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Brief report

Revaccination with 7-valent pneumococcal conjugate vaccine elicits better serologic response than 23-valent pneumococcal polysaccharide vaccine in HIV-infected adult patients who have undergone primary vaccination with 23-valent pneumococcal polysaccharide vaccine in the era of combination antiretroviral therapy

Ching-Lan Lu [a], Sui-Yuan Chang [b,c,*,1], Yu-Chung Chuang [d], Wen-Chun Liu [d], Chin-Ting Su [c], Yi-Ching Su [c], Shu-Fang Chang [c], Chien-Ching Hung [d,e,f,*]

[a] Department of Internal Medicine, National Taiwan University Hospital Hsin-Chu Branch, Hsin-Chu, Taiwan
[b] Departments of Laboratory Medicine, National Taiwan University Hospital and National Taiwan University College of Medicine, Taipei, Taiwan
[c] Department of Clinical Laboratory Sciences and Medical Biotechnology, National Taiwan University College of Medicine, Taipei, Taiwan
[d] Departments of Internal Medicine, National Taiwan University Hospital and National Taiwan University College of Medicine, Taipei, Taiwan
[e] Department of Medical Research, China Medical University Hospital, Taichung, Taiwan
[f] China Medical University, Taichung, Taiwan

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ABSTRACT

HIV-infected adults who had received 23-valent pneumococcal polysaccharide vaccine (PPV23) five years or more earlier consecutively underwent revaccination with one dose of PPV23 (127 subjects) from December 2005 through October 2007, or upon change in standard of care, non-randomly one (50) or two doses (44) of 7-valent pneumococcal conjugate vaccine (PCV7) from October 2008 through June 2010. Serologic response was defined as ≥2-fold increase in the IgG level plus a level ≥1000 ng/ml 48 weeks following revaccination. At week 48, the response rate was significantly higher in the 2-dose PCV7 group compared with that in the 1-dose PCV7 or PPV23 group (63.6% vs 32.0% vs 8.7%, respectively; $P < 0.05$). Revaccination with one dose of PCV7 (AOR, 4.57), two doses of PCV7 (AOR, 22.66), and CD4 >350 cells/μl (AOR, 3.24) and undetectable viral load (AOR, 3.87) at revaccination were statistically significantly associated with a better serologic response at week 48. Despite the limitation that study arms were neither randomized nor contemporaneous, we conclude that revaccination with PCV7 appears to elicit a better serologic response than PPV23 in the HIV-infected adults who have received PPV23 five years or more earlier (clinical trial registration number: NCT00885625).

1. Introduction

Despite widespread use of combination antiretroviral therapy (cART), the risk for invasive pneumococcal disease (IPD) in patients with HIV infection remains significantly higher when compared with the general population [1–4]. The U.S. Department of Health and Human Services (DHHS) Guidelines recommend that patients with HIV infection receive 23-valent pneumococcal polysaccharide vaccine (PPV23) and revaccination is also recommended for the HIV-infected patients whose primary vaccination with PPV23 occurs five years earlier [5]. However, studies that examine the serologic responses to revaccination among HIV-infected patients in the cART era [6–8] yielded inconsistent results due to differences in the study population, receipt of cART, duration of cART before revaccination, type of vaccine studied, and dose and sequence of vaccine administered.

While the only randomized clinical trial failed to show the benefit of PPV23 vaccination in preventing all-cause pneumonias in HIV-infected Ugandans who were not receiving cART [9], French and colleagues have demonstrated an efficacy of 74% of primary

* Corresponding authors at: Department of Internal Medicine, National Taiwan University Hospital, 7 Chung-Shan South Road, Taipei, Taiwan.
Tel.: +886 2 23123456 ext. 67552; fax: +886 2 23707772.
E-mail addresses: sychang@ntu.edu.tw (S.-Y. Chang), hcc0401@ntu.edu.tw (C.-C. Hung).
[1] Alternative corresponding author address: Department of Clinical Laboratory Sciences and Medical Biotechnology, National Taiwan University College of Medicine, 1 Jen-Ai Road Section 1, Taipei, Taiwan. Tel.: +886 2 23123456 ext. 66908; fax: +886 2 23711574.

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vaccination with PCV7 in preventing recurrent IPD due to vaccine serotypes in HIV-infected Malawians in the cART era [10]. In 2012, the Advisory Committee on Immunization Practices recommends one dose of 13-valent PCV (PCV13) for HIV-infected adult patients aged 19 years or greater [11]. However, it remains unclear whether revaccination with PCV will be more immunogenic than PPV in HIV-infected adult patients. In this 48-week follow-up study, we aimed to compare the serologic responses to revaccination with PPV23 and two different doses of PCV7 in HIV-infected adult patients who had received PPV23 five or more years earlier.

2. Patients and methods

2.1. Study population

Between December 2005 through October 2007, HIV-infected patients who were aged 20 years or greater and had undergone primary vaccination with PPV23 five years or more earlier were given a dose of PPV23 (Pneumovax® 23, Merck & Co., Inc.). After PCV7 was introduced into Taiwan, HIV-infected patients were consecutively enrolled from October 2008 through June 2010 to non-randomly undergo revaccination with either one or two doses of PCV7 (Prevenar®, Wyeth) at a 4-week interval between the two doses. Patients were excluded if they were pregnant and received immunomodulating agents and cytoreductive chemotherapy within the last three and six months, respectively. After revaccination, blood specimens were collected at baseline, and every 12 weeks afterwards for 48 weeks during their routine follow-up at the outpatient clinics for antiretroviral therapy and related HIV care. Plasma HIV RNA load (PVL) and CD4 lymphocyte count were determined every three to six months. The blood specimens were stored at −70 °C until use. The study was approved by the Research Ethics Committee of the hospital, and every patient gave written informed consent.

2.2. Determinations of anti-capsular antibody

Determinations of anti-capsular antibody levels to four pneumococcal serotypes (serotype 6B, 14, 23F, and 19F) were carried out with the use of ELISA by following the methods described previously with minor modifications [12]. Briefly, 1 ml of serum was mixed with 10 μg of cell-wall polysaccharide (CWPS) and incubated at room temperature on a rocking platform for 30 min. Capsular polysaccharides from *S. pneumoniae* serotype 14, 19F, 23F, or 6B obtained from the American Type Culture Collection (ATCC) were suspended in phosphate-buffered saline (PBS, pH7.4) at concentration of 10 μg/ml and used directly to coat wells by incubation at 4 °C overnight. After washing, blocking was done with PBS containing 1% of bovine serum albumin at 4 °C overnight. Duplicate serum samples were studied in 2-fold serial dilutions, and a laboratory reference standard for each serotype that contained known amount of IgG reactive with specific capsular polysaccharide was included in each plate as a positive control. Following washing, this first antibody incubation was performed at 37 °C for 2 h. After thorough washing of unbounded antibodies to wells, horseradish peroxidase (HRP)-conjugated goat antibody to human IgG (ZYMED LABORATORIES INC, South San Francisco, CA) at 1:2000 dilution was used to detect IgG, and the reaction is developed 10 min at dark by addition of K-blue substrate (Neogen Corporation, Lexington, KY, USA), followed by adding 1 N sulfuric acid to stop the reaction. All washings between each incubation were done with PBS buffer containing 0.05% Tween 20. Optical density was read in an ELISA reader (SpectraMAX 340, Molecular Devices, Sunnyvale, CA) at a wavelength of 450 nm, with subtraction of optical density of the appropriate blank. The concentration of IgG was calculated against a reference standard curve generated with the use of the WHO-approved reference standard 89F.

2.3. Definition of serologic response

Significant serologic response was defined as ≥2-fold increase in the IgG level plus a post-vaccination level ≥1000 ng/ml to at least two serotypes at week 48 [8,13,14]. Response rate was estimated in both intention-to-treat (ITT) population, in which patients with missing data were considered non-responders, and per-protocol (PP) population, in which patients with missing data were excluded from analysis.

2.4. Statistical analyses

All statistical analyses were performed using Stata software, version 12 (StataCorp, College Station, Texas, USA). Categorical variables were compared using χ^2 or Fisher's exact test whereas non-categorical variables were compared using one-way ANOVA with Bonferroni posthoc test or Student's *t* test. All relevant clinical and laboratory variables such as age, sex, CD4 count and PVL at vaccination were tested by univariate analysis, followed by stepwise model comparison and selection to determine the final model of multiple variable analysis. Odds ratio (OR) for each associated factor and 95% confidence intervals (CI) were also calculated. A P value <0.05 was considered as statistically significant.

3. Results

3.1. Characteristics of the study population

The study flow of pneumococcal revaccination with PPV23 or PCV7 is shown in Supplementary Fig. A. During the study period, 127 patients received one dose of PPV23 from December 2005 through October 2007; and upon change in standard of care, 50 and 44 patients non-randomly received one or two doses of PCV7, respectively, from October 2008 through June 2010. Table 1 summarizes the baseline characteristics of the study subjects. In total, 97 patients (76.4%) in the PPV23, 36 (72.0%) 1-dose PCV7, and 39 (88.6%) 2-dose PCV7 group completed 48 weeks of follow-up. There were no significant differences between patients with or without completing 48 weeks of follow-up (Supplementary Table A).

3.2. Serologic antibody responses

Sequential antibody levels to each serotype are shown in Fig. 1A to D and serologic response rates to at least two serotypes following revaccination are shown in Supplementary Fig. B. Patients in the 2-dose PCV7 group maintained significantly higher response rates than those in the PPV23 or 1-dose PCV7 group at all four time points. At week 48, the serologic response rate was significantly higher in the 2-dose PCV7 group compared with 1-dose PCV7 or PPV23 group (63.6% vs 32.0% vs 8.7%, respectively; $P < 0.05$). The results of univariate analysis for serologic responses are shown in Supplementary Tables B, C, and D. Table 2 summarizes the results of multiple logistic regression analysis to identify the factors associated with significant serologic responses. Patients receiving either one or two doses of PCV7 had a significantly higher response rate compared those receiving PPV23 ($P = 0.001$ and $P < 0.001$, respectively), so were the patients with undetectable PVL or CD4 counts >350 cells/μl at revaccination ($P = 0.03$ and $P = 0.03$, respectively). Similarly, patients receiving either one dose or two doses of PCV7 and those achieving undetectable PVL also had a higher rate of achieving ≥2-fold increase of IgG than those receiving PPV23 and those failing to achieve undetectable PVL