Equal IgG Antibody Response to Pneumococcal Vaccination in All Stages of Human Immunodeficiency Virus Disease

Marc Vandenbruaene, R. Colebunders, F. Mascart-Lemone, Y. Haerden, D. Van Hove, M. Peeters, J. Goeman, P. Van Royen, and D. Avonts

Institute of Tropical Medicine, Antwerp; Erasme Hospital and Pasteur Mérieux MSD, Brussels, Belgium

To evaluate the immunogenicity and safety of a 23-valent pneumococcal vaccine in human immunodeficiency virus (HIV)–seropositive patients, 80 men and 18 women received 1 dose of the vaccine (Pneumo 23; Pasteur Mérieux MSD, Brussels). The total IgG antibody response against all 23 *Streptococcus pneumoniae* capsular antigens was measured. Antibody levels were expressed in arbitrary units per microliter, referring to a standard curve. Geometric mean titers of the total IgG capsular antibodies on the day of vaccination and 30–45 days later were compared. The ratios of titers after and before vaccination in patients with >500, 200–500, and <200 CD4 lymphocytes/μL were 10, 10, and 12.6, respectively. Nonresponse (ratio <4) occurred in 17% of patients and was unrelated to CD4 cell count. The vaccine was well tolerated; no serious side effects occurred. In 83% of the patients with HIV infection, the total antipneumococcal IgG level was higher after vaccination.

Streptococcus pneumoniae is the most common cause of community-acquired pneumonia and the second most common cause of bacterial meningitis in the United States. Pneumococcal bacteremia-related mortality is high, even with appropriate therapy. The worldwide emergence of drug-resistant pneumococcal strains may complicate the treatment of these infections in the future [1]. Human immunodeficiency virus (HIV)–seropositive patients are at increased risk for acquiring pneumococcal infections, even at a relatively early stage of disease, before the first AIDS-defining event [2].

People with AIDS have mainly a T lymphocyte deficiency. They are still able to produce antibodies against pneumococcal antigens, because these polysaccharide antigens elicit an antibody response by direct interaction with B lymphocytes, without T cell interference [3].

Placebo-controlled clinical trials in HIV-uninfected persons give conflicting results on vaccine efficacy: Simberkoff et al. [4] demonstrated no protective effect in chronically ill patients, but Austrian et al. [5] observed a 78.5% reduction of putative pneumococcal pneumonia and a 82.3% reduction of proven pneumococcal bacteremia in healthy South African gold mine workers.

Two unpublished trials showed no difference between vaccine and placebo (HIV-negative) groups in the occurrence rate of pneumonia and bacteremia [6]. Using an indirect cohort analysis method, Butler et al. [7] found a 57% vaccine efficacy for serotypes included in the vaccine. In a policy analysis based on a hypothetical cohort of HIV-infected patients, Rose et al. [8] state that pneumococcal vaccination is a reasonable prevention strategy at all HIV-disease stages: Few vaccinations are needed to prevent hospitalizations and deaths, and the vaccination is cost-effective [8].

Although pneumococcal vaccination is recommended by the Centers for Disease Control (CDC) for all persons with HIV infection, its protective efficacy in this population is still unknown [9]. We evaluated the total IgG response to and the safety and tolerance of the 23-valent pneumococcal vaccine (Pneumo 23; Pasteur Mérieux MSD, Brussels) in different stages of HIV disease.

Patients and Methods

Study population. Between April and November 1992, 116 consecutive HIV-seropositive patients were enrolled for study; the 91 men and 25 women had a mean age of 38 years. There were 58 homosexuals, 1 injecting drug user, 43 heterosexuals, 1 transfusion recipient, and 13 patients with unknown risk for HIV infection.

Serologic analysis (immunogenicity study) was done for 98 patients from whom pre- and postimmunization blood samples were obtained and who had never received the vaccine. Eighteen patients were excluded from the immunogenicity study: 2 patients had been vaccinated with the vaccine, 2 did not receive the vaccine, and from 14 either a pre- or a postvaccination blood sample was missing.

Vaccinated patients who completed the form for self-reported side effects (n = 106) were included in the side effects analysis.

Patients were grouped according to their CD4 cell counts (>500, 200–500, <200/μL) and their 1993 CDC clinical stage (A, B, or C) [10].

Immunization. Each participant received a single dose of 0.5 mL of the 23-valent pneumococcal vaccine intramuscularly in the deltoid muscle. The vaccine contains 25 μg of each of the capsular

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The study was approved by the ethics committee of the Institute of Tropical Medicine, Antwerp. Written informed consent was obtained from all study patients.

The vaccine was provided by Mérieux, Brussels.

Reprints or correspondence: Dr. Marc Vandenbruaene, Institute of Tropical Medicine, Nationalestraat 155, B-2000 Antwerp, Belgium.

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polysaccharide types, and it contains serotypes 1–5, 6B, 7F, 8, 9N, 9V, 10A, 11A, 12F, 14, 15B, 17F, 18C, 19A, 19F, 20, 22F, 23F, and 33F.

Laboratory tests. Venous blood was collected before and 4–6 weeks after vaccination (median interval, 32 days; 25th and 75th percentiles, 27 and 38). Sera were stored at −70°C until all specimens had been collected. Pre- and postimmunization sera were tested simultaneously for pneumococcal antibodies (total IgG against all 23 serotypes).

Antipneumococcal antibodies were detected by ELISA using the 23-valent vaccine (10 μg/mL) as coating antigen. To measure specifically antipneumococcal capsular antibodies, sera were preincubated with 50 μg of free wall polysaccharide (Statens Serum Institute, Copenhagen) and then incubated at 2 different dilutions (1/1600 and 1/3200) in the ELISA plates. After 2 h of incubation at room temperature, the plates were washed and the fixed antibodies were detected by the addition of peroxidase-labeled anti-human IgG (Southern Biotech, Birmingham, AL). Orthophenylene-diamine was finally added, and absorbance was measured in a photometer (Titertek Multiscan; Program Resources, Rockville, MD) at 490 nm. Optical densities measured were converted to antigen-specific arbitrary units with a calibration curve based on the optical densities obtained from serial dilutions of an HIV-negative serum sample rich in anticapsular pneumococcal IgG (vaccine-induced pneumococcal IgG from an HIV-seronegative patient) using a semilog method of interpolation and calculation of concentrations only in the linear part of the interpolation sigmoid semilog curve. The pneumococcal specificity of the assay was demonstrated by adsorption experiments with washed, encapsulated bacteria [11].

CD4 lymphocytes were counted before vaccination using immunologic flow cytometry.

Statistical analysis. Geometric mean antibody titers before and after the vaccination were compared by Kruskal-Wallis one-way analysis of variance. The ratio of titers (after to before vaccination) was calculated for each participant. With a ratio ≥4, the vaccination was considered immunogenic (to cause an immune response to at least 1 pneumococcal serotype included in the vaccine). Nonresponse was defined as a ratio of <4.

Results

The vaccine was immunogenic in 83% of patients. On average, antibody levels increased 10-fold after vaccination. Pre- and postimmunization total IgG titers against the 23 vaccine capsular types and the ratios of titers after to before vaccination did not differ according to CD4 lymphocyte count or CDC clinical group (table 1). Of the 98 patients in the immunogenicity analysis, 17% did not respond to the vaccination. Nonresponse did not correlate with CD4 lymphocyte count or with CDC clinical group. Current smokers had lower pre- and postimmunization antibody levels than patients who never smoked.

Immunization was well tolerated. Local pain and tiredness were the most common complaints reported the day after vaccination by, respectively, 61% and 26% of the participants. There were no serious adverse events.

Table 1. Total antipneumococcal IgG levels in 98 patients with HIV infection before and after 23-valent pneumococcal vaccination.

	n	Before	After	Ratio
CD4 cell count				
>500/μL	24	4.3	42.7	10
200–500/μL	44	4.7	41.7	10
<200/μL	30	3.8	44.7	12.6
CDC stage				
A (asymptomatic)	58	4.5	43.7	9.5
B (intermediate disease)	20	3.8	41.7	11
C (AIDS)	20	4.5	43.7	9.8

NOTE. Data are geometric mean antibody titers expressed in arbitrary U/μL. No differences were statistically significant.

Discussion

The results of immunogenicity studies of pneumococcal vaccination in persons with HIV infection are conflicting. Certain studies have shown a decreased antibody response after pneumococcal vaccination in HIV-seropositive persons compared with HIV-seronegative controls, while other studies have not shown such a difference. In a study by Rodriguez et al. [11], a lower humoral immune response and a higher degree of nonresponse after pneumococcal vaccination was observed in HIV-seropositive patients with <500 CD4 cells/μL than in patients with >500 CD4 cells/μL. Janoff et al. [12] found asymptomatic HIV-positive patients to have higher levels of vaccine-specific antibodies than did patients with AIDS, although the differences were not statistically significant. In the largest immunogenicity study yet performed among persons with HIV infection, Kroon et al. [13] observed similar immune responses in patients with >300, 100–300, and <100 CD4 lymphocytes/μL. In that study, no significant difference in antibody response was observed comparing HIV-seropositive patients with seronegative controls.

Our study confirms the data of Kroon et al. [13]. We also observed a similar total IgG antibody response in patients with early, intermediate, and late HIV disease. Differences in results among the different immunogenicity studies may be explained by differences in study population, small sample sizes in some studies, and different methods of determining antibody levels.

Formation of antibody to pneumococcal vaccine is an example of a relatively simple immunologic response—a T cell–independent response because T lymphocytes are not essential for measurable antibody formation. The multiple repeating epitopes of pneumococcal polysaccharide antigens can be simultaneously recognized by many surface immunoglobulin molecules on B cells. Such multivalent cross-linking of receptors delivers a powerful activation signal, which may proceed independent of complex cellular interactions [3].

In contrast to the studies of others, we studied only total IgG antibody response against all 23 antigens in the vaccine. Our goal was to see if HIV-seropositive patients could raise

an immunologic response or not. Others have studied specific immunologic responses to some antigens, which raises the question of which antigen responses to study. Patients will remain susceptible to infection by serotypes not studied.

The protective level of antipneumococcal antibodies remains unknown for people with or without HIV infection. Failure of pneumococcal vaccination in AIDS patients has been reported [14]. A placebo-controlled clinical trial is the only way to demonstrate clearly the efficacy of pneumococcal vaccines in persons with HIV infection. Because of the low incidence of *S. pneumoniae* infection and the expected low efficacy of the pneumococcal vaccine, a large number of patients should be enrolled in such a trial. Alternatively, multicenter case-control studies could compare pneumococcal vaccination rates between HIV-infected persons with and without *S. pneumoniae* infection.

On the basis of immune-response data and cost-effectiveness calculations of a hypothetical cohort of HIV-positive subjects, pneumococcal vaccination could be recommended to HIV-seropositive patients at all stages of HIV-disease [8]. However, the CDC recommendation to vaccinate all persons with HIV infection is not widely implemented at present. In Belgium, there is no pneumococcal vaccine commercially available. Because the efficacy of the 23-valent pneumococcal vaccine among persons with HIV remains unproven, this situation will probably not change in the near future.

We recommend that placebo-controlled trials with pneumococcal vaccine should be conducted in HIV-seropositive patients to elucidate the efficacy of the vaccine in this population.

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