Risk of side effects associated with the use of nevirapine in treatment-naïve patients, with respect to gender and CD4 cell count

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Objectives
A warning about the use of nevirapine (NVP) by its pharmaceutical manufacturer has been issued in which it has been recommended that NVP should not be prescribed in patients with increased risk of toxicity based on CD4 cut-offs and gender. The aim of this study was to determine whether these recommendations are of use in preventing side effects.

Methods
This retrospective study included antiretroviral drug-naïve patients who started treatment with NVP. Patients were divided into two groups: those with high CD4 counts (H; women: CD4 count > 250 cells/µL; men: CD4 count > 400 cells/µL) and those with low CD4 counts (L; women: CD4 count < 250 cells/µL; men: CD4 count < 400 cells/µL).

Results
A total of 142 patients were included in the study, 61 in the H group and 81 in the L group. Skin rash developed in 6.56% of patients [95% confidence interval (CI) 2.67–15.70%] in the H group and in 14.81% of patients (95% CI 8.72–24.17%) in the L group (P = 0.18). Hepatotoxicity developed in 4.92% (95% CI 1.79–13.50%) and 6.17% (95% CI 2.73–13.66%) of patients with high and low CD4 cell counts, respectively (P = 1.0).

Conclusion
The recommendations not to use NVP in drug-naïve patients at increased risk of toxicity on the basis of gender and CD4 cell count do not seem to be of use in preventing the occurrence of side effects. However, a small number of patients were included in this study, and hence the possibility cannot be excluded that the recommendations are appropriate in another clinical practice setting.

Keywords: adverse events, hepatotoxicity, nevirapine, rash

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Introduction
Nevirapine (NVP) was the first nonnucleoside reverse transcriptase inhibitor approved for use in HIV-infected patients and is a widely used antiretroviral drug, the efficacy of which has been well demonstrated in numerous clinical trials. It is easy to administer and is generally well tolerated [1]. The main limitation of its use is the risk of the occurrence of potentially serious side effects, such as hepatic toxicity and hypersensitivity reactions.

In order to avert or reduce such reactions, an attempt has been made to identify the risk factors for presentation of hypersensitivity reactions or hepatotoxicity. In a retrospective analysis of Boehringer-Ingelheim databases, it was found that the risk of symptomatic hepatotoxicity was 12 times greater in women with a CD4 count above 250 cells/µL, in comparison with women with a CD4 count below 250 cells/µL (11 vs. 0.9%) [2]. In men, there was a 6.3% risk if the CD4 count was above 400 cells/µL, compared with 1.2% when the CD4 count was below 400 cells/µL [2].
9.8 (relative risk) for women with a CD4 count above 250 cells/μL and 6.4 (relative risk) for men with a CD4 count above 400 cells/μL [3]. These data are clinically significant and appear in the Summary of Product Characteristics [4], where direct reference is made to the use of this drug in the described conditions, with the recommendation that it should only be used in clinical situations where the benefits clearly outweigh the risks. This warning about NVP also appears in the guidelines for antiretroviral treatment [6,15]; the purpose of the warning is to decrease the frequency of symptomatic liver toxicity.

Analysis of the results of a large randomized clinical trial, the 2NN study, demonstrated that the rate of skin rash and hepatic events was higher in patients with CD4 counts > 200 cells/μL, and also that women with CD4 counts > 200 cells/μL had a statistically significantly increased risk of developing a rash compared with men [7]. In the EuroSIDA cohort study, in which the risk of NVP discontinuation in relation to high and low CD4 cell counts was investigated, it was observed that patients with a high CD4 cell count had an increased risk of discontinuation compared with patients with a low CD4 cell count, and the risk was higher in naïve patients [8].

The aim of this study was to determine whether or not these gender- and CD4 cell count-based recommendations are of use in preventing the side effects associated with NVP treatment.

Materials and methods

This retrospective study included all antiretroviral treatment-naïve patients who started treatment with NVP between January 1999 and January 2006, in a single Barcelona hospital.

The skin rash was classified using a previously established scale [9]. Hepatotoxicity was diagnosed when transaminases were raised by more than five times the normal value, in patients whose baseline levels had been normal, and by more than 3.5 times the baseline measurement in patients whose baseline levels were abnormal prior to commencing treatment. Clinical hepatitis was diagnosed when, in addition to raised transaminases, patients presented nausea, asthenia and/or jaundice.

A hypersensitivity reaction was diagnosed when rash and at least one of the following symptoms occurred: fever, asthenia, general malaise, myalgia and arthralgia, or multisystemic adverse effects (lymphadenopathy, mucositis, pneumonitis, myocarditis, hepatitis or interstitial nephritis) within 6 weeks of starting NVP.

The patients were divided into two groups in accordance with the recommended CD4 cell count cut-off for the use of NVP: a group with high CD4 counts (women with CD4 counts > 250 cells/μL and men with CD4 counts > 400 cells/μL), and a group with low CD4 counts (women with CD4 counts < 250 cells/μL and men with CD4 counts < 400 cells/μL). The classification was based on a CD4 cell count obtained between 2 weeks and 1 month before the initiation of highly active antiretroviral therapy (HAART) containing NVP.

To assess whether patients were coinfected with hepatitis B or C virus (HBV or HCV), serological HBV status was determined by measuring HBV surface antigen (HbsAg) in an immunoassay, and HCV status was determined by measuring HCV antibody, also in an immunoassay. Information on serological HBV and HCV status was available for all patients when they started NVP treatment, and for those who were seronegative at baseline, the serological tests were repeated if a hepatic event occurred.

The statistical analysis was carried out using Fisher’s exact test for the comparison of proportions and the Mann–Whitney U-test for the comparison of quantitative variables. Two Cox’s proportional hazard models were run, using the development of skin rash as one variable status and the development of hepatotoxicity as another variable status, the factor analysed being the categorical variable of high or low CD4 cell count, according to the above-mentioned criteria, which was adjusted by cotrimoxazole exposure in the first analysis and for hepatitis B and C in the second analysis.

Results

The study included a total of 142 patients who had commenced antiretroviral treatment containing NVP between January 1999 and January 2006. The median follow-up time from the start of the NVP therapy was 2.60 years (interquartile range 0.60–4.07). Male patients (105 individuals) accounted for 73.9% of those included in the study. In terms of CD4 cell count category (as described in the ‘Materials and methods’ section), 61 patients had high CD4 cell counts and 81 had low CD4 cell counts.

Table 1 summarizes the patients’ baseline characteristics. The year of starting NVP was 1999 for 50 patients, 2000 for 30 patients, 2001–2002 for 39 patients, and 2003–2006 for 23 patients. The nucleosides used in combination with NVP were zidovudine + lamivudine in 65 patients, stavudine + lamivudine in 34 patients, stavudine + didanosine in 33 patients, and other combinations in 10 patients (only three patients started abacavir concomitantly with NVP).

Table 2 summarizes the side effects observed, in relation to gender and CD4 cell count classification.

Irrespective of the classification used, a skin rash of any type developed in 16 patients (11.27%; 95% CI 7.08–17.53%).
representing 19.44% (95% CI 9.83–35.15%) of patients exposed to cotrimoxazole and 8.57% (95% CI: 4.62–15.51%) of patients not exposed to cotrimoxazole ($P = 0.07$). In relation to gender, these patients represented 10.48% (95% CI 5.99–17.81%) of men and 16.22% (95% CI 7.74–31.25%) of women ($P = 0.36$); all rashes in women occurred in the group with low CD4 cell counts.

Liver toxicity was present in eight patients (5.63%; 95% CI 2.92–10.73%), representing 10.71% (95% CI 3.89–27.35%) ($P = 0.19$) and 7.41% (95% CI 3.02–17.59%) ($P = 0.48$) of HBV- and HCV-infected patients, respectively. The median time before development of skin rash was 19 days (range 6–43 days). The median time for the development of hepatotoxicity was 200 days (range 6–536 days). Only three of the patients developed hepatotoxicity in the first 20 weeks after starting NVP (one in the high CD4 cell count group). The incidence of hepatotoxicity was 2.06 per 100 patients/year (95% CI 0.14–7.53): 1.68 per 100 patients/year in the high CD4 group (95% CI 0.01–6.99) and 2.52 per 100 patients/year in the low CD4 group (95% CI 0.38–8.17) ($P = 0.54$). In the Cox’s regression analysis, no differences were detected in the risk of hepatotoxicity between the CD4 cell count groups [for the high CD4 group, hazards ratio (HR) 0.49; 95% CI 0.09–2.521; and for the low CD4 group, HR 2.06; 95% CI 0.40–10.61; $P = 0.39$]. The result was similar if coinfection with HBV or HCV was included in the model.

In the Cox’s regression model, the risk of developing skin rash was higher for the low CD4 group (HR 4; 95% CI 1.22–13.16; $P = 0.01$). If cotrimoxazole was included in the model, the risk of skin rash in the low CD4 group was not statistically significant (HR 2.77; 95% CI 0.71–10.84; $P = 0.14$).

**Discussion**

The study has several limitations. It was retrospective, and it included a small number of patients, so the power was limited and there were insufficient data to enable a comprehensive multivariate analysis to be performed. However, in the clinical practice setting where this study was conducted, the recommendation not to use NVP in treatment-naive patients, based on gender and CD4 cell count, does not seem to be of use in preventing the occurrence of side effects associated with the drug.

The incidence of skin rashes was 11.3% (14.8% in the low CD4 group and 6.6% in the high CD4 group), these results being very similar to those found in other studies [1, 10]. Racial differences may be a factor in hypersensitivity reactions; a high incidence of skin rashes has been reported.

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<tr>
<th>Table 1 Baseline characteristics of patients exposed to nevirapine</th>
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<tr>
<td>CD4 count &gt; 250 cells/µL in women,</td>
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<td>&gt; 400 cells/µL in men (n = 61)</td>
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<tr>
<td>Male gender [n (%)]</td>
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<td>IDU [n (%)]</td>
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<td>Follow-up time [years] [median (IQR)]</td>
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<td>CD4 count [cells/µL] [median (IQR)]</td>
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<td>Viral load [log$_{10}$ copies/µL] [median (IQR)]</td>
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<th>Table 2 Side effects observed in patients exposed to nevirapine according to CD4 cell count</th>
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<tr>
<td>CD4 count &gt; 250 cells/µL in women and &gt; 400 cells/µL in men (n = 61) [number (%; 95% CI)]</td>
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<td>Patients with any grade III–IV side effects</td>
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<td>Skin rash</td>
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<td>Grades I–II</td>
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<td>Hypersensitivity reaction</td>
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*The patients with symptomatic hepatitis are also included in the 'Hepatotoxicity' row. CI, confidence interval.
in China [11]. In a subanalysis of patients included in the 2NN study, for which study participants were recruited in Thailand, a high incidence of skin side effects was recorded [20% with efavirenz, 21% with NVP twice a day (bid), 38% with NVP once a day (qd) and 67% with NVP + efavirenz] [12]. A higher incidence of hypersensitivity reaction at higher CD4 cell counts has been confirmed in patients without HIV infection who were exposed to NVP in the context of post-accidental-exposure prophylaxis [13]; use of NVP is consequently not advised for such patients.

An increased risk of both skin reactions and hepatotoxicity in women with high CD4 cell counts has been reported in the context of clinical trials and cohort studies [2,3,14].

The CD4 cut-offs are intended to reduce the incidence of severe hepatotoxicity, with or without rash, and therefore it is not surprising that the incidence of rash was not lower in the low CD4 group; in fact it was higher in this group, and this was probably related to the concomitant use of cotrimoxazole.

The incidence of hepatotoxicity in this study (2.06 per 100 patients/year) was lower than that reported in another study carried out in Barcelona [15]. In another multicentre study in which 613 patients treated with NVP were recruited with a median follow-up time of 43 months, fivefold or greater increases in transaminase levels were observed in <2% of cases [16]. One explanation for these differences could be that there were differences in the way researchers defined hepatotoxicity. The real incidence of hepatotoxicity associated with NVP may be lower; the adverse event developed in the first 20 weeks after starting NVP in only three of the eight patients considered to have hepatotoxicity, and with this very small number of events it would be difficult to detect a difference in frequency related to CD4 cell count.

Clinically, the differential diagnosis of hepatotoxicity associated with NVP can be difficult. Clinical signs of toxic hepatitis are uncommon, most diagnoses being made as a result of raised liver enzyme levels, which can also be caused by enzyme induction, immune reconstitution syndrome, exacerbation of hepatitis B or C, or direct hepatotoxicity, and can accompany the hypersensitivity reaction.

The main result of this study, that CD4 counts >250 cells/μL in women and >400 cells/μL in men are not a risk factor for hepatotoxicity, has also recently been reported by others. In a retrospective analysis carried out in Germany of 507 patients who started taking NVP, including antiretroviral treatment–experienced and -naïve patients, no increased risk of hepatotoxicity was found in relation to CD4 cell count in either men or women [17]. The other study was a meta-analysis of clinical trials, primarily carried out in Spain, which included 410 patients who started taking NVP in the context of simplification therapy. This study also did not find an increased risk of hepatotoxicity based on the CD4 cell count [18]. The incidence of hepatotoxicity in both these studies was very similar to that found in this study. However, these studies were carried out in pretreated patients, and the incidence of NVP-related adverse events should not be directly compared between naïve and pretreated patients. In another study that included 346 patients starting NVP-based therapy (41 naïve and 341 experienced patients), only 5.8% of patients interrupted therapy because of hepatotoxicity, and neither female gender nor CD4 count above 250 cells/μL was a risk factor for this adverse event [19]. In a study conducted in British Columbia, which included 685 antiretroviral-naïve patients starting NVP, 9.6% of patients met the definition for hypersensitivity reactions, and no variables were identified as risk factors; however, patients with both HCV coinfection and hypersensitivity reactions had a higher risk of death. These results support the current recommendations against the use of NVP in HCV-coinfected patients [20].

These contrasting results regarding the risk of toxicity in relation to gender and CD4 cell count may be explained by adverse events that have similar clinical signs (e.g. elevation of transaminases) but different pathogenic mechanisms. Clinical signs of early hepatotoxicity which are found in certain populations in the first few weeks of treatment are likely to indicate immunologically mediated hepatotoxicity, with multisystemic manifestations and a significant genetic component [21]; clinical signs appearing later, as in the patients who were treated in this study, are likely to indicate direct hepatotoxicity, which is less common.

The inferences that can be made from the results of this study may be limited because it was a retrospective study involving a small number of patients. Nevertheless, it does reflect the clinicians’ experience with the use of NVP in treatment-naïve patients in a single Barcelona hospital.

These research findings are not reported with the intention of suggesting that the precautions followed when patients are given NVP should be modified. They do highlight, however, the fact that the pathogenic mechanisms involved in the side effects associated with this drug are not sufficiently clear and that regional differences may be involved. Additional studies are needed to help clinicians make recommendations about NVP toxicity based on the individual patient’s profile.

**Acknowledgement**

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