Summary

Background. Pharmacotherapy and immunotherapy are the main treatment modalities for respiratory allergy. The aim of this paper has been to evaluate the efficacy and tolerability of subcutaneous and sublingual immunotherapy in association in allergic patients, and to demonstrate that the patients who have performed a second oral vaccination cycle after 4-5 years from the first subcutaneous treatment, derive benefits that may last for years. This is due to immune system’s plasticity.

Methods. The study was conducted in 30 allergic patients which had previously executed a full cycle of classical subcutaneous immunotherapy, with a partial remission of symptoms. After 4-5 years, they were subjected to sublingual immunotherapy for the same allergen, improving the results obtained.

Results. All the patients reported a decrease or absence of clinical symptoms, a reduction in the use of anti-allergic drugs, and lower values of PRIST and RAST after the treatment.

Conclusions. The results of this clinical study confirm the improvement of results when subcutaneous and sublingual immunotherapy are associated.

Key words
immune response; immunotherapy; sublingual immunotherapy (SLIT); T cell; vaccination

Introduction

Respiratory allergy occurs in more than 500 million persons around the world. In developed countries, allergic rhinitis affects between 10 and 25% of the general population, with an average of 23% in European countries. The risk of asthma is higher in patients with rhinitis. Allergies to grass, weed and tree pollen characteristically result in seasonal rhinitis symptoms, which correlate with the presence of allergen exposure in the environment. The primary approach to the control of the symptoms is the identification and avoidance of the causal allergens, which is often impossible for pollen. Pharmacotherapy and immunotherapy are the main treatment modalities. In contrast with pharmacotherapy, allergen injection immunotherapy has long term benefits that may persist for at least 3 to 5 years after discontinuation. These include long term remission of symptoms, a decrease in the onset of new sensitizations and, in subjects with rhinitis alone, a reduction in the likelihood of progression of their disease from rhinitis to asthma. Despite the proven efficacy to the traditional approach, there are clear limitations. These limitations lead physicians to research alternative routes of administration of immunotherapy, such as the sublingual route, or to search for molecules, such as novel adjuvants, modified natural allergens, peptide immunotherapy, recombinant allergens and their hypoallergenic variants, that will be dependent on the outcome of focused, adequately powered, and well designed clinical trials.

In this clinical study we resume the history of 30 patients, administered with a three-years classical subcutaneous immunotherapy with a partial remission of symptoms, in which the use of three-years sublingual immunotherapy for the same allergen, improved the results obtained.
Concerning the case of pollen with seasonal flowering, the drug of the maintenance phase was administered in cycles over three years and interrupted only during the period of pollination. During treatment, the patients were subjected to clinical control once a month, monitoring and checking the tolerability of the vaccine and the symptoms. At the end of the maintenance phase we carried out a follow-up at time zero, one month, three months and six months later. After twelve months, we repeated the Prick test.

Results

All the 30 patients treated reported a benefit with reduction of 80% in respiratory symptoms, complete absence of asthma in patients with allergy to Dermatophagoides, and reduction in the use of anti-allergic drugs (in all treated patients the corticosteroids therapy was no longer necessary and antihistamines just in case of need in heyday). Respiratory symptoms were evaluated on the basis of:

1. The presence of cough, rhinitis and conjunctivitis;
2. An otolaryngologist examination that verified the presence of a hyperemic mucosa on allergic basis without other deficits (ex. Nasal septum deviation);
3. Administration of RQLQ (Rhinocconjunctivitis Quality of life questionnaire).

The ocular symptoms were evaluated on the basis of an ophthalmic examination, which verified the presence of a hyperemic conjunctiva on allergic basis.

Regarding the cases of allergy to Dermatophagoides mix, the maintenance phase consisted in the daily administration of the drug for three years.

Materials and methods

In our study we enrolled 30 patients of both sexes and aged between 30 and 60 years, with chronic and/or seasonal inhalatory allergy, and who had already executed a full cycle of subcutaneous hyposensitizing therapy 4-5 years before. The patients were divided according to the allergy’s type and symptoms (Table 1).

For each patient, after the signature of informed consent, PRIST, RAST and PRICK TEST for inhalants were performed, with similar results to those observed before hyposensitizing therapy. We therefore started a new treatment with oral hyposensitizing therapy, that comprises an induction and a maintenance phase. In the induction phase, lasting 13 days, for each patient 6 bottles of 4 ml each were used, with increasing concentrations of the allergen, administered by drops in the following way:

- First bottle: 2 drops on first day, 4 drops on second day, 6 drops on third day, 8 drops on fourth day, 10 drops on fifth day, 12 drops on sixth day, 14 drops on seventh day, 16 drops on eighth day;
- The remaining five bottles: 1 drop on ninth day, 2 drops on tenth day, 3 drops on eleventh day, 4 drops on twelfth day, 5 drops on thirteenth day.

On the fifteenth day, the maintenance phase begins, where patients continue therapy with three drops per week for three years, using the third bottle, with the highest concentration of allergen. All patients were subjected to this stage, even those with sensitization to perennial allergens. In this study, we used a sublingual immunotherapy produced by Lofarma, an Italian pharmaceutical company.

Regarding the cases of allergy to Dermatophagoides mix, the maintenance phase consisted in the daily administration of the drug for three years.

Table 1 - Distribution of patients according to the allergens and symptoms.

<table>
<thead>
<tr>
<th>Allergens</th>
<th>No patients</th>
<th>Symptoms</th>
</tr>
</thead>
<tbody>
<tr>
<td>Grasses mix</td>
<td>10</td>
<td>Rhinitis, cough, conjunctivitis</td>
</tr>
<tr>
<td>Pellitory mix</td>
<td>10</td>
<td>Rhinitis, cough, conjunctivitis</td>
</tr>
<tr>
<td>Dermatophagoides mix</td>
<td>10</td>
<td>Rhinitis, cough, conjunctivitis, asthma</td>
</tr>
</tbody>
</table>

Table 2 - Comparing the RAST before and after the treatment.

<table>
<thead>
<tr>
<th>Allergens</th>
<th>RAST before the treatment</th>
<th>RAST after the treatment</th>
</tr>
</thead>
<tbody>
<tr>
<td>Grasses mix</td>
<td>300 iu</td>
<td>250 iu</td>
</tr>
<tr>
<td>Pellitory mix</td>
<td>350 iu</td>
<td>150 iu</td>
</tr>
<tr>
<td>Dermatophagoides mix</td>
<td>600 iu</td>
<td>200 iu</td>
</tr>
</tbody>
</table>
Successful of subcutaneous and oral hyposensitizing therapy in 30 patients

Discussion

In atopic allergy, type 2 helper T lymphocytes (Th2 cells) are elevated in relation to regulatory T lymphocytes (Treg cells). In healthy subjects the ratio is vice versa. It seems that tolerance generated through allergen-specific Treg cells is the immunologic reaction mode towards allergens in healthy non-atopic subjects. It has been found that hyposensitization will correct the imbalance of Th2 and Treg cells and restore the normal immune response to allergens.

Our results demonstrate the enormous effectiveness of oral immunotherapy, performed after one subcutaneous. In fact, the patients who have performed a second oral vaccination cycle 4-5 years after the first subcutaneous treatment, derive benefits that last for years after suspension of the therapy. Six years have passed from the administration of second oral vaccine, and therefore we can say that these patients present a stable and unaltered condition, until now. Those who have been subjected only to the first vaccination cycle, have showed an improvement in symptoms until 3 years after suspension the therapy. To explain how this is possible, we must refer to the concept of “biological plasticity”, that is the ability to change in response to external stimuli and then to show memory. The biological plasticity is a form of adaptation that reflects the evolution of each individual, and therefore explains why different organisms may respond to the same stimulus in different ways. The same thing happens in allergy sufferer undergoing vaccine, which will induce changes, such as the generation of antibody heritage. The Immune System maintains the memory of those systems that have been shown effective in thwarting previous attacks. Therefore, when the allergic subject is subjected to the second vaccination cycle after many years, you get a much greater benefit due to the fact that the repetition of the cycles of immunotherapy potentiates the effect of the first treatment, thus allowing to maintain the immune memory of these patients; it has a synergistic action between the two treatments, made possible precisely by the memory of the first.

Conclusions

The efficacy of allergen injection immunotherapy for allergic respiratory disease has been confirmed in systematic reviews and meta-analyses for asthma and for allergic rhinitis. The sublingual route is usually considered as an alternative to subcutaneous immunotherapy. Instead, we demonstrated that the subcutaneous and oral immunotherapy in association represents a safe and effective treatment. Considering the success of 100% obtained in our study, it symbolizes a revolution in the field of prevention, above all for patients with atopy to perennial allergens suffering serious trouble all year.

References