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Letter to the Editor

Impact of 13-valent pneumococcal conjugate polysaccharide vaccination on severe exacerbations in patients with chronic obstructive pulmonary disease and established cardiovascular disease

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To the editor

1. Introduction

Immunocompromised patients with certain underlying diseases, such as chronic obstructive pulmonary disease (COPD) or cardiovascular disease (CVD), are more susceptible to *Streptococcus pneumoniae* (pneumococcus) infection, characterised by a poor clinical course and severe disease pattern [1,2].

CVDs are the most prevalent comorbidities in patients with COPD and have been related to an increased need for hospitalisation [3], triggered by acute cardiovascular events or decompensated chronic, vascular pathologies. Our group reported that administering the 13-valent pneumococcal conjugate polysaccharide vaccine (VNC13) in patients with COPD seems to reduce the number of exacerbations that require hospital admission [4]. However, the impact of this vaccine on patients with COPD and established CVD has not been evaluated yet.

2. Materials and methods

To fill this gap, we did a sub-analysis of our former study material [4]. Briefly, a prospective, observational study in 121 patients, followed up for 18 months, was performed. Data had been collected on pulmonary function, body mass index (BMI), dyspnoea measured by the modified Medical Research Council scale (mMRC), pneumococcal vaccination status, number of exacerbations that required hospital admission in that period, as well as comorbidities. Clinical records of the 12 months prior to enrolment were analysed and patients correspondingly divided into “exacerbator” and “non-exacerbator” phenotypes [5]. Patients were categorised as subjects with COPD and CVD (COPD/CVD) if they had any of the following pathologies: ischaemic heart disease, heart failure, cardiac arrhythmia, or cerebrovascular accidents. The remaining patients were classified as subjects without cardiovascular disease (COPD/-CVD). Exacerbations identified as community-acquired pneumonia were excluded. Data collectionwas approved by the Ethics Committee of our hospital and by the Spanish Agency for Medicines and Medical Products (AEMPS).

Samples characteristics were described, according to the nature of the variable in absolute and relative frequencies, as means ± SD or medians. A possible relation between the VNC13 vaccine and its supposed effects was evaluated by means of Chi-squared and multivariate analysis (logistic regression) in order to adjust the risks. The cases observed in the follow-up period were taken into account as the number of adjustment variables allowed in our given model [5 (k + 1)], where k represents the independent variables.

3. Results

Out of 121 patients, 71 (59%) were classified as COPD/CVD. Their baseline characteristics are listed in Table 1. Of the non-vaccinated patients with COPD/CVD, 50% needed hospital admission compared to 16,1% of the vaccinated patients ($p = .007$). The vaccine-related difference in hospital admission in COPD/-CVD patients was not statistically significant (vaccinated 23% vs. non-vaccinated 13%, $p = .413$).

Multivariate logistic regression analysis showed that both CVD in non-vaccinated patients as well as in the exacerbator phenotype had an increased risk of hospital admission, resulting in ORs 9.45 ($p = .001$) and 4.1 ($p < .001$), respectively (Table 2A). The relation between cardiovascular disease and VNC13 was not significant ($p = .117$), but the value was sufficiently low as to evaluate the impact of vaccination in each of the groups. Thus, we found that the risk of hospital admission was significantly reduced in the vaccinated COPD/CVD group ($p = .024$), but not in the COPD/-CVD group ($p = .794$).

Directing the focus of analysis towards COPD/CVD patients, we observed that VNC13 vaccination reduced the risk of admission differentially, depending on the patient's exacerbating or non-exacerbating phenotype ($p = .040$). Thus, the risk was significantly reduced in non-exacerbating COPD/CVD patients (OR: 0.05, $p = .013$) (Table 2B). In fact, 43.3% of the non-vaccinated COPD/CVD non-exacerbator phenotype patients were admitted to hospital at least once compared to only 3.8% of the vaccinated ones. However, the effect in patients with COPD/CVD and an exacerbator phenotype was not significant ($p = .68$). Likewise, we did not find a significant effect of the VNC13 vaccination in COPD/-CDV patients.

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Table 1
Baseline characteristics of patients with chronic obstructive pulmonary disease.

Variables	COPD/CVD (n = 71)	COPD/-CVD (n = 50)	*p*
Age, years (mean ± SD)	74.4 ± 8.1	68.5 ± 9.6	< 0.001
Sex (% male)	90	82	0.303
BMI (mean ± SD)	29.2 ± 4.5	27 ± 5.1	0.018
Active smoker (%)	14.1	32	0.006
PYI (mean ± SD)	50 ± 19	51 ± 21	0.868
FEV_1 (L)	1.19 ± 0.38	1.25 ± 0.41	0.457
FEV_1 (%)	46.2 ± 11.62	47.3 ± 11.57	0.621
FVC (L)	2.43 ± 0.64	2.65 ± 0.76	0.095
FVC (%)	72.9 ± 16	79.4 ± 17	0.036
FEV_1/FVC (%)	49.3 ± 12	48.9 ± 13.1	0.861
Diabetes mellitus (%)	50.7	22.1	0.003
Associated respiratory pathology[a] (%)	47.8	44.2	0.813
Immunocompromised[b] (%)	22.5	16.1	0.512
Liver disease (%)	8.5	8.2	< 1
Kidney disease (%)	29.6	6.1	0.003
Charlson comorbidity index (mean ± SD)	3.2 ± 1.89	1.58 ± 0.99	< 0.001
Dyspnoea, measured by the modified Medical Research Council scale (mean ± SD)	2.18 ± 0.74	1.74 ± 0.72	0.001
Exacerbator Phenotype (%)	21%	28%	0.51
Vaccinated with VNC13 (%)	43	26	0.072

FEV_1: forced expiratory volume in the first second; FVC: forced vital capacity; BMI: body mass index; PYI: pack year index; SD: standard deviation; VNC13: 13-valent pneumococcal conjugate polysaccharide vaccine; COPD/CVD: patients with COPD and cardiovascular disease; COPD/-CVD: patients with COPD without cardiovascular disease.

[a] Asthma, interstitial diseases, bronchiectasis, sleep apnoea.

[b] inherited, HIV, systemic corticoids, or chemotherapy.

Table 2
Risk of hospital admission.

Variables	B	OR	*p*
A. Multivariate logistic regression analysis of the risk of hospital admission			
Constant	−4.06	0.02	< 0.001
Cardiovascular disease in patients not vaccinated with VNC13	2.24	9.45	< 0.001
Exacerbator phenotype	1.40	4.01	< 0.001
Vaccination with VNC13	0.32	1.38	0.79
Vaccination with VNC13 in COPD/CVD[a]	−2.27	0.10	0.117
B. Risk of hospital admission in patients with COPD/CVD vaccinated with VNC13 according to phenotype			
Non-exacerbator	−2.95	0.05	0.013
Exacerbator	0.54	1.71	0.68

B: Logistic Regression Coefficients; OR: Odds ratio; VNC13: 13-valent pneumococcal conjugate polysaccharide vaccine; COPD/CVD: patients with COPD and cardiovascular disease.

[a] Interaction effect.

4. Discussion

We conclude from this study that vaccination with VNC13 reduces the risk of hospital admission in non-exacerbating patients with COPD/CVD. For the most part, exacerbations in COPD are associated with pathogenic bacteria, such as *Haemophilus influenzae, Moraxella catarrhalis*, and pneumococcus, the latter being responsible for at least 15% of them [6]. A number of epidemiological studies have shown that pneumococcal infection increases the risk of acute cardiovascular events by two to eight times [7]. Different causes have been postulated for this association: on the one hand the infectious process in itself [8] and on the other hand the fact that pneumococcus acts as a potent antigen on the immune-inflammatory mechanism of atherosclerosis. Binder et al. observed a decrease in atherosclerotic plaques of 40% after administering VNP23 (23-valent pneumococcal polysaccharide vaccine) in an animal model [9]. Lamontage et al. found that subjects who received VNP23 had a significantly reduced risk of acute coronary events (OR 0.53, 95% CI 0.40–0.70) [10]. The authors proposed "antigen mimicry" between oxidized LDL (low-density lipoprotein) and pneumococcus. The IgM antibodies against pneumococcus generated by vaccination recognised the oxidized LDL and reduced its uptake by macrophages, which in turn reduced atheroma plaque formation.

In our study, vaccination with VNC13 lowered the number of hospital admissions in non-exacerbating COPD/CVD patients. The detected benefit could be related to the immunity generated by the vaccine as well as its possible cardioprotective properties, although no studies corresponding to the latter have been published yet. However, we did not observe the effect in COPD/CVD patients with an "exacerbator" phenotype. What could explain this finding is that the pathogens involved in exacerbations are not the same as those in subjects that do not suffer frequent aggravations. Particularly relevant among these pathogens are *Haemophilus influenzae*, enterobacteria, and *Pseudomonas aeruginosa*.

The main limitations of our study are the small sample size in COPD/-CVD, the inter-observer variability in ruling out pneumonic processes by chest X-rays, and omission of respiratory sampling during exacerbations. To our knowledge, this is the first "real-life" study to assess the impact of VNC13 on patients with COPD/CVD. However, we must point out that the observed effect of VNC13 did not pass the Hosmer Lemeshow test, and the interaction effect between vaccine and CVD was no significant, so that the explanatory power of the model is limited. Studies with a larger sample size are needed to particularly corroborate these findings.

Authors' contribution

Juan Marco Figueira Gonçalves: concept and design of the manuscript; data collection, analysis, and interpretation; manuscript drafting, revision, and final approval.

Miguel Ángel García Bello: concept and design of the manuscript; analysis, and interpretation; manuscript drafting, revision, and final approval.

Natalia Bethencourt Martín: data collection; manuscript revision and final approval.

David Díaz Pérez: data collection; manuscript drafting, revision, and final approval.

Lina Inmaculada Pérez-Méndez: data analysis and interpretation; revision and final approval of the manuscript.

Conflict of interest

L.I. Pérez-Méndez was a lecturer in the Research Methodology programme of the Vaccine Academy of Pfizer.

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All authors have read and given their approval to the final version of the manuscript and declare to have met the requirements for authorship.

All authors have made substantial contributions to the design of this manuscript and assume responsibility for its content.

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