Prospective, controlled study of a polyvalent pseudomonas vaccine in cystic fibrosis—three year results

D T LANGFORD AND J HILLER

Department of Clinical Immunology, Wellcome Research Laboratories, Beckenham and Department of Paediatrics, City Hospital, Nottingham

SUMMARY Thirty four children with cystic fibrosis allocated to pseudomonas vaccine and control groups were studied for three years. No significant differences were observed in the numbers colonised by Pseudomonas aeruginosa or in the overall disease progress of the two groups.

The unique nature of Pseudomonas aeruginosa infection in cystic fibrosis and its rarity in other classes of patient suggests that the cystic lung environment offers very favourable growth conditions. A gradual transition of the organism from a non-mucoid to a mucoid form has been observed and both forms may be isolated from the sputum during this transition. The mucoid form is virtually impossible to eradicate from the sputum once it is established. High values of antipseudomonal antibodies in cystic fibrosis are associated with severe pulmonary disease and the possibility of antigen/antibody complexes enhancing alveolar damage has been raised. Although it was acknowledged that enhancement of antibody concentrations by vaccination might be of little value in established mucoid infections it was considered reasonable to study the prophylactic value of vaccination in uncolonised patients in an attempt to prevent the initial colonisation with non-mucoid Ps aeruginosa.

A controlled study of pseudomonas vaccine in guinea pigs subjected to intratracheal challenge had shown good protection against pseudomonas pneumonia, and although this was not a model for cystic fibrosis, it provided additional rationale for a human study.

Materials and methods

The vaccine used in this study was a polyvalent pseudomonas vaccine (Lot PEV01, Wellcome) which is a freeze dried, blended extract of 16 international serotypes of Ps aeruginosa.

Thirty four cystic fibrosis patients aged 2 to 18 years with repeatedly negative sputum or cough swab cultures for Ps aeruginosa were divided into two groups, matched for age and sex. The allocation into groups was performed with no knowledge of clinical details. Seventeen children (5 boys, 12 girls; mean age 7-2 years) received vaccine while the remaining 17 (8 boys, 9 girls; mean age 7-3 years) were not immunised and served as a control group. Written, informed consent was obtained from all parents.

The vaccine group received three subcutaneous injections of the polyvalent pseudomonas vaccine at monthly intervals and a further injection at 12 monthly intervals from the start of the study. The dose was 0-25 ml for those under 12 years and 0-5 ml for those aged 12 years or more. Most of the patients entered the study between March and May 1980; seven were entered between then and the end of 1981. Follow up is reported to the end of 1982 for yearly investigations such as radiographs but to the middle of 1983 for culture isolates. Several patients originally allocated to a group acquired pseudomonas infection after the study began but before they could be entered and vaccinated. This led to some imbalance in sex distribution.

Blood samples were collected before each injection in the vaccine group and at yearly intervals in the controls. These were assayed for full blood count, liver function tests, urea and electrolytes, immunoglobulin classes, and selected serotype-specific pseudomonas antibodies using an ELISA technique. Sputum or cough swab cultures were obtained each time the child was seen, usually every two months. A chest radiograph was taken at the beginning of the study and yearly thereafter, avoiding acute infective episodes; this was scored by two
observers using the Chrispin-Norman method.\(^6\) An overall clinical assessment was made at the same time using the Shwachman scoring system,\(^7\) and peak expiratory flow was also measured. Any isolates from the cultures were sent to the Public Health Laboratory Service, Colindale, for serotyping.

A \(t\) test was used to compare control patients with vaccinated patients. In addition, subgroups of patients infected and uninfected at the end of the study with \(P\text{s aeruginosa}\) were identified, and the four subgroups so defined were examined by analysis of variance for any interaction of vaccination and pseudomonas infection on the clinical parameters. Analysis of variance showed an interaction at approximately the 10\% level of significance for most of the nine analyses and at the 1\% level in one, thus making separate comparisons of the four subgroups appropriate.

**Results**

**Comparison of all controls with all vaccinated patients.** The age and sex distribution of the groups is shown in the Figure, and it can be seen that although the groups were equivalent for age, there was a predominance of girls in the vaccine group. The two groups showed small differences with regard to age at diagnosis and mode of presentation of the disease. The mean age at diagnosis in vaccinated patients was 19 months (range 0 to 13 years) and in the control patients 24 months (range 0 to 8 years). Three vaccinated patients presented with meconium ileus compared with four patients in the control group.

There were no reactions to the vaccine apart from one mild local response. No differences were noted between the groups in terms of blood counts, blood chemistry, or immunoglobulin assays.

The antibody responses to a selection of the 16 serotype antigens as measured by ELISA were equivalent to those seen in healthy adult volunteers, and it was of interest that initial titres before vaccination were lower than in healthy adults. The responses to some serotypes were poor. Colonisation with \(P\text{s aeruginosa}\) induced much higher titres than vaccination and these rises were observed against multiple serotypes. This indicates the presence of a common antigen in the vaccine, although the vaccine is serotype specific in protection assays in animals. This suggests that ELISA assays using vaccine antigen do not correlate with protection.

The Chrispin-Norman scores for the radiographs, the Shwachman scores, and the peak flow values available for study are shown in Tables 1, 2 and 3 respectively. Some early values for peak flow were missing, and this reduced the number of evaluable patients for this parameter. The Chrispin-Norman scores showed a trend towards higher scores in the vaccinated subjects compared with the controls but this did not attain statistical significance. No significant differences were seen in any variable either at

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**Figure**  
*Age and sex distribution of vaccinated and control subjects with cystic fibrosis.*

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\(^{6}\) Langford and Hiller.

\(^{7}\) Results.
the start of the trial or in changes in subsequent years when both groups were compared.

**Comparison of subgroups**

**Controls and vaccinated subjects infected by pseudomonas**
Seven controls and six vaccinated subjects developed established infection with *Ps aeruginosa* as defined by three or more positive cultures at three year follow up. Sixty five per cent of isolates from vaccinated subjects and 74% of isolates from controls were non-mucoid strains, and although in some patients the progression from non-mucoid to mucoid was observed with time, in others either the opposite pertained or there was no observed trend. Mixed cultures were occasionally found. There was no significant difference in the numbers infected or in the length of time before infection became established (Table 4). The age and sex of the subgroups were also very similar.

The vaccinated group had larger decreases in Shwachman scores by 1981 and 1982 than the control group (P<0-05 and P<0-01). A larger fall in peak flow was also observed in the vaccinated subjects (P<0-05) but a significantly higher mean peak flow on entry (P<0-001) was also observed.

**Controls and vaccinated subjects uninfected by pseudomonas**
No significant differences were seen for any variable.

**Controls infected and uninfected by pseudomonas**
The infected controls had larger decreases in Shwachman scores by 1982 than the uninfected group.
(P<0.05) but no differences were observed in other variables.

Vaccinated subjects infected and uninfected by pseudomonas
The infected, vaccinated subjects had larger decreases in Shwachman scores by 1980, 1981, and 1982 (P<0.01, P<0.001, and P<0.01) and also a greater fall in peak flow (P<0.05).

Discussion
The possibility of benefit from prophylactic vaccination has been raised by many workers in the field but no controlled studies have been conducted. This study shows that vaccination has so far failed to reduce the rate of pseudomonas colonisation. The study also shows that patients colonised with Ps aeruginosa experienced more rapid clinical deterioration as assessed by Shwachman scores than those remaining uncolonised. In addition, a more rapid decrease in Shwachman scores and peak flow measurements occurred in those patients who were vaccinated and colonised compared with those who were only colonised. These differences, however, are based on small numbers of patients and must be interpreted with caution regardless of the statistical values. Nonetheless, the changes observed in clinical parameters so far raise the possibility that vaccination may increase immune complex formation, and in the absence of any observed benefit the present trial is continuing without further yearly vaccinations.

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References

Correspondence to Dr D T Langford, Clinical Immunology Department, Wellcome Research Laboratories, Beckenham, Kent.

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