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OCCURRENCE OF PNEUMOCYSTIS PNEUMONIA IN HIV-INFECTED PATIENTS AND THE INTERFERENCE OF THE HIGHLY ACTIVE ANTIRETROVIRAL THERAPY

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ABSTRACT: From the beginning of the AIDS epidemic, pneumocystis pneumonia (PCP) has been distinguished as one of the most frequent opportunistic diseases with high morbid-mortality. As from 1996, the advent of the highly active antiretroviral therapy (HAART) has changed the characteristics of such epidemic by reducing its related diseases and, as a result, AIDS-related mortality. With the purpose to estimate PCP occurrence and HAART interference, 376 HIV-infected or AIDS patients were studied from January 1992 to December 2002. Among them, 58 (15.5%) PCP cases were found. There was a higher occurrence of PCP in the group of patients in which HAART was not used, with 40 (69.0%) of the episodes. As regards the studied period, a tendency to a linear reduction in annual PCP incidence was observed. The mean of T CD_4^+ lymphocytes in the patients with PCP (117 cells/mm^3) was significantly lower when compared to that of the other individuals (325 cells/mm^3). Therefore, this study suggests a temporal reduction in PCP occurrence related to HAART use with higher T CD_4^+ lymphocyte counts. Nevertheless, this opportunistic infection still shows significant incidence in AIDS patients. (NCT00516581)

KEY WORDS: AIDS, pneumocystis pneumonia, antiretroviral treatment, T CD_4^+ lymphocytes.

CONFLICTS OF INTEREST: There are no conflicts.

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INTRODUCTION

Pneumocystis pneumonia (PCP), an infection caused by the fungus *Pneumocystis jiroveci* (formerly *P. carinii*), has gained importance since the first AIDS description in June 1981. In the first decade of such epidemic, PCP occurred in up to 80.0% of individuals with AIDS and was responsible for two-thirds of its defining diseases, thus being the most frequent opportunistic disease (8, 11, 13).

As from 1995, the advent of HAART has allowed a rapid reduction in PCP incidence. In the United States, from 1992 to 1995, the rate of PCP episodes per AIDS patient within a year dropped from 21.5% to 3.4%, as estimated from 1996 to 1998 (8, 11). In Europe, such rate dropped from 49.0%, as of prior to March 1995, to 3.0% after March 1998 (9, 15). In Brazil, that figure dropped from 27.7%, as of 1980 to 1988, to 11.9% in 1998 and 1999 (4). Among all opportunistic infections, PCP showed the highest reduction tendency.

On the other hand, even in developed countries as well as in those with access to antiretroviral drugs, such as Brazil, PCP still remains as the most common opportunistic infection in AIDS patients (4,8). This study aimed at analyzing PCP occurrence in relation to HAART use, T CD_4^+ lymphocyte count and the temporal distribution of cases.

PATIENTS AND METHODS

Patients

From a total of 820 patient charts, 376 HIV-infected individuals were randomly selected. Such individuals were over 14 years old and had been assisted by the Infectious Diseases Division of the Department of Tropical Diseases and Imaging Diagnosis of the Botucatu Medical School, UNESP. The period from January 1992 to December 2002 was retrospectively analyzed. In order to diagnose HIV infection, the performance of two reagent enzyme-linked immunosorbent assay (ELISA) serological tests and confirmation by the Western Blot technique, whenever necessary, were observed. This study was approved of by the Research Ethics Committee of the Botucatu Medical School, UNESP.

PCP Episode and Antiretroviral Scheme Used

During the whole period of study, the presence of the presumptive clinical diagnosis established by the assisting doctor and the indication of specific treatment were

characterized as a PCP episode. Isolation and etiological identification laboratory methods were not used to characterize PCP in this study, since such tests are rarely ordered during the work routine.

As regards antiretroviral therapy, the patients were divided into two groups:

- Non-use of HAART: 171 patients who had never been given antiretroviral drugs or who used therapy with one or two nucleoside reverse transcriptase inhibitors (NRTI).
- Use of HAART: 205 patients who received therapy with two NRTI and one non-nucleoside reverse transcriptase inhibitors (NNRTI), or two NRTI and one protease inhibitor (PI), or therapies with more than three drugs.

As for PCP patients, the antiretroviral drugs prescribed in the last six months prior to such episode were selected, and as for the other individuals, the selected scheme was that which was closer to the study completion.

T CD_4^+ Lymphocyte Count

The routine applied by the Botucatu Blood Bank was performed by using specific monoclonal antibodies CD_4^+ (RD_1) ("Coulter® Monoclonal, Antibodies, Reagents") and flow-cytometer reading. The results were expressed by means of the absolute number of cells per mm^3.

Statistical Analysis

The Chi-Square and Odds-Ratio statistics were used in order to analyze the contingency tables for cross classifying data. The groups of patients were compared by using analysis of variance (calculation of statistics F and p). The level of significance adopted was 5%. Software SPSS® 13.0 for Windows® was used for data processing.

RESULTS

Of the 376 patients studied, 229 (60.9%) were males and 147 (39.1%) were females; 298 (79.3%) were white and 78 (20.7%) non-white, with a mean age of 32.2 years (variation from 14 to 63 years). There was no statistical difference between the groups as regards such two variables ($p>0.05$).

PCP episodes were found in 58 (15.5%) patients, and of these, 18 (31.0%) were using HAART, whereas 40 (69.0%) were not, as shown in Table 1. In the group of patients with PCP, no difference was observed in the mean of T CD_4^+ lymphocytes

among those undergoing HAART or not (p=0.379), but prophylaxis using sulfamethoxazole-trimethoprim was associated with protection against the PCP episode (p>0.001).

The distribution of the 58 PCP episodes in the period under study in relation to the total number of patients accumulated annually is represented in Figure 1.

T CD_4^+ lymphocyte count was recovered in 327 individuals, and in those with PCP, the mean was 117.6 cells/mm^3. For patients without PCP, the mean was 325.5 cells/mm^3, according to Table 2.

Table 1. Association of antiretroviral therapy and the episode of pneumocystis pneumonia (PCP). Calculated statistics and comments.

PCP / Therapy	Present	
	Number	Percentage
Without HAART	40	69%
HAART	18	31%
Total	58	100%

Hypothesis	Calculated Statistic	Significance	Comment
Without HAART = HAART	$\chi^2 = 15.26$ ODDS RATIO: 2.66	$p < 0.001$	Without HAART > HAART

Without HAART: patients who never received antiretroviral drugs or to whom therapy with one or two nucleoside reverse transcriptase inhibitors (NRTI) were prescribed.

HAART: patients who received potent combination antiretroviral therapy.

p: significance.

Table 2. Association between T CD_4^+/mm^3 lymphocyte count and pneumocystis pneumonia (PCP) episode. Calculated statistics and comments.

PCP / CD_4^+/mm^3	Present	Absent
Mean	117.6	325.5
Median	59.0	273.0
Standard Deviation	118.9	295.0
Minimum – Maximum	1–511	2–2681

Hypothesis	Calculated Statistic	Significance	Comment
Present = Absent	F = 26.75	p = 0.001	Present < Absent

p: significance

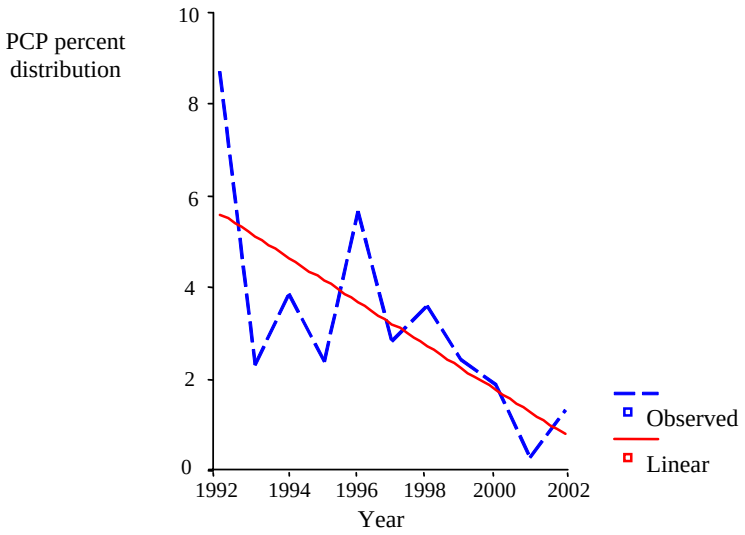

Figure 1. Percent distribution of the 58 pneumocystis pneumonia (PCP) cases in relation to the total number of patients assisted, annually accumulated, and their linear distribution from January 1992 to December 2002.

Calculated Statistic: $R^2 = 0.48$; F = 8.31

DISCUSSION

The findings in this study as regards the sample's characterization, such as gender distribution, age and skin color, are in agreement with those in Brazil (2) in the same period, and there was no statistical difference between the groups ($p>0.05$), which shows homogeneity between them.

In this study, HAART use for at least six months was related to a smaller chance of PCP occurrence. Sixty-nine percent of the episodes were concentrated in patients without HAART, and the comparison with individuals from the other group showed significant statistical difference ($p<0.001$) and increased risk for PCP (Odds Ratio: 2.66). When the distribution of PCP episodes in the studied period was analyzed, a temporal reduction in the incidence, characterized by a tendency to a linear drop (R^2: 0.48), was observed.

One of the major limitations of studies involving PCP diagnosis is its etiological confirmation. The pathogen is rarely recovered in common expectoration, hence, in routine work, the diagnosis is achieved in a presumptive fashion by considering unspecific clinical, radiographic and laboratory findings, such as lactic dehydrogenase dosage and arterial gasometry (14). Methods such as expectoration induced by saline solution inhalation and bronchial alveolar lavage by brushing, as obtained from bronchoscopy and transbronchial, transthoracic and thoracotomic biopsies, are more sensitive techniques; however, they are costly and can be related to high complication rates and increase in hospitalization time (1).

Historically, PCP, which had always been the most common opportunistic disease defining AIDS, was also the one exhibiting the largest reduction after the strategies of prophylactic use with sulfamethoxazol-trimethoprim at the beginning of the 1990s and particularly after HAART introduction as of 1996. The number of cases of other rather frequent opportunistic infections, such as neurotoxoplasmosis and neurocryptococcosis, was also reduced, but less intensively than that of PCP (4, 6, 7, 9, 10, 12, 15).

In countries with few resources and where access to HAART is not ensured, PCP incidence is still very high; therefore, studies on the occurrence of such opportunistic disease become a tool which can possibly evaluate successful outcomes in the therapeutic approach to AIDS patients (3). In Brazil as well as in other countries which ensure access to antiretroviral drugs, a tendency to the highest reduction in PCP occurrence has been observed (2, 4, 6, 7, 9, 10, 12, 15).

Additionally, the patients who did not use HAART showed shorter survival periods and more severe progression marking conditions as well as higher death risks when compared to those utilizing PIs (4–7, 9). Therefore, it is plausible to assume that the reduction in PCP incidence is, in fact, associated with antiretroviral treatment, since it recovers, at least partly, the individual's immunologic conditions, thus promoting an increase in the number of T CD_4^+ lymphocytes mainly as a result of virological control with a reduction in the HIV plasma viral load to undetectable or very low levels.

T CD_4^+ lymphocyte count was also related to PCP occurrence in this study, since the patients with the disease showed significantly lower counts than those in the group without PCP ($p=0.001$). In various observational cohorts, the risk for PCP development is largely increased in patients with T CD_4^+ lymphocyte counts lower than 200 cells/mm^3 (8, 11, 13).

The possible explanations for the occurrence of PCP and other opportunistic infections in patients receiving HAART would be the therapeutic failure triggered by resistance of HIV to antiretroviral drugs and the lack of adherence to the therapeutic regimen and prophylaxis schemes, variables which were not investigated in this study.

Additionally, reduction in PCP incidence may be related to other factors, such as seeking medical care at an earlier stage, which allows a proper clinical and therapeutic approach (4).

In conclusion, HAART use and higher TCD_4^+ lymphocyte counts are associated with reduction in PCP occurrence. Also, there was a tendency to reduction in PCP occurrence in the studied period (1992–2002).

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