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Impact of 13-valent pneumococcal conjugate polysaccharide vaccination on exacerbation rates of COPD patients with moderate to severe obstruction

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ABSTRACT

Introduction. One of the main microorganisms described as the cause of exacerbations of chronic obstructive pulmonary disease (COPD) is *Streptococcus pneumoniae*. The aim of this study was to evaluate the impact of the 13-valent pneumococcal conjugate polysaccharide vaccine (PCV13) on COPD patients with regard to the development of exacerbations and the possible differential effect according to the patients' phenotype.

Material and methods. Prospective observational study of patients with COPD and FEV_1 (forced expiratory volume in the first second) ≤ 65% and 18-month follow-up. Main variables: vaccination status with PCV13, phenotype "frequent exacerbator" or "non-exacerbator", number of exacerbations, hospitalization, and deaths. A descriptive statistical analysis was performed according to the nature of the variable and an inferential analysis with $CI_{95\%}$, bivariate contrasts, and multivariate analysis. Statistical level 5%. The statistical packages EPIDAT 3.0 and SPSS version 21.0 were used.

Results. A total of 121 patients were included. Twenty-four percent were identified as phenotype exacerbators. Thirty-six percent were vaccinated with PCV13. During follow-up, 68% of the patients had at least one exacerbation and 27% required hospitalization. We observed similarity ($p > 0.05$) in the number of exacerbations and deaths; however, the rate of hospitalization in the vaccinated group was 18% compared to 32% in the non-vaccinated one. In the multivariate adjustment (control for phenotype), the adjusted OR for risk of hospitalization was 2.77 in the non-vaccinated group ($p = 0.044$).

Conclusions. Not vaccinating with PCV13 almost triples the risk of hospitalization in patients with COPD.

Keywords: COPD; vaccine; pneumococcus; exacerbation; phenotype

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Impacto de la vacunación neumocócica de polisacáridos conjugados 13-valente en las exacerbaciones de pacientes con enfermedad pulmonar obstructiva crónica con obstrucción al flujo aéreo moderada-muy grave

RESUMEN

Introducción. Uno de los principales microorganismos descritos como causante de las exacerbaciones de la Enfermedad Pulmonar Obstructiva Crónica (EPOC) es el *Streptococcus pneumoniae*. El objetivo de este estudio es evaluar el impacto de la administración de la vacuna neumocócica de polisacáridos conjugados 13-valente (VNC13) en pacientes con EPOC en lo que respecta al desarrollo de exacerbaciones y el posible efecto diferencial según perfil del paciente.

Material y métodos. Estudio observacional prospectivo de 18 meses de seguimiento de pacientes con EPOC y FEV_1 ≤ 65%. Variables principales: estado de vacunación con VNC13, fenotipo "exacerbador" o "no exacerbador", número de exacerbaciones, ingresos y fallecimientos. Se realizó un análisis estadístico descriptivo según la naturaleza de la variable y un análisis inferencial con $IC_{95\%}$, contrastes bivariados y análisis multivariante. Nivel de significación 5%. Se emplearon los paquetes estadísticos EPIDAT 3.0 y SPSS versión 21.0.

Resultados. 121 pacientes fueron incluidos. El 24% se etiquetaron como fenotipo exacerbador. Un 36% estaban vacunados con VNC13. Durante el seguimiento, el 68% de los pacientes presentaron al menos una exacerbación y un 27% requirió ingreso. Observamos similitud ($p > 0,05$) en el número de exacerbaciones y fallecimientos, sin embargo el porcentaje de ingresos en los vacunados fue del 18% frente a 32% en el grupo de no vacunados. En el ajuste multivariado (controlando por el fenotipo del paciente) se observa un $OR_{ajustado}$ de 2,77 de riesgo de ingreso en el grupo no vacunado ($p=0,044$).

Conclusiones. La falta de vacunación con VNC13 en pacientes con EPOC casi triplica el riesgo de ingreso hospitalario.

Palabras clave: EPOC; vacuna; neumococo; exacerbaciones; fenotipo

INTRODUCTION

Streptococcus pneumoniae (pneumococcus) is a grampositive, encapsulated, facultative anaerobic bacterium, which frequently colonises the human nasopharynx. To date, pneumococcus is divided into more than 93 serotypes according to the chemical and antigenic structure of the capsular polysaccharides. Between 15 and 20 of these serotypes cause the majority of pneumococcal diseases worldwide[1,2], among them severe forms of invasive pneumococcal disease (IPD)[3], non-bacteraemic community-acquired pneumonia[4], acute otitis media[5], and exacerbations of chronic obstructive pulmonary disease (COPD)[6].

Since 1992, administering the polysaccharide pneumococcal vaccine against 23 serotypes (PPV23) has been recommended both in patients over 65 and in groups at risk of pneumococcal infections, such as chronic respiratory diseases like COPD, bronchiectasis, cystic fibrosis, interstitial pulmonary fibrosis, and pneumoconiosis[7]. Although available evidence on the efficacy of PPV23 in COPD concludes that there is a decrease in episodes of pneumococcal pneumonia, it has not been shown to provide clear benefit in terms of reducing exacerbations[8,9].

In 2012, the General Directorate of the Spanish National Health and Pharmacy System approved active immunisation with a 13-valent pneumococcal conjugate polysaccharide vaccine (PCV13) for IPD prevention in adults over 50, to which the recent results obtained by the CAPITA study on prevention of non-bacteraemic pneumococcal pneumonia added[10-12]. However, its role in reducing exacerbations in COPD patients has not yet been evaluated.

The clinical course of COPD is often worsened by episodes of clinical instability, termed aggravations or exacerbations. It is estimated that COPD patients suffer between one and four exacerbations per year. However, their occurrence does not follow a normal distribution. Some patients do not have exacerbation events at all, while others undergo exacerbations repeatedly, the latter being a group of patients with a high risk of morbimortality. The cut-off point to consider a patient exacerbator has been varying over time. Currently, patients with two or more events per year are referred to as frequent exacerbators[13].

The objective of this study was to evaluate the mid-term impact of PCV13 administration on COPD patients with moderate to very severe airflow obstruction with regard to the development of infectious exacerbations, particularly in patients requiring hospital admission, and a potentially differential effect according to the patients' profile.

MATERIALS AND METHODS

The study was conducted as a prospective observational study of a cohort of COPD patients (codes CIE10: J44-J44.9) treated at the outpatient clinic of the Pneumology Service in the southern Health Care Area of Tenerife, who met the following criteria: preceding follow up by the Pneumology Service for at least one year; aged over 40; active or former smoker of more than ten packs of cigarettes per year or sustained exposure to other harmful, volatile agents; post-bronchodilator forced expiratory volume in 1 second (FEV1)/forced vital capacity (FVC) < 70%; FEV1 ≤ 65% of the predicted value.

After their inclusion in the study, each patient was monitored for 18 months (or until their death) based on their computerised medical history (CMH). The main variables for inclusion were the pneumococcal vaccination status (vaccinated patients began their 18-month follow-up period with the date of vaccination), the number of exacerbations, as well as hospital admissions in that period. Acute episodes of clinical instability were considered as infectious exacerbations when they comprised sustained worsening of respiratory symptoms beyond their daily variations (cough, expectoration, dyspnoea or both) and required the prescription of outpatient (moderate exacerbation) or hospital (severe exacerbation) antibiotic treatment for their control. This information was obtained from the CMH. Exacerbations that were identified as community-acquired pneumonia were excluded.

The CMH from the 12 months prior to study inclusion of either patient was analysed to assign them the clinical phenotype 'frequent exacerbator' or 'non-exacerbator'. COPD patients were defined as frequent exacerbators when they had suffered two or more exacerbations in the preceding year[13]. These exacerbations had to be at least 4 weeks apart from the end of treatment of the earlier exacerbation or 6 weeks from the beginning of that exacerbation in untreated cases to differentiate the new event from a previous therapeutic failure. Additionally recorded variables were age, sex, smoking habits (active smoker, former smoker or non-smoker) as well as smoking intensity by means of the pack-year index (PYI), body mass index (kg/m^2), BODEx index, influenza vaccination, and mortality from any cause during follow up. The Charlson index was used to record associated comorbidities, although other conditions not included in this index were also taken into account for being considered of special relevance, such as the history of myocardial infarction, arterial hypertension, and arrhythmias, among others. Outcomes of the pulmonary function tests were also recorded, and the patients were categorised according to the four degrees of severity collected in the 2009 GOLD guidelines[14] and according to the GOLD 2011[15] categories.

The estimated sample size was 120 patients for a hospital admission probability of 25%, a 95% confidence level, and an accuracy of at least 5% in a limited population of 203 cases of COPD with moderate to very severe airflow obstruction, recorded at the specialised outpatient clinic of Pneumology in this district of the health care service, which gave a sample fraction of over 50%.

Subsequent to follow up completion, sample characteristics were described according to the nature of the variable (nominal, ordinal, or scale) in absolute and relative frequencies,

means ± SD, or medians and P_{25}–P_{75}. The possible relationship between PCV13 vaccination and its potential effects was then evaluated in a bivariate (chi-square, Student's t, Fisher's exact, or Mann-Whitney U test) and a multivariate (logistic regression) manner in order to adjust the risks. The number of adjustment variables allowed in our model, given the cases observed in the period [10 (k + 1)] (where k are the independent variables)[16], and the goodness-of-fit test (Hosmer and Lemeshow test) were taken into account.

All hypothesis contrast tests were performed with a significance level of 5%. Likewise, the prevalence of vaccination, prevalence of frequent exacerbator phenotype in patients with COPD with moderate to very severe airflow obstruction, and the probability of exacerbation requiring hospital admission were calculated applying the 95% CI. Calculations and contrasts were performed using the statistical packages SPSS version 21.0 and EPIDAT 3.0. For sample size calculation, we used the C.M.T. Glaxo Wellcome software.

The study was approved by our hospital Ethics Committee as well as the Spanish Agency for Medicines and Medical Products (AEMPS).

RESULTS

A total of 121 patients were included in the study. Their baseline characteristics are described in table 1. The mean age of 72 years stands out; patients were mostly overweight men, and more than 20% classified as active smokers. Following the GOLD 2009 and GOLD 2011 classification, patients were allocated mainly to stages II-III and category D, respectively. Cardiovascular comorbidities were the most common ones (58% of the patients) with an average Charlson index of 2.5 ± 1.7. An exacerbating phenotype was assigned to 24% of the patients, $CI_{95\%}$ [16–32%].

The proportion of PCV13 vaccinated patients was 36.4%, which provided an estimate of the prevalence of coverage of 27–45%, $CI_{95\%}$. PPV23 vaccination was registered in 9.1% of the patients (solely or combined with PCV13), and 44.6% were vaccinated against influenza. There was no statistically significant difference between percentages of PCV13 vaccinated COPD patients of the frequent exacerbator and the non-exacerbator phenotype (p = 0.52), (figure 1).

Approximately one third of the patients did not exhibit exacerbations. The cumulative incidence of hospital admission during the 18-month follow up reached 27%, $CI_{95\%}$ [19% -35%]. There were 27 deaths recorded throughout the study period.

In the joint distribution of PCV13 vaccination and its possible effects (total number of exacerbations, number of hospital admissions, and deaths throughout the study period), total exacerbations and deaths were similar in vaccinated as well as non-vaccinated patients (shown in table 2). However, the proportion of hospital admissions in vaccinated subjects was 18% compared to 32% in the non-vaccinated group (risk difference of 14%, OR_{crude} = 2.16), a difference that approached the level

Table 1 | Basal Characteristics of COPD Patients (n=121)

Patients number	121
Mean age (years)	72 ± 9.18
Sex	
Men	105 (86.8%)
Women	16 (13.2%)
Mean BMI (kg/m^2)	28.28 ± 4.88
Smoking status	
Non-smoker	2 (1.7%)
Active smoker	26 (21.5%)
Former smoker	93 (76.9%)
Pack-year index	50.79 ±19.91
Pulmonary function	
FEV1 (%)	46.6 ± 11.5
FVC (%)	75.6 ± 16.7
FEV1/FVC (%)	49.0 ± 12.4
FEV1 (L)	1.21 ± 0.39
FVC (L)	2.52 ± 0.70
Cardiovascular disease[a]	71 (58.7%)
Respiratory pathology[b]	65 (53.7%)
Diabetes mellitus	29 (24.0%)
Immunosuppression[c]	24 (19.8%)
Chronic liver disease	10 (8.3%)
Chronic kidney disease	24 (19.8%)
GOLD 2009	
I	0 (0%)
II	52 (43.0%)
III	59 (48.8%)
IV	10 (8.3%)
GOLD 2011	
A	11 (9.1%)
B	21 (17.4%)
C	21 (17.4%)
D	68 (56.2%)
Charlson index (mean)	2.5 ± 1.7
BODEx	3.25 ± 1.52

Values are expressed as patients numbers [%] or mean ± SD. FEV1: forced expiratory volume in the first second; FVC: forced vital capacity; BMI: body mass index; GOLD: Global Initiative on Obstructive Lung Disease. [a]Cardiac arrhythmia, ischemic heart disease, and cardiac insufficiency. [b]Asthma, interstitial diseases, bronchiectasis, sleep apnoea. [c]Congenital, HIV, systemic corticosteroids, and chemotherapy.

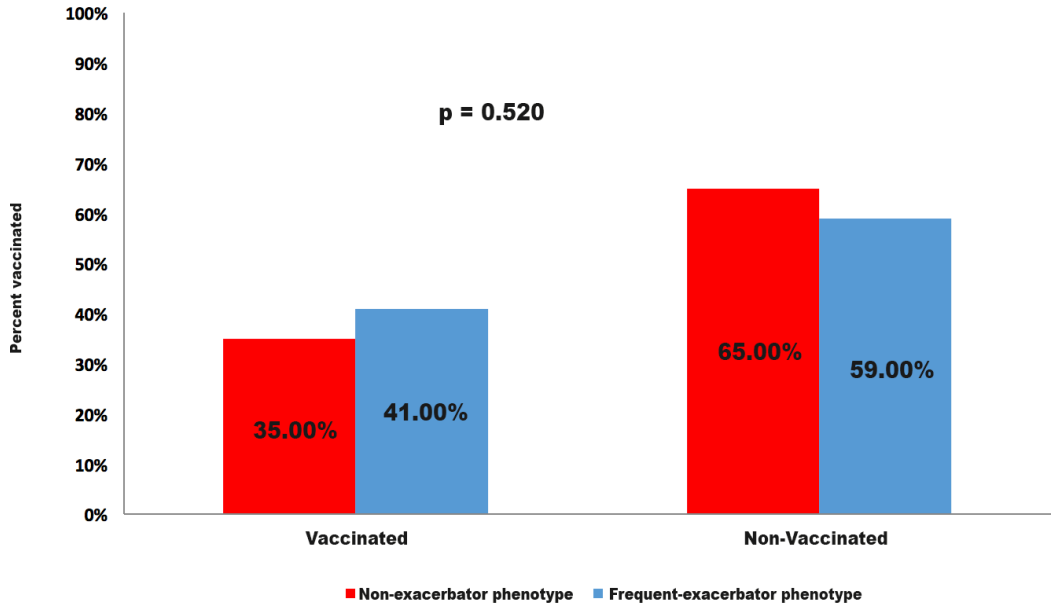

Figure 1 Percentages of PCV13 vaccination according to phenotypes

of statistical significance (p = 0.067) in this unadjusted association analysis.

The final logistic regression model was obtained adjusting for clinical phenotype, a characteristic that had been validated not to be associated with vaccination (figure 1). That allowed to detect a risk of hospitalisation almost three times higher among non-vaccinated patients compared to vaccinated ones ($OR_{adjusted}$ = 2.77, p = 0.044, table 3). The interaction between the two variables was not significant (p = 0.252) and was therefore excluded from the final model.

DISCUSSION

The following conclusions were drawn from this study: 1) The pneumococcal vaccination rate among the COPD patients treated at our specialised pneumology clinic is insufficient. 2) The risk of hospital admission is tripled in non-vaccinated COPD patients with moderate to very severe airflow obstruction.

Local defence mechanisms are altered in COPD patients. These alterations allow microorganisms, which in normal conditions would be eliminated by the organism, to persist and chronically colonise the airway[17], thus favouring the onset of aggravations. These episodes are associated for the most part with the activity of bacteria such as *Heamophilus influenza*, *Moraxella catarrhalis*, and *Streptococcus pneumoniae*, the latter being responsible for at least 15% of COPD exacerbations[6]. In addition, *S. pneumoniae* serotypes differ between study entities. In the course of COPD exacerbations, serotypes 19A, 3, 14, and 15B are the most frequently isolated, and serotypes 3, 19A, 14, and 7F are the most common ones in episodes of pneumococcal pneumonia[18].

To date, pneumococcal infection has been approached from two fronts: 1) specific antibiotic therapy and 2) active immunisation. With regard to the former, it has not been possible to achieve totally satisfactory results given the high percentage of resistance to the commonly used antibiotics[19-22]. As for active immunisation, there are two types of vaccination, the PPV23 and the PCV13. Although PPV23 has traditionally been recommended for patients with chronic respiratory diseases, it is currently known to have a main drawback that is its uneven immunogenicity, especially in subjects over 65. However, COPD patients usually belong to this age group. On the other hand, studies which evaluated the immunogenicity of PCV13 in subjects over 50 years of age have shown that this vaccine elicits a significantly higher antibody response than PPV23 for 8 of the 12 shared serotypes[23,24]. From the clinical point of view, the CAPITA study demonstrated a 75% decrease in IPD development and a 46% decline in non-bacteraemic pneumococcal pneumonia in adults vaccinated with PCV13[12].

As for COPD patients, there is evidence available for the efficacy of PPV23 in terms of a decrease in episodes of pneumococcal pneumonia, especially in patients below 65 and with a FEV1 of less than 40%, but without any improvement in numbers of exacerbations, mortality, or first episode of community-acquired pneumonia[8,9,25]. Studies on the efficacy of PCV13 are scarce. The available evidence describes an enhanced immunogenicity compared to PPV23, especially in COPD subjects without previous pneumococcus vaccina-

Table 2 Difference between PCV13 vaccinated and non-vaccinated COPD patients during the 18-month follow up

	Vaccinated (n=44)	Non-vaccinated (n=77)	*p*
No. exacerbations Median [P25-P75]	1 [0 - 1]	1 [0 - 2]	0.171[a]
No. exacerbation % (n)	61.4% (27)	68.8% (53)	0.404[b]
Hospital admission % (n)	18.2% (8)	32.2% (25)	0.067[c]
Death % (n)	25.0% (11)	21.0% (16)	0.592[b]

[a]Mann-Whitney U test. [b]Chi-square. [c]Fisher's exact.

Table 3 Multivariate logistic regression analysis of the risk of hospital admission

	OR	CI 95%	Wald	p
No. vaccinated	2.77	1.03–7.50	4.043	0.044
Frequent-exacerbator phenotype	6.30	2.44–16.30	14.42	0.001

Goodness of fit. Hosmer and Lemeshow test p=0,511; overall % predicted 75,2%

tion[26]; but there are no studies evaluating the clinical impact on these patients.

Similar to the results obtained by Walters et al. with PPV23[8], we did neither find any decrease in the overall incidence of exacerbations nor in all-cause mortality in patients vaccinated with PCV13. However, we did detect differences after adjusting the analysis for the patient's phenotype, especially in severe exacerbations. The COPD patients who had not received PCV13 vaccine had a three times higher risk of hospital admission compared to the vaccinated ones. Our findings are consistent with a study published by Montserrat-Capdevila et al.[27], who describe that PPV23 reduces exacerbation events in COPD patients. However, their sample age was below the one analysed in this study (68 years ± 11,60) and the patients had mostly mild airway obstruction. It is likely that the benefit of PCV13 vaccination found in this work was due to the described greater immunogenicity within the herein studied age group.

In this study, the vaccination rate against pneumococcus is far from optimal, with numbers below 50%. Multiple studies, carried out in Spain, show that the pneumococcal vaccination coverage is deficient, with an overall rate in the population over 65 of 53%[28]. Given this scenario, Fernández Ruiz et al.[29] evaluated the aspects involved in the incorrect implementation of vaccination recommendations according to the levels of care. At hospital level, the main obstacles were the difficulty to access the patient's vaccination history followed by ignorance of the recommendations, while in primary care the main problems were mistrust or rejection among patients[30,31]. In the case of this study, the low rate of PCV13 vaccination may have been due to patient mistrust regarding its beneficial effects, as all patients were offered counselling by both the responsible pulmonologist and the nurse.

Therefore, in view of the presented data, PCV13 appears to be effective in reducing serious, infectious exacerbations in COPD patients with moderate to very severe airflow obstruction. The main limitation of this study is, on the one hand, the small sample size. A larger sample would have most likely provided significant differences that could not be detected in this work. On the other hand, although data collection excluded exacerbations that were described as ongoing pneumonic processes, their presence cannot be ruled out given the interobserver variability with respect to the interpretation of the chest X-ray as well as the low sensitivity of the latter in detecting incipient pneumonic processes. Finally, a correct collection of respiratory samples during exacerbations could have provided information on the microorganism involved in the process and been related to the vaccination status. One of the advantageous points of this study was that the sample group also included non-vaccinated COPD patients from the same base population.

To conclude, this work represents an observational study; therefore more specific studies should be designed to evaluate the efficacy of PCV13 in these patients.

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CONFLICTS OF INTEREST

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

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