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Rapid progression of carotid lesions in HAART-treated HIV-1 patients

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Abstract

To obtain data on the evolution of carotid lesions, we evaluated 133 patients at their first antiretroviral regimen, followed for at least 2 years; 77 treated with protease inhibitors (PIs): Group A and 56 with non-nucleosidic reverse transcriptase inhibitors (NNRTIs): Group B. All patients were subjected to carotid ultrasonography. In Group A, among the previously normal patients 22.5% developed lesions, 40% remained normal, 37.5% shifted to other antiretroviral regimens. Among the 37 previously pathologic patients, 46% worsened, 19% were stable, in 8% the lesions had disappeared, 27% shifted. In Group B, among the previously normal patients, 12.7% developed lesions, 80.8% remained unaltered, 6.5% shifted. Among the previously pathologic patients, 12.5% worsened, lesions reversed in 25%, remained stable in 50% and 12.5% shifted to PI. At statistical analysis, in Group A both the percentage of patients developing new lesions and the percentage of patients who worsened was significantly higher. In conclusion, we evidenced a more rapid onset of lesions in patients treated with PIs with respect to patients treated with NNRTIs and towards a more rapid evolution of the previous lesions. The shift from PIs to NNRTI/3 NRTI seems related to a lower rate of evolution. Interestingly, a disappearance of lesions was detected in both groups.

Keywords: HIV; Antiretroviral therapy; Intima-media thickness; Color-doppler ultrasonography; Carotid plaques

1. Introduction

Treatment with protease inhibitors (PI) has been associated with the onset of metabolic disturbances, such as insulin resistance and lipodystrophy [1–4]. Moreover, various vascular complications (stroke, angina pectoris and myocardial infarctions) have been described in patients subjected to prolonged treatment with this class of antiretrovirals. These observations prompted the hypothesis that PI can determine an atherosclerotic damage of the vascular wall [5–8]. Moreover, compared with untreated patients, those receiving PI seem more prone to endothelial dysfunction [9] and coronary artery calcifications [10]. However, in spite of these observations, the actual role of these molecules in increasing the risk of cardio- and cerebro-vascular events in HIV-positive patients still remains a highly controversial issue.

Ultrasound color-doppler is a well-established, non-invasive method for measuring the degree of atherosclerosis. Furthermore, the examination can be conducted early in the development of atherosclerosis and can be used to detect the progression of the lesions.

In previous reports within the premature vascular lesions and antiretroviral therapy study (PREVALEAT), a higher than expected prevalence of premature carotid lesions was observed in HIV-1-infected patients treated with PI-including regimens compared to naive or non-nucleosidic reverse tran-

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scriptase inhibitors (NNRTI)-treated patients with color-doppler ultrasonograpy of the epiaortic vessels [11].

In the present study, to obtain data on the evolution of the lesions, a subgroup of these patients was followed for a period of at least 2 years from the start of therapy.

2. Patients and methods

The patients evaluated had been enrolled in the PREVALEAT study which had selected a total of 293 HIV-1-positive patients at their first antiretroviral regimen [11]. The group included 160 subjects submitted to follow-up, 77 of whom were being treated with PI-based regimens (Group A) and another 56 with NNRTI-based regimens (Group B). In Group A, 34 patients were treated with regimens based on indinavir/ritonavir, 25 with nelfinavir, 12 with saquinavir/ritonavir, 6 with lopinavir/ritonavir. In Group B, 26 patients were treated with regimens based on nevirapine and 30 with efavirenz. The patients were submitted to an initial color-doppler ultrasonography after at least 12 months of therapy and to a second doppler after a further 12 months. Intima characteristics, pulsation and resistance indexes, minimal, peak and mean speed were evaluated. Atherosclerotic plaques were described. Subjects affected by hypertension were excluded from the study. The main patient characteristics are reported in Table 1.

All patients were subjected to ultrasonography of the epiaortic vessels using a last generation power color-doppler with 7.5 mgHz probes. Characteristics of the intima, pulsation index, resistance index, minimal speed, peak speed and mean speed were evaluated; an intima-media thickness (IMT) of >1 mm was considered to be pathological [12]. Atherosclerotic plaques, if present, were described. A carotid was classified as being affected by plaque if there was a localized thickening >1.2 mm that did not uniformly involve the whole left or right common carotid bifurcation with or without flow disturbance [13,14]. Ultrasonography was performed by physicians specifically trained on carotid vessels (LA, PF and FS) with at least a 10-year experience in the ultrasound color-doppler technique and at least 1000 documented epiaortic examinations. They were blinded to the patient's antiretroviral therapy. Moreover, during the study, periodical meetings were held using filmed reports aimed at the comparison and standardization of the technique. Patients were submitted to the investigation in a supine position after at least 10 min of acclimatization in a comfortable room. Patients were informed that the investigation was non-invasive. The common, internal, and external carotid vessels were examined in the short and long axis. The percentage of stenosis was always quantified by calculating the stenosis areas in the short axis using a strong magnification. This was intended to distinguishing correctly the real lumen from plaques markedly hypoechoic with the color- or the power-doppler The speed measurements were performed at an 45–60° inclination with respect to the lumen. The morphological investigation of the plaque was performed using both ultrasonography and the ultrasound power color-doppler in order to better characterize the profile of the plaque and the IMT [15–18]. None of the patients was subjected to angiography because of poor patient compliance to an invasive procedure. Moreover, previously published literature confirms that the technique used is the gold standard for investigation of carotid plaques [19]. Risk factors for cardiovascular diseases were evaluated, such as familial history (angina, myocardial infarction, cerebral stroke and transitory ischemic attack), sedentary life (<1 h/week of sport activity), cigarette smoking, alcohol consumption (>80 g/day), active drug addiction, hyperglycemia (>110 mg/dl), hypercholesterolemia (>200 mg/dl) and hypertriglyceridemia (>200 mg/dl); in addition, risk factors for HIV-1 infection including Center for Disease Control and Prevention (CDC) stage, CD4 cell count, viral load and antiretroviral therapy were assessed. No patients used lipid-lowering drugs.

The statistical analysis was performed using the chi-square test and the F-Fisher exact test when necessary.

The ethics committee of the hospital approved the study and the patients provided informed written consent.

3. Results

In Group A, at baseline, 40 patients (52%) were normal while 37 (48%) showed lesions of the epiaortic vessels. At follow-up, among the previously normal patients, 9 (22.5%) developed lesions while 16 (40%) remained normal. The remaining 15 (37.5%) shifted to other antiretroviral regimens. The lesions developed were: seven pathologic IMT, one plaque and one pathologic IMT plus plaque.

Among the 37 previously pathologic patients of the A Group, 17 (46%) showed worsening of the lesions, 7 (19%) were stable and in 3 (8%) the lesions had disappeared. The remaining 10 (27%) shifted to other regimens. Among the worsened patients 3 had pathologic IMT, and 14 pathologic IMT plus plaques (see Fig. 1).

In Group B, at baseline 48 (86%) were normal and 8 (14%) had lesions. At follow-up, among the previously normal patients, 6 (12.7%) developed lesions while 39 (80.8%) remained unaltered. Three patients (6.5%) shifted to other regimens, one to PI, two to 3 nucleosidic reverse transcriptase inhibitors (NRTI). The lesions developed were: four pathologic IMT, one plaque and one pathologic IMT plus plaque.

Among the eight previously pathologic patients of the B Group, one (12.5%) worsened with increase of IMT, while the pathologic IMT reversed in two (25.0%), the lesions remained stable in four (50.0%) and one patient (12.5%) shifted to 3 NRTI (see Fig. 2).

Pulsation and resistance indexes, minima speed and peak speed resulted normal in all the patients.

When comparing the previously healthy patients who developed lesions in the Groups A and B, a significantly