Levels of Proinflammatory Cytokines in Plasma after Pneumococcal Immunization in Human Immunodeficiency Virus Type 1-Infected Patients

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To ascertain if immunization with pneumococcal polysaccharide vaccine is associated with rises in the levels of proinflammatory cytokines in the plasma of human immunodeficiency virus type 1 (HIV-1)-infected patients, the levels of tumor necrosis factor alpha (TNF-α) and interleukin-6 (IL-6) were measured serially after immunization. IL-6 levels rose an average of 2.2- and 2.1-fold 6 and 8 h after immunization, respectively, but TNF-α levels remained unchanged. The levels of these cytokines were stable in unimmunized controls. Immunization with pneumococcal polysaccharide vaccine induces increases in the levels of IL-6 in the plasma of persons with HIV-1 infection.

Since persons with human immunodeficiency virus (HIV) type 1 (HIV-1) infection are at greater risk for infection with Streptococcus pneumoniae, immunization of these individuals with pneumococcal polysaccharide vaccine is recommended (3). Interleukin-6 (IL-6) production can be induced by stimulation of monocytes with polysaccharide capsular constituents of gram-positive organisms in vitro (12), and increased levels of proinflammatory cytokines in serum have been noted during the course of infections with gram-positive organisms (4, 14). Immunization with live, attenuated vaccines can transiently increase the levels of proinflammatory cytokines in the plasma of non-HIV-1 infected subjects (6, 8). We conducted the present study to ascertain whether increases in the levels of proinflammatory cytokines in plasma are seen after immunization of HIV-1-infected patients with pneumococcal polysaccharide vaccine.

Six HIV-1-infected patients who were receiving medical care at the University Hospitals of Cleveland and Rush-Presbyterian-St. Luke’s Medical Center, who had not received the pneumococcal polysaccharide vaccine in the previous 6 years, and whose physicians prescribed immunization with pneumococcal polysaccharide vaccine were invited to participate in this study. Immunized patients had a mean CD4 cell count of 239 cells/μl (range, 10 to 780 cells/μl); four were receiving combination antiretroviral therapy. Five HIV-1-infected patients not receiving pneumococcal vaccine served as controls. Their mean CD4 cell count was 452 cells/μl (range, 10 to 780 cells/μl), and all were receiving combination antiretroviral therapy. No patient had a concurrent opportunistic infection. All patients gave informed consent.

A pneumococcal polysaccharide vaccine (Lederle) containing 25 μg each of 23 different polysaccharide serotype antigens was administered intramuscularly in the deltoid region. No other vaccines or skin tests were administered simultaneously. Blood was drawn into EDTA-containing Vacutainer tubes before immunization and also at 2, 4, 6, 8, and 24 h after immunization. Blood was drawn from unimmunized HIV-1-infected controls at the same intervals.

Plasma samples were stored at −70°C and were assayed in batches. Immunoreactive tumor necrosis factor alpha (TNF-α; Medgenix, Fleurus, Belgium) and IL-6 (R&D Systems, Minneapolis, Minn.) were measured by enzyme-linked immunosorbent assay. The lower limits of detection for these assays are 0.65 pg/ml for IL-6 and 16 pg/ml for TNF-α. The levels of TNF-α and IL-6 in plasma are stable over 7 to 13 weeks in patients with stable HIV-1 disease, with median coefficients of variation of 13 and 29%, respectively (5).

Mean plasma IL-6 levels rose significantly (P = 0.022; t test for comparison between means at 0 and 6 h) after immunization with pneumococcal polysaccharide vaccine, peaking at between 2 and 6 h and returning to the baseline level after 24 h in all patients. The mean plasma IL-6 levels in controls did not rise significantly (Fig. 1). Each of the six immunized patients experienced a rise in plasma IL-6 level during this period, with the increase ranging from 0.34 to 7.61 pg/ml. Baseline plasma TNF-α levels were above the detection limits in five of the six immunized patients and in the five control patients. For calculation of means, samples with levels that fell below the limit of detection were assigned a value of 16 pg/ml. Plasma TNF-α levels did not rise after immunization with pneumococcal polysaccharide vaccine and remained stable in the unimmunized controls (Fig. 2). None of the patients developed a fever during the 8 h of observation.

In summary, we found transient but significant increases in plasma IL-6 levels but not plasma TNF-α levels after immunization with pneumococcal polysaccharide vaccine in HIV-1-infected patients. IL-6 is produced by monocytes, B lymphocytes, and other cells and is necessary for the terminal differentiation of B lymphocytes into antibody-producing plasma cells (1). In vitro, monocyte stimulation with capsular polysaccharides of gram-positive organisms induces IL-6 production (14). IL-6 production can be induced through TNF-dependent and TNF-independent pathways (7). Our data suggest that administration of pneumococcal polysaccharide vaccine induces expression of IL-6 through a mechanism that may be independent of TNF-α expression, although enhanced TNF-α expression at the site of cellular interactions cannot be excluded by these
In vitro, IL-6 can enhance the production of HIV-1 (12, 13), and IL-6 is synergistic with TNF-α in the induction of latent HIV-1 expression (11). Although we could not measure changes in plasma HIV-1 RNA levels in this 24-h study, vaccine-induced expression of IL-6 may explain the rises in plasma HIV-1 RNA levels seen after immunization with pneumococcal polysaccharide vaccine (2).

Plasma IL-6 levels may exhibit diurnal variation, increasing late in the evening in non-HIV-1-infected subjects (10). In the present study, plasma IL-6 levels remained stable in unimmunized subjects, supporting the concept that the observed rises in plasma IL-6 levels in the immunized patients were due to immunization with pneumococcal polysaccharide vaccine.

There are some limitations to this study. We did not administer placebo to the control subjects, so an effect of injection and not the immunogen on plasma IL-6 levels, although unlikely, cannot be excluded. Controls tended to have higher CD4 cell counts than the immunized patients. Although changes in plasma IL-6 levels might vary according to CD4 cell count, we could find no relationship between increases in IL-6 levels and CD4 cell counts (data not shown).

In conclusion, our study shows that immunization with pneumococcal polysaccharide vaccine transiently increases plasma IL-6 levels in persons with HIV-1 infection.

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