

Immunogenicity of 13-Valent Conjugate Pneumococcal Vaccine in Patients 50 Years and Older with End-Stage Renal Disease and on Dialysis

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Patients with end-stage renal disease (ESRD) and on dialysis are at increased risk of pneumococcal disease. We evaluated the immunogenicity of the 13-valent pneumococcal conjugate vaccine (PCV13) in this population. Eligible patients with ESRD and on dialysis were given a single dose of PCV13. The concentrations of serum antibodies against 13 pneumococcal capsular polysaccharides were measured at the baseline and at 2 and 12 months postvaccination. A response to the vaccine was defined as a ≥ 2 -fold increase in antibody concentration from that at the baseline and an absolute postvaccination value of at least 1 $\mu\text{g/ml}$. Seventeen patients completed the study. Increases in the concentrations of antibodies to the vaccine serotype were demonstrated 2 months after vaccination. The geometric mean antibody concentrations at 12 months postvaccination declined by 38% to 72% compared to those measured at 2 months postvaccination. A response to at least 1 serotype in the vaccine was seen in all patients at both 2 and 12 months postvaccination. The overall rate of the response to each individual vaccine serotype varied between 23.5% and 94.1% at 2 months postvaccination and 23.5% and 65% at 12 months postvaccination. Pain at the injection site was the most common local reaction. Vaccination with PCV13 induces antibody responses to vaccine serotypes in patients with ESRD and on dialysis at 2 months postvaccination. However, the decline in antibody concentrations at 12 months postvaccination with a conjugate pneumococcal vaccine requires further study. (This study has been registered at ClinicalTrials.gov under registration no. NCT01974817.)

Patients with end-stage renal disease (ESRD) and on dialysis are predisposed to infections with *Streptococcus pneumoniae* (1). Mortality rates from pneumonia in dialysis patients are about 10 to 16 times higher than those in the general population (2, 3). Furthermore, the emergence of multiple-antibiotic-resistant pneumococcal strains has added to this therapeutic challenge. This has led to an increased focus on vaccination for the prevention of pneumococcal diseases in this subset of patients.

End-stage renal disease is associated with disorders of the adaptive immune system, which result in decreases in antigen-presenting function, the T-cell-mediated immune response, and immunological memory (4, 5). These patients are thus at risk of vaccine hyporesponsiveness. There is evidence of a decreased immunologic response to the 23-valent pneumococcal polysaccharide vaccine (PPSV23) in patients undergoing dialysis compared to that in the general population (6, 7). Moreover, a rapid decline in anti-pneumococcal IgG levels is observed in patients with ESRD within 1 year after vaccination with PPSV23 (8).

PPSV23 predominantly induces a T-cell-independent immune response, and hence, immunologic memory is not achieved (9, 10). Conjugate polysaccharide vaccines, which incorporate a protein carrier (diphtheria toxin cross-reactive material 197 [CRM₁₉₇]) to the purified capsular saccharides of *S. pneumoniae*, elicit a more robust immunological memory (9). The 13-valent pneumococcal conjugate vaccine (PCV13) includes serotypes 19A, 7F, 3, 5, and 6A, which are the most common causes of pneumococcal pneumonia in adults >50 years of age (11). The response to PCV13 in patients with ESRD and on dialysis has not been well studied, and data on long-term immunogenicity after vaccination in this subset of patients are lacking.

The primary objective of this study, which is registered at ClinicalTrials.gov under registration no. NCT01974817, was to

assess the immunogenicity of PCV13 in adults over age 50 years with ESRD and on dialysis.

(This work was presented at the 55th Interscience Conference on Antimicrobial Agents and Chemotherapy, San Diego, CA, 17 to 21 September 2015 [12].)

MATERIALS AND METHODS

Patients. Adults over 50 years of age in the Lansing, MI, area who had ESRD and who were undergoing dialysis were recruited between March 2013 and November 2013. Patients were excluded if they had a history of *S. pneumoniae* infection, had received pneumococcal vaccination within the preceding 5 years, were HIV positive, had functional or anatomic asplenia, or had received immunosuppressive medications or gamma globulin within the previous 6 months. Patients were also excluded from the study if they had any serious unstable medical conditions which the investigators believed would preclude participation in the study.

The study was approved by Michigan State University's Institutional Review Board, and written informed consent was obtained from the subjects prior to entry into the study.

Vaccine and administration. All patients received a single dose of 0.5 ml of PCV13 (Prevnar 13; lot G54897; Wyeth Pharmaceuticals Inc.) ad-

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TABLE 1 Demographics and characteristics of study patients^a

| Characteristic | Baseline value |
|---|---------------------|
| Mean \pm SD age (yr) | 62.6 \pm 9.05 |
| Sex (no. of males/no. of females) | 9/8 |
| No. (%) of patients of the following race: | |
| White | 9 (52.9) |
| Black | 6 (35.3) |
| Hispanic | 1 (5.9) |
| Pacific Islander | 1 (5.9) |
| Mean \pm SD no. of days on dialysis before enrollment | 1,851 \pm 1,631.5 |
| No. (%) of patients who had received pneumococcal vaccination >5 years earlier ^b | 11 (64.7) |
| No. (%) of patients with the following comorbid medical conditions: | |
| Diabetes mellitus | 13 (76.4) |
| Hypertension | 13 (76.4) |
| Congestive heart failure | 5 (29.4) |
| Coronary artery disease | 4 (23.5) |
| Chronic obstructive pulmonary disease | 3 (17.6) |
| Previous renal transplant | 1 (5.9) |

^a Data are for a total of 17 patients.^b More than 5 years prior to enrollment in the study.

ministered intramuscularly in the deltoid area. This dose of the vaccine contains approximately 2.2 μ g polysaccharides of pneumococcal serotypes 1, 3, 4, 5, 6A, 7F, 9V, 14, 18C, 19A, 19F, and 23F and approximately 4.4 μ g of serotype 6B individually conjugated to 34 μ g CRM₁₉₇ carrier protein. Each dose of the vaccine also has 100 μ g polysorbate 80, 295 μ g succinate buffer, and 125 μ g aluminum as an aluminum phosphate adjuvant. The vaccine was supplied in single-dose syringes and stored at 2°C to 8°C. Blood samples were drawn prior to vaccination and at 2 months and 12 months after vaccination. Serum was stored at -20°C until it was assayed. All specimens were assayed within 2 months of collection.

Laboratory methods. The levels of antibodies to each of the 13 serotypes contained in the conjugate vaccine were measured by multianalyte immunodetection (MAID; Focus Diagnostics, Cypress, CA). These panels utilize the Food and Drug Administration standard reference serum 89-S as the calibration standard (13). This test is based on the Luminex flow cytometric system for performing multiple assays simultaneously, though

the specific analytical detail of the assay has not been published. Serum samples were assayed for the concentrations of antibodies to serotypes 1, 3, 4, 5, 6A, 6B, 7F, 9V, 14, 18C, 19A, 19F, and 23F. The lower limit of detection for this test is 0.3 μ g/ml. Increases in concentrations measured by MAID were determined by dividing the postvaccination concentration by the prevaccination concentration. A vaccine serotype response was defined as a ≥ 2 -fold increase in antibody concentration and an absolute postvaccination concentration of at least 1 μ g/ml (14).

Statistical analysis. Specific antibody concentrations were expressed as the geometric mean. Comparisons of antibody concentrations pre- and postvaccination were performed using paired Student's *t* test. A *P* value of <0.05 was considered statistically significant.

RESULTS

A total of 25 patients were enrolled in the study from March to November 2013. Four patients died due to non-vaccine-related causes during the follow-up period. Two patients moved out of the area and were lost to follow-up. One patient decided to discontinue dialysis, and another underwent renal transplantation and thus was no longer eligible to continue in the study. Data for 17 patients were available for final analysis. Baseline patient characteristics are shown in Table 1. Most patients (76.4%) were diabetic, and 11/17 (64.7%) had received pneumococcal vaccination more than 5 years prior to enrollment in the study.

Antibody concentrations. Table 2 shows the geometric mean antibody concentrations (GMCs) at the baseline and at 2 and 12 months postvaccination. The increase in antibody concentrations at 2 months postvaccination compared to the concentrations at the baseline was statistically significant for the concentrations of antibodies to all 13 serotypes contained in PCV13. However, the increase in antibody concentrations at 12 months postvaccination compared to the concentrations at the baseline was statistically significant only for the concentrations of antibodies to serotypes 5, 19F, 6B, and 18C.

The geometric mean antibody concentrations at 12 months postvaccination declined by 38% to 72% compared to the antibody concentrations at 2 months postvaccination. This difference was statistically significant (*P* < 0.05) for the concentrations of antibodies to several serotypes, as shown in Table 2.

Vaccine response. Figure 1 displays the responses of the patients to the vaccine serotypes at 2 months and 12 months

TABLE 2 Antibody response as GMCs^a

| Serotype | GMC (μ g/ml) at: | | <i>P</i> value between GMC at baseline and 2 mo | GMC (μ g/ml) at 12 mo postvaccination | <i>P</i> value between GMC at: | |
|----------|-----------------------|----------------------|---|--|--------------------------------|----------------|
| | Baseline | 2 mo postvaccination | | | Baseline and 12 mo | 2 mo and 12 mo |
| 1 | 0.99 (0.54–1.82) | 3.53 (1.85–6.75) | 0.009 | 1.46 (0.80–2.64) | 0.44 | 0.004 |
| 3 | 0.47 (0.33–0.67) | 1.88 (0.82–4.30) | 0.035 | 0.79 (0.43–1.46) | 0.11 | 0.04 |
| 4 | 0.44 (0.33–0.58) | 0.92 (0.54–1.58) | 0.023 | 0.57 (0.37–0.87) | 0.059 | 0.023 |
| 5 | 0.79 (0.46–1.37) | 7.35 (3.15–17.13) | 0.011 | 2.80 (1.30–6.01) | 0.045 | 0.006 |
| 6A | 0.56 (0.42–0.74) | 6.80 (2.78–16.61) | 0.014 | 1.93 (0.86–4.32) | 0.077 | 0.027 |
| 14 | 2.09 (0.81–5.39) | 13.84 (6.69–28.63) | 0.048 | 5.95 (3.07–11.52) | 0.61 | 0.078 |
| 19F | 1.36 (0.70–2.63) | 9.99 (6.23–16.04) | 0.03 | 4.56 (2.90–7.18) | 0.026 | 0.048 |
| 23F | 0.62 (0.39–0.99) | 6.12 (2.47–15.20) | 0.01 | 2.24 (1.11–4.52) | 0.057 | 0.018 |
| 6B | 0.57 (0.34–0.96) | 8.35 (3.35–20.78) | 0.009 | 3.08 (1.49–6.36) | 0.013 | 0.015 |
| 7F | 1.04 (0.54–1.99) | 5.71 (2.82–11.55) | 0.03 | 2.48 (1.29–4.77) | 0.07 | 0.04 |
| 18C | 1.14 (0.57–2.27) | 7.86 (4.26–14.51) | 0.021 | 4.23 (2.48–7.19) | 0.003 | 0.052 |
| 19A | 2.18 (0.90–5.24) | 9.86 (4.45–21.82) | 0.039 | 3.11 (1.38–6.99) | 0.33 | 0.042 |
| 9V | 1.11 (0.65–1.90) | 3.47 (2.08–5.79) | 0.042 | 1.36 (0.88–2.09) | 0.827 | 0.016 |

^a Data are for a total of 17 patients. Data in parentheses are 95% confidence intervals.

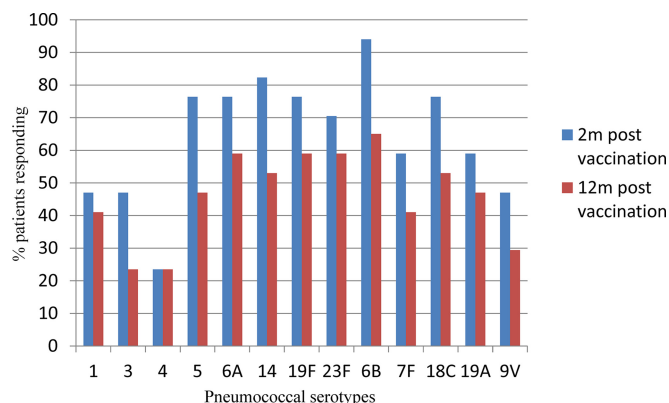


FIG 1 Percentage of patients responding to each serotype ($n = 17$). 2m and 12m, 2 and 12 months, respectively.

postvaccination. All patients responded to at least 1 serotype at both 2 months and 12 months postvaccination, while a response to >75% of the vaccine serotypes was observed in 9/17 (53%) patients at 2 months postvaccination and in 4/17 (23.5%) patients at 12 months postvaccination. Responses to <25% of the vaccine serotypes were observed in 6/17 (35.3%) patients at 12 months postvaccination. The best response noted was to vaccine serotype 6B, with 16/17 (94.1%) patients responding to that serotype at 2 months postvaccination. Responses to serotypes 19A and 7F were seen at 2 months postvaccination in 10/17 (58.8%) patients each, while the response rate at 12 months postvaccination decreased to 47% (8/17) and 41.2% (7/17), respectively. Similarly, there was a significant decrease in the antibody response at 12 months postvaccination compared to that at 2 months postvaccination for the other vaccine serotypes except serotype 4.

Adverse effects after vaccination. An adverse reaction to vaccination was observed in 4/25 (16%) patients. Local reactions were reported by 2 patients. These reactions were mild and included injection site pain in both patients. Additionally, mild redness at the injection site was noted in one of the patients with injection site pain. Systemic reactions were mild and were noted by 2 patients. Both patients reported generalized muscle pain and fatigue after vaccination which resolved within 48 h.

DISCUSSION

Patients with ESRD and on dialysis have altered immunity, which increases the risk of severe infections (4, 5). The burden of pneumococcal disease in patients with ESRD is high, with *S. pneumoniae* being the cause of more than half of the reported cases of pneumonia in dialysis patients (1). Patients with chronic kidney disease (CKD) who do not mount an adequate response to PPSV23 are more likely to develop pneumococcal infections than patients who respond to the vaccine (15).

A recent study identified serotype 19A to be the most common serotype responsible for pneumococcal pneumonia in adults >50 years of age in the United States, followed by serotypes 7F/A, 3, 5, and 6A (11). In our study, the best response to the serotypes in PCV13 was to serotypes 5 and 6A, with 13/17 (76.5%) patients each responding to these serotypes at 2 months. The lowest response was to serotype 3 (47% of patients). Thus, in dialysis patients, PCV13 elicited a good antibody response at 2 months postvaccination to the common pneumococcal serotypes responsible

for almost 75% of cases of pneumococcal pneumonia in U.S. adults >50 years old.

To the best of our knowledge, this is the first study to evaluate the immunological response to conjugate pneumococcal vaccines in adult patients with ESRD and on dialysis. In children on dialysis, a trial with a 7-valent conjugate pneumococcal vaccine demonstrated antibody responses against at least one serotype in all patients at 60 days postvaccination (16). Only 9/24 (37.5%) children on dialysis achieved a 4-fold rise in the concentrations of antibodies to at least five of the seven serotypes over the concentrations at the baseline. In our study, a response to 10 out of the 13 serotypes in the vaccine was seen in a majority of patients at 2 months postvaccination.

We observed a significant decrease in the concentrations of antibodies to most of the PCV13 serotypes at 12 months postvaccination, and the overall rate of response to individual serotypes was also poor at 12 months postvaccination. A similar decrease in antibody concentrations, often within the first year after vaccination, has been observed in patients with chronic renal disease after vaccination with PPSV23 (8). In a study of patients with renal failure and on hemodialysis, both IgG1 and IgG2 concentrations doubled 4 weeks after vaccination with PPSV23 (8). However, the antibody concentrations decreased at 1 year, with diabetic and hypertensive patients demonstrating the greatest decline.

The reasons for the rapid decline of antibody concentrations in dialysis patients are likely multifactorial. ESRD has been associated with disturbance of the adaptive immune system, with a resulting decrease in immunological memory (4, 5). Moreover, gradual removal of a proportion of the serum antibody level may occur during dialysis and may contribute to the reduction in antibody concentrations.

Our study has several limitations. First, the sample size was small, and there was further attrition of the patient population, as mentioned above. For ethical reasons, we did not have a control group who could be given a placebo injection. Additionally, we decided not to compare PCV13 with PPSV23, as several authors have reported a less than adequate response to vaccination with PPSV23 in patients with renal failure and immunocompromised patients (17, 18). Finally, our study did not assess clinical pneumococcal disease.

In conclusion, patients with ESRD and on dialysis demonstrated an antibody response to PCV13 that decreased at 12 months postvaccination. Additional studies of the response of this unique population to a conjugate pneumococcal vaccine with measurement of antibody concentrations at longer intervals are needed.

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