ABSTRACT

Background: A short-term immunotherapy vaccine for the treatment of pollen allergy has been developed utilising L-tyrosine adsorbed allergoids. The reduced number of injections could provide advantages over long-term therapy schedules. This would improve compliance and support application of specific immunotherapy (SIT) to a greater extent. We report a multicenter study to evaluate the efficacy and safety of this treatment in a clinical practice setting.

Methods: Patients (n = 1808) with a diagnosis of sensitivities to various pollens and symptoms of allergic asthma and/or allergic rhinitis and/or allergic conjunctivitis were selected. The vaccine formulation was made up according to individual sensitivities and contained L-tyrosine adsorbed allergoids. The patients were treated with a 3-injection initial course followed by a 3-injection maintenance course. Efficacy was measured by consumption of symptomatic medication compared with that in the previous season (p < 0.001). In addition, in 80% of the patients, the physician's assessment was either “good” or “very good”. These outcomes were unaffected by the closeness of the treatment course to the onset of the pollen season. Tolerability was good and most local and systemic reactions were mild.

Conclusions: The treatment of pollen-allergic patients with a short-term SIT using a 6-injection pollen allergoid/L-tyrosine vaccine in a clinical practice setting provided a high level of efficacy with a low incidence of mainly mild adverse events.

mo de medicación antialérgica sintomática en com-
paración con la estación anterior y por valoración del 
médico según una escala con cinco posibles valores. Se registraron los efectos adversos.

**Resultados:** La eficacia se evidenció por una con-
siderable disminución de los síntomas y del uso de 
medicación comparados con la estación anterior (p < 0,001). También la valoración por parte del inves-

tigador fue “buena” o “muy buena” en el 80 % de 
los casos. Estos resultados eran independientes de 
la proximidad entre tratamiento y el inicio de la esta-
ción de polen. La tolerancia fue buena, con reaccio-
nes locales y sistémicas de carácter leve.

**Conclusiones:** El tratamiento de pacientes alé-
gicos al polen con sit con pauta de corta duración, 
6 dosis de alergoides de polen adsorbidos en L-tirosina, en una situación normal de práctica clínica, 
ha mostrado una alta eficacia con una baja incidien-
cia de reacciones adversas, de carácter leve en su 
mayoría.

**Palabras clave:** Alergoide. L-tirosina. Asma. Polen. 
Inmunoterapia de corta duración. Conjuntivitis.

**INTRODUCTION**

There is ample evidence that the prevalence of se-
asonal and perennial allergic rhinitis is increasing 
worldwide. Patients with these conditions are fre-
cently treated with antihistamines and/or steroids 
which alleviate symptoms but do not provide any 
cure. Allergic symptoms may certainly be reduced by 
avoidance measures with some success; however, 
aeroallergens (particularly pollens) are the most diffi-
cult to avoid. The only allergy treatment available that is capable of providing long-term relief is specific im-
munotherapy (SIT) which is thought to act via sti-
mulation of the Th1 lymphocyte response or by 
anergy of Th2 activity. SIT may also prevent or slow 
down the “allergic march” in children by reducing 
the development of asthma which unfortunately is 
still a life-threatening disease.

Useful advances in the design of SIT vaccines have resulted in improved efficacy and tolerability. 
Conversion of allergens to allergoids (ie chemical 
modification of allergens) increases the potential to-
lerability of a vaccine by reducing the reactivity with 
specific IgE whilst maintaining the ability to induce specific IgG. Depot adjuvants provide a slow aller-
goid release mechanism which both assists safety 
and promotes the immune response. Most SIT vac-
cines are now standardised, providing reproducible 
potencies and thus encouraging efficacy and tolera-
bility.

This study utilises an L-tyrosine adjuvanted aller-
goid vaccine that is specifically designed for pollen 
allergy SIT (TA Mix top, Bencard Allergie 

**PATIENTS AND METHOD**

In this study 1808 patients with symptoms of aller-
gic asthma and/or allergic rhinitis and/or allergic conj-
junctivitis were recruited from 200 centres in 
Germany. These conditions were diagnosed to be es-
entially due to sensitisation by combinations of po-
llens from the following flora: a 12-grasses mix 
cultivated rye, birch/alder/hazel trees, or the weeds 
plantain or mugwort.

Patients received subcutaneous injections of a po-
llen allergoid mixture according to their individual sensitisation profile, as prescribed by their physician. 
Pollen extracts were semi-purified, modified with 
glutaraldehyde and adsorbed onto 3 % L-tyrosine. 
A summary of those formulations that were prescri-
bbed is given in the results section. Initial therapy was 
given using three injections at 1-2 week intervals, 
consisting of 0.5 ml allergoid/L-tyrosine suspension 
at 300, 800 and 2000 standardised units (SU) respec-
tively. This was followed by maintenance therapy 
with three further top doses (2000 SU) given at injec-
tion intervals of 1-4 weeks. All initial treatments and 
the majority of maintenance treatments (82 %) were
administered before the start of the appropriate pollen season.

Efficacy was recorded in two ways. Firstly, an opinion of therapeutic success given by the physician was taken using a five-point scale ("very good" to "worsened"). Secondly, the consumption of anti-allergic medication was monitored, comparing to that used in the previous pollen season. The pollen seasons were not significantly different regarding severity.

Physicians assessed the tolerability of both initial and maintenance courses by employing a three-point scale ("very good", "good", "less good"). Local and systemic reactions were recorded for both courses.

Statistical evaluation for differences in continuous data was done by the Wilcoxon signed rank test and differences in frequencies or percentages were calculated by the chi²-test.

RESULTS

A total of 1808 patients were studied including 55% females and 45% males. The mean and median ages were 30 years (standard deviation = 14 years), with the majority of patients between 10 and 39 years of age. The youngest subject was 6 years and the oldest 67 years old. A minority of patients (31%) had undergone previous hyposensitisation treatment, the vaccines most frequently formulated with grasses/rye, birch or alder pollen extracts (50%, 34% and 20% of patients, respectively).

Diagnosis of pollen allergy was made using a combination of tests. These comprised: skin prick tests 89%, case history 83%, RAST 40%, and provocation in 11% of patients. Allergic sensitisations of the patients are displayed in table I.

Physicians prescribed vaccines containing appropriate combinations of allergoids to match the individual sensitisations of the patients. The majority of patients (72%) was treated with grasses/rye (n = 651) or birch/alder/hazel (n = 467), respectively. For brevity, only those combinations prescribed for 20 or more patients are illustrated (table II). A summary of the symptoms presented by the patients in the pre-treatment pollen season is given in figure 1. Conjunctivitis and rhinitis predominated, followed by asthma occurring in 39% of the patients and atopic eczema and urticaria in smaller minorities (18% and 6% respectively).

Efficacy of treatment was reported from 1558 patients (fig. 2). Therapy success was found to be either very good or good in 80% of the patients, and a moderate success was reported in 13%.

In patients treated with grasses/rye (n = 578) or birch/alder/hazel (n = 392) similar results were reported with very good/good therapy success in 76% and 83% of patients. Moderate success was achieved in 16% and 10%, respectively (fig. 3).

![Figure 1.—Symptoms of patients in pollen season prior to treatment.](http://www.elsevier.es)

Table I

<table>
<thead>
<tr>
<th>Sensitisation</th>
<th>Patient numbers</th>
<th>Percentage of patients</th>
</tr>
</thead>
<tbody>
<tr>
<td>Grasses/rye</td>
<td>1216</td>
<td>67</td>
</tr>
<tr>
<td>Birch/ald/alder/hazel</td>
<td>768</td>
<td>42</td>
</tr>
<tr>
<td>Birch</td>
<td>489</td>
<td>27</td>
</tr>
<tr>
<td>Mugwort</td>
<td>298</td>
<td>16</td>
</tr>
<tr>
<td>House dust mites</td>
<td>161</td>
<td>9</td>
</tr>
<tr>
<td>Animal epithelia</td>
<td>130</td>
<td>7</td>
</tr>
<tr>
<td>Plantain</td>
<td>97</td>
<td>5</td>
</tr>
<tr>
<td>Food</td>
<td>74</td>
<td>4</td>
</tr>
<tr>
<td>Moulds</td>
<td>46</td>
<td>3</td>
</tr>
</tbody>
</table>

Table II

<table>
<thead>
<tr>
<th>Allergoid combination</th>
<th>Patient numbers</th>
<th>Percentage of patients</th>
</tr>
</thead>
<tbody>
<tr>
<td>Grasses/rye</td>
<td>651</td>
<td>42</td>
</tr>
<tr>
<td>Birch/ald/alder/hazel</td>
<td>467</td>
<td>30</td>
</tr>
<tr>
<td>Grasses/rye and birch</td>
<td>164</td>
<td>10</td>
</tr>
<tr>
<td>Grasses/rye and birch/alder/hazel</td>
<td>80</td>
<td>5</td>
</tr>
<tr>
<td>Grasses/rye and mugwort</td>
<td>73</td>
<td>5</td>
</tr>
<tr>
<td>Birch</td>
<td>61</td>
<td>4</td>
</tr>
<tr>
<td>Mugwort</td>
<td>42</td>
<td>3</td>
</tr>
<tr>
<td>Grasses/rye and birch and mugwort</td>
<td>21</td>
<td>1</td>
</tr>
<tr>
<td>Total</td>
<td>1559</td>
<td>100</td>
</tr>
</tbody>
</table>

![Graph showing symptoms of patients in pollen season prior to treatment.](http://www.elsevier.es)
Efficacy, as quantified by reduction in the use of anti-allergic medication, is shown in figure 4 (n = 1554). Medication consumption sharply diminished: regular use went down from 43% to 8% of the patients, and frequent use dropped from 37% to 13%. The overall reduction in medication was a highly significant effect \( p < 0.001 \) which was also observed in patients treated with grasses/rye or birch/alder/hazel \( p < 0.001 \) (figs. 5 and 6).

These reductions were also seen in a further analysis dividing patients into an “early” and “late” therapy group, depending on the date of their final maintenance course injection. The first group \( n = 821, 47\% \) had the last injection before the end of February and the second group \( n = 927, 53\% \) from March onwards. In both groups medication consumption was reduced \( p = 0.46 \). Therapy success was estimated “very good” in 35% and 33% of patients, and a “good” rating was achieved in 44% and 48% (“early” and “late” groups respectively). A moderate success was reported by 13% (“early” group) and 14% (“late” group). Unchanged patients were seen in 7% (“early” group) and 5% (“late” group). Worsening of symptoms was reported in 1% (“early” group). The therapy was estimated to be equally successful in both groups \( p = 0.36 \).

Tolerability was reported by the physicians in three classifications (table III). Data from 1744 patients (initial course) and 1379 patients (maintenance course) were evaluated.

The tolerability was clearly high with a total of 94% of the patients with a “very good” and “good” rating treated with the initial course, and a 97% total for the same ratings for the patients at the maintenance stage. This slight difference was statistically significant \( p = 0.04 \).

Local and systemic reactions following treatment with both the initial and maintenance courses are summarised in table IV. A total of 12,788 injections was evaluated (7748 initial course, 5040 maintenance course). The vast majority of reactions were of a mild nature, and most events either did not require medication or were just treated by cooling. Patients treated with the maintenance course showed a significant reduction in the incidence of local reactions compared to that found with the initial course \( p = 0.02 \). There were no significant differences in local or systemic reactions comparing the pre-seasonal and co-seasonal therapy group.

Severe systemic reactions were reported from 6 patients corresponding to a percentage of 0.05% (initial course) and 0.06% (maintenance course). In 3 cases the reaction was found to be local. The remaining 3 systemic reactions occurred during initial therapy; two reactions were correlated to the injection, 1 reaction was probably correlated. From these 3 reactions classified as “severe” one anaphylactic...
reaction occurred and was successfully treated
(Tavegil, Solu-Decortin i.v.). The symptoms dis-appeared after 30 minutes. The second of these "severe"
reactions was sublingual itching whereas a descrip-
tion of symptoms was missing in the third case. No
serious systemic reaction was reported.

Therapy was discontinued for 140 patients (7.7 %),
the major reasons being lack of co-operation or a
concomitant disease, as shown in table V.

DISCUSSION

The short term immunotherapy in this study has
some special features regarding its potential use.
Firstly, there is the capability of patient specific mix-
tures to suit virtually all patients with allergy to
common pollens, ie those monosensitised and polysensi-
tised. Secondly, the allergoid/L-tyrosine combination
offers efficacious and safe treatment with a compara-
tively low number of injections, which assists com-
pliance and saves time for both physician and patient.

Impressive efficacy was judged by physicians,
with a positive overall response for SIT given for
93 % of the patients, leaving only 6 % with symp-
toms unchanged and 0.4 % worsened. The results
were confirmed in a subgroup analysis. Patients tre-
et with grasses/rye or birch/alder/hazel achieved
very good/good therapy success in 76 % and 83 %
respectively. Efficacy was also demonstrated by
substantially reduced medication consumption, parti-
cularly regarding regular and frequent use. The ef-
fact was statistically highly significant (p < 0.001).
This reduction in antiallergic medication was also re-
ported in patients treated with grasses/rye or birch/al-

Table III

<table>
<thead>
<tr>
<th>Classification</th>
<th>Patient numbers</th>
<th>Percentage of patients</th>
</tr>
</thead>
<tbody>
<tr>
<td>Initial course</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Very good</td>
<td>1148</td>
<td>66</td>
</tr>
<tr>
<td>Good</td>
<td>482</td>
<td>28</td>
</tr>
<tr>
<td>Less good</td>
<td>114</td>
<td>6</td>
</tr>
<tr>
<td>Maintenance course</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Very good</td>
<td>961</td>
<td>70</td>
</tr>
<tr>
<td>Good</td>
<td>370</td>
<td>27</td>
</tr>
<tr>
<td>Less good</td>
<td>48</td>
<td>3</td>
</tr>
</tbody>
</table>

Table IV

<table>
<thead>
<tr>
<th>Course</th>
<th>Reaction</th>
<th>Percentage</th>
</tr>
</thead>
<tbody>
<tr>
<td>Initial (7748 injec-</td>
<td>Local reactions</td>
<td>1.85</td>
</tr>
<tr>
<td>tions)</td>
<td>(redness/swelling &gt; 5cm diameter)</td>
<td></td>
</tr>
<tr>
<td></td>
<td>Mild systemic reactions</td>
<td>0.76</td>
</tr>
<tr>
<td></td>
<td>(e.g., rhinitis, conjunctivitis)</td>
<td></td>
</tr>
<tr>
<td></td>
<td>Severe systemic reactions</td>
<td>0.05</td>
</tr>
</tbody>
</table>
| Maintenance (5040 injec-
| tions)                | Local reactions                               | 1.2        |
|                       | (redness/swelling > 5cm diameter)              |            |
|                       | Mild systemic reactions                        | 0.44       |
|                       | (e.g., rhinitis, conjunctivitis)               |            |
|                       | Severe systemic reactions                      | 0.06       |

...
with respect to the last injection before pollen season.

Similar results, although with small patient numbers were reported elsewhere\(^9,10\). The authors reported a very good/good therapy success in 73% (grasses/rye) and more than 80% (birch/alder/hazel) respectively. Moreover a marked reduction in medication consumption was reported in these studies with grass- or tree-pollen allergic patients\(^9,10\).

Tolerability of the treatment was encouragingly high; “very good/good” ratings were given by 94% of the patients after the initial course, and 97% of the patients after the maintenance course. The difference was statistically significant (\(p = 0.04\)).

Local and systemic reactions were mainly mild. Local reactions from the maintenance course were significantly lower than those from the initial course (\(p = 0.02\)), which is possibly an indication of some desensitisation already resulting from the first three injections. Severe systemic reactions were very limited (initial course 0.05% ; maintenance course 0.06% of injections), with no statistical difference between therapies. No serious systemic reactions were reported.

Some maintenance courses were administered co-seasonally. One may speculate that the additional exposure during pollen season might be detrimental to safety. But those patients given co-seasonal maintenance therapy showed no significant differences in local or systemic reactions in comparison to the pre-seasonal therapy group. It may be concluded that the good tolerability of this short-term immunotherapy which has been reported elsewhere\(^9,10\) was confirmed in this study.

In summary, this study has shown that short term SIT has provided a successful treatment of pollen-allergic patients with allergic asthma and/or allergic rhinitis and/or allergic conjunctivitis. Since this data involved large patient numbers the results of smaller studies could be confirmed.

In a clinical practice setting, a pollen allergoid/L-tyrosine vaccine has provided high efficacy with a low incidence of adverse events which were mainly mild in nature. The convenient dosage with 6 injections could improve compliance and may support wider application of specific immunotherapy (SIT) in future.

### REFERENCES

5. EU notes for guidance on allergen products, 1996 (CPMP/BWP/243/96).