Eur J Med Res (2008) 13: 343-348 © I. Holzapfel Publishers 2008

HEPATOTOXICITY IN PATIENTS PRESCRIBED EFAVIRENZ OR NEVIRAPINE

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Abstract

Aim: For several years Nonnucleoside reverse transciptase inhibitors (NNRTIs) in antiretroviral therapy have been associated with hepatic side effects. Particularly the hepatotoxic potential of Nevirapine is well analysed today.

We performed a prospective, multicenter study to compare the hepatotoxicity of Efavirenz (EFV) with that of Nevirapine (NVP) and to investigate further risk factors.

Material and Methods: The study included HIV-1-infected patients from five clinics and private medical practices in southwestern Germany who initiated an antiretroviral therapy with NVP or EFV between July 1998 and December 2001. Among 296 patients in total, 151 received EFV and 145 received NVP. Laboratory tests during the course of treatment included liver enzymes, HIV-RNA and CD4 cell-count. Additionally, signs of clinical hepatitis were recorded. Hepatotoxicity was graded in the manner of Sulkowsky et al. (2000), who used a scale modified from that of the AIDS Clinical Trials Group.

Results: Hepatitis C virus and hepatitis B virus were detected in 10.1% and 4.1% of patients, respectively. The overall rate of severe hepatotoxicity (grade 3 to 4 elevations in aspartate aminotransferase and/or alanine aminotransferase) was 2 of 151 (1.3%) in patients prescribed EFV and 3 of 145 (2.1%) in patients prescribed NVP. Mild-to-moderate hepatotoxicity (grade 2 elevation) was observed in 6.0% (EFV) and 3.4% (NVP) of patients. Incidence of mild-to-moderate and severe hepatotoxicity did not differ significantly between the study groups. 3 of 14 patients (2.1%) with grade 2 elevation of liver enzymes (LEE) and 4 of 5 patients (80%) with grade 3 to 4 LEE were symptomatic. Only risk factor for the development of mild-to-moderate hepatotoxicity was hepatitis C coinfection.

Conclusion: Increases of liver enzymes during therapy with NVP or EFV are not unusual, but are mostly mild-to-moderate and asymptomatic. LEE occurs just as frequent in patients prescribed EFV as in patients prescribed NVP.

Key words: HIV, Hepatotoxicity, Nevirapine, Efavirenz, LEE

INTRODUCTION

Since the introduction of highly active antiretroviral therapy (HAART) about 10 years ago, prognosis of patients with HIV infection has dramatically improved. Both HIV-related morbidity and mortality has declined significantly (Palella et al. 1998, Cameron et al. 1998, van Sighem et al. 2003). Due to increased life expectancy of HIV infected patients long-term side effects of antiretroviral therapy are becoming more and more important, among which hepatic toxicity with highest priority. In contrast to class-specific side effects of nucleoside reverse tranciptase inhibitors (NRTIs) such as lactic acidosis (John et al. 2001, Walker et al. 2002) or increased cadiovascular risk under therapy with protease inhibitors (PIs) (Rhew et al. 2003), hepatotoxicity occurs in all of the three classes (NRTI, PI, NNRTI). Among NNRTIs the hepatotoxic potential of Nevirapine was analysed the most in detail. However, only a few studies have examined the hepatic side effects of Efavirenz. We performed a prospective, multicenter study to compare the hepatotoxic potential of Efavirenz and Nevirapine and to investigate further risk factors for hepatotoxicity.

MATERIAL AND METHODS

This study included HIV-1-infected patients from five clinics and private medical practices in southwestern Germany who have initiated an antiretroviral therapy with NVP or EFV between July 1998 and December 2001. NVP and EFV were prescribed with NRTIs and/or PIs according to the judgement of the individual clinician, so that therapy contained 3 or more antiretroviral agents. To be included, patients could be either antiretroviral therapy-naive or –experienced, but had not been treated with NVP or EFV before. Demographic data like age, sex, risk group for HIV-1 transmission, previous use of antiretroviral drugs, prescribed antiretroviral medication, and Centers for Disease Control (CDC) stage at the start of this study were collected from the patients' medical records. If available, results of current hepatitis B virus (HBV) and hepatitis C virus (HCV) serologies were also documented, in some cases without current serology we had to go back to earlier laboratory tests. Patients with a reactive

serum HCV antibody by immunoassay and those with a positive HBV surface antigen (HBsAg) by immunoassay were considered to have chronic infection. We recorded the pretreatment serum levels of aspartate aminotransferase (AST), alanine aminotransferase (ALT), HIV viral load and CD4 cell count. These values had to be collected within three months before the start of the therapy to be valid. During the course of treatment all patients had laboratory testing every eight weeks including once more AST, ALT, HIV viral load (by branched-DNA-method or polymerase chain reaction) and CD4 cell count. Data collection terminated after 88 weeks of therapy with NVP/EFV or at the end of course of treatment, regardless of the reason for discontinuation. Hepatotoxicity was graded in the manner of Sulkowsky et al. (2000), who used a scale modified from that of the AIDS Clinical Trials Group. Patients with normal AST and ALT levels prior to treatment had their peak AST and ALT levels graded relative to the upper limit of normal (ULN): grade 0 (<1.25 × ULN), grade 1 (≥1.25 × ULN ≤2.5 × ULN), grade 2 (>2.5 × ULN ≤5 × ULN), grade 3 (>5 × ULN ≤10 × ULN) or grade 4 (>10 × ULN). To avoid selection bias favouring the inclusion of persons with elevated serum AST or ALT levels (>ULN) prior to treatment, these patients were graded relative to their baseline AST and ALT levels (BLV): grade 0 (<1.25 × BLV), grade 1 (≥1.25 × BLV ≤2.5 × BLV), grade 2 (>2.5 × BLV ≤3.5 × BLV), grade 3 (>3.5 × BLV ≤5 × BLV) or grade 4 (>5 × BLV). To classify patients with grade 2, 3 or 4 hepatotoxicity as either symptomatic or asymptomatic, the medical records of these patients were screened for evidence of clinical signs and symptoms during therapy with EFV/NVP. Furthermore, we recorded all available information on the etiology of liver enzyme elevation (e.g. acute viral hepatitis).

Statistical analysis was performed as follows: Pretreatment demographic and clinical data were compared between treatment groups using chi² test for categorical variables and Mann-Whitney test for continuous variables. Mann-Whitney test was also used to compare incidence of moderate hepatotoxicity (grade 2) and severe hepatotoxicity (grade 3 and 4) between NVP and EFV treatment group. Time to event analysis was performed by using Kaplan-Meier survival curves. To assess risk factors for moderate and severe hepatotoxicity we used a multivariate logistic regression. In addition, we performed a univariate analysis using the Fisher test for categorical variables and the Mann-Whitney test for continuous variables. Variables considered in these analyses were sex, age, risk group, HBV and HCV infection, naivety of antiretroviral therapy, concurrent PI use, number of drugs used in previous HAART regimens, duration of previous therapy, AST, ALT, CD4 cell count, and HIV RNA level prior to treatment. All reported p values are 2-sided; a p value of less than 5% was considered significant. Data was analyzed using SAS version 8.2.

Results

Patient Characteristics

Between July 1998 and December 2001 296 patients initiated antiretroviral combination therapy containing either EFV or NVP. Baseline characteristics of these 296 patients did not differ significantly between the EFV and NVP subgroup, except for sex, risk group, median CD4 cell count and median HIV RNA level (Table 1).

Liver Enzyme Elevation (LEE)

Incidence of mild-to-moderate LEE (grade 2) for all patients was 14 of 296 (4.7%); 9 of 151 (6.0%) among the EFV group and 5 of 145 (3.4%) among the NVP group. 7 of 296 patients (2.4%) developed a severe LEE (grade 3 or 4); 4 of 151 (2.6%) in the EFV group and 3 of 145 (2.1%) in the NVP group. While screening the medical records an obvious cause of the LEE was found in 2 cases. 2 patients of the EFV group had an acute HBV infection. We excluded these 2 patients from our analysis of outcome and risk factors leaving 5 cases of severe LEE (1.7%). Among these 2 of 151 (1.3%) were in the EFV group and 3 of 145 (2.1%) were in the NVP group. There were no significant differences between the incidence of grades of LEE among the EFV and NVP group (Mann-Whitney test, $p = 0.75$).

Patients prescribed EFV developed mild-to-moderate LEE in week 24 (IQR 16-72) and severe LEE in week 16 and 24. Among patients prescribed NVP, mild-to-moderate LEE occurred in week 16 (IQR 12-36) and severe LEE in week 16 (2 patients) and 48 (1 patient). Time to development of mild-to-moderate and severe LEE did not differ significantly between the study groups (log rank test $p = 0.79$).

LEE and Chronic Viral Hepatitis

We also examined the effect of chronic HBV and HCV infection. HBsAg was found in 11 (3.9%) and HCV antibodies in 29 (9.8%) of 296 patients. Only 1 patient (0.34%) was positive for HBsAg as well as for HCV antibody. 3 patients with a positive HBsAg developed LEE grade 2, none of the patients with HBV coinfection experienced severe LEE. We performed a time to event analysis using a Kaplan-Meier survival curve. Patients, who were positive for HbsAg, developed more rapidly LEE than patients without this marker (log rank test $p = 0.003$).

Among the patients with HCV coinfection LEE occurred in 3 cases: Two patients developed mild-to-moderate LEE, one severe LEE. We did not find any difference between the hepatotoxicity-free survival time in patients with positive HCV antibodies compared with patients with negative HCV antibodies (log rank test $p = 0.4$).

Risk Factors for LEE

To assess risk factors for mild-to-moderate and severe LEE we performed a univariate analysis using the Fisher test for categorical variables and the Mann-Whitney test for continuous variables. Only the presence of HBsAg was associated with the development of grad 2-4 LEE (Table 2).

In addition, we made use of a multivariate logistic regression analysis. Again, only chronic HBV infection

Table 1. Baseline characteristics of the study population.

	EFV Regimen n = 151 (51.0)	**NVP Regimen n = 145 (49.0)**	**p value**
Age	38 (33-44)	38 (34-50)	.30
Sex			.04
Male	115 (76.2)	124 (85.5)	
Female	36 (23.8)	21 (14.5)	
Risk group			.02
Homosexual	80 (52.9)	77 (53.1)	
Heterosexual	32 (21.2)	16 (11.0)	
Injection drug use	21 (13.9)	22 (15.2)	
Use of blood products	6 (4.0)	4 (2.8)	
country of origin	10 (6.6)	24 (16.6)	
unknown	2 (1.3)	2 (1.4)	
CDC stage			.77
A1	1 (0.7)	4 (2.8)	
A2	19 (12.6)	19 (13.1)	
A3	4 (2.6)	8 (5.5)	
B1	3 (2.0)	3 (2.1)	
B2	54 (35.8)	46 (31.7)	
B3	25 (16.6)	26 (17.9)	
C1	0 (0.0)	0 (0.0)	
C2	4 (2.6)	3 (2.1)	
C3	38 (25.2)	34 (23.4)	
unknown	3 (2.0)	2 (1.4)	
HbsAg positive	7 (4.6)	5 (3.4)	.61
HCV antibody positive	18 (11.9)	12 (8.3)	.30
Median AST (U/l)	13 (10-19)	12 (10-16)	.33
Median ALT (U/l)	16 (12-25)	16 (10-24)	.26
Median CD4 cell count (cells/mm³)	317 (192-496)	393 (244-558)	.03
Median HIV-RNA (copies/mL)	5481 (72-59779)	100 (50-8000)	<.0001
Naive for antiretrovirals	34 (22.5)	32 (22.1)	.93
Previous duration of treatment with antiretrovirals (months)	26 (2-45)	27 (1-43)	.91

Sex, risk group, CDC stage, HBsAg, HCV antibody and naivity for antiretrovirals are presented as number (percent). Statistical comparison was performed by using the chi² test. AST, ALT, CD4 cell count and HIV-RNA, age and previous duration of treatment are shown as median (IQR). Statistical comparison was determined with the Mann-Whitney test.

Table 2. Risk factors for grade 2-4 LEE.

Risk factor	**OR**	**95%CI**	**P value**
Sex	1.55	0.53-4.48	.38
Age	-	-	.42
Risk group	-	-	.86
HBsAg positive	5.58	1.38-22.66	.03
HCV antibodies positive	1.74	0.48-6.34	.42
Pretreatment AST	-	-	.95
Pretreatment ALT	-	-	.73
Pretreatment CD4 cell count	-	-	.51
Pretreatment HIV-RNA	-	-	.75
Naive for antiretrovirals	0.64	0.18-2.26	.58
Previous duration of treatment	-	-	.47
Number of drugs in previous antiretroviral therapy	-	-	.60
Co-therapy with PIs	0.97	0.12-7.77	> .99

Univariate risk factor analysis was performed with Fisher test for categorical variables and Mann-Whitney test for continuous variables. Odds ratio (OR) and confidental intervall (CI) are shown for all categorical variables with 2 variations.

was independently associated with the development of grade 2-4 LEE (p = 0.009, OR = 5.4, CI 1.3-22.1).

Clinical Outcomes

None of the patients with LEE developed liver failure or died as a result of liver disease in the subsequent follow-up. Among the 14 patients with mild-to-moderate LEE, 3 patients (of this 2 patients prescribed EFV and 1 patient prescribed NVP) showed clinical symptoms like nausea, vomitus, rash, abdominal pain and fever. 2 of them continued therapy, and a follow-up showed declining liver enzymes. 1 patient aborted therapy, liver enzymes of this patient declined too. The 11 remaining patients with grade 2 LEE continued therapy with EFV/NVP and presented without exception declining LEE in follow-up.

Among the 5 patients with severe LEE under therapy with EFV/NVP, 4 patients (2 patients prescribed EFV and 2 patients prescribed NVP) developed clinical symptoms. 3 of these 5 patients concluded antiretroviral therapy with EFV/NVP therapy. Follow-up showed dropping transaminases in all 3 cases. 2 patients presented declining liver enzymes despite of continuation of therapy.

Discussion

One of the most discussed subjects in current HIV therapy are hepatic side effects of antiretroviral drugs. They occur in all classes of antiretroviral drugs (den Brinker et al. 2000, Sulkowsky et al. 2000, Wit et al. 2000, Monforte et al. 2001, Nunez et al. 2001, Puoti et al. 2003). But in particular the use of NNRTIs, a common component of antiretroviral therapy, has been associated with the development of hepatotoxicity in a large number of studies (Martin-Carbonero et al. 2003, Martínez et al. 2001, Palmon et al. 2002, Prakash et al. 2001, Sulkowsky et al. 2002, Monforte et al. 2001, Wit et al. 2002). Among the NNRTIs, NVP is examined best (Powderly 2004, Martínez et al. 2001, Cattelan et al. 1999, de Maat et al. 2003, Gökengin, Yamazhan 2002, Gonzáles deRequena et al. 2002, Piliero, Purdy 2002, Prakash et al. 2001) wheras there are only a few studies, that deal with the hepatotoxicity of EFV.

The aim of this study was to investigate the incidence of hepatotoxicity associated with the first use of EFV and NVP in a cohort of 296 patients in southwestern Germany. In opposite to findings of earlier studies (Martin-Carbonero et al. 2003, Sulkowsky et al. 2002), severe LEE was rarely seen in our cohort (1.3% among patients prescribed EFV versus 2.1% among patients prescribed NVP). This result might be explained by the very low occurrence of factors in our patient population that might potentiate NNRTI-associated hepatotoxicity, such as chronic HBV and HCV infection. The findings of Palmon et al. (2002) also support this theory. Patients with severe LEE presented almost all clinical symptoms, but none of these patients developed liver failure. Therefore LEE in our cohort can not be considered as a life-threatening event. Mild-to-moderate LEE occurred more frequently, however in most cases LEE was asymptomatic and decreased despite of continuation of therapy, so that other effects such as concurrent drug exposure and alcohol consumption might have played a major role in that.

Some authors found higher rates of hepatotoxicity among patients prescribed NVP compared to patients prescribed EFV (Law et al. 2003, Sulkowsky et al. 2002, Martin-Carbonero et al. 2003). However, we can not confirm these results, incidences of mild-to-moderate and severe hepatotoxicity did not differ significantly between the EFV and the NVP group.

Concerning the time of detection of hepatotoxicity, results of published studies are not uniform. While de Maat et al. (2003) observed LEE already after 28 days of therapy with NVP, Sulkowsky et al. (2002) noticed LEE only after 137 days (patients prescribed NVP) and 100 days (patients prescribed EFV). Two types of antiretroviral-associated hepatotoxicity are actually discussed: an early and a late onset. The early occurring form (less than 12 weeks after initiation of therapy) frequently goes along with rash, eosinophilia, fever and arthralgia and seems to be based on an immune-mediated mechanism. The second form with a late onset (after more than 12 weeks of therapy) is supposed to rely on an intrinsic toxic effect of the drug (Martinez et al. 2002). Mild-to-moderate hepatotoxicity in our cohort occurred after a median of 24 weeks (168 days) in the EFV group and after a median of 16 weeks (112 days) in the NVP group, no patient developed severe hepatotoxicity before week 16 of therapy and only 1 patient with hepatotoxcity developed rash. These findings support the theory, that more likely an intrinsic toxic effect of EFV and NVP caused hepatotoxicity in our patient population. Unfortunately we had no data about the plasma levels of EFV and NVP during therapy to investigate this in more detail.

We also analysed risk factors for the development of hepatotoxicity. Because of the low incidence of severe hepatotoxicity we determined risk factors for all patients with at least mild-to-moderate hepatotoxicity. The analysis showed, that only coinfection with HBV was significantly associated with hepatotoxicity during therapy with EFV or NVP. Sulkowsky et al. (2002), who also investigated risk factors for hepatotoxicity of EFV/NVP, additionally found a connection between HCV coinfection and hepatotoxicity. Several studies about antiretroviral therapy associated hepatotoxicity confirmed this connection (Martinez et al. 2001, Puoti et al. 2003, Wit et al. Nunez et al. 2001). We suppose, that because of the very low incidence of chronic HCV infection (10.1%) in our patient population we can not proof this risk factor hypothesis. Early in 2004 Boeringer Ingelheim published an updated product information for Viramune®. It includes a new paragraph about the association of higher pretreatment CD4 cell count (women > 250 cells/mm^3, men > 400 cells/mm^3) and hepatotoxicity. Our analyses did not show any association between these parameters, but we can not rule out the existence of such a correlation. Maybe we did not discover it because of the relative low number of patients with hepatotoxicity (n = 19). An alternative explanation for the failure of evidence might be, that 11 of the 19 patients with hepatotoxicity were treated with EFV instead of NVP. Risk

factors for hepatotoxicity under therapy with EFV might differ slightly from these of NVP. Controlled studies will be necessary to investigate these differences.

There are several limitations, that could affect the results of this study: First, we performed a prospective, multicenter study, but had to renounce of a randomisation to get a sufficient large patient population. The missing randomisation led to an unequal distribution of some baseline characteristics. We found differences between the two study groups concerning distribution of sex, risk group, median CD4 cell count and median HIV-RNA in copies/mL. None of these factors was a risk factor for the development of hepatotoxicity, so that an effect on the incidence of hepatotoxicity should be unlikely but can not be ruled out. Second, a current hepatitis serology was not available for all patients; for some patients we had to resort to earlier laboratory tests. Changes in hepatitis serology results might not be recognized. Third, patients with a reactive serum HCV antibody by immunoassay were considered to have chronic infection. However, only 90% of the patients with reactive antibodies had detectable plasma HCV RNA (Thomas et al. 2000), therefore the effect of the HCV infection might had been underestimated.

In summary during therapy with NVP or EFV increases of liver enzymes were not unusual, but were mostly mild-to-moderate and asymptomatic. Clinical hepatitis was rarely seen and fully reversible after withdrawal of EFV/NVP. Incidence of mild-to-moderate and severe hepatotoxicity did not differ significantly between the two study groups, so that we recommend frequent monitoring of liver enzymes as well for patients treated with NVP as for patients treated with EFV.

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Received: February 13, 2008 / Accepted February 24, 2008

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