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SHORT REPORT

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Response to PCV13 vaccination in patients with multiple myeloma versus healthy controls

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ABSTRACT

Infections are a major cause of morbidity and mortality in individuals with multiple myeloma (MM). These individuals exhibit humoral dysfunction and show a suboptimal response to pneumococcal polysaccharide vaccine (PPV23). Since pneumococcal conjugate vaccine (PCV13) elicits a T cell dependent response, it is recommended in patients with multiple myeloma. This study compares the initial response to PCV13 and durability of the response at 6 months in patients with multiple myeloma versus normal controls. Seven patients with multiple myeloma and 18 control patients were enrolled in the study. Streptococcal pneumonia serotype IgG titers were drawn at baseline, day 30, and day 180 after MM patients and controls received PCV13. Although vaccination with PCV13 produced a similar initial response in patients with multiple myeloma compared to control subjects, the duration of response may have waned in patients with multiple myeloma as compared to control subjects.

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Introduction

Multiple myeloma (MM) is a common lymphoproliferative disorder that remains incurable despite dramatic improvement in overall survival rates.[1] Infectious complications result in death in approximately 45% of MM patients, and two-thirds of these infections are due to pneumonia.[2,3] Vaccination is one the strategies employed to help reduce the threat of infection in this at-risk patient population.

Individuals with MM have historically received vaccination with pneumococcal polysaccharide vaccine (PPV23, Pneumovax®). MM patients have defects in their humoral immunity, and show a suboptimal immune response to PPV23.[4,5] Pneumococcal conjugate vaccine (PCV13, Prevnar), demonstrates greater immunogenicity through a T cell dependent response, leading to longer lasting immunologic memory.[6] Individuals with MM theoretically have intact T cell function, and therefore may respond better to PCV13 as compared to PPV23. As compared to PPV23, PCV13 has consistently demonstrated a non-inferior response to all pneumococcal serotypes and a significantly greater response to the majority of common serotypes in the general population.[7]

Despite the fact that existing guidelines recommend vaccinating MM patients with PCV13,[8] there is paucity of data for this vaccination strategy.[9] We therefore compared the immune response to PCV13 in patients with MM versus normal controls. Our understanding of vaccine response will be crucial in establishing a successful, tailored approach to infection prevention, thereby further addressing a leading complication in these patients, and potentially decreasing associated morbidity and mortality.

Results and discussion

A total of 25 patients were enrolled in the study – 18 normal controls and 7 patients with MM. The mean age was 70.3 ± 5.2 years for normal controls, versus 65.1 ± 12.7 years for MM patients. 3/18 (16.6%) of the normal controls were males, versus 4/7 (62.5%) males in the MM group. In the MM group, no patients had recently undergone autologous bone marrow transplant, 3/7 (42.9%) were receiving chemotherapy during this study, 2/7 (28.9%) had smoldering disease. The median time since diagnosis of MM was 30 months (range 0–133 months).

The initial responses of both groups to 12/13 IgG serotypes used in PCV13 are reported in the attached figure (Figure 1). There was no statistically significant difference in immediate response to PCV13 vaccine between MM patients (3/7 responders) and normal controls (7/18 responders). The durability of response was measured by looking at the number of patients at 6 months in each group that had maintained an adequate response. Only 1/3 of the responders in the MM group had maintained a response, as compared to 7/7 responders in the control group ($p = 0.02$). In both the MM and control patients who maintained an adequate response at 6 months, the responding serotypes remained the same over the duration of the study.

Additionally, age alone did not affect the initial immune response ($p = 0.37$) or response at six months suggestive of memory ($p = 0.59$). Gender alone also did not affect the initial

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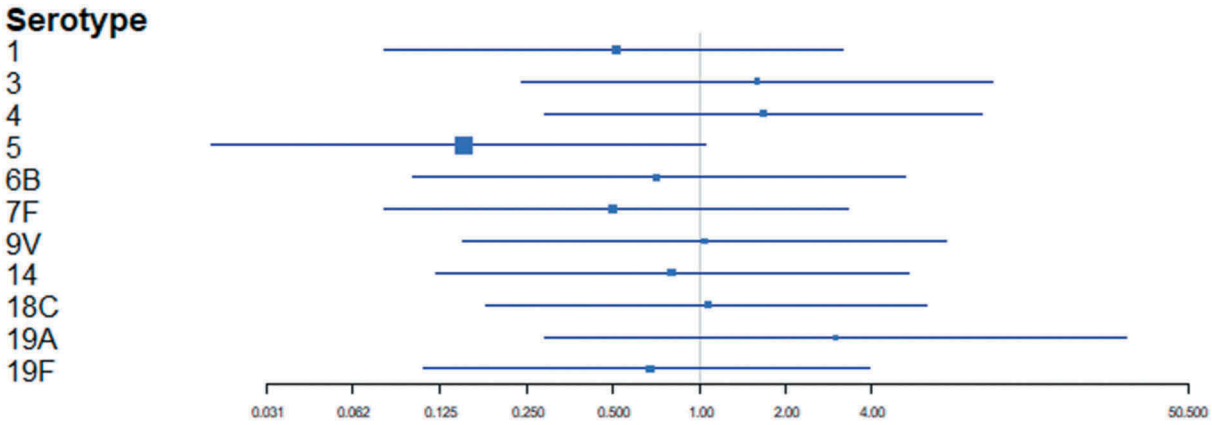

Figure 1. Odds ratio of response by IgG serotype with 95% CI

immune response (p = 0.86) or memory at six months (p = 0.76). In a multivariate analysis, gender and age together also did not affect the initial immune response (p = 0.66) or memory at six months (p = 0.76).

MM patients have abnormal humoral immunity, and may therefore not adequately respond to vaccination with PPV23. Therefore, the current guidelines recommend using PCV13 for vaccination against streptococcus pneumoniae in MM patients.[8] Our results show that vaccination with PCV13 produces a similar immunologic response in MM patients as compared to normal controls, but the duration of response to vaccination may wane at 180 days, as compared to the control group.

For a definition of an immune response, we chose commonly checked immunologic parameters used in the clinical management of primary and secondary immunodeficiency. Although interpretation of an adequate response to pneumococcal vaccination remains debatable, we used the most widely accepted criteria. This evaluation of checking pre and post vaccination IgG titers is different from the definition of vaccine efficacy used by the FDA,[10] and likely explains our lower than expected rates of vaccine responders, particularly in group of normal controls. Although this is different than endpoints needed for vaccine approval, we think it is most relevant to clinical practice, and remains one of the best clinical predictors for protection against infection with streptococcus pneumoniae. Given their known humoral defects, the authors feel that clinicians should be encouraged to complete this type of evaluation more often in MM patients.

There are limitations of our study, most notably the small numbers of MM patients that were enrolled. Due to successful vaccination programs, such as routine series of three vaccinations for patients with MM undergoing autologous stem cell transplant, it was difficult to find MM patients who had not previously been vaccinated with PCV13. Despite the small number of MM patients, the authors feel that these results serve as a proof of concept that vaccination in MM patients may not be the most efficacious strategy in preventing infection with streptococcus pneumoniae. We hope these findings lead to additional, larger studies on this topic. Lastly, the lower than expected rates of responders to PCV13, particularly in the group of normal controls, is likely explained by our defined clinical criteria for response to vaccination.

Despite these considerations, the authors feel the findings are noteworthy, and this remains the only study to date to show that MM patients respond to PCV13 vaccination similarly to normal controls, but may not maintain a sustained response over time. MM patients may therefore remain at risk of pneumococcal infection despite vaccination, and it remains imperative to be vigilant about additional strategies to prevent infectious complications in this high risk population.

Methods

In this prospective cohort study, patients were enrolled at Rochester Regional Health from December 2015 through October 2016. All patients meeting criteria were offered enrollment in the study. Inclusion criteria included any patient with multiple myeloma or patients > 65 years old in whom pneumococcal vaccination was indicated as standard of care. Exclusion criteria included the following: 1) prior history of PCV13, 2) PPV23 within the past 1 year, 3) previously diagnosed immunodeficiency or other immunosuppressive states, 4) active malignancy, 5) immunotherapy or immunochemotherapy within 6 months, 6) therapy with immunoglobulin replacement, 7) chronic oral corticosteroids at an equivalent dose of prednisone > 10 mg daily. Appropriate patients were enrolled consecutively

The primary endpoint was the response of IgG titers to pneumococcal serotypes after PCV13 in subjects with MM compared to normal controls. The secondary endpoint was the duration of IgG response to pneumococcal serotypes in patients with MM compared to normal controls. Patients received PCV13 and had baseline titers for IgG serotypes for streptococcus pneumoniae at visit 1. We used ELISA (fluoroimmunoassay) to measure treatment response. Follow up IgG titers were drawn on day 30 (± 7 days) and day 180 (± 30 days). Individual serotype response was defined as following:[11]

If the baseline titer < 1.3 μg/ml, increase 2-fold to above 1.3 μg/ml OR increase 4-fold
If the baseline titer was > 1.3 μg/ml, increase 2-fold
Overall response in individuals was defined as response in > 70% of the serotypes.

Vaccine response was compared between the two groups for antibody titers of 12/13 IgG serotypes in PCV13. Given the small

sample size, Fischer's exact test was used to analyze odds ratio significance for the 2 × 2 contingency tables. Type I error rate was set less than 0.05. The odds ratio confidence intervals were derived from the log odds ratios using standard methods. SAS® University edition was used for analysis. Binary logistic regression was used to assess the effect of gender and age on the categorical variables of initial immune response and memory.

Key points

- Vaccination with PCV13 produces a similar initial response in patients with multiple myeloma as compared to normal controls.
- Duration of response to PCV13 may wane in patients with multiple myeloma as compared to normal controls.

Disclosure of potential conflicts of interest

No potential conflict of interest was reported by the authors.

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