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Original Research Article

Long-term efficacy and safety of treatment with nevirapine plus nucleoside reverse transcriptase inhibitors for HIV-1 infection: An eight-years follow-up

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ABSTRACT

Background: The aim of this retrospective study is to evaluate long-term efficacy and safety of highly active antiretroviral therapy (HAART) regimens based on nevirapine (NVP) plus nucleoside reverse transcriptase inhibitors (NRTIs), with particular regard to NVP's effect on liver function and lipid profile, in both HAART-experienced patients and naïve.
Material and methods: We have continuously treated with NVP for at least 8 years a total of 197 HIV-1 positive patients (126 males, 71 females) and we have followed-up them over a eight-years period: 54.7% of them were HAART-experienced patients and have switched to NVP for simplification, intolerance or dyslipidemia, while 45.3% were naïve to antiretroviral drugs. Co-infection with hepatitis C viruses was detected in 20% of patients. Viral load, CD4+ cell count, liver enzymes and lipid profile were investigated on 2, 4, 6 and 8 years follow-up controls, retrospectively.
Results: The initial positive anti-viral answer obtained with NVP have been lasting in time in all patients. The patients which were continuously treated with NVP kept undetectable viral load from 2 to 8 years follow-up controls. None of these patients developed liver toxicity. An increased in of γ-GT levels occurred in the first two years of treatment, then they remained stable; AST and ALT levels showed no significant variations. Lipid levels remained in normal range, with a significant improvement of HDL-cholesterol in naïve patients.
Conclusion: Long-term treatment with NVP is safe and effective, and it do not require use of statins in both experienced and naïve patients.

1. Introduction

Nevirapine (NVP) has been known in years as a well tolerable antiretroviral drug that is able to stimulate long-lasting immunological response [1–5].

NVP reported side effects, including liver toxicity, rash and anaphylactic reactions, most frequently occur within 6th–18th therapy week [1,6]. Men and women with CD4+ cell count, respectively, above 400 cell/mm^3 and above 250 cell/mm^3, along with HBV/HCV co-infected patients, have more possibility to develop side effects, as well as heavy drinkers and people with HLA-DRB*0101 genetic profile [7]. It could be necessary, in some cases, to stop therapy because of adverse reaction: therapy interruption has been performed in both HAART-experienced patients (i.e., people that has been previously treated with antiretroviral drugs) with low CD4+ cell count at the nadir and high at basal drug level, and naïve patients with low CD4+ cell count. Thus, these two kinds of patients seem to have the same possibility to develop adverse reactions/require treatment discontinuation [8,9].

Despite this, NVP have many advantages. It is possible to switch from efavirenz (EFV) to immediate full dose NVP [10–12]. NVP can be employed in preventing peripartum HIV transmission, and the standard dose is also recommended for HIV-1 positive woman with a low CD4+ cell count [13]. In addition, EFV-intolerant patients successfully switching to NVP show an improvement of psychical/neurological side effects and lipid profile. Given its potential to regulate blood lipid levels (e.g., increasing HDL-cholesterol), NVP can reduce cardiovascular risk in HIV-1-positive patients [14,15]. Thus, using NVP may incentivize long-term adherence to HAART. Because of its good penetration through the haematic-encephalic barrier and into interstitial spaces, NVP can reduce cognitive deterioration in those patients who have persistently undetectable plasma HIV-RNA during HAART, while the virus is obtainable in their encephalic liquid [16]. The drug process remains unaltered

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during pregnancy: NVP passes quickly through the placenta and guarantees an effective antiretroviral prophylaxis [17]. Finally, NVP is quite cheap, whereas other commonly used anti-retroviral drugs are very expensive: given the increasing life expectancy of HIV-infected patients, the benefits of NVP cost-efficiency should be considered.

The aim of this retrospective study is to evaluate the long-term efficacy of NVP-based HAART regimens and to estimate safety of NVP, with particular regard to its effect on liver function and lipid profile, on both naïve and HAART-experienced patients.

2. Materials and methods

Our retrospective study starting from 1999 has involved a total of 350 HIV-1 positive patients consecutively. These patients have received a combination therapy of NVP plus a spectrum of reverse transcriptase inhibitors (nucleoside or nucleotide) (NRTIs) including azathioprine (AZT), lamivudine (3TC), emcitrabine (FTC), tenofovir (TDF), didanosine (DDI) and stavudine (D4T). Our patients received NVP tablets (cp) by 200 mg two times a day or 400 mg once a day associated with at least two NRTIs.

Between 1999 and 2010, 153 patients (43.7%) have discontinued therapy: 83 patients (54.3%) discontinued either because of lack of adherence to NVP-based combination therapy or failure or resistance of the same, while 70 (45.7%) discontinued because of side effects such as rash and liver toxicity. Among patients who prematurely disrupted NVP-treatment, those HIV and HCV/HBV co-infected (*n*, 37) stopped NVP after seven weeks, whereas those non co-infected (*n*, 33) discontinued treatment on week eight.

On the last follow-up control in 2010, we assessed that a total of 197 of 334 patients (54.5%) were continuously treated for eight years, with NVP-based combination therapy: 101 people received NVP plus AZT-37C, 42 NVP plus FTC and TDF, 20 NVP plus D4T-3TC and 18 NVP plus AZT-DDI. Patients' general characteristics were investigated before they started NVP-combination therapy, and are provided in Table 1.

Ninety-nine of 181 patients (54.6%) were received HAART-experienced patients: they have switched to NVP because of simplification, intolerance or failure, or dyslipidemia (i.e., hypertriglyceridemia, hypercholesterolemia) (Table 1).

HIV-1 viral load, CD4+ cell count, liver enzymes and lipid profile have been evaluated at baseline and on 2, 4, 6 and 8 years follow-up controls. There was no limit to restrictive inclusion of patients according to the values of CD4+ cell count or viral load at baseline. Written informed consent has been obtained from study participants.

3. Results

Among, 197 patients, the median duration of therapy from the moment of recruitment has been of 9.5 ± 1.5 years.

Thirty-six patients (18.2%) were HCV/HBV and HIV co-infected. They were considered patients with co-infection HIV/HCV, as they were stable and with as liver impairment at baseline not superior to grade 2. Those HBV/HIV co-infected were asymptomatic.

Starting from 2-years follow-up control until 8-years control, HIV-1-RNA was undetectable in all patients, and the average CD4+ cell count increased about 250 cell/mm^3 from baseline value (Table 2). In naïve patients viral charge has been decreasing into the first 6 months of therapy (range 3–9 months).

Table 1
General baseline characteristics of examined NVP-patients.

Total patients (pts)	197
Age median (years ± SD)	49 ± 10.7
Sex	
Male (*n*; %)	126; 69.6
Female (*n*; %)	71; 30.4
CDC stage	
A (*n*; %)	98; 59
B (*n*; %)	57; 29
C (*n*; %)	42; 22
HIV transmission category	
IVDU (*n*; %)	29; 14.7
Heterosexual (*n*; %)	69; 35
Homosexual (*n*; %)	52; 27.2
Other or unknown (*n*; %)	47; 24.6
Pts switched to NVP (*n*; %)	113; 59.1
CD4/mm^3 (median; range)	450; 30–1600
VL copies/ml, Bayer bDNA (median; range)	
In 33 pts:	100,000 (51–500,000)
Failure/poor tolerability	
In 80 pts:	<50
Simplification	52 pts
Dyslipidemia	28 pts
NVP-naïve pts (*n*; %)	84; 43.9
CD4/mm^3 (median; range)	386; 11–986
VL c/ml at baseline Bayer bDNA (median; range)	87,000; 20,000–214,000
HVB/HCV and HIV co-infected pts	41 (21.4)
HCV-RNA positive pts	30
HBsAg/HCV-RNA pts	6
HBsAg-positive pts	5

Between baseline and six-year follow-up control, we observed an increasing γ-GT trend that was greater in HCV/HBV and HIV co-infected patient. Then, γ-GT levels remained stable between six and eight-year control in both patients' groups. Otherwise, ALT and AST remained stable through the years in patients without HCV/HBV infection, and minimal changes were detectable in HCV/HBV and HIV co-infected patients (that showed higher baseline liver enzymes) (Table 3). Thus, no significant alterations of global liver function were detected during the follow-up period in all patients (Table 3).

In experienced patients, total and LDL-cholesterol levels slightly increased through the years but remained within standard range. In these patients, triglycerides levels showed a decrease from baseline on four-year control, that resulted to be not statistically significant at 4-year control ($p = 0.07$); mild decrease in HDL-cholesterol levels was observed (Table 4). Among naïve patients, HDL-cholesterol levels progressively increased from baseline ($p = 0.01$), while triglycerides levels showed a decreasing, with low fluctuations, trend. In the same group, registered total and LDL-cholesterol levels demonstrated no significant variations (Table 4). None of the patients were assuming neither statins nor other lipid-lowering drugs.

4. Discussion

We have observed that long-term use of NVP represents a safe and effective therapeutic approach. The initial positive anti-viral answer obtained with NVP have been lasting in time in both experienced and naïve patients. Our patients continuously treated with

Table 2
Viral load and CD4+ cell count follow-up.

	Baseline	2 years	4 years	6 years	8 years
CD4/mm^3 (median; range)	414; 12–1233	548; 102–1309	671; 220–1546	683; 210–1480	660; 200–1340
HIV-1 RNA copies/ml (Bayer bDNA) range	70,000; 49–500,000	<50	<50	<50	<50