Pneumo-CLL study: Immunogenicity of the Currently Recommended Pneumococcal Vaccination Schedule in Patients with Chronic Lymphocytic Leukaemia.

PROTOCOL

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1. Introduction

Patients with chronic lymphocytic leukaemia (CLL) are at increased risk of both invasive pneumococcal disease (IPD) and community acquired pneumonia (CAP) caused by Streptococcus pneumoniae [1-3]. Therefore, international guidelines recommend pneumococcal vaccination for all CLL patients, preferably before initiation of treatment. The recommended vaccination schedule consists of Prevenar13®, a 13-valent pneumococcal conjugated vaccine (PCV13) followed 2 months later by Pneumovax23, a 23-valent polysaccharide vaccine (PPSV23) [4, 5].

The immunological efficacy of this sequential vaccination schedule in CLL patients is unknown. Previous studies have only investigated responses to either PCV13 or PPSV23 alone (Table 1) [6-15]. Responses to PPSV23 alone are poor in CLL patients [7, 9, 10, 14, 15]. Responses to the 7-valent pneumococcal conjugated vaccine (PCV7) or PCV13 are higher compared to responses to PPSV23, but lower compared to responses in healthy individuals [6, 8, 15]. More advanced disease stage and lower baseline IgG negatively influence responses to vaccination (Table 1) [6, 14, 15].

Table 1

Study	Year	N (final analysis)	Population	Vaccination schedule	Serologic respone definition	Response rate	Factors associated with response
A) Studies investigating schedules containing conjugated vaccines (PCV7/PCV13)							
Sinisalo et al (8)	2007	73	n=49 CLL (15% steroids, 22% chemo, 80% Binet A, median disease duration 2 years); n=24 healthy	PCV7 only	≥ 2 fold IgG rise AND serotype specific IgG ≥ 0.35 mcg/l for at least 6/7 PCV7 serotypes	24% CLL; 71% controls	Less advanced disease; no past or ongoing chemotherapy; normal IgG.
Paiarski et al (6)	2014	39	Treatment naive CLL (n=24); Healthy (n=15)	PCV13 only	≥2 fold Total anti-pneumococcal IgG	58.3% CLL; 100% controls	Lower stage of CLL, higher total IgG
Andrick et al (11)	2017	8	n=4 CLL + ibrutinib; n= 4 CLL - ibrutinib	PCV13 only	≥2-fold increase in 3 or more out of 13 serotypes	Ibrutinib 0%; No Ibrutinib 100%	X
Svensson et al (15)	2018	128	Treatment naive CLL patients	PCV7 versus PPSV23 (RCT)	Serotype specific OPA titers to PCV13 serotypes > Lowel Limit of Quantification (OPA titers = interpolated reciprocal serum dilution resulting in complement-mediated killing of 50% of the assay bacteria)	PCV13: 32% ; PPSV23 21%	Less advanced disease; higher total l IgG
Lindström et al (13)	2018	24	CLL, follow-up study of Sinisalo 2007	PCV7 5 years before	Serotype specific IgG ≥ 0.35 mcg/l (per serotype)	For individual serotypes 29-71% of the patients were still protected	X
Lindström et al (12)	2019	28	CLL (n=20); healthy controls (n=8), follow-up study of Sinisalo 2007	PCV7 and 5 years later PPSV23	Serotype specific IgG for all PCV7 serotypes AND PPSV23 serotype 5 and 7	10-15%	Healthy controls had higher responses to all serotypes
B) Studies investigating PPSV23 only							
Hartkamp et al (14)	2001	24	57% Rai 0-1; 28% prior chemothrapy; median disease duration >36 months	PPSV23	Protection: 2/3 serotypes 20% above cut-off based on reference adult hyperimmune plasma pool; Response: >2 fold increase + protection (defintition above)	Response: 22% Protection: improved from 38% to 50% after vaccine;	Higher disease stage + lower baseline IgG; prior chemotherapy negatively impacted responses
Sinisalo et al (7)	2001	27	n=14 Binet A, n=8 Binet B n=9 Binet C), median disease duration 3 years.	PPSV23	A significant proportionate change in total anti-pneumcoccal IgG (no cut-off value given)	0%	X
van der Velden et al (9)	2007	49	CLL >50% RAI 0; 20% previous chemotherapy	PPSV23 (with or without ranitidine)	Response =>4 fold increase in IgG to 3 serotypes; Protection: ≥0,35 mcg/ml	Response: 1% response; 'Protection' increased from 45%-59%	Ranitidine did not generate better responses
Safdar et al (10)	2008	32	87% had previous chemotehrapy and 73% anti-CD20	PPSV23 (n=7); PPSV23 + G-CSF injections (n=25)	≥2-fold IgG rise and level >0.5mcg/ml for all 6 measured seorypes	0% (0-17% per individual serotype)	G-CSF did not generate better responses

2. Objective

The aim of this observational cohort study is to assess the immunogenicity of the currently recommended vaccination schedule of PCV13 followed by PPSV23 in CLL patients.

3. Study design

As part of routine care, all adult CLL patients naïve to pneumococcal vaccination and cared for in the participating centers receive one dose of Prevenar13® followed by one dose of Pneumovax23® 2 months later. According to the current local standard of care for immunosuppressed individuals, the response to vaccination is assessed by measuring pneumococcal antibody levels before and 4-8 weeks after vaccination [16, 17]. In this non-interventional cohort study we will ask informed consent to all vaccinated CLL patients to collect their clinical data and laboratory results for study purposes.

4. Inclusion criteria

All adult CLL patients

- naïve to pneumococcal vaccination,
- having received one dose of Prevenar13®,
- followed by one dose of Pneumovax23® 2 months later,
- in whom pneumococcal antibody levels before and 4-8 weeks after vaccination are measured, and
- in whom a complete data collection is possible.

5. Data collection

After we obtain informed consent clinical data will be collected according to a standardized electronic case report form (Castor EDC). Variables included in the case report form are:

- sex
- smoking behaviour
- age at the moment of the PCV vaccine administration
- comorbidities (charlson comorbitiy index)
- before vaccination (as determined in the 6 weeks prior to vaccination)
  - Rai stage (I/II/III)
  - past or ongoing chemotherapy
  - ongoing steroid treatment
  - past or ongoing therapy with a monoclonal anti-CD20 antibody (and date of last infusion)
  - total IgG level
  - lymphocyte count, haemoglobin and platelet level
- pre-vaccination pneumococcal IgG levels
- post-vaccination pneumococcal IgG levels
- date of PCV and PPSV23 vaccine administration
- date of antibody measurements

Laboratory methods and definitions

Serotype-specific pneumococcal immunoglobulin G (IgG) concentrations to 5 pneumococcal serotypes shared across both vaccines (6B, 9V, 14, 19F, 23F) and 4 serotypes unique to PPSV23 (8, 15B, 20, 33F) will be determined in the immunology laboratory of the UMC Utrecht. A validated multiplex immunoassay will be used (Luminex® technology). Serologic response will be defined as a ≥4-fold increase in serotype specific anti-pneumococcal IgG for ≥70% of measured. Serologic protection will be defined as an antibody concentration ≥1.3 mcg/ml for ≥70% of all measured serotypes, according to the definition of the *American Academy of Allergy, Asthma & Immunology* [18]. In addition, because most previous studies (Table 1) used the WHO cut-off for protection in infants (≥0.35 mcg/ml) we will also analyse our data by the infant correlate of protection to be able to compare our results with previous studies [19].

6. Data Analysis

The primary outcome of the study is serologic response rate (SRR) after vaccination. Secondary outcomes of interest are serologic protection rates (SPR) after vaccination analysed by the 2 most widely accepted serologic cut-offs described above, geometric mean antibody concentrations before and after vaccination, and factors associated with response to vaccination, such as age, treatment status and disease stage. To this end, we will perform a multivariable logistic regression analysis, starting with all previously mentioned clinical variables of interest and using a stepwise backward selection method based on p-value <0.1. For data analysis, we will use IBM SPSS version 24.0 (Chicago, Illinois) software. We will apply an α significance level of 0.05. Means and standard deviations will be presented for normally distributed data, and medians and interquartile ranges for non-normally distributed data. The $\chi 2$ test will be used for dichotomous variables and the Student t test or Mann-Whitney U test for normally or non-normally distributed continuous variables, respectively. The Wilcoxon signed-rank test will be used to compare median pre- and post-vaccination antibody concentrations.

7. Ethical considerations and privacy

For this non-interventional study, participants are not exposed to additional study procedures. Vaccination and assessment of vaccination responses are according to local standard of care. A waiver for medical ethical assessment has been issued by the Medical Ethical Committee of the Amsterdam UMC-Location AMC. Informed consent will be asked of each individual patient for use of their data for research purposes. A data protection impact analysis will be performed in collaboration with privacy advisors of all participating hospitals.

8. References

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