Abstract. – Background. The effectiveness and safety of specific immunotherapy (SIT) in allergic diseases such as asthma have been increasingly questioned, some authors practically advocate to eliminating SIT as a therapeutic option for allergic patients, since the risks associated with this form of asthma treatment might be higher than the possible positive effects.

Observations. We emphasize that several authors comment on the frequency of reactions to SIT without a sound competence. Therefore, the scope of the present study was to ascertain whether this form of therapy is safe and effective in pediatrics. Denying SIT is a misleading issue since in children not cured with SIT a risk factor for persistence of respiratory symptoms is the ongoing sensitivity to allergens.

Conclusion. SIT consists in the administration of specific allergic extracts at progressively higher doses, with the aim to achieve a state of immunological tolerance and subsequently a reduction of clinical manifestations caused to the patients by the same allergens. We demonstrate that SIT is safe and effective in children.

Key Words:
Pediatric SIT, Pediatric asthma, Allergic rhinitis, Very early onset, Adverse reactions, Persistence of respiratory symptoms.

Introduction

Since 19871 a wealth of guidelines and indications for SIT with inhalant allergens and/or venoms have been proposed and published within the following years by a number of organizations and scientific societies all over the world. These include the WHO (World Health Organization)2,3, the EAACI (European Academy of Allergy and Clinical Immunology)4, the International Consensus Report on Asthma5, the Global Strategy for Asthma Management and Prevention6, the International Consensus Report on Rhinitis7, the BSA CI (British Society for Allergy and Clinical Immunology)8, the AAAAI (American Academy of Allergy, Asthma, and Immunology), and the ACAAI (American College of Allergy, Asthma, and Immunology)9. Physicians and scientists from different countries convened at the WHO headquarters in Geneva in January 1997, to analyze the science and indications for specific immunotherapy (SIT) for treating allergic diseases. They published their position papers in several journals related to allergy, asthma and immunology, including Journal of Allergy and Clinical Immunology, Annals of Allergy, Asthma and Immunology, and Allergy in 199810,11 and highlighted that SIT should be evaluated as an effective treatment for allergic asthma, if carried out correctly, suitable allergen extracts are used, and the therapeutic indications are exactly followed according to germane indications.

Is SIT safe in children?

Several recommendations against performance of SIT in children have been stressed12,13, underlining13 that children < 5 years present a significantly greater risk of systemic reactions14. We have stressed15 that several significant topics were omitted:
1) the children were subjected to a rush protocol, which is known to provoke more reactions,
2) the children had neither premedication nor preventive measures; the authors were conscious of the risks, therefore the patients were hospitalized for the first night of treatment,
3) the authors hypothesized that the hospitalization increased the rate of reactions because of its psychologic impact14.
Akçakaya et al. have treated 88 children with SIT, and reported adverse reactions in 12 children (0.2%). However, only one child suffered from anaphylaxis (1.1%) = one case out 5760 injections = 0.017%. The remaining 11 children had reactions consisting in laryngoedema, wheezing, urticaria, etc, all treated with epinephrine and antihistamines.

Wells has discussed the different incidence and severity of systemic reactions (SR) to SIT between the Oklahoma and Atlanta practice. He stressed that the figures in his practice were about one third of that reported by Tinkelman et al. The actual difference was between 0.02% (1/4700) and 0.08% (1/1600).

However, many reports have discussed the occurrence of SRs to SIT. A number of fatalities after SIT have been also rarely reported, since Lamson in 1929 first described a death from anaphylaxis after SIT. The prevalence of SRs in adults has been estimated between 5% and 44% for grass SIT, and between 7 and 50% for mite SIT, whereas at present there are a few data in children. According to these studies performed on a small number of children with asthma, SR rate was actually zero using a mite extract, and between 80 to 100% using a highly purified and standardized mold extract. We summarize in Table 1 the most recent data of SRs in children, in Table 2 the details of two cases of shock, and in Table 3 those of 7 fatal cases, while Table 4 demonstrates that FRs in children are statistically nonexistent.

We have treated with SIT a number of children (see below), observing adverse reactions in 0.09% injections and, contrary to Akçakaya et al., one case of shock out of 47247 injections = 0.0021% and in 0.089% of 1119 treatments.

It is very striking that in this study the case of shock was provoked in a child receiving Dermatophagoides pteronyssinus (Der p) extracts, with statistical significant differences compared to children treated with pollen extracts (p < 0.0001). Therefore, Der p is the most immunogenic allergen for children, with a considerable correlation with Akçakaya et al. In three studies, we observed only local reactions successfully treated with drug therapy. In 300 children with asthma due to Der p or pollens, only 5 children (2.5%) had reactions consisting in urticaria (3 cases) and wheezing (2 cases) (0.006% of treatments), caused by hyperdosage which subsided reducing the dosage.

Is SIT effective in children?

We have treated with SIT 1443 children aged 2-14 years. During three years we have prospectively observed 67 children with correctly diagnosed asthma due to pollinosis, 39 children with monosensitization to Alternaria alternata, and 300 children with respiratory allergy due to Der p or pollens also treated for three years with an allergenic extract and evaluated as above. Statistically significant differences were observed between children receiving SIT and those drug-treated. Among the 1056 children treated with SIT, 0.08% had adverse reactions, compared to 0.04% in the group treated with drugs. The difference was statistically significant (p < 0.0001).

Table I. Systemic reactions (SR) in children during SIT.

<table>
<thead>
<tr>
<th>Authors</th>
<th>Year</th>
<th>No. of SR</th>
<th>Age (y)</th>
<th>No. of inj</th>
</tr>
</thead>
<tbody>
<tr>
<td>Lin et al</td>
<td>1993</td>
<td>3/374 (8%)</td>
<td>2-9</td>
<td>139/513.368 (2.9%)</td>
</tr>
<tr>
<td>Businco et al</td>
<td>1995</td>
<td>41/1443 (3.7%)</td>
<td>2-14</td>
<td>41/45979 (0.08%)</td>
</tr>
</tbody>
</table>

Table II. Cases of shock in children during SIT.

<table>
<thead>
<tr>
<th>Case</th>
<th>Based on children</th>
<th>Based on injections</th>
</tr>
</thead>
<tbody>
<tr>
<td>A. Akçakaya</td>
<td>1.1%</td>
<td>0.017%</td>
</tr>
<tr>
<td>Businco</td>
<td>0.09%</td>
<td>0.0021%</td>
</tr>
</tbody>
</table>
The natural evolution of asthma from childhood to adulthood has been the subject of several studies. Asthma onset within the first year is certain in 34.5-56.2% of babies, and a greater proportion (82.4%) is manifest between the 4th and the 7th year of life. Further, asthma is present in 90% of children aged 8 years or less. Therefore, the most severe cases have an early onset, and the allergic component of asthma is most pronounced in children and adolescents. Even slight, newly diagnosed asthma is accompanied with features of ongoing mucosal inflammation and desquamation of bronchial epithelium, and elastic fibers in the bronchial walls are destroyed by long-standing asthma. Bronchoalveolar lavage findings and mucosal biopsies in asthmatic children aged 1-15 years have revealed bronchial inflammation and collagen deposition below the basement membrane, showing that both inflammation and remodelling occur early in life. Therefore, our studies demonstrate the effectiveness of SIT in children with respiratory allergy.

We also observed a whole remission of asthmatic manifestations in the children that regularly completed the SIT cycle. In all our studies, the controls were treated with all antiasthma medications available with statistically significant differences compared to children receiving SIT. A's regards the immunologic correlates, serum IgE levels significantly decreased, paralleled by an 8.8-fold increase in the IgG levels. Therefore, our studies have definitely established ITS effectiveness in pediatric age, positively influencing the natural history of respiratory allergies.

Is specific immunotherapy safe and effective in children?

### Table III. Fatal reactions in 7 children aged 7-18 years during SIT (1973-1989).

<table>
<thead>
<tr>
<th>Cases</th>
<th>Cause</th>
</tr>
</thead>
<tbody>
<tr>
<td>1</td>
<td>Known error of SIT administration and incorrect dose of epinephrine</td>
</tr>
<tr>
<td>2</td>
<td>Probable error of dosage and delay in the treatment</td>
</tr>
<tr>
<td>3</td>
<td>Did not wait in the doctor's office</td>
</tr>
<tr>
<td>4</td>
<td>Did not wait in the doctor's office</td>
</tr>
<tr>
<td>5</td>
<td>Wheezing at time of injection and during the 24-48 previous hours</td>
</tr>
<tr>
<td>6</td>
<td>No known error</td>
</tr>
<tr>
<td>7</td>
<td>No known error</td>
</tr>
</tbody>
</table>

Data from 27, 36.

### Table IV. FR in children aged 7-18 years during SIT (1973-1989).

<table>
<thead>
<tr>
<th>Based on years considered</th>
<th>Based on injections</th>
</tr>
</thead>
<tbody>
<tr>
<td>1 case</td>
<td>Every 2 + 1/2 years</td>
</tr>
<tr>
<td></td>
<td>Every 20 × 10⁷</td>
</tr>
</tbody>
</table>

Data from 15.
References


3) Current status of allergen immunotherapy: shorted-

4) MALLING H, WEEKE B. Immunotherapy: position paper of the European Academy of Allergy and Clinical Immunology. Allergy 1993; 14: 9-35.


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