

Sublingual Immunotherapy in Polysensitized Patients: Effect on Quality of Life

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■ Abstract

Background: Quality of life (QOL) is an important issue in allergic rhinitis and has been evaluated in a number of studies that have shown how it is impaired in untreated patients and improved by effective treatment. However, there are no data concerning QOL after sublingual immunotherapy (SLIT) in polysensitized patients.

Objective: To evaluate the effect, in real-life clinical practice, of SLIT on QOL in a population of polysensitized patients with allergic rhinitis.

Methods: We prospectively evaluated 167 consecutively enrolled polysensitized patients with allergic rhinitis. QOL was measured in all cases with the Rhinoconjunctivitis Quality of Life Questionnaire at baseline and after 1 year of SLIT (performed in approximately 70% of cases using single allergen extracts provided by the same manufacturer).

Results: The most frequent causes of sensitization were grass pollen, Parietaria, and house dust mites. The mean number of sensitizations per patient was 3.65. SLIT was performed with 1 extract in 123 patients (73.6%), with 2 extracts in 31 patients (18.6%), and with more than 2 extracts in 13 patients (7.8%). The mean values of all the QOL items improved significantly ($P < .01$ in all cases), with the following reductions noted: activities, 3.96 to 2.89; sleep, 2.07 to 1.56; general problems, 2.16 to 1.5; practical problems, 3.69 to 2.58; nasal symptoms, 3.57 to 2.50; eye symptoms, 2.92 to 1.83; and emotional aspects, 2.2 to 1.44.

Conclusions: This study provides evidence that QOL can be improved in polysensitized patients treated with SLIT, and that the use of just 1 or 2 allergen extracts seems to be sufficient and effective in terms of improving QOL.

Key words: Allergic rhinitis. Polysensitization. Sublingual immunotherapy. Quality of life.

■ Resumen

Antecedentes: La calidad de vida (CDV) es un factor importante en la rinitis alérgica y se ha evaluado en múltiples estudios que han mostrado su deterioro en pacientes no tratados y su mejora mediante tratamientos eficaces. No obstante, no se dispone de datos sobre la CDV tras inmunoterapia sublingual (ITSL) en pacientes polisensibilizados.

Objetivo: Evaluar el efecto, en la práctica clínica real, de la ITSL sobre la CDV en una población de pacientes polisensibilizados con rinitis alérgica.

Métodos: Se realizó una evaluación prospectiva de 167 pacientes polisensibilizados con rinitis alérgica incluidos consecutivamente. La CDV se midió en todos los casos con el Cuestionario de Calidad de Vida en la Rinoconjuntivitis al inicio y al cabo de 1 año de la ITSL (realizado en aproximadamente el 70% de los casos utilizando extractos de un solo alérgeno proporcionados por el mismo fabricante).

Resultados: Las causas más frecuentes de sensibilización fueron el polen de gramíneas, el polen de parietaria y los ácaros del polvo doméstico. El número medio de sensibilizaciones por paciente fue de 3,65. La ITSL se realizó con 1 extracto en 123 pacientes (73,6%), con 2 extractos en 31 pacientes (18,6%) y con más de 2 extractos en 13 pacientes (7,8%). Los valores medios de todos los ítems de CDV mejoraron significativamente ($p < 0,01$ en todos los casos), y se notificaron las reducciones siguientes: actividades, de 3,96 a 2,89; sueño, de 2,07 a 1,56; problemas generales, de 2,16 a 1,5; problemas prácticos, de 3,69 a 2,58; síntomas nasales, de 3,57 a 2,50; síntomas oculares, de 2,92 a 1,83; y aspectos emocionales, de 2,2 a 1,44.

Conclusiones: En este estudio se proporcionan evidencias de que es posible mejorar la CDV en pacientes polisensibilizados tratados con ITSL, y de que el uso de extractos de solo 1 ó 2 alérgenos parece ser suficiente y eficaz para mejorar la CDV.

Palabras clave: Rinitis alérgica. Polisensibilización. Inmunoterapia sublingual. Calidad de vida.

Introduction

Allergic rhinitis (AR), a very common condition with increasing prevalence in the general population, is the most frequent immunoglobulin (Ig) E-mediated disease [1-3]. It is classically divided into seasonal AR and perennial AR according to the type of allergens involved and the period of symptoms [4]. Seasonal AR is mainly caused by outdoor allergens such as pollen, whereas perennial AR is caused by indoor allergens such as house dust mites, pets, and cockroaches. This classification system was revised by the Allergic Rhinitis and its Impact on Asthma (ARIA) workgroup to cover frequency and duration of symptoms [5]. The new classification defines AR as either intermittent (symptoms for fewer than 4 days a week or fewer than 4 consecutive weeks) or persistent (symptoms for more than 4 days a week or more than 4 consecutive weeks). Additionally, symptoms are graded as mild, moderate, or severe depending on their impact on daily activities and quality of life (QOL). Some comparative studies have found no equivalence between either seasonal and intermittent AR or perennial and persistent AR, hence the proposal that these subtypes do not represent the same status of disease [6-8]. Another important aspect of AR is polysensitization. Although AR symptoms start in early childhood with monosensitization [9], the tendency to become sensitized to multiple allergens soon becomes apparent. A further factor influencing QOL is the frequent association between AR and asthma; indeed AR is the most relevant risk factor for the onset or worsening of asthma [5,10].

Allergen-specific immunotherapy (SIT) has an important role in AR management. Its aim is to reduce allergy symptoms and the need for medication by inducing clinical and immunological tolerance toward the offending allergen [11,12]. Sublingual immunotherapy (SLIT) is a commonly prescribed form of SIT in Europe [11]. Its efficacy has been recognized in consensus documents [5,13] and confirmed by meta-analyses

of patients with AR [14] and asthma [15]. Polysensitization can be a crucial factor when choosing the allergen extract to be used for immunotherapy, and indeed many allergists prefer not to prescribe SIT in polysensitized patients.

Nevertheless, no studies to date have investigated the impact of SLIT on QOL in polysensitized patients. The aim of this study was to evaluate the effect of 1-year SLIT on QOL, measured by a validated questionnaire, in a population of polysensitized patients with AR.

Methods

Study Design

The study was conducted in 16 allergy centers uniformly distributed throughout Italy. It was designed to include representative samples of the general population and to detect new cases. The study was approved by the review boards of all the participating centers and informed consent was obtained from all participants. All the patients were evaluated at baseline (V1) and after 1 year of SLIT (V2).

Patients

A total of 418 patients with AR and/or asthma that visited the participating centers in the study period were prospectively evaluated [16]. A detailed clinical history was taken and a complete physical examination performed. The patients were included in the study on the basis of a diagnosis of AR and/or asthma and documented polysensitization. The diagnosis of intermittent or persistent AR and assessment of severity were made on the basis of type and duration of symptoms combined with a positive skin prick test (SPT) according to validated criteria [5]. Diagnosis and assessment of asthma severity were based on the Global Initiative for Asthma criteria [17].

Skin Tests

SPTs were performed and evaluated as described by the European Academy of Allergy and Clinical Immunology [18]. The panel consisted of house dust mites (*Dermatophagoides farinae* and *Dermatophagoides pteronyssinus*), cat and dog dander, grass mix, Compositae mix, *Parietaria officinalis*, birch, hazel, olive tree, *Alternaria tenuis*, *Cladosporium*, and *Aspergillus* mix (Stallergenes, Milan, Italy).

QOL

QOL assessment was based on the Rhinoconjunctivitis Quality of Life Questionnaire, which consists of 28 items distributed in 7 domains: sleep problems (3 items), general problems (7 items), practical problems (3 items), nasal problems (4 items), eye symptoms (4 items), activities (3 items), and emotions (4 items) [19]. Responses are scored on a 7-point Likert scale, while domains and overall scores are scored on a 0-to-6 scale, with lower scores indicating better QOL. When evaluating the effects of SLIT on QOL, a reduction of at least 1 point after treatment is considered clinically relevant [19].

SLIT

In order to ensure the uniformity of data, only patients who had received allergen extracts from the same manufacturer (Stallergenes, Antony, France) were evaluated. SLIT was administered according to the build-up and maintenance schedules recommended by the manufacturer. The choice of allergen extract was based on the demonstration of a relationship between sensitization and history. In other words, it was attempted in all cases to identify a cause-effect relationship between allergen exposure and symptom occurrence. All SLIT-related adverse events were recorded on diary cards.

Statistical Analysis

Continuous and/or discrete parameters were reported as means (SD), medians (interquartile range), and frequencies. Categorical parameters were reported in contingency tables. The significance of the differences between QOL scores at V1 and V2 was calculated using the *t* test for paired data, and 95% confidence intervals were reported for the mean of the differences. The analysis also considered level of severity, type of sensitization, and type of allergen used at the beginning of SLIT. Statistical significance was set at a *P* value of <.05. Statistical analysis was performed using the BMDP Dynamic statistical package (BMDP Statistical software, Inc., Los Angeles, California, USA).

Results

We evaluated 167 patients (89 males, 78 females; mean (SD) age, 28.2 [12.8] years). The patients' demographic and clinical characteristics are reported in Table 1 and the SPT results are shown in Table 2. The most frequent causes of sensitization were grass pollen, *Parietaria pollen*, and house dust mites. Thirty-eight patients (20.8%) had 2 sensitizations,

Table 1. Demographic Data and Clinical Characteristics of Patients^a

Patients, No.	167
Age, y	
Mean (SD)	29.2 (12.8)
Median (25-75 IQR)	27.6 (19.3-37.8)
Sex	
Male	78 (46.7)
Female	89 (53.3)
Diagnosis	
Rhinitis	89 (53.3)
Asthma	3 (1.8)
Rhinitis and asthma	75 (44.9)
Rhinitis	
Mild intermittent	4 (2.4)
Moderate-severe intermittent	24 (14.3)
Mild persistent	25 (15)
Moderate-severe persistent	111 (66.5)
Asthma	
Intermittent	37 (22.2)
Mild persistent	16 (9.6)
Moderate persistent	21 (12.6)
Severe Persistent	4 (2.4)

Abbreviation: IQR, interquartile range.

^aData are presented as no. (%) of patients unless otherwise indicated.

Table 2. Skin Prick Test (SPT) Results Expressed as Absolute and Relative Values

SPT	No.	%
<i>Dermatophagoides</i>	72	43.11
5-grass mix	133	79.64
Wall pellitory	79	47.31
Olive	53	31.74
Tree mix	65	38.92
Cypress	18	10.78
Compositae	51	30.54
Ragweed	25	14.97
<i>Alternaria</i>	21	12.57
Cat dander	40	23.95
Dog dander	31	18.56
Other	21	12.57

Table 3. Allergen Extracts Used for Sublingual Immunotherapy

Allergen Extract	No. of Treatments	%
House dust mites	68	40.72
Grass pollen	53	31.74
Parietaria pollen	33	19.76
Olive pollen	19	11.38
Betulaceae pollen	11	6.59
Compositae pollen	6	3.59
Cypress pollen	6	3.59
<i>Alternaria</i>	6	3.59

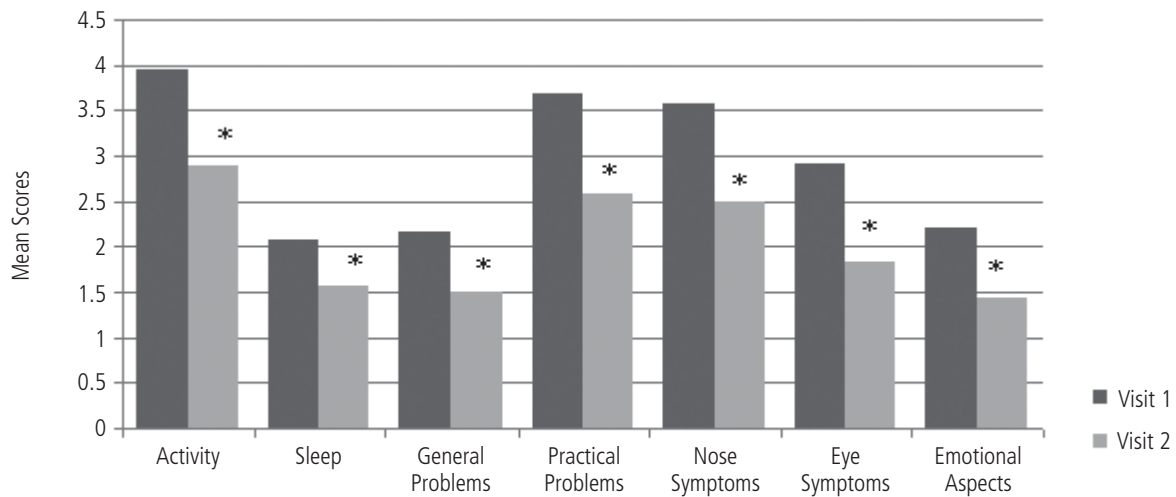


Figure. Changes in health-related quality of life scores before and after sublingual immunotherapy.

53 (29%) had 3 sensitizations, 31 (16.9%) had 4 sensitizations, 20 (10.9%) had 5 sensitizations, 12 (6.6%) had 6 sensitizations, and 11 (6%) had more than 6 sensitizations. The mean number of sensitizations per patient was 3.65.

SLIT was performed in 123 patients (73.6%) with a single allergen extract, in 31 patients (18.6%) with 2 extracts, and in 13 patients (7.8%) with more than 2 extracts. House dust mites and grass pollen were the most common extracts (Table 3).

Analysis of severity, type of sensitization, and type of allergen did not reveal any significant differences.

In the group of patients treated with a single allergen extract ($n=123$), there were local reactions in the mouth in 41 patients (33.3%), gastrointestinal reactions in 16 patients (13%), and mild respiratory reactions in 2 patients (1.6%). In the group treated with 2 or more extracts ($n=44$), there were 16 local reactions (36.4%), 8 gastrointestinal reactions (18.2%), and 1 mild respiratory reaction (2.3%). The differences between the 2 groups were not significant. Three patients with gastrointestinal reactions dropped out because of the adverse effects. No severe systemic reactions were reported.

The mean QOL scores as assessed by the Rhinoconjunctivitis Quality of Life Questionnaire decreased significantly from 3.96 at V1 to 2.89 at V2 ($P<.01$). The Figure shows the mean values of the individual items assessed at V1 and V2. Importantly, these were all significantly reduced.

Discussion

AR is characterized by an inflammatory response that causes the onset of symptoms. Nasal obstruction is the most prominent manifestation of allergic inflammation and has the greatest impact on QOL [8,9]. Polysensitization, which is frequently diagnosed during allergy testing, is an

immunological phenomenon that is both clinically significant and epidemiologically relevant, as reported in recent surveys [20-22]. The increasing number of sensitizations seems to characterize the natural history of allergic patients and may represent a typical development pattern of IgE-mediated hypersensitivity. Polysensitization may be associated with a different clinical picture than that seen in monosensitized patients, particularly in terms of poorer quality of life [16]. The clinical relevance of polysensitization is confirmed by the high mean number of sensitizations found in our cohort. Another important aspect regarding clinical relevance is the possible influence of physician attitude on the management of allergic disease, particularly with regards to the prescription of immunotherapy. Indeed, many physicians prefer not to prescribe SIT to patients with multiple sensitizations. Allergists, for their part, tend to choose just 1 or sometimes 2 extracts when administering SLIT to polysensitized patients.

QOL evaluation is an important tool in the study of AR in both clinical and therapeutical trials. With this study, we aimed to explore, for the first time, the impact of SLIT on QOL in polysensitized patients in real-life clinical practice. We found a number of interesting outcomes. Firstly, there was a considerable number of sensitizations per patient in our cohort (3.65). Confirming the trend observed among allergists in Europe to limit the number of extracts used in immunotherapy [23], we found that a single extract was chosen in almost three quarters of patients and that few allergens were used in the rest. This approach would appear to be correct as it led to a significant improvement in QOL. Secondly, all the QOL aspects investigated were significantly affected by SLIT. This is a meaningful outcome that confirms the high effectiveness of immunotherapy. The effect of SLIT on QOL was clinically relevant for activities, practical problems, and nasal and ocular symptoms. This is interesting as these are the aspects that have

been found to be affected most in AR [24]. Indeed, patients with AR frequently describe nose and eye symptoms as troublesome and annoying and report that they affect daily life activities and cause practical problems. The results of our study, thus, obtained from a large number of patients, confirm that SLIT with 1 or 2 allergen extracts can significantly improve the QOL of polysensitized patients.

Another aspect to be considered is the safety and tolerability of SLIT. Treatment-related adverse reactions can understandably have a negative effect on patients' perception of QOL. The only available study on the safety of SLIT according to the number of extracts used was conducted in children; in that study, adverse events (mostly mild and self-resolving), were reported in 42% of patients treated with a single allergen and in 40% of those treated with multiple allergens, this difference being clearly nonsignificant [25]. The safety in the present study was quite good, with comparable rates of local reactions in the mouth and gastrointestinal reactions in patients treated with a single extract or with 2 or more extracts; only 3 patients (1.8%) withdrew because of repeated gastrointestinal reactions.

These observations support the notion that polysensitization is a relevant aspect in allergic patients and must be carefully evaluated, particularly if immunotherapy is being considered. In any case, polysensitization should not be a counterindication for immunotherapy. In our cohort, the choice to limit SLIT to 1 or 2 allergen extracts proved to be sufficient and effective in terms of improving QOL.

Our study has certain limitations. The selection of patients was conditioned by including only those who received allergen extracts manufactured by the same company, the choice of extract was based on subjective criteria, and there was no control group.

In conclusion, this study provides evidence that SLIT conducted using 1 or 2 allergen extracts can improve the QOL of polysensitized patients. Further studies are needed to confirm these findings.

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