

A comparison of the clinical and immunological effects of an alum-precipitated five-grass extract with a conjugated two-grass extract in the desensitization of hay fever

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Summary

Thirty-nine patients with pollen hay fever were randomly allocated to receive either an alum-precipitated five-grass extract (Allpyral®) or a two-grass conjugated extract (Conjuvac®) prior to the 1982 pollen season.

Efficacy was assessed by means of symptom scores, drug usage and specific IgE and IgG antibody response. Both nasal and eye symptom scores were significantly higher during the pollen season in those patients receiving Allpyral. Specific IgE and IgG measured after the pollen season showed similar rises in each group. Seven patients showed a marked elevation in specific IgE and nine a marked elevation in specific IgG, but no patient showed both. Those with a high specific IgE level tended to be younger. Symptom scores bore no relation to either specific IgE or IgG antibodies. Side-effects were mainly local and were equal in both groups.

Introduction

Immunotherapy has been used for prophylaxis of hay fever or pollen rhinitis for over 70 years (Noon, 1911) though the first controlled trial of its efficacy was not published until 1954 by Frankland and Augustin. Controlled studies have since confirmed its role in the palliation of symptoms compared with placebo (Kerr & Murchison, 1963; Norman, Winkenwerder & Lichtenstein, 1972). However, the possibility of local and systemic side-effects and the inconvenience of a large number of injections have continued to be a disadvantage. Attempts have been made to purify and alter the pollen antigen to increase their immunogenicity, while reducing side-effects. Preparations made by extracting pollen with pyridine and adsorbing onto alum have been widely used and shown to be safe and effective when compared with aqueous pollen extracts or depot pollen emulsions (Frankland & Noelipp, 1966; Munro-Ashman, 1966). Glutaraldehyde-treated grass pollen-tyrosine adsorbate (Pollinex) has the advantage of a short course and fewer side-effects (Symington, O'Neal & Kerr, 1977).

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but may not give such a high level of clinical effectiveness as other vaccines (Verstraeten & Wheeler, 1978).

It would appear that most grass pollens have a number of common antigens (Milner & Tees, 1972). Löwenstein (1978) showed that immunological partial identity exists between the antigen of timothy and those of cocksfoot, rye and false-oat grass pollens. Therefore reducing the number of pollens in an extract may give equal or improved efficacy by reducing unwanted antigenic stimulation (Brown, Thantrey & Jackson, 1979), though this approach has yet to be proven (Davies, 1983).

Conjuvac is a new preparation which consists of partially purified extracts of two pollens in equal proportions conjugated to sodium alginate which acts as an adjuvant. It is suggested that this may maintain the immunogenicity of the pollen extract while reducing the induction of allergic reactions (Taylor, Sheldon & Spicer, 1981). This study compares the clinical and immunological effect of Allpyral®, an alum-precipitated five-grass extract (timothy, rye, cocksfoot, Yorkshire fog and meadow grass pollen) with Conjuvac®, a two-grass conjugated extract (timothy and cocksfoot).

Patients and methods

The study comprised of thirty-nine patients, aged between 8 and 50 years, with at least 2 years' history of seasonal pollen rhinitis, who were attending an allergy clinic. The diagnosis was based on a seasonal history and positive skin-prick tests to pollen extract (Dome). Several patients also had allergic rhinitis caused by other allergens mainly housedust mite and a few had mild asthmatic symptoms. Twenty-two had undergone immunotherapy in the past.

The patients were alternately allocated into two groups and the treatment given pre-seasonally. One group received nine weekly injections of an alum precipitated five-grass extract (Allpyral) starting with a dose of 20 PNU (protein nitrogen units) and rising to 4000 PNU. The other group received a conjugated two-grass extract (Conjuvac) rising from 1 AUR (activity units by RAST) to 800 AUR over eleven weekly injections. In both groups doses were reduced when severe local reactions occurred and then slowly built up to a maximum dose. Side-effects were recorded independently by nursing staff. The patients finished their injections 2–4 weeks before the start of the pollen season. No maintenance injections were given.

The patients were provided with symptom cards to record the presence and severity of symptoms from the 16 May to the 31 July 1982. The symptoms charted were: eyes—itching, swelling and watering; nose—sneezing, blockage and watering; chest—wheezing. The symptoms were scored as: 1: mild, 2: moderate, 3: severe. For analysis of the scores the 21 days between 17 May and 6 June were taken as the pre-pollen season. This was compared with the pollen season which was designated as the 42 days between 15 June and 25 July. All patients had access to oral antihistamines for use when required. The Glasgow pollen count was measured using a Hirst-Volumetric spore trap.

The symptom scores were handled in two ways. To show a temporal relationship with the pollen count, the average daily score of the group was taken and related to the daily pollen count. Otherwise the symptoms scores were analysed as the average daily score for each individual patient over the pre-pollen and pollen season.

Venous blood samples were taken before hyposensitization and following the pollen season. Serum from the samples were stored at -20°C pending analysis. Total IgE was measured by a double antibody-modified PRIST assay (Gliech, Averbeck &

Swedland, 1971), grass-specific IgE by a radioallergosorbent test (Gliech & Jacob, 1975), and both antibodies results measured as ng/ml. Specific IgG antibodies were measured by a double antibody technique and results expressed against a test serum and expressed in arbitrary test units (tu/ml) (Foucard & Johansson, 1976).

Symptoms scores were analysed for significance by appropriate *t*-testing but the antibody results were not of a normal distribution and therefore, non-parametric methods were used (Wilcoxon's rank sum tests).

Results

One patient receiving Conjuvac had to discontinue treatment because of a severe local reaction. Other side-effects are noted in Table 1. Ten patients failed to complete diary cards satisfactorily. Antibody levels before and after treatment were available in thirty-five patients. The results of thirteen Conjuvac and twelve Allpyral patients were available to be analysed for both antibody results and diary scores. The patients had a mean age of 22 years (11–39 years) in the Allpyral group and 25 years (8–52 years) in the Conjuvac group. Similar numbers in each group had previously been desensitized.

The average nasal daily symptom score of the two groups of patients is shown in Fig. 1 along with the daily pollen count. The average scores per day per patient out of a total of three during the pre-pollen season in the Conjuvac and Allpyral groups were similar: 0.65 ± 0.14 s.d. and 0.63 ± 0.27 s.d., respectively. Both groups had an increase in symptoms during the pollen season but the symptom score in the Allpyral group (1.31 ± 0.29 s.d.) was significantly higher than the Conjuvac group (0.81 ± 0.18 s.d.) ($P < 0.05$). Analysing the symptom scores per patient rather than per day over the two periods showed that both groups had similar scores pre-seasonally. During the pollen season the Allpyral group had a statistically significant rise in symptoms ($P < 0.01$) but the Conjuvac group did not. The differences between the two groups at this time did not reach statistical significance (Fig. 2). Only three patients in each group developed a wheeze during the pollen season. Seven out of thirteen in the Conjuvac group had eye symptoms while eleven out of twelve in the Allpyral group had similar symptoms, though these tended to be more severe than in the Conjuvac group (Fig. 3).

Twelve patients out of eighteen in the Conjuvac group and twelve out of seventeen in the Allpyral group showed a rise in total IgE following desensitization. The rise in

Table 1. Side-effects

Reactions	Conjuvac (21 patients)	Allpyral (18 patients)
Local		
None	3	3
Minor	10	9
Frequent	0	2
Severe	8	4
Systemic		
Wheeze	1	2
Rhinitis	1	0
Treatment discontinued	1	0

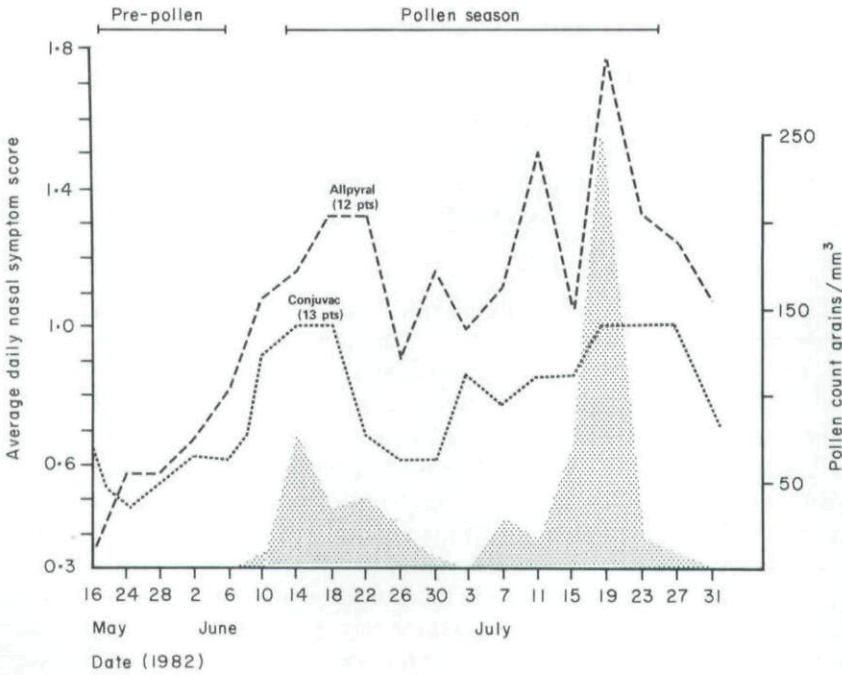


Fig. 1. Average daily nasal symptom score for Allpyral and Conjuvac groups, and pollen count during the 1982 summer season.

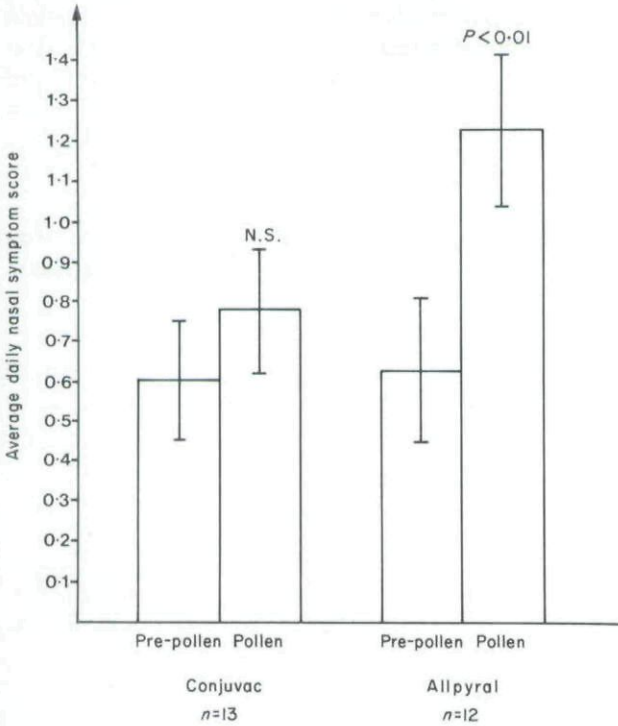


Fig. 2. Average nasal symptom score for the pre-pollen and pollen seasons for both the Conjuvac and Allpyral groups.

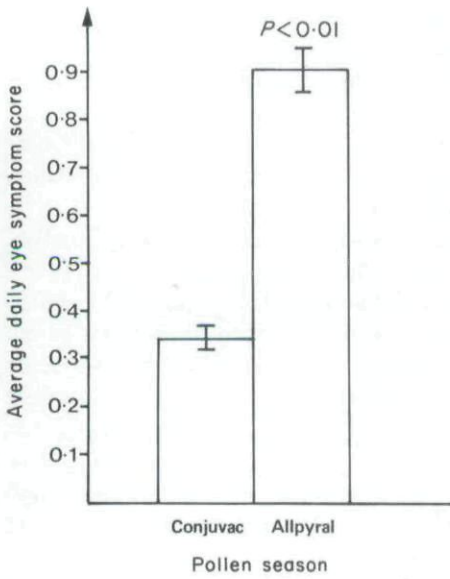


Fig. 3. Average daily eye symptom score for both groups during the pollen season.

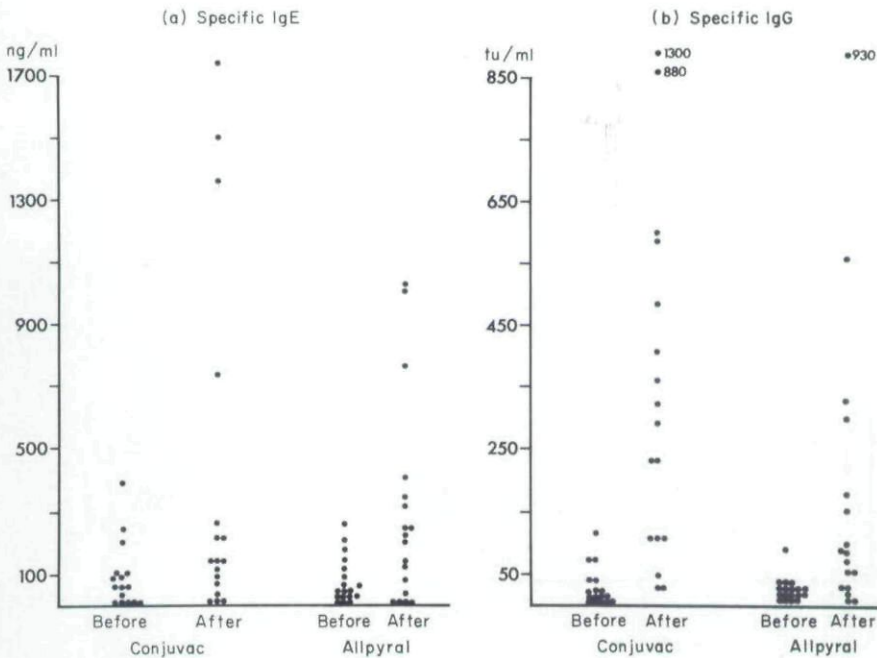


Fig. 4. Alterations in specific IgE and IgG before and after desensitization.

total IgE was significant in the Conjuvac group ($P=0.05$) but not in the Allpyral group. There was no difference in total IgE when compared in both groups before and after the pollen season. The specific IgE and IgG had similar baselines before treatment in each desensitization group. There was a highly significant rise of both specific IgE and specific IgG ($P < 0.01$) (Fig. 4) after desensitization. The rises were similar whether Allpyral or Conjuvac was given. Twelve patients in the Conjuvac group but only seven in the Allpyral group had a greater than ten-fold increase in specific IgG.

There appeared to be no relationship between specific IgE and specific IgG before desensitization, most levels being below $400 \mu\text{g/ml} + 400 \text{ tu/ml}$, respectively. Figure 5 shows the changes that occurred after desensitization and at the end of the pollen season. In nineteen patients, there was a mild elevation in both antibodies. Seven patients showed a striking elevation in specific IgE but no dramatic increase in specific IgG. In nine patients specific IgG rose to a great extent without a corresponding increase in specific IgE. No patient had a large increase in both antibodies. The patients who mounted a high specific IgE response tended to be younger with a mean age of 16 years (8–28 years), than the group as a whole and than those who developed a high specific IgG who had a mean age of 26 years (17–44) ($P < 0.05$). Symptom scores were

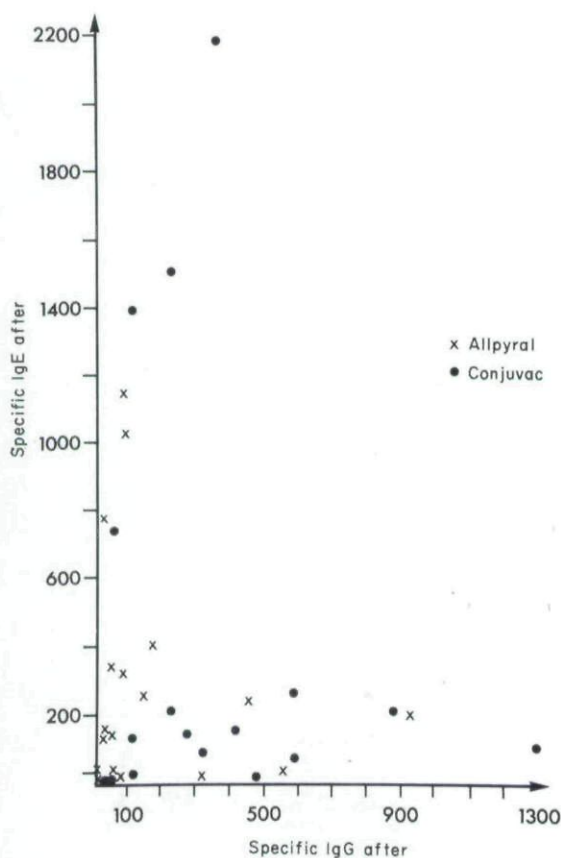


Fig. 5. Specific IgG and IgE after desensitization.

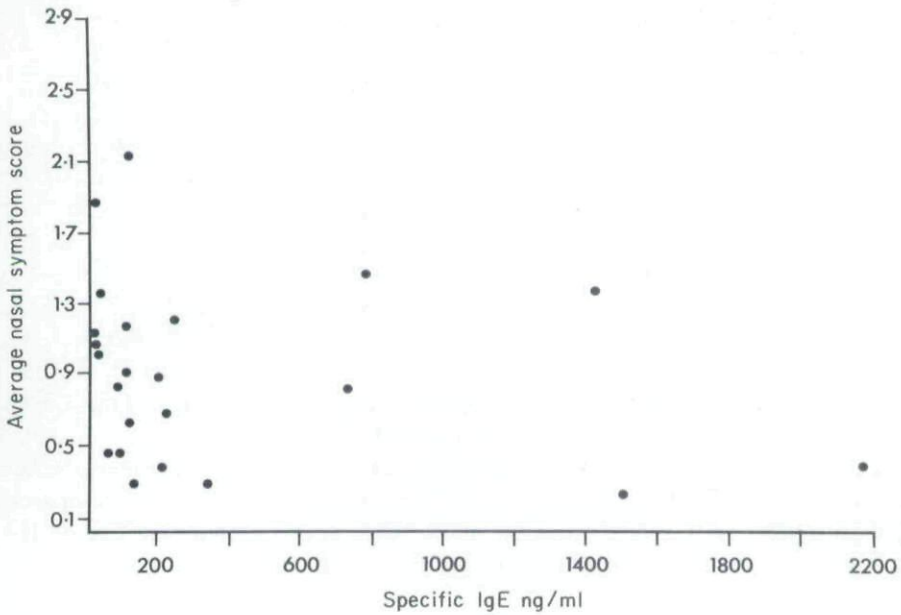


Fig. 6. Average nasal symptom score during the pollen season plotted against specific IgE.

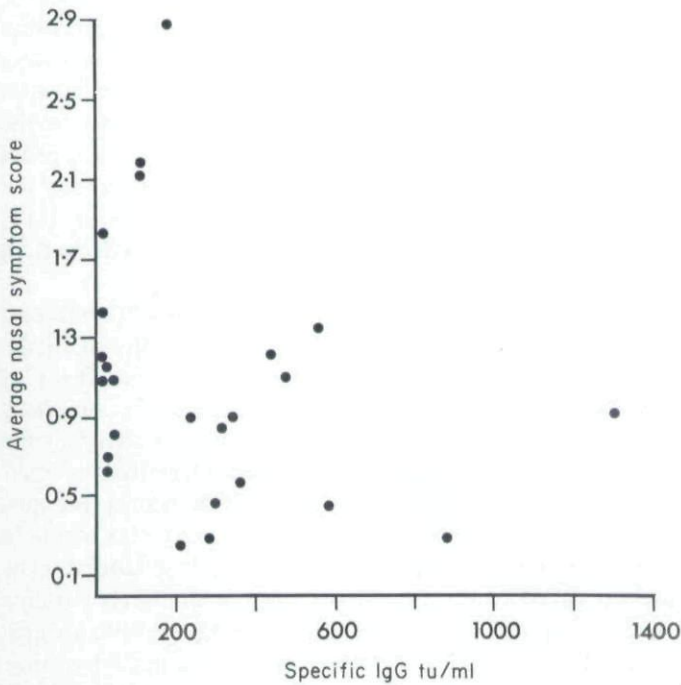


Fig. 7. Average nasal symptom score during the pollen season plotted against specific IgG.

Table 2. Patient acceptability

	Conjuvac	Allpyral
Improved symptoms	16/18	12/18
Would repeat next year	17/18	15/18

similar in each group. In fact, symptom scores appeared to bear little relationship to either the specific IgE (Fig. 6) levels or the specific IgG level (Fig. 7).

Both treatments were generally acceptable to patients with a slightly higher number in the Conjuvac group feeling that treatment had improved their symptoms compared with previous years (Table 2). Three patients in the Conjuvac group and four in the Allpyral group required antihistamines during the pollen season.

Discussion

We have compared the effect of an accepted and proven depot pollen extract Allpyral (Munro-Ashman, 1966; Brown, Thantrey & Jackson, 1979) with Conjuvac a new pollen-alginate conjugate over the 1982 pollen season in Glasgow. More than 75% of patients thought that desensitization had helped their hay fever compared to previous years, giving similar results to other published series (for review see Davies, 1983). However, patients still developed seasonal symptoms and occasionally required other medications such as decongestants and antihistamines. Pre-pollen symptoms were evenly matched. Both groups had an increase in symptoms during the pollen season but the increase in both nasal and eye symptoms was significantly greater in the Allpyral group, suggesting that Conjuvac gave a superior clinical result. This appears to be in keeping with previous laboratory and clinical suggestions that reduction of the number of pollens in a vaccine may improve efficacy (Taylor, Sheldon & Spicer, 1981; Brown, Thantrey & Jackson, 1979). Claims that Conjuvac had less side-effects than other vaccines were not substantiated (Bruno, 1982).

Recent studies with insect venom immunotherapy, showing good correlation between alteration in antibody levels and efficacy, has reawakened interest in the concept of the induction of IgG as 'blocking antibody' to explain the effects of immunotherapy (Lesso, Sobotka & Lichtenstein, 1976). Both vaccines in our study induced similar rises in specific IgE and specific IgG. Although it is known that the seasonal rise in specific IgE is partially suppressed by immunotherapy, we like the other authors found no correlations between specific IgE levels and clinical results (Stenius, Wide & Seymour, 1971; Lichtenstein *et al.*, 1973). Age, however, may play a role in antibody response as those who mounted a high specific IgE response tended to be significantly younger, a factor not taken into account in some publications. All patients had a rise in specific IgG. The changes were similar after desensitization in both groups. Looking at specific IgE and specific IgG, there appeared to be two distinct subgroups. One developed a very high specific IgG level and the other a very high specific IgE level, but no patients developed both. No other factors, such as previous desensitization,

initial antibody levels or type of desensitization used seemed to relate to the final levels. Our observations could suggest a common perhaps age-related controlling pathway. Clinical effectiveness, as judged by symptoms scores, have no relationship to either high specific IgG or high specific IgE. This agrees with other studies which have shown only slight or no correlation with specific IgG levels in hay fever (Gliech *et al.*, 1977; Foucard & Johansson, 1978; Lichtenstein *et al.*, 1973).

Studies performed with ragweed hay fever show that the efficacy of desensitization depends on the cumulative dosage and that symptoms continue to improve over several years desensitization (Norman, 1980). Though this is only a 1-year study we have shown that Conjuvac has similar immunological effects to Allpyral and despite reduction of the vaccine to two grasses has superior clinical results.

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