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Association between PCV13 pneumococcal vaccination and risk of hospital admissions due to pneumonia or sepsis among patients with haematological malignancies: a single-centre retrospective cohort study in Israel

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ABSTRACT

Objectives Patients with haematological malignancies receiving immunosuppressive therapy are at highest risk of invasive pneumococcal disease. Our goal was to investigate whether vaccination of haematological patients with pneumococcal 13-valent conjugated vaccine (PCV13) prior to therapy initiation is associated with decreased hospital admissions due to pneumonia or sepsis within 12 months.

Design and setting A longitudinal retrospective cohort study was conducted at the haematology unit of Carmel Medical Center, Israel.

Participants Information on adult patients (>18 years) who were diagnosed between 1 January 2009 and 30 December 2019 with haematological malignancies and received immunosuppressive therapy was retrieved from the electronic health records. Patients with haematological malignancies who received the PCV13 vaccination during or after initiation of the immunosuppressive therapy were excluded from the study.

Outcome measures A multivariate logistic regression model was performed to determine whether PCV13 vaccination is associated with fewer hospital admissions due to pneumonia or sepsis.

Results The cohort included 616 patients, of which 418 (67%) patients were not vaccinated and 198 (33%) were vaccinated. Within 12 months, 15.1% (n=63) of non-vaccinated patients compared with only 7.1% (n=14) of the vaccinated patients were hospitalised due to pneumonia or sepsis. The logistic regression analysis demonstrated that receiving PCV13 vaccination is associated with 45% (OR=0.45, 95% CI: 0.246 to 0.839, p=0.012) reduced odds of being hospitalised due to pneumonia or sepsis in patients with haematological malignancies receiving immunosuppressive therapy.

Conclusion This is the first observational study to demonstrate the association between PCV13 vaccination and hospital admissions in patients with haematological malignancies receiving immunosuppressive therapy. Patients receiving PCV13 vaccination before immunosuppressive therapy initiation had significantly reduced odds of hospitalisation due to pneumonia or sepsis compared with non-PCV13-vaccinated patients.

Strengths and limitations of this study

- The study data are retrieved from Clalit Health Services database, which documents all types of vaccinations and hospital admissions.
- All hospital admissions due to pneumonia or sepsis were verified by the authors via review of the patient chart and discharge summary.
- The study is an observational, single-centre study, and causality cannot be directly inferred.
- The control group consisted of comparable historical controls.

INTRODUCTION

Haematological malignancies are the most common cause of cancer-related deaths.[1] The lifetime probability to develop non-Hodgkin's lymphoma (NHL) in the USA is 1 in 42 for males, and 1 in 54 for females.[1] The age-adjusted mortality rate from NHL is 4.4/100 000 for females and 7.3/100 000 for males.[1] The underlying malignancy and the immunosuppressive therapy place people at risk of severe infection, which is a frequent cause of death. Patients with multiple myeloma (MM), for example, have frequent infectious complications resulting in death in approximately 45% of the patients, two-thirds of these infections are due to pneumonia.[2] In a national-level US study, the cumulative incidence of severe sepsis was 43 cases per 1000 people living with NHL.[3] The relative risk of

severe sepsis in those with NHL was 10 times greater than observed in the population without cancer.[3]

In patients with haematological malignancies, several factors predispose to infectious complications, including immune deficiencies associated with the primary malignancy and the use of multiple lines of cytotoxic therapy that are frequently associated with prolong neutropenia and bone marrow failure. These complications usually lead to increased risk of serious infections requiring hospitalisation.[4,5]

One of the most serious infectious complications is invasive pneumococcal disease (IPD), defined as isolation of *Streptococcus pneumoniae* from a normally sterile body site (typically blood or cerebrospinal fluid).[6] Among adults with haematological malignancies, the IPD incidence is estimated to be 0.5% per year since diagnosis, 50-fold higher than in the general population.[7]

Primary prevention of IPD relies on two available pneumococcal vaccines: the pneumococcal 13-valent conjugated vaccine (PCV13) and the pneumococcal 23-valent polysaccharide vaccine (PPSV23). A low antibody response to PPSV23 has been described in the general elderly population as well as in patients with haematological malignancies, including patients with MM and lymphoma.[8] PCV13, however, demonstrates a greater immunogenicity through a T cell-dependent response, leading to longer lasting immunological memory.[2]

The effectiveness of PCV13 in preventing pneumonia was demonstrated in the community-based CAPITA Study, with 84 496 adults over 65 years of age.[9] The CAPITA Study showed a vaccine efficacy of 45.6% to prevent community-acquired pneumonia and 75% to prevent IPD.[9] Other studies performed with the PPSV23 have revealed less than 40% protective antibody levels after vaccination.[10 11]

The Infectious Diseases Society of America (IDSA), as well as other organisations, such as the Israel Ministry of Health (MoH), published recommendations regarding the vaccination of immunocompromised patients.[8] The proper timing of immunisation in patients with cancer is a key component of achieving efficient vaccine protection. In general, patients with malignancy should receive the PPSV23 4–6 weeks prior to chemotherapy, and no later than 2 weeks prior to chemotherapy initiation. The PCV13 vaccination is given as a single dose in addition to PPSV23.[12 13]

The immune response following PCV13 vaccination in patients with haematological malignancies was evaluated.[11 12] PCV13 vaccination in patients with chronic lymphocytic leukaemia, for example, induces an immune response in a considerable proportion of patients (58%) although less than in healthy controls (100%).[14] Individuals with MM have historically received the PPSV23 vaccination, but this has usually resulted in a suboptimal immune response, most probably due to a defect in their humoral immunity system.[2] Poor immune function and suboptimal response to pneumococcal vaccine, which contribute to the high rates and increased IPD-related mortality, were observed in patients with haematological malignancies and patients following organ or bone marrow transplantation.[7]

Several unresolved questions are still present regarding the use of PCV13 in various groups of patients. The effect of PCV13 vaccine on preventing IPD prior to the initiation of immunosuppressive therapy in patients with haematological malignancies has not been rigorously tested. Additionally, a paucity of data exists regarding vaccine effectiveness in patients treated with targeted therapy against B or T lymphocytes.[15] In this paper, we conducted a retrospective cohort study to assess whether vaccination of haematological patients with PCV13 prior to chemotherapy and/or biological therapy initiation was associated with decreased hospital admissions due to pneumonia or sepsis within 12 months of therapy initiation.

METHODS

Study design and setting

A longitudinal retrospective cohort study was conducted at the haematology unit of Carmel Medical Center (CMC), Haifa, Israel, between 1 January 2009 and 30 December 2019. The data were retrieved from the electronic health records (EHRs) and the computerised databases of Clalit Health Services (CHS). Retrieved data included patients' clinical and personal characteristics, namely, vaccination status, hospitalisation (dates and cause) and type of therapy (chemotherapy and/or biological therapy).

Study population

The study population included patients with haematological malignancies (with the exception of patients with acute leukaemia). PCV13 vaccination was recommended to all patients as soon as it became available for general use, that is, as of 1 June 2016. This retrospective analysis included two groups of patients: those who did not receive the PCV13 vaccination and patients who received PCV13 vaccination prior to initiation of immunosuppressive therapy.

Inclusion and exclusion criteria

The study included records of patients over 18 years old who have received chemotherapy and/or biological therapy. We excluded patients who were not members of CHS due to unavailability of follow-up data. We also excluded patients with acute leukaemia, due to the paucity of patients and the aggressive nature of the disease, and patients who received the PCV13 vaccination after immunosuppressive therapy was commenced.

Study variables

The dependent variable was the first hospitalisation due to pneumonia or sepsis within 12 months after initiation of biological therapy and/or chemotherapy. The EHR of our healthcare system is very accurate in recording vaccination status. The decision regarding patient hospitalisation due to pneumonia or sepsis was made according

to the diagnosis on discharge documentation, based on the following criteria: fever, dyspnoea, leucocytosis, and chest X-ray or chest CT. Accurate data regarding results of blood cultures were not available due to initiation of antibiotics therapy prior to drawing blood cultures in a significant proportion of patients. Therefore, we could not accurately assess the proportion of positive blood cultures.

The independent variable was vaccination with PCV13.

Control variables included demographic variables, such as age, gender, country of birth, marital status (eg, married, single or lives alone) and place of living. General clinical variables included functional status according to ECOG (Eastern Cooperative Oncology Group) performance scale.[16] The disease-specific clinical variables are as follows: age at treatment; primary haematological disease (lymphoproliferative disease, myeloproliferative disease and MM); type of immunosuppressive therapy (chemotherapy and/or biological therapy); risk of severe neutropenia (<500 neutrophils/µL—high, moderate or low) (more than 7 days, less than 7 days, no neutropenia); and splenectomy status.[17]

Vaccination procedure

The PCV13 vaccination procedure was commenced at CMC on 1 June 2016 and included an intramuscular injection of 0.5 mL of polysaccharides from 13 pneumococcal serotypes conjugated to a non-toxic diphtheria toxin (Prevenar, Pfizer, USA).

Statistical analyses

Descriptive statistics (frequency, means and SD) were performed to describe patients' demographic and clinical characteristics. Statistical significance of differences and associations between vaccinated and non-vaccinated patients, and between those who were or were not hospitalised due to pneumonia or sepsis within 12 months of treatment initiation, were analysed using a Student's t-test for continuous variables and χ^2 test for categorical variables. To determine the contribution of the PCV13 vaccine to the risk of first hospitalisation due to pneumonia or sepsis within 12 months, a multivariate logistic regression model controlling for known confounders was performed. Variables were entered into the regression model if a statistically significant association ($p<0.05$) was found in the bivariate associations with the dependent variable. All statistical analyses were carried out using SPSS statistical software V.23.

Patient and public involvement

There was no patient or public involvement.

RESULTS

The study population included 616 patients; of these, 67% (n=418) patients did not receive PCV13 vaccine and 33% (n=198) received PCV13 vaccine prior to initiation of immunosuppressive therapy.

Table 1 Demographic and clinical characteristics of vaccinated and non-vaccinated patients

	Non-vaccinated (n=418, 67%)	Vaccinated (n=198, 33%)	
Variable	**N (%)**	**N (%)**	**P value**
Gender			0.219
Male	229 (54.8)	98 (49.5)	
Female	189 (45.2)	100 (50.5)	
Country of birth			0.079
Israel	209 (50)	114 (57.6)	
Not Israel	209 (50)	84 (42.4)	
Living area			0.621
City	318 (76.1)	147 (74.2)	
Rural	100 (23.9)	51 (25.8)	
Family status			0.773
Married	319 (76.3)	149 (75.3)	
Not married	99 (23.7)	49 (24.7)	
Splenectomy			0.309
Yes	6 (1.4)	1 (0.5)	
No	412 (98.6)	197 (99.5)	
Haematological diagnosis			0.043
Lymphoid malignancy	318 (76.1)	160 (80.8)	
Myeloid malignancy	32 (7.7)	5 (2.5)	
Multiple myeloma	68 (16.3)	33 (16.7)	
Age at treatment			0.372
19–65	154 (36.8)	82 (41.4)	
66–75	137 (32.8)	66 (33.3)	
76+	127 (30.4)	50 (25.3)	
ECOG performance score			0.001
Dependent	37 (8.9)	4 (2)	
Not dependent	381 (91.1)	194 (98)	
Treatment type			0.035
Chemotherapy	131 (31.3)	49 (24.7)	
Biological	19 (4.5)	18 (9.1)	
Combined treatment	268 (64.1)	131 (66.2)	
Risk of neutropenic fever			0.098
High risk	65 (15.6)	28 (14.1)	
Moderate risk	335 (80.1)	153 (77.3)	
Low risk	18 (4.3)	17 (8.6)	

ECOG, Eastern Cooperative Oncology Group.

Table 1 describes the participants' sociodemographic and clinical characteristics. Among non-vaccinated patients, 36.8% were aged between 18 and 65 years, 32.8% were between 66 and 75 years, and 30.4% were older than 76 years (table 1). In the vaccinated group, 41.4% were aged between 18 and 65 years, 33.3% were between 6 and 75 years, and 25.3% were older than 76 years (p=0.372). More independent patients (according to ECOG performance score) were documented in the vaccinated

patients' group compared with the non-vaccinated (98% vs 91.1%, p=0.001). The most prevalent haematological diagnosis was lymphoid malignancy (76.1% among the non-vaccinated and 80.8% among the vaccinated), followed by MM (16.3% among the non-vaccinated and 16.7% among the vaccinated) and myeloid malignancy (7.7% among the non-vaccinated and 2.5% among the vaccinated). Most of the patients had a moderate risk of neutropenic fever (non-vaccinated—80.1%, vaccinated—77.3%).

Table 2 presents the association between the demographic and clinical characteristics and the rate of hospitalisation due to pneumonia or sepsis within 12 months after immunosuppressive therapy initiation. Among patients who were admitted within 12 months after therapy initiation, due to pneumonia or sepsis, non-vaccinated patients were the vast majority (81.8% vs 18.2%, p=0.005). A significant association was found between age at treatment and hospitalisation rates. As anticipated, in both groups, patients older than 76 years of age had higher rates of hospitalisation compared with younger patients between 18 and 65 years of age (p=0.014). The highest rates of hospitalisation were found among the patients with myeloid malignancy and MM compared with patients with lymphoid malignancy (p=0.01).

Table 3 shows a logistic regression analysis of factors associated with 12-month hospitalisation due to pneumonia or sepsis. Vaccinated patients had reduced odds of hospitalisation due to pneumonia or sepsis within 12 months since treatment initiation (OR=0.45, 95% CI: 0.246 to 0.839, p=0.012). Additionally, older age (76+ years) was associated with increased hospitalisation odds relative to the age group 19–65 years (OR=2.082, 95% CI: 1.102 to 3.934, p=0.024). The type of haematological malignancy was not significantly associated with the odds of hospitalisation.

Table 2 Association between demographic and clinical characteristic and hospitalisation rates due to pneumonia or sepsis within 12 months

	No admission within 12 months	Admission within 12 months	
	N (%)	N (%)	P value
Vaccination status			0.005
Vaccinated	184 (43.1)	14 (18.2)	
Non-vaccinated	335 (65.9)	63 (81.8)	
Gender			0.446
Male	283 (52.5)	44 (57.1)	
Female	256 (47.5)	33 (42.9)	
Haematological diagnosis			0.01
Lymphoid malignancy	428 (79.4)	50 (64.9)	
Myeloid malignancy	28 (5.2)	9 (11.7)	
Multiple myeloma	83 (15.4)	18 (23.4)	
Country of birth			0.41
Israel	286 (53.1)	37 (48.1)	
No Israel	253 (46.9)	40 (51.9)	
Family status			0.476
Not married	132 (24.5)	16 (20.8)	
Married	407 (75.5)	61 (79.2)	
Living area			0.972
City	407 (75.5)	58 (75.3)	
Rural	132 (24.5)	19 (24.7)	
ECOG performance score			0.359
Dependent	34 (6.3)	7 (9.1)	
Not dependent	505 (93.7)	70 (90.9)	
Risk of neutropenic fever			0.975
High risk	81 (15)	12 (15.6)	
Moderate risk	427 (79.2)	61 (79.2)	
Low risk	31 (5.8)	4 (5.2)	
Splenectomy			0.886
No	533 (98.9)	76 (98.7)	
Yes	6 (1.1)	1 (1.3)	
Treatment type			0.635
Biological treatment	33 (6.1)	4 (5.2)	
Chemotherapy treatment	154 (28.6)	26 (33.8)	
Combination treatment	352 (65.3)	47 (61)	
Age at treatment			0.014
19–65	218 (40.4)	18 (23.4)	
66–75	173 (32.1)	30 (39)	
76+	148 (27.5)	29 (37.7)	

ECOG, Eastern Cooperative Oncology Group.

DISCUSSION

In this study, we investigated the association between PCV13 vaccination and hospital admissions due to pneumonia or sepsis in a cohort of patients with haematological malignancies, within 12 months since initiation of therapy. This study is the first to demonstrate in a large cohort of patients with haematological malignancies that PCV13 vaccine administration prior to immunosuppressive therapy is associated with reduced odds of hospital admission due to pneumonia or sepsis, and that vaccination was associated with a 55.6% reduced odds of hospitalisation. These significant results support the latest IDSA-recommended guidelines to vaccinate patients with haematological malignancies with PCV13 prior to immunosuppressive therapy, which later have also been adopted by international organisations, such as the Israel MoH.[18 19]

For this study, we used the CHS data warehouse that comprises information from patients' EHRs and administrative data. This is a unique database which encompasses all records of vaccinations in any care setting as well as patients' demographics, all clinic visits, disease characteristics, treatment and hospital admissions. All vaccination records were verified by the study authors including vaccine date.

Prior to our study, the effectiveness of PCV13 in preventing pneumonia was only demonstrated in the community-based CAPITA Study.[20] Although patients

Table 3 Logistic regression analysis of factors associated with 12-month hospitalisation due to pneumonia or sepsis

Variable	OR	95% CI Lower	95% CI Upper	P value
Non-vaccinated (reference)				
Vaccinated	0.454	0.246	0.839	0.012
Age at treatment				
19–65 (reference)				
66–75	1.915	1.022	3.588	0.043
76+	2.082	1.102	3.934	0.024
Haematological diagnosis				
Lymphoid malignancy (reference)				
Multiple myeloma	1.704	0.936	3.101	0.081
Myeloid malignancy	2.092	0.919	4.762	0.079

undergoing immunosuppressive therapy were previously recommended to be vaccinated with PCV13 prior to treatment initiation,[12] no study has demonstrated the clinical benefit in reducing severe pneumonia or sepsis, and hospital admissions following vaccination with PCV13 in these patients.

As anticipated, factors other than PCV13 vaccination also influence the risk of admission due to pneumonia or sepsis.[21] In our cohort, age >65 years old and the type of malignancy were associated with increased risk of hospital admission due to pneumonia or sepsis, in the bivariate analysis. The regression analysis demonstrated, however, that the PCV13 vaccination has a protective effect controlling for age and the type of malignancy. The IPD incidence among patients with haematological malignancies is 0.5% per year, which is 50-fold higher than in the general population.[7] However, no data were found regarding hospitalisation rates due to IPD or sepsis in patients with haematological malignancies.

The main strength of our study is our ability to retrieve accurate information on all hospital admissions in a large cohort of patients treated in our medical centre over a period of 10 years. To verify that the reason for hospital admissions was pneumonia or sepsis, we reviewed the EHR of all study participants. Blood culture data were limited as in a significant proportion of patients, the antibiotic treatment was initiated prior to drawing blood cultures. We therefore could not make any conclusion regarding the incidence of invasive pneumococcal infection. Although our retrospective study is inherently limited (compared with a randomised trial), our findings demonstrate similarity in sociodemographic and clinical characteristics between vaccinated and non-vaccinated patients, except for type of disease, treatment modalities and functional dependency. This difference might have been the result of differences in patients' age and thus differences by disease were no longer statistically significant after controlling for age groups in the multivariate regression. Treatment modality differences between vaccinated and non-vaccinated treatment might be explained by the mix of patients' malignancies and changes in treatment protocols over the last decade, namely, the use of a combination of biological and chemotherapy treatment. This change is in concomitant with patients' vaccination. Notably, these differences lost significance regarding hospital admission in the regression analysis.

This study demonstrates for the first time the association between PCV13 vaccination in a group of patients at high risk of infection—patients with haematological malignancies—and risk of adverse outcomes, such as infections requiring hospitalisation. Further research in large cohorts of patients, stratifying by diverse risk factors and using randomised trial study designs, is needed in order to examine the PCV13 vaccination outcomes regarding hospitalisation, survival rates and economic impacts.

Contributors RD preform the data collection, analysis and writing the manuscript. ED, ES and MP designed the study, analysed the data and wrote the manuscript. MP is the guarantor of the study.

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Competing interests None declared.

Patient and public involvement Patients and/or the public were involved in the design, or conduct, or reporting, or dissemination plans of this research. Refer to the Methods section for further details.

Patient consent for publication Not required.

Ethics approval This study involves human participants and was approved by the Carmel Medical Center Helsinki Committee (CMC-20-0005) and by the Faculty of Social Welfare and Health Sciences Ethics Committee, University of Haifa (approval no. 351/20).

Provenance and peer review Not commissioned; externally peer reviewed.

Data availability statement Data are available upon reasonable request. Identifiable individual participant data will not be available; however, aggregated, anonymised data will be available on request from the corresponding author.

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