' QoL. Accordingly, we believe that olfactory testing in AR patients prior to immunotherapy is of great clinical importance for appropriate patient selection and consultation for treatment outcomes related to QoL results.

Declaration of Conflicting Interests

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