Subcutaneous Immunotherapy Improves the Symptomatology of Allergic Rhinitis

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Abstract

Introduction The relevance of allergic rhinitis is unquestionable. This condition affects people's quality of life and its incidence has increased over the last years.

Objective Thus, this study aims to analyze the effectiveness of subcutaneous injectable immunotherapy in cases of nasal itching, sneeze, rhinorrhea and nasal congestion in allergic rhinitis patients.

Methods In the present study, the same researcher analyzed the records of 281 patients. Furthermore, the researchers identified allergens through puncture cutaneous tests using standardized extracts containing acari, fungi, pet hair, flower pollen, and feathers. Then, the patients underwent treatment with subcutaneous specific immunotherapy, using four vaccine vials for desensitization, associated with environmental hygiene. The authors analyzed conditions of nasal itching, sneeze, rhinorrhea, and nasal congestion throughout the treatment, and assigned them with a score ranging from zero (0), meaning absence of these symptoms to three (3), for severe cases. The symptoms were statistically compared in the beginning, during, and after treatment.

Results In this study, authors analyzed the cases distribution according to age and the evolution of symptomatology according to the scores, comparing all phases of treatment. The average score for the entire population studied was 2.08 before treatment and 0.44 at the end. These results represent an overall improvement of ~79% in symptomatology of allergic rhinitis in the studied population.

Conclusion The subcutaneous immunotherapy as treatment of allergic rhinitis led to a reduction in all symptoms studied, improving the quality of life of patients, proving itself as an important therapeutic tool for these pathological conditions.

Keywords
- allergy
- rhinitis
- hypersensitivity
- allergen immunotherapy
- injections
- subcutaneous
- symptoms

Introduction

Allergic rhinitis is a type of disease with high worldwide incidence.[1–3] The International Study of Asthma and Allergies in Childhood (ISAAC) released studies showing prevalence rates of allergic rhinitis among Brazilian children and adolescents of 25.7% and 29.6%), respectively.[4] Furthermore, the

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Allergic Rhinitis and its Impact on Asthma (ARIA) project classifies allergic rhinitis as a risk factor for the development of asthma, alerting to its impact on quality of life and high social costs.[5–7] The ARIA project also proposed a new classification to allergic rhinitis severity, replacing the terms perennial and seasonal rhinitis with mild, moderate or severe intensity, persistent or intermittent. In the United States, it is estimated that 30 million people suffer from allergic rhinitis, causing high absenteeism, which corresponds to more than 3.8 billion dollars per year in financial costs.[3,8]

In addition, there is evidence that allergic rhinitis is frequently undertreated, mainly in its moderate and severe/intense persistent forms.[6,9] The management of patients with allergic rhinitis involves proper pharmacological therapies, including allergen immunotherapy.[8,10,11] Subcutaneous injection with allergen-specific immunotherapy (SIT) is indicated for patients with refractory symptoms, being considered the only treatment capable of modifying the course of allergic rhinitis and asthmas. However, less than 5% of allergic patients have undergone immunotherapy, mainly due to the long term for treatment and allergy side effects, which demonstrates the complexity of this therapy. Moreover, different authors show that the actual beneficial effects and security of immunotherapy remain unclear.[2,11–15] One option for such cases could be the use of interleukin 5 (IL-5). This cytokine relates to the suppression of the allergens' synthesis, demonstrating the possible clinical efficiency of immunotherapy.[14,16] Thus, the use of this therapy in respiratory allergies can be an attempt at inactivation of allergen-specific Th1 and Th2 cells, decreasing the production of IgE in B lymphocytes, modulating the immune response.[10]

Objective

Therefore, the aim of this retrospective study is to analyze the effectiveness of an injectable immunotherapy in cases of nasal itching, sneeze, rhinorrhea, and nasal congestion in allergic rhinitis patients.

Materials and Methods

In the current study, the authors analyzed 281 patient records, independent of seasons, at the beginning and end of treatment, attended to over 11 years, of both genders, aged 3 to 69 years old, with a clinical diagnosis of allergic rhinitis and bronchial asthma associated, without other apparent allergic etiologies.

The researchers diagnosed patients with positive puncture cutaneous tests, using standardized extracts containing acari, fungi, pet hair, flower pollen, and feathers. After diagnosis, the patients received specific desensitizing vaccines of Alergofar® (purified allergens, Rio de Janeiro, RJ, Brazil) at a private practice in the city of Jundiaí, São Paulo State, Brazil. The study was approved by Ethics Committee of the Faculty of Medicine of Jundiaí (process number 127/2007–Jundiaí, São Paulo, Brazil). The identity of all patients was preserved.

The allergic rhinitis symptoms analyzed in this study were: itching, sneezing, watery rhinorrhea, and nasal congestion. The same researcher and examiner, in the same office, quantified these conditions according to signs and symptoms proposed by some authors, and modified for this report throughout the entire study period. The scoring was as follows:

Zero (0) = absence of symptom; 1 = mild symptoms: occasional itching and sneezing, nasal rhinorrhea, and/or secretion sensation in the throat and/or occasional nasal congestion; 2 = moderate symptoms: itching and sneezing several times per day, rhinorrhea several times per day and/or frequent throat clearing, and nasal congestion with buccal breathing; 3 = severe/intense symptoms: itching and sneezing interfering with daily activities, constant nasal rhinorrhea, and coughing and/or speech alteration, buccal breathing with interference of sleep, and damage in sense of odors due to nasal congestion.

The researchers obtained five mean scores per symptom for each patient: at the beginning of treatment, and at the end of the first, second, third, and fourth vaccine dose. Any subsequent booster treatments were disregarded. The researcher performed skin prick tests in the forearm of all patients. Equipment for orotracheal intubation and ventilation were always available.

In this analysis, the authors observed patients' reactions to house dust mites (*Dermatophagoides farinae, Dermatophagoides pteronyssinus, Blomia tropicalis, Aleuroglyphus ovatus, Suidasia pontificiae*, and *Tyrophagus putrescentiae*), fungus/spores, pet hair, flower pollen, wool, and feathers. The histamine was used as a positive control and the response to saline solution (0.9%) as a negative control. Any others forms were defined as positive responses. The responses in relation to histamine were also classified as mild, moderate, and severe/intense, similar to those described in literature.[17]

Patients were included according to the following inclusion criteria: 1) age over 3 years; 2) clinical symptoms compatible with those for allergic rhinitis/asthma; 3) disease that had not been responsive to conventional treatments, including environmental control; 4) positive skin tests; 5) possibility of having received specific desensitization treatment; 6) vaccines received of the same origin; 7) underwent only subcutaneous treatment; 8) use of four vials of allergen extracts re-suspended in aluminum hydroxide at increasing concentrations. The study's exclusion criteria were: 1) younger than 3 years old; 2) patients with uncertain diagnosis (with mildly allergic rhinitis); 3) good response to conventional treatments; 4) discontinued treatment; 5) patients who did not attend the clinical visits; and 6) patients hypersensitive to the vaccine components; 7) rhinitis due to other causes. The sample can be considered representative of the studied population, as it takes into account similar socio-economic levels of good standing, good housing conditions, access to health services, and appropriate nutrition. All treated patients received detailed written recommendations for environmental control and hygiene, food for a dye-free diet and an acaricidal solution containing benzyl benzoate to control acari, all of them standardized to avoid influence over the outcome. During treatment, patients were not allowed to use drugs, such as: steroidal anti-inflammatory, acetylsalicylic acid,

antihistamines, oral decongestants, or corticosteroids, except in cases of acute episodes or when prescribed and monitored by the main researcher. All patients received instructions to report the use of any medication during therapy and answered questions concerning this in the periodical reassessment visits.

The applied vaccine was always the Alergofar® (Rio de Janeiro, Brazil). The total period of treatment was 14 months. The first vial (doses) contained a weak concentration of allergens (0.008 skin reactivity units [SRU]) administered at intervals of 7 days (8 increasing doses of 0.1 to 0.8ml). The second vial contained a medium concentration of allergens (0.08 SRU) applied at intervals of 10 days (8 increasing doses of 0.1 to 0.8ml). The third vial contained a strong concentration of allergens (0.8 SRU) and was administered at intervals of 14 days (8 increasing doses of 0.1 to 1.0ml). The fourth vial contained an extra-strong concentration (8 SRU) and was administered at intervals of 21 days divided into 9 doses (0.1, 0.2, 0.3, 0.5, 0.6, 0.8, 1.0, 1.0, and 1.0ml). The patients were consistently monitored for 15–30 minutes after each administration.[18] They underwent reassessment after the end of each vaccine vial. In case of an acute episode of rhinitis exacerbation, the researchers administered oral antihistamines for a few days. According to literature, this common approach does not alter the results or the evaluation of treatment efficacy. Moreover, for control purposes, the researchers always evaluated the patients after administering this drug.[19]

Statistical Analysis

The authors compared results statistically during the entire treatment and reported the mean, median, and values range. They applied the Wilcoxon test to evaluate the difference between the symptom scores (nasal itching, sneezing, rhinorrhea, and nasal congestion) before, during and after vaccine therapy. A level of significance of 5% was adopted. Data were analyzed using the SAS 9.1 software (USA).

Results

The population studied was of 281 patients, including 167 (59.4%) males and 114 (40.6%) females, totaling 8,992 applications performed. There was no significant difference in relation to gender.

Ages ranged from 3 to 69 years old, with a mean in relation to "n" of 17.4 ± 11.7 years. Approximately 50% of the sample was younger and over 50% was older than 14.4 years (median), as seen in ►**Table 1**.

In the results, it is also possible to observe the incidence of each symptom of allergic rhinitis at four levels of intensity in the population studied ($n = 281$) before treatment with specific desensitizing vaccines.

►**Fig. 1** shows mean symptom scores before treatment. The overall mean score corresponds to the sum of all individual symptom scores divided by the number of patients studied ($n = 281$), and then divided by four, which represents the number of symptoms evaluated during each stage of desensitization treatment.

Table 1 Median distribution of the patients by age

Age groups (years)	Patients "n"	%
3–6	29	10.3
6–12	91	32.4
12–18	64	22.8
18–24	40	14.2
24–30	15	5.4
30–42	31	11.0
42–54	7	2.5
54–70	4	1.4
Total	**281**	**100**

The mean scores at the end of vaccine therapy are shown in ►**Figs. 2**, **3**, **4**, and **5**, respectively.

►**Table 2** summarizes the mean score of each symptom of allergic rhinitis before treatment and at the end of immunotherapy.

The authors observed significant differences among the four symptoms studied between the beginning and the end of immunotherapy ($p < 0.05$; Wilcoxon test). With respect to itching, there were significant differences ($p < 0.05$) found in all stages of treatment, except between the second and third vial ($p = 0.225$). The mean initial score (1.89 ± 1.20) was significantly higher than the final score (0.35 ± 0.69; $p < 0.001$).

There were also significant differences ($p < 0.05$) pertaining to sneezing in all stages of treatment, except between the second and third vial ($p = 0.196$). The mean initial score (2.27 ± 0.97) was significantly higher than the final score (0.51 ± 0.78 $p < 0.001$). Rhinorrhea scores also differed significantly ($p < 0.05$) between all stages of treatment, except between the first and second vial ($p = 0.347$) and between the second and third vial ($p = 0.2154$), but the mean initial of score (1.84 ± 1.15) was significantly higher than the final score (0.37 ± 0.68, $p < 0.001$).

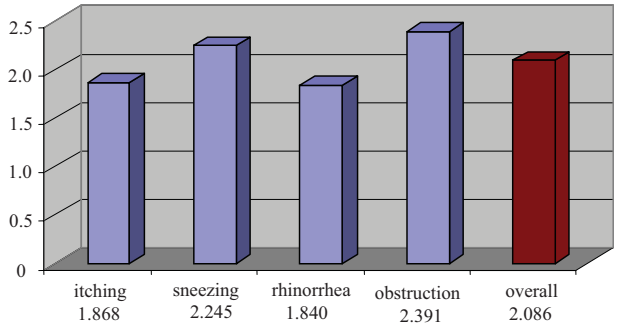

Fig. 1 Mean score in relation to symptom in allergic rhinitis; at the beginning of immunotherapy ($n = 281$). 0 = absence of symptom; 1 = mild symptom; 2 = moderate symptom; 3 = intense/severe symptom.

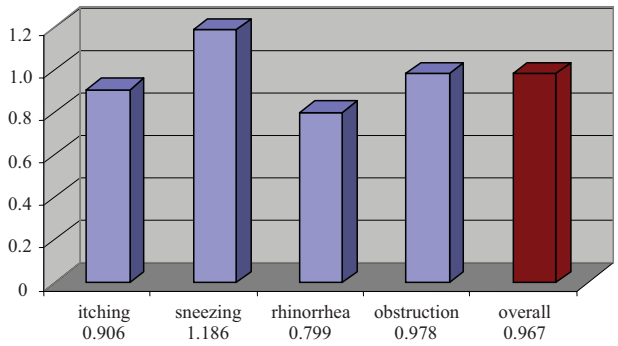

Fig. 2 Mean score of allergic rhinitis at the end of the first vial of vaccine therapy ($n = 281$). 0 = absence of symptom; 1 = mild symptom; 2 = moderate symptom; 3 = intense/severe symptom.

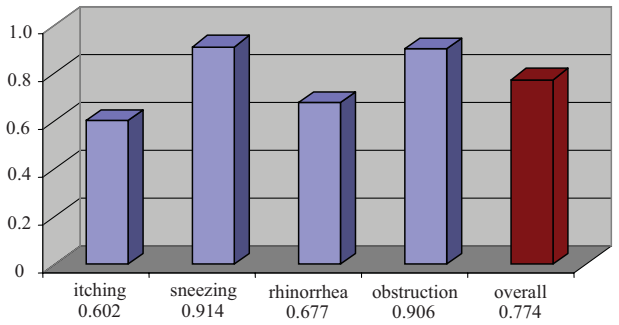

Fig. 4 Mean score of allergic rhinitis at the end of the third vial of vaccine therapy ($n = 281$). 0 = absence of symptom; 1 = mild symptom; 2 = moderate symptom; 3 = intense/severe symptom.

The scores obtained for nasal congestion also differed significantly ($p < 0.05$) in all stages, except between the first and second vial ($p = 0.658$) and between the second and third vial ($p = 0.327$). The mean initial score (2.41 ± 0.97) was significantly higher than the final score (0.54 ± 0.85; $p < 0.001$).

The comparison of total score obtained in combination with the four symptoms, showed significant differences ($p < 0.05$) in all stages of treatment, with the mean initial score (8.41 ± 2.63), being higher than the final score (1.75 ± 2.03; $p < 0.001$).

Discussion

In the present study, the researchers did not observe significant differences in relation to gender. The mean age of the patients was 17.4 ± 11.7 years (range of 3–69 years), with ~50% of the sample younger and over 50% older than 14.4 years old (median). The majority of patients were children and adolescents. According to literature, the immunotherapy for allergic rhino-conjunctivitis and allergic asthma is more effective in children and young adults than in older adults.[10]

The researchers used standardized diagnostic and therapeutic procedures for all patients and analyzed the records, ensuring the study's confidentiality and criteria. Skin tests are recognized as effective and precise tools for the etiological diagnosis of allergic rhinitis.[5,10,14–17] Confirming this, a study that included 117 patients with persistent rhinitis demonstrated positive reactions to *Dermatophagoides farinae* (78%), *Dermatophagoides pteronyssinus* (75%), and *Blomia tropicalis* (77%).[20] These tests must be interpreted 15 to 20 minutes after puncture, in an interval that should not be exceeded since skin reactions tend to fade over time.[17] Anergic patients, or those under the effect of some medications, such as systemic decongestants, cold medicines, and antihistamines, may show negative responses to all allergens tested, including histamine. Systemic or topical corticosteroids do not alter the result of these skin tests.

In addition, in applying these tests, the use of physiological saline is recognized as a negative control and must be compared with all the allergens tested.[17] Lastly, desensitization treatment has been and should always be indicated for patients with symptoms refractory to conventional treatments and with the combination of environmental hygiene to reduce exposure to the allergens.[2] In the present study, an acaricidal solution containing benzyl benzoate was prescribed for environmental hygiene, to reduce the population of mites according to literature.

As for desensitizing vaccines, they do not interact with systemic and topical antihistamines, disodium cromoglycate, or corticosteroids because they are not conventional drugs, but extracts of allergens. Furthermore, there are no

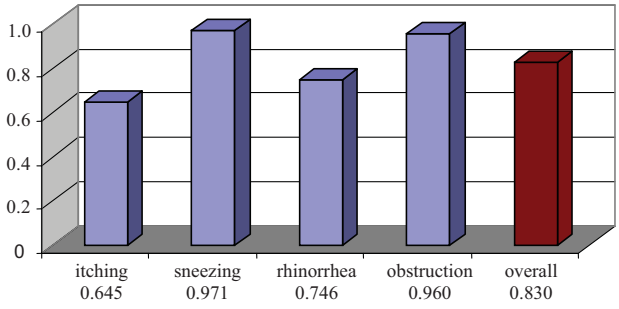

Fig. 3 Mean score of allergic rhinitis at the end of the second vial of vaccine therapy ($n = 281$). 0 = absence of symptom; 1 = mild symptom; 2 = moderate symptom; 3= intense/severe symptom.

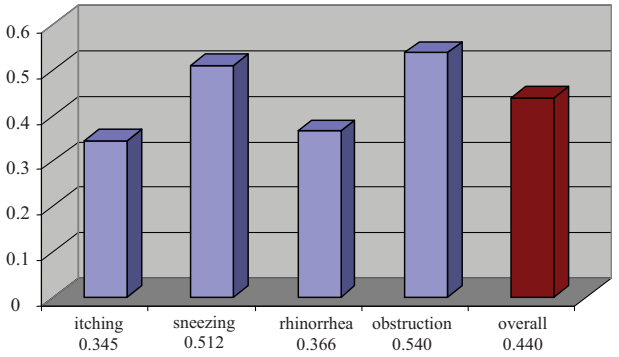

Fig. 5 Mean score of allergic rhinitis at the end of the fourth and last vial of vaccine therapy ($n = 281$). 0 = absence of symptom; 1 = mild symptom; 2 = moderate symptom; 3 = intense symptom.

Table 2 Mean score of allergic rhinitis at the end of vaccine therapy ($n = 281$). 0 = absence of symptom; 1 = mild symptom; 2 = moderate symptom; 3 = intense/severe symptom

Symptom	Itching	Sneezing	Rhinorrhea	Nasal congestion
Mean scores (before treatment)	1.86*	2.24*	1.84*	2.39*
Mean scores (end of treatment)	0.34*	0.51*	0.36*	0.54*

Mean.
*Significantly different ($p < 0.05$).

restrictions to subsequent complementary surgeries, such as anatomical deformities correction of nasal septum and/or hypertrophy of the nasal conches.[10,14,15]

In general, this allergen immunotherapy consists of the treatment of allergic disease through the administration of gradually increasing doses of allergen. Currently, this is considered a more efficient form of immune tolerance induction, compared to that described in 1911.[21] This study reports vaccine concentrations as SRU (Standard Reactivity Unit), a standard unit considered ideal for the purpose. The first vial of vaccine contained a weak concentration of allergens (0.008 SRU), the second presented a medium concentration (0.08 SRU), the third presented an elevated concentration (0.8 SRU), and the fourth presented a very elevated concentration (8 SRU). The researchers recorded alterations in symptoms at the end of each vaccine vial, excluding sporadic doses.[22] The equivalence of SRU/milliliter, microgram/milliliter (µg/ml), and International Units (IU), allow for the comparison with other studies, similar to: 1) mild concentration: contains 0.008 SRU = 0.00625 µg = 0.01 IU; 2) moderate: 0.08 SRU = 0.0625 µg = 0.1 IU; 3) Strong: 0.8 SRU = 0.625 µg = 1 IU; 4) very elevated: 8 SRU = 6.25 µg = 10 IU. According to international standards, the minimum concentration at the end of treatment must be 4 IU/ml, equivalent to 2.5 µg/ml. In the present study, researchers used 2.5 times this concentration, plus the minimum quantity recommended at the end of treatment.

This treatment should be applied subcutaneously; intradermal or intramuscular applications are inadequate and can reduce the efficacy of desensitization treatment. In this respect, a study proposed the injection of allergens in minor doses into the lymph nodes with a short-term treatment.[13] These factors are important in subcutaneous immunotherapy (SCIT),[23] as well as the quality of the allergen extract[24] and time of action. However, the duration of allergen effects is mainly related to individual characteristics, similar to those described in literature, which show rates ranging from 0–50%.[25]

Nonetheless, most studies consider this allergy therapy safe, despite some reports of a potential risk of anaphylaxis,[12] episodes of asthma, urticaria, angioedema,[13] and erythema multiforme.[26] A prospective, multicenter, placebo-controlled trial was conducted in patients submitted to depigmented allergen extract. The patients received four injections of increasing doses at weekly intervals followed by monthly addition dosage, totaling 5,923 doses. In this case, five patients presented local reactions and 27 presented systemic reactions.[27] Some researchers also suggest reducing the dose in cases of local or systemic reaction[18] and excluding asthmatic patients, since they are particularly vulnerable to adverse reactions.[19] In the present study, there was no reaction observed in samples.

The present study, however, did not exclude asthmatic patients. In fact, it included 63 patients with this condition. The authors did exclude one patient because he presented bronchospasm after each dose applied, even at higher dilutions. The responsible researcher and an experienced nurse applied the injections and, according to literature, consistently had intubation and ventilation equipment available.[19] In the present study, the patients were controlled and monitored for 15 to 30 minute after each dose administration to detect immediate adverse reactions. No systemic reactions

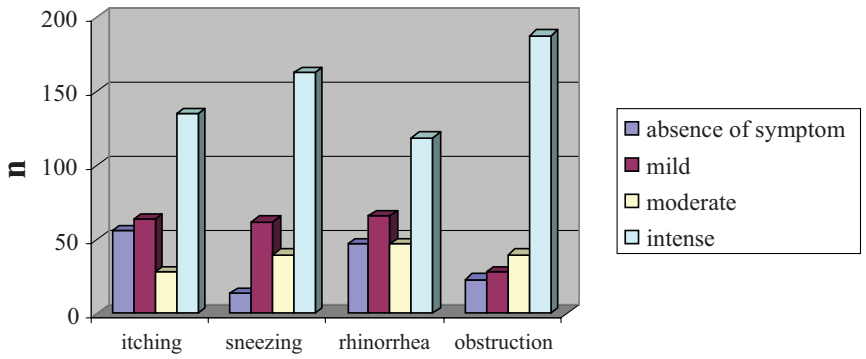

Fig. 6 Incidence of each symptom of allergic rhinitis at four levels of intensity in the population studied ($n = 281$) before treatment with specific desensitizing vaccines.

occurred after 8,992 applications; only some mild local reactions were observed but did not require interventions, which indicate eminent tolerability and assurance of treatment. Differently, others studies show the occurrence of reactions after treatment, as well as the need for frequent drug intervention in 0.13% of cases.[2]

In the present results (►**Fig. 6**), most of the patients studied had severe symptoms, which were mainly sneezing and nasal congestion, followed by itching and rhinorrhea (►**Fig. 1**). After the first dose, nasal congestion was the symptom with the greatest reduction (►**Fig. 2**). Followed by rhinorrhea and nasal congestion in the second dose (►**Fig. 3**), whereas after the third dose, the authors observed improvement of all symptoms (►**Fig. 4**). Final data on the improvement of symptoms were demonstrated after the last vaccine dose (►**Fig. 5**). These findings indicate two important qualitative moments in symptoms improvement during this immunotherapy: one after the first dose and the other after the fourth.

Similarly, other studies have shown improvement of symptoms after this treatment.[2,7] Immunotherapy has also been used to treat different cases, leading to reduced symptoms and in the need for medications, aside from a substantial improvement in quality of life. It is indicated to patients that cannot avoid exposure to allergens and in situations where pharmacologic therapy has not rendered positive results. Specific immunotherapy to treat allergic rhinitis in elderly patients was efficient and had no collateral effects. In addition to the clinical benefit, there was also improvement in the cutaneous test.[2,19,22,28–31]

Moreover, with respect to the controversy about the season in which the study is initiated or conducted, this cannot be considered a bias factor in the evaluation of symptoms, because all the patients included in the present report were followed in a continuously during treatment, refuting, for example, the seasoned report of 120 patients concretely allergic to grass and rye pollen.[32]

Finally, ►**Table 2** shows the comparison of mean scores before and after treatment, also demonstrated by ►**Figs. 1** and **5**. The authors calculated the mean score obtained from the four main rhinitis by dividing individual scores by four, in that the maximum score was three. This resulted in a score of 2,086 in the beginning of treatment and 0.440 after the last vaccine dose, which corresponds to an overall symptom improvement of 79% in patients with allergic rhinitis with or without asthma. The authors also obtained intermediate scores during treatment, demonstrating the progressive improvement of symptoms. Significant differences ($p < 0.05$) were observed for all comparisons performed. The mean initial score (8.41 ± 2.63) was higher than the final score (1.75 ± 2.03) ($p < 0.001$).

Thus, the study shows that specific immunotherapy is a relevant approach in blocking the progression of rhinitis and asthma, mainly in selected cases.[4,18,33]

Conclusion

Subcutaneous immunotherapy demonstrated efficacy in decreasing the symptoms of itching, sneezing, rhinorrhea, and nasal congestion in patients with allergic rhinitis, proving to be an important therapeutic tool against this pathological condition.

Acknowledgments

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