Subcutaneous Immunotherapy in Northern Israel: Efficacy and Safety

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ABSTRACT: Background: The efficacy of subcutaneous immunotherapy for the treatment of allergic rhinitis, allergic conjunctivitis, allergic asthma and stinging insect hypersensitivity has been demonstrated in several studies. Objectives: To investigate the effectiveness and side effects of immunotherapy in Israel and the relationship between local and systemic side effects. Methods: This retrospective study was based on patient records and a computerized database for drug dispensing over a 5 year period. Success was rated as partial or complete. Side effects were classified as local or systemic. Systemic side effects were further classified according to severity, as mild (cutaneous), moderate (respiratory symptoms), or severe (cardiovascular). Results: Of the 135 patients on aero-allergen immunotherapy who reached maintenance, 120 (88.9%) exhibited complete or partial improvement and 15 (11.1%) did not improve. All of the 44 patients on hymenoptera immunotherapy reached effective maintenance doses. The mean percent side effects calculated per treatment (injection) were 2.49 for local and 1.58 for a systemic reaction during the build-up phase, and 1.13 and 1.12 during the maintenance phase, respectively. Rates of systemic reactions were 1.3% for cutaneous, 1.14% for respiratory and 0.97% for cardiovascular reactions during the build-up phase, and 1.11%, 0.53%, and 0.51% during the maintenance phase, respectively. The odds of systemic reactions were significantly higher in patients with local reactions both in the build-up phase (P = 0.03) and in the maintenance phase (P = 0.0003). The number of annual medications dispensed per patient decreased from 31.5 to 26.0 during the first year after reaching maintenance, and to 22.5 in the second year. Pharmaceutical costs were 67% lower 1 year after the start of the maintenance phase, compared to the year before the start of immunotherapy, and 63% lower in the second year (P = NS). Conclusions: Immunotherapy was effective and safe. Recognizing the benefits and safety of immunotherapy by physicians and health authorities is necessary to provide better care for allergic patients.

KEY WORDS: immunotherapy, subcutaneous immunotherapy, allergy, atopy, asthma, efficacy, safety, side effects

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Several double-blind, placebo-controlled randomized clinical trials have demonstrated the effectiveness of subcutaneous immunotherapy for the treatment of allergic rhinitis, allergic conjunctivitis, allergic asthma, and stinging insect hypersensitivity [1-6]. Based on immunotherapy practice parameters, allergen immunotherapy is considered for patients who present with sensitivities to clinically relevant allergens [1]. The decision to begin immunotherapy depends on factors such as patient preference and acceptability, expectations for adherence, medication requirements, response to avoidance measures, and adverse effects of medications. The efficacy of immunotherapy may vary around the world due to differences in climate, the nature of aero-allergens and their distribution. The risks of local and systemic side effects in both the build-up and maintenance phases remain key considerations in the decision to administer subcutaneous immunotherapy.

The World Health Organization 1998 position paper on allergen immunotherapy stated that local reactions to immunotherapy are not predictive of systemic reactions [7]. Since then, retrospective studies have both supported [8,9] and challenged [10] this conclusion. In the present study we investigated the efficacy and safety of immunotherapy administered in northern Israel over a 5 year period.

PATIENTS AND METHODS

This was a retrospective cohort study covering 5 years of follow-up. We reviewed the medical records of all individuals insured by Clalit Health Services, the largest health management organization in Israel, who were treated with subcutaneous immunotherapy at HaEmek Medical Center and at allergy satellite clinics in northern Israel during the 5 year period 2006–2011. All immunotherapy treatments, both aero-allergen and hymenoptera, were administered according to clinical guidelines using a standard schedule of 24 weeks. The actual schedule was modified according to side effects [1,11]. Our approach was immunization to clinically relevant allergens rather than to a single allergen [8]. Patients on aero-allergen immunotherapy were maintained with appropriate...
recommended doses of 1000–4000 bioequivalent allergy units or the recommended amount of allergen measured by weight/volume [1].

Partial success of aero-allergen immunotherapy was defined as a meaningful reduction in symptoms and improved quality of life, as assessed by patients and physicians. Complete success was defined as a state in which no further allergic symptoms required treatment, according to patients’ medical records. For hymenoptera hypersensitivity, immunotherapy was defined as successful once a patient reached an effective therapeutic maintenance dose, namely 100 µg of honey bee, wasp, or yellow jacket protein.

Side effects were classified as local or systemic. Local reactions were measured by a ruler after each injection and recorded in the patient’s records by the nurse. Reactions were classified as local when an injection was followed by redness, swelling and pruritus at the site of the injection with a > 20 mm wheal formation. Systemic side effects were further classified by their severity according to a modification of the World Allergy Organization systemic reaction grading [13-16]: mild for presentation in the skin (urticaria), moderate for respiratory symptoms (irritation sensation in the throat, cough, shortness of breath, wheezing, acute exacerbation of asthma), and severe for cardiovascular system symptoms. For a diagnosis of asthma, a previous diagnosis of asthma with proof of reversibility on pulmonary function tests and response to bronchodilators was acceptable. Side effects were recorded in the patient’s medical records at the time of their occurrence. For calculating frequency of systemic side effects according to severity, we considered the more severe presentation of each event. For example, if a patient suffered urticaria and shortness of breath, the systemic side event was considered moderate and not mild. To examine associations between local and systemic side effects we calculated the probability/odds ratio of systemic side effects developing in patients who developed local side effects. We assessed side effect rates per patient and per treatment (injection) for both the build-up and maintenance phases. Since the effect of aero-allergen immunotherapy may continue to improve after reaching the maintenance phase, especially for seasonal allergy, we evaluated the success rates 1 and 2 years after maintenance was reached.

**USE OF MEDICATIONS**

Data on the medications related to rhinitis and asthma treatment were collected from the Clalit Health Service computerized database for drug dispensing. Medications included oral first- and second-generation antihistamine alone or combined with pseudoephedrine, nasal corticosteroids, nasal and ocular antihistamines, bronchodilators, inhaled corticosteroids, and ICS+LABA. The data were analyzed and compared for three time periods: the year preceding initiation of immunotherapy and during the first and second years after reaching maintenance doses.

**STATISTICAL ANALYSIS**

Demographic and clinical patient characteristics were compared by the degree of treatment success using the Kruskal-Wallis test for continuous variables, and chi-square tests or Fisher exact tests for categorical data. Chi-square tests were also used to examine the dependence of side effects on type of allergy. The Wilcoxon two-sample test was used to analyze differences in type of allergy. Relations between the local and systemic side effects in the build-up and maintenance phases were analyzed using the chi-square test; odds ratio (95% confidence interval) was also presented. Since pharmaceutical costs did not follow normal distribution, the Wilcoxon signed rank test was performed to assess a possible statistically significant reduction in medication purchases and costs between the 12 months preceding immunotherapy and the first and second years after reaching maintenance dose. Statistical significance was set at \( P < 0.05 \). Statistical analysis was performed with the SAS 9.2 Software.

This study was approved by the national Ethics Review Board of Clalit Health Services. The Ethics Review Board waived the need for informed consent because of the retrospective design of the study.

**RESULTS**

During the study period 232 patients received subcutaneous immunotherapy [Table 1]. The mean age of those receiving aero-allergen immunotherapy was 26.2 years (range 6–73) and 25.5 years (range 3–60) for those receiving hymenoptera immunotherapy. Males comprised 48.4% (88 patients) and 74.0% (37 patients) of those receiving aero-allergen and hymenoptera immunotherapy respectively. A total of 179 patients reached maintenance doses: 135 of 182 patients (74.2%) on aero-allergen and 44 of 50 (88%) on hymenoptera immunotherapy. Of the patients who did not reach the maintenance phase, 28 were still in the build-up phase at the end of the study and 25 dropped out before reaching maintenance. Thirty-seven patients dropped out during the maintenance phase.

<table>
<thead>
<tr>
<th>Table 1. Demographics of the study population (232 on immunotherapy)</th>
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</thead>
<tbody>
<tr>
<td><strong>Gender</strong></td>
</tr>
<tr>
<td>Male</td>
</tr>
<tr>
<td>Female</td>
</tr>
<tr>
<td>Total</td>
</tr>
<tr>
<td><strong>Ethnicity</strong></td>
</tr>
<tr>
<td>Jewish</td>
</tr>
<tr>
<td>Arab/Non Jewish</td>
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<tr>
<td>Mean age (yr) (range)</td>
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</tbody>
</table>
The main reason for drop-out was inconvenience attending the clinic to receive treatment (80% during the build-up phase and 65% during the maintenance phase), followed by relocation, pregnancy, and other diseases. The mean time to reach maintenance was 261.57 ± 193.7 days (8.72 ± 6.46 months), median 203 days (6.77 months). The mean time that patients received aero-allergen immunotherapy was 5.54 ± 2.39 years (median 4.55) as compared to 5.57 ± 2.59 years (median 4.53) for hymenoptera immunotherapy.

Of the 135 patients on aero-allergen immunotherapy who reached maintenance, 120 (88.9%) exhibited complete or partial improvement, and only 15 (11.1%) did not improve. Complete resolution was reported in 86.1% of patients (31/36) treated for more than 5 years, compared to 60.5% (23/38) treated for 3–5 years (P = 0.0132, OR 4.04, 95% CI 1.2843–12.7303).

No correlation was found between success rate and age at the start of therapy, gender, or ethnic origin. Treatment success did not correlate with patients’ primary allergic conditions, i.e., allergic rhinitis with or without conjunctivitis, asthma, or any combination of these. None of the allergens used for immunotherapy exhibited any correlation with the success rate.

The mean percentage of side effects calculated per treatment (injection) was 2.4% for local and 1.58% for systemic reactions during the build-up phase, and 1.13% and 1.12% during the maintenance phase, respectively. For systemic reactions the rates were 1.3% for cutaneous, 1.14% for respiratory and 0.97% during the build-up phase, and 1.11%, 0.53% and 0.51% during the maintenance phase, respectively.

Table 2 presents the association of local and systemic side effects during the build-up and maintenance phases. Patients with local side effects either in the build-up phase or maintenance phase were significantly more likely to have systemic side effects during these phases (P = 0.03 and 0.0003, respectively). Patients with systemic side effects in the build-up phase were significantly more likely to have systemic side effects in the maintenance phase (P < 0.0001). Local side effects were significantly more common in patients who had such side effects in the build-up phase (P = 0.0063). There was no correlation between the occurrence of local side effects during the build-up phase and systemic effects in the maintenance phase.

The number of medications dispensed per patient per year decreased from 31.5 before immunotherapy to 26.0 (by 17.5%) during the first year after reaching maintenance, and to 22.5 (by 28.6%) in the second year (P = NS). Similarly, pharmaceutical costs were 67% lower 1 year after the start of the maintenance phase, compared to the year before the start of immunotherapy, and 63% lower in the second year (P = NS) [Figure 1]. There was no statistically significant difference in pharmaceutical costs between the year before the start of immunotherapy and either the first or second year after reaching maintenance for any class of medication.

### Table 2. Outcome and success rate of immunotherapy

<table>
<thead>
<tr>
<th>Aero-allergen (n (%))</th>
<th>Hymenoptera (n (%))</th>
<th>Total (n (%))</th>
</tr>
</thead>
<tbody>
<tr>
<td>Started</td>
<td>182</td>
<td>50</td>
</tr>
<tr>
<td>Completed build-up</td>
<td>135</td>
<td>44</td>
</tr>
<tr>
<td>Completely or partially improved</td>
<td>120 (88.9)</td>
<td>44 (100)</td>
</tr>
<tr>
<td>Not improved</td>
<td>15 (11.1)</td>
<td>0 (0)</td>
</tr>
</tbody>
</table>

Partial success of aero-allergen immunotherapy was defined as a meaningful reduction in symptoms and improved quality of life, as assessed by patients and physicians. Complete success was defined as a state in which no further allergic symptoms required treatment, according to patients’ medical records. For hymenoptera hypersensitivity, immunotherapy was defined as successful once a patient reached an effective therapeutic maintenance dose of 100 µg honey bee, wasp, or yellow jacket protein.

### Table 3. Odds ratio for the development of side effects in the build-up and maintenance phases, with associations between local and systemic side effects

<table>
<thead>
<tr>
<th>Effect investigated</th>
<th>OR</th>
<th>95%CI</th>
<th>P value</th>
</tr>
</thead>
<tbody>
<tr>
<td>Build-up phase</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Systemic side effects in patients with local side effects (n=232)</td>
<td>1.87</td>
<td>1.06–3.31</td>
<td>0.03</td>
</tr>
<tr>
<td>Maintenance phase</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Systemic side effects in patients with local side effects (n=179)</td>
<td>3.40</td>
<td>1.71–6.74</td>
<td>0.0003</td>
</tr>
<tr>
<td>Mixed (build-up and maintenance phases)</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Systemic side effects during the maintenance phase in patients with systemic side effects during the build-up phase on (n=179)</td>
<td>6.38</td>
<td>3.17–12.81</td>
<td>&lt; 0.0001</td>
</tr>
<tr>
<td>Local side effects during the maintenance phase in patients with local side effects during the build-up phase (n=179)</td>
<td>2.49</td>
<td>1.28–4.84</td>
<td>0.0063</td>
</tr>
<tr>
<td>Systemic side effects during the maintenance phase in patients with local side effects during the build-up phase (n=179)</td>
<td>NS</td>
<td></td>
<td>0.18</td>
</tr>
</tbody>
</table>

### DISCUSSION

This 5 year historical study demonstrated the efficacy and safety of subcutaneous aero-allergen and hymenoptera immuno-
therapy. All patients receiving hymenoptera immunotherapy were tolerant to the maintenance dose of 100 µg. Of patients treated by aero-allergen immunotherapy, 89% showed significant improvement. These findings concur with previous data on the efficacy of immunotherapy [1,2,7]. Moreover, the improvement reached shortly after reaching the maintenance dose, as described here, concurs with previous documentation [17]. Nevertheless, comparisons among studies are limited since the success rate of immunotherapy depends on the appropriate selection of patients with acceptable levels of compliance and on the administration of effective doses of clinically relevant allergens. Most studies on this subject have compared symptom scores between patients who are and are not treated with immunotherapy. However, little data are available regarding the proportion of patients actually reporting a meaningful benefit from immunotherapy, as reported in this study.

In this study, treatment efficacy was not associated with patients’ primary allergic conditions, i.e., allergic rhinitis with or without conjunctivitis or asthma. While immunotherapy is known to prevent the development of asthma in patients with allergic rhinitis [18,19], these findings support the notion that the condition of asthma, once controlled in a patient with allergic rhinitis, should not be a factor in determining whether or not to initiate immunotherapy.

The lack of association between reported clinical improvement and age, gender, ethnic background, and treatment against a particular allergen, supports the notion of a universal pathophysiology of allergic disease, with similar courses in populations in different environments. The duration of immunotherapy is determined by the physician and patient after considering the benefits and risks associated with discontinuing or continuing treatment [1]. There are presently no specific tests or clinical markers for identifying which patients will relapse and which will remain in long-term clinical remission after stopping immunotherapy. Nevertheless, we found significantly greater success rates in patients treated for 5 years or more compared to those treated for 3 years, suggesting that reaching efficacy with immunotherapy may take longer than generally thought and that efficacy may increase with time. Our findings support the benefit of continuing immunotherapy beyond 3 years, preferably 5 years. Longer duration requires particularly good patient adherence. This highlights the importance of careful patient selection and ensuring that the patient understands the treatment and its requirements. In addition, prolonged immunotherapy may require greater support by health care providers.

In this study, the cost of asthma medication decreased markedly from the point that maintenance was reached, continuing for another 2 years. This trend supports the efficacy of immunotherapy by demonstrating that the reported improvement in symptoms was not due to an increased use of medications. Although reductions in medication costs per patient did not reach statistical significance, they may be meaningful when considering health care costs for a population of patients with allergies. This finding concurs with those reported by a previous retrospective study [20]. Controlled clinical studies have shown that clinical symptoms and the quantity of medication required to control symptoms are valid measures of efficacy [1]. Furthermore, guidelines for allergen immunotherapy clinical trials recommend that a combined symptom–medication score be used as a primary outcome measure [1,13].

The rates of systemic reactions observed in the current study were similar to those reported in the literature [21-25]. Nevertheless, the development of systemic and potentially life-threatening side effects among some patients, albeit few, supports recommendations that immunotherapy be administered under the supervision of trained medical staff proficient in recognizing and treating anaphylactic reactions.

This study demonstrated statistically significant associations between the appearance of local side effects and the later emergence of both local and systemic side effects. Local side effects may predict systemic side effects in both the build-up and maintenance phases. It follows that patients with local reactions should be monitored particularly carefully, and that modification of doses be considered. It is well established that local reactions to hymenoptera may indicate an increased risk that systemic reactions will develop [1]. Our findings support a similar tendency regarding local reactions to aero-allergens. On the other hand, patients can be counseled that local reactions will be less frequent when maintenance is achieved. Most of the existing data on associations between local and systemic reactions are based on retrospective cross-sectional studies [8-10]. In contrast, this is a historical cohort study of patients treated with immunotherapy over a 5 year period, with separate consideration of the build-up and maintenance periods as well as the 2 year period after achieving maintenance. The limitations of this study are that it was retrospective and not controlled.

CONCLUSIONS

This study showed that immunotherapy is effective and safe and is associated with a trend of reduced medication use and costs for rhinitis and asthma. Local side effects presenting in the build-up and maintenance phases may predict systemic side effects. Recognizing the benefits and safety of immunotherapy in allergic patients is necessary for physicians and health authorities in providing better care and treatment.

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Capsule

Negative regulation of the NLRP3 inflammasome by A20 protects against arthritis

Rheumatoid arthritis is a chronic autoimmune disease that affects 1–2% of the world’s population and is characterized by widespread joint inflammation. Interleukin-1 is an important mediator of cartilage destruction in rheumatic diseases, but our understanding of the upstream mechanisms leading to production of interleukin-1β by macrophages significantly enhances Nlrp3 inflammasome-activated caspase-1 activation, pyroptosis and interleukin-1β secretion by soluble and crystalline Nlrp3 stimuli. In contrast, activation of the Nlrp4 and AIM2 inflammasomes is not altered. Importantly, increased Nlrp3 inflammasome activation contributes to the pathology of rheumatoid arthritis in vivo, because deletion of Nlrp3, caspase-1 and the interleukin-1 receptor markedly protects against rheumatoid arthritis-associated inflammation and cartilage destruction in A20myel-KO mice. These results reveal A20 as a novel negative regulator of Nlrp3 inflammasome activation, and describe A20myel-KO mice as the first experimental model for studying the role of inflammasomes in the pathology of rheumatoid arthritis.

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