The Role of Passive Immunization in HIV-Positive Patients*

A Case Report

Velko Veljkovic, PhD; Radmila Metlas, PhD; Djorde Jevtic, PhD; and William W. Stringer, MD, FCCP

An HIV-positive patient presented with pulmonary tuberculosis as her AIDS-defining diagnosis in 1993 and was effectively treated with 12 months of standard antituberculosis medications (isoniazide, rifampin, and pyrazinamide for 2 months). She received zidovudine for 6 weeks at the time of her diagnosis; however, because of patient preference, she has not received subsequent standard HIV medications (7 years). Her CD4 count at the time of diagnosis (1993) was 297/μL. Monthly passive immunotherapy was administered (fresh frozen plasma from HIV-negative blood donors with a significant titer for the anti-vasoactive intestinal peptide [VIP]/NTM antibody) from December 1993 to June 1994. Her CD4 count increased to >400/μL during the passive immunotherapy and has remained stable for the past 6 years. The rational for the use of anti-VIP/NTM antibodies preparations in HIV, the possible mode of action of anti-VIP/NTM antibodies, the use of Ig preparations, and the role of exercise as a natural source of anti-VIP/NTM antibodies are discussed. This case report supports the potential therapeutic use of anti-VIP antibodies for treatment of HIV disease. (CHEST 2001; 120:662–666)

Key words: aerobic exercise; AIDS; anti-vasoactive intestinal peptide/NTM antibodies; HIV; Ig preparations; passive immunization; tuberculosis

Abbreviations: AZT = zidovudine; OC = oral candidiasis; OD = optical density; TB = tuberculosis; VIP = vasoactive intestinal polypeptide

Despite enormously costly clinical and scientific efforts worldwide, the AIDS pandemic continues to spread at an alarming rate due to the lack of a safe and effective AIDS vaccine. Current HIV therapy is also quite toxic, expensive, and increasingly less effective due to the generation of more aggressive resistant HIV strains. Thus, clinicians are faced with an urgent need for effective, less toxic, nondrug-related therapies for HIV disease. Among the most promising approaches are those directed toward better utilization of the natural capacities of the host immune system against HIV.

Rationale for Clinical Experiment Design

The earliest clinical trials of passive immunization in HIV-positive patients provided conclusive evidence that antibodies to HIV-1 clear virus from the bloodstream to an undetectable level (by polymerase chain reaction) and maintains long-term neutralization of viremia. These preliminary results have accelerated further research, resulting in development of therapeutic immune preparations containing a mix of concentrated anti-HIV-1 antibodies derived from the healthy HIV-infected individuals (HIV hyperimmune globulin) or immunized animals (porcine-derived hyperimmune Ig to HIV-1).

Neurath and coworkers have reported differences in the spectrum of antibodies against HIV-1 gp120 in two groups of HIV-infected individuals, those who remained healthy for at least 10 years, and those who developed AIDS within 5 years of the onset of infection. They found that antibodies which recognized the peptide 280–306 derived from C-terminus of the second conserved region (C2) of gp120 of the HIV-1 isolate BH10 were significantly more prevalent in asymptomatic carriers than in AIDS patients. It has been speculated that absence or disappearance of these antibodies may represent a possible factor contributing to the development of AIDS. The origin of these antibodies remains unclear because the domain 280–306 of the C2 region is nonimmunogenic in humans. Based on the structural and informational similarities between the peptide RSANFTDNAKTHVQLNESVEIN (peptide NTM) encompassing residues 280–302 of HIV-1 gp120 and the human vasoactive intestinal polypeptide (VIP), it has been proposed that antibodies identified by Neurath and coworkers represent natural anti-VIP autoantibodies. It has also been demonstrated that sera from HIV-negative asthma patients contains high titers of natural anti-VIP antibodies with peptide NTM reactivity.

Correlation between the titer of VIP/NTM reactive antibodies and AIDS progression indicates that these antibodies may be an important factor in control of the disease. Using the above information, we considered the
possibility of applying passive immunization, based on these antibodies, as a therapy for HIV disease. One of the important questions concerning this therapy concerned the possible source of the human VIP/NTM antibodies. Paul and Said\(^1\) reported the presence of anti-VIP autoantibodies in normal HIV-negative human sera. Starting from these results, we have screened sera collected from 393 HIV-negative blood donors by enzyme-linked immunosorbent assay based on the peptide NTM. Results of this analysis demonstrated that approximately 5% (21 of 393 donors) of the tested sera contain significant titer of the anti-VIP/NTM antibodies corresponding to optical density (OD) value \(> (\text{OD mean} + 2 \text{ SD})\); (Fig 1). Based on these results we decided to use selected normal HIV-negative sera containing high titer of the natural VIP/NTM reactive antibodies for passive immunization therapy of an HIV patient.

**Case Report**

A 35-year-old female IV drug user presented with pulmonary tuberculosis (TB) as her index AIDS diagnosis in November 1993. The clinical pattern of TB was typical of the reactivation, with chest radiography showing left upper lobe infiltration. The subsequent culture revealed *Mycobacterium tuberculosis* with a sensitive organism. The standard anti-TB therapy (isoniazide, rifampin, and pyrazinamide for 2 months) was effective and completed in November 1994 (12 of months of therapy). At the time of diagnosis (November 1993), her CD4 cell count was 297/\(\mu\)L (26.8%), her p24 antigen was negative, and her hematologic parameters allowed the introduction of zidovudine (AZT) therapy.

She was treated with oral AZT for 6 weeks after her diagnosis, and she remained clinically stable; however, mild oral candidiasis (OC) developed. During this period of AZT therapy, her CD4 cell count decreased to 253/\(\mu\)L (17.7%). Due to patient dissatisfaction with AZT treatment and the fall in her CD4 count, an alternative treatment was offered to the patient. She accepted, and AZT treatment was discontinued.

**Treatment**

The passive immunization protocol used for this patient was presented and approved by the local institutional review board.

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(Figure 1. Reactivity to VIP in sera collected from 393 healthy, HIV-negative blood donors. Twenty-one of 393 donors (5.3%) exceeded (by 2 SD) the average OD of 0.275.)

(Figure 2. Change in the CD4 count per microliter and the CD4 fraction (percentage) for the first 1,750 days (5 years) after the initial (6 months) immunotherapy.)

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**Laboratory Findings**

The reactivity of patient’s serum to the peptides NTM and VIP was initially weak (OD < 0.25, a level of reactivity that corresponds to normal HIV-negative sera), but rose significantly after the immunotherapy infusions (OD, > 0.6). Subsequently, it remained high (OD, 0.65 to 0.73) until July 1995. Her CD4 count rose from a pretreatment value of 253/\(\mu\)L to 413/\(\mu\)L and 560/\(\mu\)L after 22 weeks and 32 weeks, respectively. In September 1995, it was 452/\(\mu\)L, peaked to 920/\(\mu\)L in July 1996, and decreased to 411/\(\mu\)L in May 1997 (Fig 2). It is important to point out that the percentage of CD4 cells, which represents an important predictor of development of AIDS,\(^{10}\) increased although her total CD4 count decreased (Fig 2). Her viral load was 125,000 copies per milliliter (Amplicor System; Roche Diagnostics; Indianapolis, IN) on June 1994.

During the last 2 years, her CD4 count has been stable around 400/\(\mu\)L (last value May 1999). Figure 3 shows the marked increases in neutralizing anti-V3 antibody concentration with passive infusion therapy in this patient. Note the parallel increases in CD4% and total CD4 count during this period of therapy (Fig 2).

**Follow-up**

Even though pulmonary TB usually occurs relatively early in the course of HIV infection, with CD4 count well above 200/\(\mu\)L, it is clear that reactivation of a latent TB infection is related to early (subclinical) HIV-induced immunodeficiency. Most AIDS patients will continue to have progression of their immune deficiencies if untreated, especially when other signs of immune dysfunction are present (eg, OC). Using the definition of AIDS prior to the use of pulmonary TB as an AIDS-defining event, the median time to progression to AIDS after OC was 70 weeks among patients who are not receiving antiretroviral therapy, (AIDS Clinic, Institute for Infections and Tropical Diseases, Belgrade, Yugoslavia). One thousand milliliters of fresh frozen plasma selected from HIV-negative blood donors with a significant titer for the anti-VIP/NTM antibody (Fig 1) was administered monthly for 6 consecutive months (from December 30, 1993, to June 20, 1994).
while >80% of patients with OC would develop AIDS after 3 years. Therefore, we consider this case unusual, as she has not progressed after >6 years from OC and TB and her CD4 cell count remained >400/µL for >5 years. Her last CD4 cell count was in May 1999, as she has been reluctant to undergo further laboratory examination. She remains disease free without symptoms at the time of this case report and receives regular office evaluations. Her OC is under control with intermittent fluconazole therapy.

**Discussion**

**Possible Mode of Action of NTM/VIP-Reactive Antibodies**

One of important obstacles in control of HIV infection by the host immune system relates to the phenomenon of “deceptive imprinting.”14 According to this theory, immediately after HIV infection, immunodominant epitopes of HIV produce selective pressure on the immune system, which induces and maintains its deceptive state. Therefore, the immune system is only able to recognize those HIV variants carrying epitopes that are identical or very close to the “original antigenic sin” presented initially after infection. In this way, later variants that evolve from the first autologous virus are unrecognized by the immune system and escape neutralization. At this point, since the immune system is prevented from appropriately addressing the HIV infection, it starts to produce natural autoantibodies that are able to neutralize the virus by attacking its sensitive and highly conserved sites (C-terminus of the second conserve conserved region of gp120). The putative protective role of anti-VIP/NTM antibodies could be attributed to the multipathway mode of action, including the following: (1) blocking the “secondary interaction” between HIV-1 gp120 and CD4 molecule,15–17 (2) impairing HIV infectivity,18–20 (3) blocking intermolecular interaction within the oligomeric envelope complex,21 (4) inactivation of gp120 by its proteolysis with the anti-VIP/NTM antibodies,22,23 and/or (5) maintenance of the immune network dynamic.24,25

**Therapy With HIV-Positive vs HIV-Negative Plasma and Ig Preparations**

Despite the initial optimism based on a promising preliminary clinical results (especially in prevention of HIV-1 transmission from mother to child), passive immunotherapy is not a common intervention in current HIV therapy. The principle problem appears to be the therapeutic component (neutralizing anti-V3 antibodies) present in plasma and Ig preparations collected from HIV-positive individuals. The V3-loop as a principal neutralizing determinant of HIV-1 gp120 elicits type-specific but not group-specific antibodies.26 This means that efficacy of this therapy potentially depends on the “immunologic compatibility” between HIV-1 isolates from donor(s) and acceptor (patient). There are data that point out the possibility that antibodies elicited by V3-loop, as well as by some epitopes from gp41, may be potentially harmful rather than protective, because they can enhance HIV-1 infection.27–30 It has been also reported that gp120 protein structure might encode idiotopes. In this way idiotope-bearing gp120, either soluble or expressed in multiple form on the surface of the cell, can influence the immune response in idiotype Id-anti-Id fashion.31,32 These data, together with other harmful effects of anti-gp120 antibodies, have been reviewed,33 pointing out the significant therapeutic advantage of HIV-negative plasma preparations enriched with anti-VIP/NTM antibodies in comparison with application of HIV Ig.

**Exercise as a Natural Source of VIP/NTM Reactive Antibodies**

Although infusion therapy appears promising in this case report, other less invasive mechanisms to produce high titers of VIP/NTM reactive antibodies may be feasible. An interesting article by Paul and Said in 198813 showed that autoantibodies to VIP were present in plasma from 29.6% of healthy (non-HIV-positive) human subjects who habitually performed aerobic muscular exercise (running, cycling, swimming, aerobic dancing, and/or weight training, three or more workouts per week for a year or more prior to study entry), compared to 2.3% of healthy subjects who did not. The antigenic stimulus for the formation of these autoantibodies could not be identified from their data; however, acute exercise has been shown to be associated with a brisk increase plasma levels of VIP.34,35 It is certainly plausible to theorize that these antibodies may have been produced in response to increased VIP levels during exercise.
Aerobic exercise training has been demonstrated in a number of studies to have beneficial effects in HIV-positive individuals, including increased fitness (as measured by lactate acidosis threshold and maximal oxygen uptake) and improvements in skin test reactivity to Candida antigen, without adverse effects on CD4 counts or viral loads. Finally, quality of life is significantly improved with aerobic exercise training relative to a nonexercising control group.

Therefore, passive infusion and aerobic exercise would both appear to be very promising adjunctive therapies for HIV infection. Indeed, aerobic exercise may prove to be an ideal nondrug adjunctive therapy to increase the titer of anti-VIP/NTM antibodies, improve immune status, aerobic fitness, and quality of life in HIV-positive individuals. Passive infusion and aerobic exercise training to increase the titer of anti-VIP/NTM antibodies would appear to warrant further investigation in HIV-positive individuals.

REFERENCES


Pneumocystis carinii Pneumonia in Pregnancy*

Hussain Ahmad, MD; Nirav J. Mehta, MD; Vivek M. Manikal, MD; Teresita J. Lamoste, MD; Edward K. Chapnick, MD; Larry I. Lutwick, MD; and Douglas V. Sepkowitz, MD

Objective: To report five new cases of Pneumocystis carinii pneumonia (PCP) and to review and analyze the existing reports on the subject.

Method: Five new cases of PCP during pregnancy are described. The cases, case series, and related articles on the subject in the English language were identified through a comprehensive MEDLINE search and reviewed.

Results: More than 80% of women with AIDS are of reproductive age, and PCP is the most common cause of AIDS-related death in pregnant women in the United States. Among 22 reviewed cases, the mortality rate was 50% (11 of 22 patients), which is higher than that usually reported for HIV-infected individuals with PCP. Respiratory failure developed in 13 patients (59%), and mechanical ventilation was therefore required, and the survival rate in patients requiring mechanical ventilation was 31%. Maternal and fetal outcomes were better in cases of PCP during the third trimester of the pregnancy. A variety of treatment regimens were used, including sulfamethoxazole-trimethoprim (SXT) alone or in combination with pentamidine, steroids, and efornithine. The survival rate in patients treated with SXT alone was 71% (5 of 7 patients) and for those treated with SXT and steroids was 60% (3 of 5 patients), with an overall survival rate in both groups of 66.6% (8 of 12 patients).

Conclusion: PCP has a more aggressive course during pregnancy, with increased morbidity and mortality. Maternal and fetal outcomes remain dismal. Treatment with SXT, compared to other therapies, may result in an improved outcome. Withholding appropriate PCP prophylaxis may adversely affect maternal and fetal outcomes.

Key words: AIDS; Pneumocystis carinii pneumonia; pregnancy; sulfamethoxazole-trimethoprim

Abbreviations: LDH = lactate dehydrogenase; PCP = Pneumocystis carinii pneumonia; SXT = sulfamethoxazole-trimethoprim

The number of women with HIV disease in the United States has been steadily increasing during the past decade. The greatest increase in AIDS incidence was observed in heterosexually infected women born between 1970 and 1974.1 As of 1995, > 80% of women with AIDS were of reproductive age; among pregnant women, Pneumocystis carinii pneumonia (PCP) was the most common cause of AIDS-related death in the United States.2 Although there have been sporadic reports of PCP in pregnancy, there has been no comprehensive review in order to provide guidelines regarding its management in pregnancy. This article presents five cases of PCP in pregnant women as well as a review of the literature.

CASE REPORTS

Case 1

A pregnant 34-year-old African-American woman presented at 27 weeks of gestation with a 3-week history of shortness of breath, fever, and cough. On admission to the hospital, she had a temperature of 37.2°C, a respiratory rate of 30 breaths/min, and oral thrush. CBC count showed no leukocytosis and a predominance of polymorphonuclear cells. The lactate dehydrogenase (LDH) level was 284 IU/L, and the CD4 count was 27 cells/µL. An arterial blood gas analysis done with the patient breathing room air revealed a PaO2 of 60 mm Hg with an alveolar-arterial gradient of 53. The chest radiograph showed bilateral interstitial infiltrates, and an abdominal sonogram showed a gravid uterus at 24 weeks and a viable fetus. She was empirically treated with sulfamethoxazole-trimethoprim (SXT), erythromycin, and oral prednisone. PCP was diagnosed using BAL. SXT was continued with a tapering dose of oral prednisone for 21 days. She was discharged and was readmitted to the hospital at 33 weeks of gestation with labor pains of a few hours in duration. She had noticed no fetal movements over the previous 2 weeks, and an abdominal sonogram confirmed fetal death. She vaginally delivered a macerated fetus (male, weighing 605 g), complicated by retained placenta and endometritis, but she recovered and was discharged home.

Case 2

A 31-year-old white woman was admitted to the hospital with respiratory distress at 29 weeks of gestation with a 10-day history of a minimally productive cough and shortness of breath. Laboratory studies revealed LDH level of 1,294 IU/L and a CD4 count of 24 cells/µL. The chest radiograph showed diffuse bilateral interstitial infiltrates. She was presumptively treated for PCP with IV SXT and...