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SUPPORTING INFORMATION

Additional supporting information may be found online in the Supporting Information section.

DOI: 10.1111/all.14215

Impact of immunotherapy on quality of life in patients with house dust mite allergic rhinitis

To the Editor,

Allergic rhinitis (AR) is the most frequent noninfectious rhinitis and the most common allergic disease. In addition, its prevalence is increasing worldwide.[1] The most common allergens that trigger the disease are grass pollen and house dust mite (HDM).

Quality of life (QOL) is defined as a large ensemble of physical and psychological characteristics which assess problems that concern lifestyle. The impact of AR in QOL has been observed for long time, particularly in patients with moderate to severe and persistent symptoms.[2,3] Disease-specific QOL questionnaires have shown good levels of discrimination validity in AR[4] and are instruments of interest to clinicians.

We performed a prospective study with patients referred to the Department of Otolaryngology of the Hospital Universitario Central de Asturias between 2012 and 2017, to evaluate the effect of AIT on patients' QOL. To be included, patients should meet the following criteria: (a) positive skin test to *Dermatophagoides pteronyssinus*, (b) negative skin test to other airborne allergens, (c) no previous treatment with AIT and (d) moderate-severe and persistent AR according to ARIA criteria.[2] Those patients who did not complete the AIT treatment properly were excluded from the study. All patients provided informed consent to participate in the study, previously approved by the Ethics Committee of our hospital (project number 222/19).

After diagnosis of AR, patients received recommendations about allergen avoidance and started medical treatment with nasal corticosteroids (mometasone furoate/ fluticasone furoate daily) and oral antihistamines (bilastine 20 mg once a day). In those patients poorly controlled with symptomatic treatment after 6 months, AIT was offered. Patients were informed in detail about the options, and sublingual (SLIT) or subcutaneous (SCIT) immunotherapy was chosen according to their preferences. Symptomatic treatment was continued only the first six months of AIT.

We employed SLITone$^{ULTRA®}$ and Pangramin$^{PLUS®}$ (ALK-Abelló SA). SLITone$^{ULTRA®}$ is presented in Standardized Reactivity Units

TABLE 1 Differences in quality of life questionnaires before and after treatment

Questionnaire	Symptomatic treatment			Allergen immunotherapy			Comparison
MiniRQLQ	Before	After	Difference	Before	After	Difference	Differences t test
Dimension	Mean ± SD	Mean ± SD	Mean ± SD	Mean ± SD	Mean ± SD	Mean ± SD	*P*-value
Activities	7.10 ± 4.04	6.94 ± 4.46	−0.16 ± 4.13	7.50 ± 4.57	4.13 ± 3.44	−3.37 ± 4.42	<.001
Practical problems	6.69 ± 3.43	5.98 ± 3.20	−0.71 ± 3.54	7.88 ± 3.28	4.13 ± 2.91	−3.75 ± 3.55	<.001
Nose symptoms	11.16 ± 4.42	10.24 ± 4.26	−0.92 ± 4.83	11.42 ± 4.42	6.15 ± 4.00	−5.27 ± 4.93	<.001
Eye symptoms	6.68 ± 6.21	6.65 ± 6.03	−0.24 ± 5.35	7.00 ± 5.34	4.40 ± 4.43	−2.60 ± 5.74	.033
Other symptoms	7.18 ± 4.55	6.96 ± 5.27	−0.22 ± 5.08	6.60 ± 4.84	4.35 ± 4.31	−2.25 ± 4.52	.034
Total MiniRQLQ	39.00 ± 18.44	36.76 ± 19.59	−2.24 ± 18.59	40.40 ± 17.55	23.17 ± 16.79	−17.23 ± 18.21	<.001
Questionnaire	**Symptomatic treatment**			**Allergen immunotherapy**			**Comparison**
ESPRINT-15	Before	After	Difference	Before	After	Difference	Differences t test
Dimension	Mean ± SD	Mean ± SD	Mean ± SD	Mean ± SD	Mean ± SD	Mean ± SD	*P*-value
Symptoms	15.51 ± 6.55	13.96 ± 6.36	−1.55 ± 5.85	15.08 ± 6.28	8.83 ± 5.97	−6.25 ± 6.56	<.001
Daily activities	6.59 ± 4.78	6.18 ± 4.64	−0.41 ± 4.54	6.90 ± 4.66	3.90 ± 4.10	−3.00 ± 4.77	.006
Sleep	7.35 ± 5.62	7.04 ± 5.60	−0.31 ± 5.09	7.60 ± 5.12	3.90 ± 4.00	−3.69 ± 5.07	.001
Psychological well-being	7.24 ± 5.35	6.37 ± 5.33	−0.86 ± 5.05	6.77 ± 5.19	3.87 ± 4.15	−2.90 ± 5.21	.046
Total ESPRINT-15	36.69 ± 18.01	33.55 ± 19.72	−3.14 ± 16.36	36.40 ± 18.31	20.50 ± 16.51	−15.90 ± 18.19	<.001

(SRU) and administered as drops in single-dose containers of 0.2 mL. The active extract was *Dermatophagoides pteronyssinus* 100% (15 μg/mL Derp1 and 10 μg/mL Derp2 in 300 SRU). Pangramin$^{PLUS®}$ is an injectable solution standardized in specific treatment units (STU). We administered an extract of *Dermatophagoides pteronyssinus* 100% (2 μg/mL Derp1 and 2 μg/mL Derp2 in 1000 STU). Allergen extract concentrations were reported by the laboratory ALK-Abelló. The treatment schedules for SLIT and SCIT were as follows:

- SLIT (SLITone$^{ULTRA®}$)
  - Initiation: 50 SRU/d for five consecutive days followed by 150 SRU/d for five additional consecutive days.
  - Maintenance: 300 SRU/d until 3-year treatment is completed.
- SCIT (Pangramin$^{PLUS®}$)
  - 100 STU/ml for 3 weeks
    - 1st week: 0.2 mL.
    - 2nd week: 0.4 mL.
    - 3rd week: 0.8 mL.
  - 1000 STU/ml for 4 weeks
    - 1st week: 0.1 mL.
    - 2nd week: 0.2 mL.
    - 3rd week: 0.4 mL.
    - 4th week: 0.8 mL.
  - 1000 STU/mL: 0.8 mL two weeks after the last dose, and afterwards, every 4 weeks until 3-year treatment is completed.

Patients who declined AIT treatment formed the control group. In these patients, symptomatic treatment with intranasal corticosteroids and oral antihistamines was continued.

To assess patients' QOL, we used two validated questionnaires: MiniRQLQ and ESPRINT-15. MiniRQLQ is a shorter version of the Rhinoconjunctivitis Quality of Life Questionnaire (RQLQ),[5] one of the instruments most frequently used to measure health-related QOL in AR, and validated for use in Spain in 2004.[6] The questionnaire consists of 14 items grouped in five dimensions: activities, practical problems, nose symptoms, eye symptoms and other

TABLE 2 Minimal clinical important difference in AIT group

	SLIT		SCIT	
	MiniRQLQ	ESPRINT-15	MiniRQLQ	ESPRINT-15
Patients with MCI reduction[a]	20	20	11	11
Patients with MCI increase[a]	1	1	2	3
No clinical important difference	11	11	7	6
	32		20	

[a]The cut-off point was established at ±0.7 in MiniRQLQ and at ±0.9 in ESPRINT-15.

symptoms. ESPRINT-15 is a QOL questionnaire developed out of a longer 28 item version which was developed in Spain by Valero et al.[7] The shorter version includes 15 items grouped in four dimensions: symptoms, daily activities, sleep and psychological well-being.

MiniRQLQ and ESPRINT-15 questionnaires were provided and completed between October and January the first time (Table S1). Both questionnaires were provided and completed again 3 years after the beginning of the treatment (AIT or symptomatic), in the same time of year (October-January).

A total of 103 patients were included in the study: 52 formed the AIT group (32 patients received SLIT and 20 patients SCIT) and 51 the control group. Both groups showed a significant improvement in QOL after 3-year treatment. However, the AIT group had statistically significant greater improvement in their scores in comparison with the control group. These differences were observed in the global scores and in each dimension separately as well (Table 1).

Based on previous studies, we considered a MCID value of 0.7 for MiniRQLQ[5] and 0.9 for ESPRINT-15.[8] In our cohort, patients treated with AIT showed a mean difference in MiniRQLQ of −1.23 (range −4.21 to 1.57) and −1.14 (range −4.43 to 1.86) in ESPRINT-15 (Table 2).

Inside the AIT group, patients who opted for SCIT or for SLIT and who finished the 3-year course of AIT reported very similar changes in both QOL questionnaires (MiniRQLQ P = .910, ESPRINT-15 P = .529), but the study was underpowered to detect any differences between both active groups. The subgroup of patients with better QOL before the treatment (those ones with total scores below the first decile) did not show significant improvement in MiniRQLQ questionnaire (P = .114), while their differences in ESPRINT-15 did reach statistical significance (P = .035). However, patients with worse QOL before the treatment (total scores in the highest quartile) showed a significant greater reduction in their scores in relation to the whole series in MiniRQLQ (−2.5 vs −1.23, P < .001) and ESPRINT-15 scores (−2.5 vs −1.14, P < .001).

Based on our findings, AIT provides significant improvement in health-related quality of life of patients with AR and is better than symptomatic treatment in those patients who complete a 3-year AIT course. Subcutaneous immunotherapy (SCIT) and sublingual immunotherapy (SLIT) have similar results in these terms, although further studies, with an adequate power calculation to show differences between both AIT modalities, are needed to confirm the comparable effect of both formulations. In addition, the use of QOL questionnaires may help the clinician to take better decisions about treatment, given that patients with worse QOL are more likely to benefit from AIT treatment.

CONFLICT OF INTEREST

The authors declare no conflict of interest.

AUTHOR CONTRIBUTIONS

Alvarez-Marcos C designed and directed the study. Rodrigo JP and Llorente JL participated in the clinical phase, primarily in patients' follow-up. Pedregal-Mallo D and Pacheco E collected and processed the data, performed statistical analysis and wrote the manuscript. Alvarez-Marcos, Rodrigo and Llorente reviewed the manuscript and provided critical feedback. All authors agree with the final version.

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