Cardiovascular risk factors in patients on long-term treatment with nevirapine- or efavirenz-based regimens

Paolo Maggi1*, Chiara Bellacosa1, Valentina Carito1, Francesco Perilli2, Antonio Lillo2, Anna Volpe1, Giovanna Trillo1, Domenico Angiletta2, Guido Regina2 and Gioacchino Angarano1

1Institute of Infectious Diseases, Policlinico, University of Bari, Bari, Italy; 2Unit of Vascular Surgery, Policlinico, University of Bari, Bari, Italy

*Corresponding author. Tel: +39-080-559-2134; Fax: +39-080-547-8333; E-mail: p_maggi@yahoo.com

Received 4 September 2010; returned 18 October 2010; revised 18 November 2010; accepted 6 December 2010

Objectives: The aim of this study was to evaluate the cardiovascular risk among patients treated for more than 5 years with regimens based on nevirapine or efavirenz.

Patients and methods: A total of 276 patients were retrospectively evaluated, 156 of whom were treated with nevirapine and 120 with efavirenz, by examining traditional risk factors and detecting the presence of subclinical carotid lesions with colour-Doppler ultrasonography.

Results: When comparing the data at baseline and follow-up in the nevirapine group, total cholesterol, low-density lipoprotein cholesterol (LDLc) and triglycerides showed a significant decrease, while high-density lipoprotein cholesterol increased. Ultrasound data, obtained in a subgroup of 67 patients, did not show significant changes for those treated with nevirapine. In the efavirenz group, total cholesterol, LDLc, triglycerides, glycaemia, body mass index and the number of patients with a pathological ultrasound significantly increased. When comparing the two groups at baseline and follow-up, nevirapine patients had significantly higher values of total cholesterol, LDLc and triglycerides at baseline, while total cholesterol and LDLc differed nonsignificantly at follow-up; triglycerides became significantly lower in the nevirapine arm with respect to the efavirenz group. Glycaemia was comparable between the two groups at baseline, while it was significantly lower in the nevirapine group at follow-up. The number of pathological ultrasound findings was significantly higher in the efavirenz group at follow-up.

Conclusions: Patients treated with nevirapine demonstrated a better lipid and glucose profile and a lower tendency to develop subclinical atherosclerotic lesions.

Keywords: non-nucleoside reverse transcriptase inhibitors, antiretroviral therapy, colour-Doppler ultrasonography, subclinical carotid lesions

Introduction

Although the introduction of highly active antiretroviral therapy (HAART) has produced a sharp reduction in mortality, cardiovascular (CV) disease has progressively emerged as a significant cause of morbidity and mortality among HIV-1-positive HAART-treated patients. Studies conducted on mega-cohorts have shown a possible correlation between HAART therapy based on protease inhibitors (PIs) and the risk of developing CV manifestations, whereas, until now, regimens based on non-nucleoside reverse transcriptase inhibitors (NNRTIs) seem to be relatively CV-friendly.1–4 However, data are scarce regarding a direct comparison between regimens based on the two main NNRTIs, nevirapine and efavirenz, especially among patients on long-term treatment.

The objective of the present study was to evaluate the CV risk among patients treated for more than 5 years with regimens based on nevirapine or efavirenz by examining traditional risk factors and the detection of subclinical carotid lesions by means of colour-Doppler ultrasonography.

Methods

From January to December 2009, all patients regularly attending our outpatient facility who had been treated with NNRTI-based regimens for at least 5 years were considered for the present study. A total of 276 patients were evaluated, 156 of whom were treated with nevirapine and 120 with efavirenz.

In the nevirapine group, 41.67% (65) were HAART-naive, 62.18% (97) were males and the median age was 43.36 years (range 20–76). The median treatment period was 79.5 months (range 60–130). In the efavirenz group, 35.83% (43) were HAART-naive, 58.33% (70) were males...
and the median age was 40.93 years (range 21–73). The median treatment period was 79.5 months (range 60–130).

Among patients shifted to NNRTIs from previous antiretroviral regimens, 87 (55.77%) had been treated with a PI-based regimen in the nevirapine group and 65 (54.17%) had been treated with a PI-based regimen in the efavirenz group.

All data, which were collected when initiating therapy regarding hepatitis C virus (HCV) and/or hepatitis B virus (HBV) co-infection, familial history of CV disease (defined as a first-degree relative (parent, sibling or child) who had a history of myocardial infarction or ischaemic stroke at age <55 years in men and <65 years in women), sedentary life (defined as <1 h per week of sport activity), cigarette smoking (defined as at least 100 cigarettes during the person’s life, and the last cigarette smoked <6 months previously), alcohol abuse (defined as alcohol consumption >80 g/day) and active drug addiction, were periodically examined and re-evaluated during follow-up. Because these retrospective data were obtained from active drug addiction, were periodically examined and re-evaluated during follow-up. Because these retrospective data were obtained from the database of the Premature Vascular Lesions and Antiretroviral Therapy (PREVALEAT) study, an ongoing cohort started in 1998, the above definitions were adopted at the start of the PREVALEAT study.5

Patients with a past history of CV disease, diabetic patients or those treated for dyslipidaemia, and patients with a confirmed virological failure were excluded from the study.

Values were recorded at baseline and during follow-up for fasting total cholesterol, low-density lipoprotein cholesterol (LDLc), high-density lipoprotein cholesterol (HDLc), triglycerides, glycaemia, blood pressure, body mass index (BMI) and blood pressure. Hypertension was defined as a systolic/diastolic blood pressure ≥130/≥85 mmHg according to the Third Adult Treatment Panel of the National Cholesterol Education Program (NCEP-ATP III) classification.6

In a total of 67 patients (36 in the nevirapine group and 31 in the efavirenz group) colour-Doppler ultrasonography of the epi-aortic vessels had been performed when initiating therapy and it was repeated at follow-up. In the nevirapine group the median period of ultrasonographic follow-up was 7 years (range 4–10) and that in the efavirenz group was 7 years (range 3–10). Ultrasonography was performed using a latest-generation power colour-Doppler with 7.5 MHz probes (Acuson Sequoia 512). Ultrasonography was performed by physicians with specific training on carotid vessels, with at least 15 years of experience with the ultrasound colour-Doppler technique and approximately 10000 documented epi-aortic examinations. In addition, they were blind to the patient’s treatment history and status, and unaware of the diagnosis. After being informed about the non-invasive nature of the investigation, the patients were placed in a supine position after at least 10 min of acclimatization in a comfortable room. The common carotid, bifurcation and at least the first 2 cm of the internal and external carotid vessels were examined in the short and long axis using high magnification; this technique assisted in correctly distinguishing the real lumen from plaques markedly hypoechoic with the colour or power Doppler. The morphological investigation of the plaque was performed using both ultrasonography and ultrasound power Doppler in order to better characterize the profile of the plaque and the intima–media thickness (IMT).7–10 An IMT greater than 0.9 mm was considered pathological while an artery was classified as affected by plaques if the IMT was greater than 1.2 mm.

Statistical analysis was performed using Student’s t-test for paired and unpaired samples, and the χ² and Fisher tests. The Ethics Committee of the hospital approved the study and the patients provided informed written consent.

Results

As shown in Table 1, at baseline, data regarding gender, period of treatment, revised CDC classification, percentage of HAART-naive patients, previous PI-based antiretroviral treatment, HCV and/or HBV co-infection, familial history of CV disease, sedentary life, cigarette smoking, alcohol abuse and active drug addiction did not differ statistically between the nevirapine and efavirenz groups. However, the median age was significantly higher in the nevirapine group.

| Table 1. Demographic data and risk factors for the two groups at baseline |
|-----------------------------|-----------------------------|-----------------------------|
| Age, median (range)         | Nevirapine (156 patients)   | Efavirenz (120 patients)    | P               |
| Male gender, no. of patients (%) | 43.36 (20–76)               | 40.93 (21–73)               | 0.02            |
| HAART period of treatment (months), median (range) | 97 (62.18)                  | 70 (58.33)                  | 0.61            |
| HAART-naive, no. of patients (%) | 79.5 (60–130)               | 79.5 (60–130)               | 0.9             |
| Previous PI-based treatment, no. of patients (%) | 65 (41.67)                  | 43 (35.83)                  | 0.38            |
| Familial history, no. of patients (%) | 87 (55.77)                  | 65 (54.17)                  | 0.23            |
| Sedentary life, no. of patients (%) | 35 (22.44)                  | 22 (18.33)                  | 0.4548          |
| Cigarette smoking, no. of patients (%) | 126 (80.77)                 | 103 (85.83)                 | 0.3328          |
| Alcohol abuse, no. of patients (%) | 101 (64.74)                 | 80 (66.67)                  | 0.7987          |
| Active drug addiction, no. of patients (%) | 11 (7.05)                   | 10 (8.33)                   | 0.8196          |
| HCV, no. of patients (%) | 50 (32.05)                   | 28 (23.33)                  | 0.110           |
| HBV, no. of patients (%) | 3 (1.92)                     | 6 (5.00)                    | 0.15            |
| HCV+HBV, no. of patients (%) | 2 (1.28)                     | 2 (1.67)                    | 0.79            |
| Revised CDC stage (Atlanta, GA, USA, 1993)\(a\), no. of patients (%) | 77 (49.36)                  | 61 (50.83)                  | 0.48            |
| A                          | 47 (30.13)                   | 28 (23.33)                  |                |
| B                          | 32 (20.51)                   | 31 (25.83)                  |                |

\(a\)The two groups showed a non-statistically significant distribution among the different CDC stages (\(x^2, P = 0.5\)). All groups were simultaneously compared using the \(x^2\) test for the contingency table 8×2 (\(P = 0.48\)). Statistically significant \(P\) values are shown in bold.
In the nevirapine patient group, 110 patients at baseline were treated with a backbone based on thymidine-based drugs (zidovudine or stavudine) plus lamivudine, 18 patients with didanosine plus stavudine, 14 patients with zidovudine plus didanosine and 14 patients with non-thymidine analogues (tenofovir or abacavir) plus lamivudine or emtricitabine. During the follow-up all the patients shifted to non-thymidine-based backbones.

Among the patients in the efavirenz group, at baseline, 30 were treated with a backbone based on thymidine analogues (zidovudine or stavudine) plus lamivudine and 90 subjects with non-thymidine analogues (tenofovir or abacavir) plus lamivudine or emtricitabine. During follow-up, all patients shifted to non-thymidine-based backbones.

When comparing the data at baseline and during follow-up in the nevirapine group, total cholesterol, LDLc and triglycerides showed a significant decrease during the treatment period and HDLc increased significantly, while glycaemia and BMI did not show significant variations. The number of patients with documented hypertension increased significantly during follow-up. In the nevirapine group ultrasound data did not show significant changes between baseline and follow-up. See Table 2.

As also shown in Table 2, total cholesterol, LDLc, triglycerides, glycaemia and BMI significantly increased in the efavirenz group, whereas HDLc did not show significant variations. The number of patients with documented hypertension did not increase from baseline to follow-up, while a significant number of patients demonstrated pathological findings at the end of follow-up compared with baseline.

Comparison of the two groups of patients at baseline and the end of follow-up (Table 3) showed that patients in the nevirapine group had significantly higher values of total cholesterol, LDLc and triglycerides at baseline; in contrast, total cholesterol and LDLc did not differ significantly at follow-up while triglycerides were significantly lower with respect to the efavirenz group. Glycaemia was comparable between the two groups at baseline, whereas it became significantly lower in the nevirapine group at follow-up. At follow-up, the percentage of pathological findings at ultrasound was significantly higher in the efavirenz group. No differences between baseline and follow-up values were observed for the other parameters evaluated (HDLc, BMI and hypertension).

**Discussion**

There is an increasing concern regarding the CV risk among HIV-1-positive patients, which is related not only to the possible role of PIs but also to HIV itself, as this virus appears to result in a 2-fold increase in acute myocardial infarction. In this scenario, there is an urgent need for CV-friendly antiretroviral regimens, especially for patients on long-term treatment.

Nevirapine showed a favourable lipid profile when compared with PIs, although this is only documented by studies conducted with regimens rarely used at present. More importantly, direct comparisons of nevirapine and efavirenz regimens have been conducted, showing a better lipid profile among nevirapine-treated patients. The main limitations of these studies, however, are that they explored only the metabolic outcome of patients (an important risk factor for CV, but not the only one) and did not consider subclinical organ damage; in addition, data regarding long-term treatment with these regimens are lacking.

Our findings show a better lipid and glucose profile among long-term nevirapine-treated patients, together with a tendency to decreasing values of total cholesterol, LDLc and triglycerides over time, and increasing values of HDLc. In contrast, in the efavirenz group we observed a trend towards increasing total cholesterol, LDLc, triglycerides, BMI and glycaemia. However, as the value of triglycerides was the only statistically different parameter between the two groups at follow-up, we conclude that both regimens seem generally safe among patients on long-term treatment from the metabolic point of view. The tendency for an increase in the percentage of nevirapine patients with high...
blood pressure is not easy to explain and deserves further investigation. It can be hypothesized that the significantly higher median age in this group, together with the non-significantly greater number of patients with familial CV disease, could have influenced this datum.

Measurement of carotid IMT with colour-Doppler ultrasonography was found to be a non-invasive, sensitive and highly reproducible technique for identifying and quantifying atherosclerotic lesions, even at a very premature stage. It is a well-validated research tool and is widely used in clinical practice. The American Heart Association (AHA) and NCEP-ATP III have endorsed the use of carotid IMT for CV risk assessment. In preventive medicine, IMT measurement is especially important for subjects with an intermediate CV risk, i.e. for subjects with a 10 year risk of CV disease between 6% and 20%.20,21 In our study, patients treated with efavirenz showed a significant tendency to have pathological ultrasound findings when compared with the nevirapine group.

In conclusion, patients treated with nevirapine demonstrated a better lipid and glucose profile and a lower tendency to develop subclinical atherosclerotic lesions.

**References**


