ORIGINAL RESEARCH ARTICLE

Drug Safety 2009; 32 (2): 147-158
0114-5916/09/0002-0147/$49.95/0

Hepatotoxicity Associated with Long- versus Short-Course HIV-Prophylactic Nevirapine Use

A Systematic Review and Meta-Analysis from the Research on Adverse Drug events And Reports (RADAR) Project

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Abstract

Background and objective: The antiretroviral nevirapine can cause severe hepatotoxicity when used 'off-label' for preventing mother-to-child HIV transmission (PMTCT), newborn post-exposure prophylaxis and for pre- and post-exposure prophylaxis among non-HIV-infected individuals. We describe the incidence of hepatotoxicity with short- versus long-course nevirapine-containing regimens in these groups.

Methods: We reviewed hepatotoxicity cases among non-HIV-infected individuals and HIV-infected pregnant women and their offspring receiving short- (≤4 days) versus long-course (≥5 days) nevirapine prophylaxis. Sources included adverse event reports from pharmaceutical manufacturers and the US FDA, reports from peer-reviewed journals/scientific meetings and the Research on Adverse Drug events And Reports (RADAR) project. Hepatotoxicity was scored using the AIDS Clinical Trial Group criteria.

Results: Toxicity data for 8216 patients treated with nevirapine-containing regimens were reviewed. Among 402 non-HIV-infected individuals receiving short- (n = 251) or long-course (n = 151) nevirapine, rates of grade 1–2 hepatotoxicity were 1.99% versus 5.30%, respectively, and rates of grade 3–4 hepatotoxicity were 0.00% versus 13.25%, respectively ($p < 0.001$ for both comparisons). Among 4740 HIV-infected pregnant women receiving short- (n = 3031) versus long-course (n = 1709) nevirapine, rates of grade 1–2 hepatotoxicity were

0.62% and 7.04%, respectively, and rates of grade 3–4 hepatotoxicity were 0.23% versus 4.39%, respectively ($p < 0.001$ for both comparisons). The rates of grade 3–4 hepatotoxicity among 3074 neonates of nevirapine-exposed HIV-infected pregnant women were 0.8% for those receiving short-course ($n = 2801$) versus 1.1% for those receiving long-course ($n = 273$) therapy ($p < 0.72$).
Conclusions: Therapy duration appears to significantly predict nevirapine hepatotoxicity. Short-course nevirapine for HIV prophylaxis is associated with fewer hepatotoxic reactions for non-HIV-infected individuals or pregnant HIV-infected women and their offspring, but administration of prophylactic nevirapine for ≥2 weeks appears to be associated with high rates of hepatotoxicity among non-HIV-infected individuals and HIV-infected pregnant mothers. When full highly active antiretroviral therapy (HAART) regimens are not available, single-dose nevirapine plus short-course nucleoside reverse transcriptase inhibitors to decrease the development of HIV viral resistance is an essential therapeutic option for PMTCT and these data support the safety of single-dose nevirapine in this setting.

Background

Nevirapine, a non-nucleoside reverse transcriptase inhibitor approved by the US FDA, is used in highly active antiretroviral therapy (HAART) combination regimens for the treatment of HIV infection.[1] Unlike nucleoside analogue reverse transcriptase inhibitors, nevirapine does not require phosphorylation to an active metabolite.[2] Marked plasma HIV viral load suppression has been shown to occur shortly after initiation of nevirapine-containing antiretroviral regimens.[3] Major adverse reactions, including skin rashes and hepatotoxicity, occur in approximately 3% of HIV-infected individuals who receive long-course nevirapine-containing HAART regimens, with higher rates being noted among women and individuals with higher CD4 lymphocyte counts.[4-6] In the African population, long-term nevirapine usage (>14 days) has been associated with hepatotoxicity in 6.5% of those treated.[7]

Nevirapine has excellent bioavailability following oral administration, and possesses a long plasma and intracellular half-life.[1,2] Because of a favourable pharmacokinetic profile, short-term nevirapine or nevirapine-containing combination antiretroviral regimens have been used for the prevention of mother-to-child HIV transmission (PMTCT), including infant post-exposure prophylaxis, as well as for both pre- and post-exposure prophylaxis among non-HIV-infected individuals. Single-dose nevirapine administered to a woman at the onset of labour, followed by a single dose of nevirapine administered to the infant post-partum, is the foundation of HIV prevention programmes in resource-limited settings. The WHO PMTCT guidelines include single-dose nevirapine, administered to both mother and infant, in all prevention strategies for women who do not qualify for HAART for their own disease.[8] This by definition includes all pregnant women with CD4 cell counts >250 cells/mm^3 and highlights the importance of defining the risk of liver toxicity in pregnant women taking short-course nevirapine, especially women with CD4 cell counts >250 cells/mm^3.

We and many others have previously shown dissimilar adverse drug reaction rates when products are used in a fashion other than those approved by regulatory agencies, such as the FDA.[9-11] Hence, these off-label uses require further investigation from a safety perspective. We hypothesized that rates of toxicity would differ based on treatment duration. Therefore, we stratified patients to short- and long-course prophylaxis. In this article we review toxicity reports

from non-HIV-infected individuals and HIV-infected pregnant women and their offspring for information on rates and severity of hepatotoxicity following the use of nevirapine-containing HIV prophylaxis regimens.

Methods

We wished to compare adverse events between a population with nevirapine drug concentrations at steady state and a population with non-steady-state drug concentrations. After four to five drug half-lives, a patient's nevirapine concentration reaches 94–97% of steady state, respectively. The serum half-life of nevirapine is known to be extended in non-HIV-infected patients,[12] HIV-infected pregnant women[13] and neonates.[13] In these groups, the median half-life is 56.7 hours, 61.3 hours and 54 hours, respectively. If we assume that the half-life is 60 hours in all of the populations, 240–300 hours (10–12.5 days) are required to ensure that a patient has reached steady state. Hence, we wished to compare those patients who received <13 days of therapy to those who received >14 days of therapy. We actually separated data into short- (≤4 days of treatment) and long-course (≥5 days of treatment) therapy. The division of data was not arbitrary. Upon examination of data distributions, we noted a dichotomy of therapy duration. No published reports included information on intermediate duration of nevirapine administration (5–14 days). Since no patients received 5–14 days of therapy, patients described in long-course therapy actually received treatment for >14 days. The data were conveniently statistically divided, but the separation was justified in pharmacokinetic theory. As such, our definition of long-course therapy is consistent with previous evaluations.[14]

Investigators

Investigators with the National Institutes of Health (NIH)-funded Research on Adverse Drug events And Reports (RADAR) project[11] conducted a systematic review of reported hepatotoxicity events among non-HIV-infected individuals and HIV-positive pregnant women and their offspring who received nevirapine as part of HIV-prophylaxis regimens.

Study Definitions

Nevirapine therapy was defined as 'short course' if ≤4 days of nevirapine was administered, or 'long course' if ≥5 days of nevirapine therapy was given.Severe hepatotoxicity was defined using the AIDS Clinical Trial Group (ACTG) criteria for grade 3 or 4 (ALT, AST, alkaline phosphatase and/or total bilirubin levels >5 times the upper limit of normal).[15] Mild hepatotoxicity was defined as an ACTG grade of 1 or 2 (levels >1.5–5 times the upper limit of normal for ALT, AST, alkaline phosphatase and/or total bilirubin).

Data Sources

RADAR investigators obtained case descriptions of nevirapine-associated hepatotoxicity for the years 1994 through to 2005, and identified cases of hepatotoxicity associated with nevirapine use. Case reports and series were identified with MEDLINE (via PubMed) electronic searches using Medical Subject Headings (MeSH) terms 'prevention of mother to child transmission', 'PMTCT', 'post-exposure prophylaxis', 'PEP', 'post-exposure prophylaxis of the infant', 'PEPI', 'HIV occupational exposure', 'hepatic toxicity', 'HIV prophylaxis' and 'adverse reactions to nevirapine'; and from abstracts from HIV conferences held from 1992 to 2005. Additionally, pharmacovigilance data from pharmaceutical manufacturers were also reviewed. Adverse Event Reporting System data were reviewed for the following information: initial date of adverse event reporting, pharmacovigilance programme where the case was initially reported (pharmaceutical supplier or MedWatch) and patient characteristics, including socio-demographics, clinical and laboratory findings, types and dates of use of nevirapine, and clinical evaluation of causality, treatment and outcome. Information was collected through the use of a case report form developed specifically for nevirapine-associated hepatotoxicity. The searches were limited to studies in the English language.

As no denominator data were available for the aforementioned sources of data, rates were not

able to be calculated from these sources. Therefore, rates of nevirapine-associated hepatic toxicities among non-HIV-infected individuals were obtained from (i) an unpublished phase I trial in which non-HIV-infected volunteers received nevirapine (Bennett CL, unpublished observations); (ii) a survey of occupational health programmes in Chicago, IL, USA, through which nevirapine-containing post-exposure prophylaxis regimens were prescribed following occupational exposures to HIV-infected blood or body fluids;[16] (iii) a report from a post-HIV-exposure prophylaxis programme in London;[16] and (iv) other reports of nevirapine use among healthcare workers, healthy volunteers and community members with non-occupational HIV exposures. Rates of nevirapine-associated hepatic toxicities among HIV-infected pregnant women and their offspring were obtained from (i) adverse event reports from phase III clinical trials evaluating HIV-prophylaxis regimens among pregnant women; and (ii) retrospective case series. An independent pair of adverse event researchers (CB, JP) determined whether adverse events included in the various data sources met criteria for inclusion in the study. Reports considered unreliable in their reporting of toxicity rates were not included.

Analysis

Adverse event rates were integrated across studies by cumulating fractions. Central tendency (point) estimates of hepatotoxicity incidence were compared between groups using the Fisher's Exact test.[17] Dispersion estimates of hepatotoxicity incidence were compared between groups by computing a 95% confidence interval separately for each group and assessing whether there was a confidence interval overlap. For pregnant women and for healthcare workers, the analyses included separate event comparisons involving severity grades 1–2, and severity grades 3–4. A third analysis included any events (severity grades 1–4).

Results

Twenty-nine studies were included in our analysis; 10 studies were excluded. All 29 studies provided data for the systematic review and meta-analysis.

A summary of all reports included in this study can be found in the supplementary material ('ArticlePlus') at http://drugsafety.adisonline.com.

Clinical Findings

Hepatotoxicity data for 8216 patients treated with nevirapine-containing antiretroviral regimens were reviewed, including (i) 4740 pregnant women treated for PMTCT, of whom 3031 (64%) received short-course regimens (table I); (ii) 3074 infants of HIV-infected women who received nevirapine at birth, of whom 2801 (91%) received short-course regimens (table II); and (iii) 402 non-HIV-infected

Table I. HIV-infected pregnant women (prevention of mother-to-child HIV transmission)

Study name	No. of patients	Grade 1–2 events (%)	Grade 3–4 events (%)
Short-course[a] nevirapine			
PACTG 250, #1[18]	10	0 (0.00)	0 (0.00)
PACTG 250, #2[18]	7	0 (0.00)	0 (0.00)
HIVNET 012[19,20]	306	2 (0.65)	1 (0.33)
Subtotal	**323**	**2 (0.62)**	**1 (0.31)**
SAINT[21]	655	NR	0 (0.00)
PHPT-2[22]	1411	NR	1 (0.07)
PACTG 316[23]	642	NR	5 (0.78)
Subtotal	**3031**	**NR**	**7 (0.23)**
Long-course[b] nevirapine			
Lyons et al.[14]	139	28 (20.14)	7 (5.04)
PACTG 1022[24]	17	1 (5.88)	4 (23.53)
Kramer et al.[25]	125	11 (8.80)	3 (2.40)
Joao et al.[26]	188	2 (1.06)	0 (0.00)
Fregonese et al.[27]	15	0 (0.00)	0 (0.00)
KiBS[28]	155	12 (7.74)	6 (3.87)
Phanuphak et al.[29]	157	2 (1.27)	4 (2.55)
Subtotal	**796**	**56 (7.04)**	**24 (3.02)**
DREAM[30]	778	NR	46 (5.91)
Money et al.[31]	57	NR	4 (7.02)
Tonwe-Gold et al.[32]	78	NR	1 (1.28)
Subtotal	**1709**	**NR**	**75 (4.39)**

a 1–4 days of therapy.

b ≥5 days of therapy.

DREAM = Drug Resource Enhancement against AIDS and Malnutrition; **HIVNET** = HIV Network for Prevention Trials; **KiBS** = Kisumu (Kenya) Breastfeeding Study; **NR** = not reported; **PACTG** = Pediatric AIDS Clinical Trials Group; **PHPT-2** = Perinatal HIV Prevention Trial 2; **SAINT** = South African Intrapartum Nevirapine Trial.

Table II. Infants born to HIV-infected women (post-exposure prophylaxis of the infant)

Study name	No. of patients	Grade 1–2 events (%)	Grade 3–4 events (%)
Short-course[a] nevirapine			
PACTG 316[33]	714	NR	1 (0.14)
HIVNET 012[20]	320	NR	2 (0.63)
SAINT[21]	633	NR	18 (2.84)
PHPT-2[34]	708	NR	1 (0.14)
NVAZ[35]	426	NR	0 (0.00)
Subtotal	**2801**	**NR**	**22 (0.79)**
Long-course[b] nevirapine			
HIVNET 023[36]	75	NR	0 (0.00)
SIMBA[37]	198	NR	3 (1.52)
Subtotal	**273**	**NR**	**3 (1.10)**

a 1–4 days of therapy.

b ≥5 days of therapy.

HIVNET = HIV Network for Prevention Trials; **NR** = not reported; **NVAZ** = Nevirapine-AZT (zidovudine); **PACTG** = Pediatric AIDS Clinical Trials Group; **PHPT-2** = Perinatal HIV Prevention Trial 2; **SAINT** = South African Intrapartum Nevirapine Trial; **SIMBA** = Stopping Infection from Mother to child via Breastfeeding in Africa.

patients who received nevirapine-containing pre- and post-exposure HIV antiretroviral prophylaxis, of whom 251 (62%) received short-course regimens (table III, figure 1 and figure 2). Data for neonates were available only for event comparisons involving severity grades 3–4.

Hepatotoxicity after receiving a single dose of nevirapine for PMTCT of HIV was rare, occurring in 0.23% of 3031 HIV-infected pregnant women and 0.79% of their 2801 newborns. Rates of hepatotoxicity were also low (1.10%) among the 273 newborn infants of HIV-infected mothers who received long-course nevirapine regimens. In contrast, higher rates of hepatotoxicity were noted with long-course nevirapine-containing antiretroviral regimens administered to non-HIV-infected individuals receiving pre- or post-exposure HIV prophylaxis, and to HIV-infected women. In terms of severity, the rates of hepatotoxicity among 1709 HIV-infected pregnant women who received long-course nevirapine therapy were 7.04% for those with grade 1–2 hepatotoxicity (n = 796 with reported data) and 4.39% for those with grade 3–4 hepatotoxicity (n = 1709) [table I, figure 1 and figure 2]. Among 251 non-HIV-infected individuals who received short-course nevirapine-containing regimens for pre- or post-exposure HIV prophylaxis, 1.99% experienced grade 1–2 hepatotoxicity and none had grade 3 or 4 reactions. In contrast, among 151 non-HIV-infected individuals who received 2–4 weeks of nevirapine monotherapy or nevirapine-based combination antiretroviral therapy for HIV pre- or post-exposure prophylaxis regimens, grade 3 or 4 hepatotoxicity developed in 13.25% after a median of 14 days of treatment (range 8–35 days) [table III, figure 1, figure 2 and table IV]. Nine of these individuals also reported skin rash. Among 14 HIV-infected pregnant women with CD4 lymphocyte counts >250 cells/mm^3 who were enrolled in a phase III clinical trial evaluating nevirapine versus nelfinavir-based HAART, two (14.3%) developed grade 3 or 4 hepatotoxicity after 5 and 26 weeks of nevirapine-containing HAART, respectively.[24]

Specific instances of severe nevirapine-associated hepatotoxicity in the MedWatch database were reviewed. Among 33 non-HIV-infected individuals who developed nevirapine-associated hepatotoxicity after pre- or post-exposure HIV prophylaxis, three developed severe hepatotoxicity. One 33-year-old female nurse developed

Table III. Non-infected adults (pre-exposure prophylaxis and post-exposure prophylaxis)

Study name	No. of patients	Grade 1–2 events (%)	Grade 3–4 events (%)
Short-course[a] nevirapine			
Rey et al.[38]	120	5 (4.17)	0 (0.00)
Livrozet et al.[39]	131	0 (0.00)	0 (0.00)
Subtotal	**251**	**5 (1.99)**	**0 (0.00)**
Long-course[b] nevirapine			
Puro et al.[40]	12	2 (16.67)	2 (16.67)
Johnson et al.[16]	8	0 (0.00)	5 (62.50)
Bernasconi et al.[41]	16	0 (0.00)	0 (0.00)
Benn et al.[42]	41	2 (4.88)	5 (12.20)
Bennett CL, unpublished observations	41	4 (9.76)	4 (9.76)
Jackson et al.[20]	33	0 (0.00)	4 (12.12)
Subtotal	**151**	**8 (5.30)**	**20 (13.25)**

a 1–4 days of therapy.

b ≥5 days of therapy.

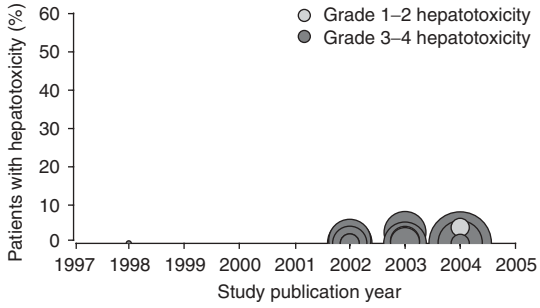

Fig. 1. Short-course nevirapine: patients with hepatotoxicity by study year as a function of study size.

grade 3 hepatotoxicity. Initially, she experienced malaise and fatigue following 8 days of a nevirapine-containing post-exposure prophylaxis regimen. Severe hepatotoxicity resolved following 1 month of prednisone therapy.[44] Grade 3 hepatotoxicity persisted for 2 months in a 38-year-old male physician following discontinuation of 14 days of administration of a nevirapine-containing post-exposure prophylaxis antiretroviral regimen. The toxicity subsequently resolved following a 2-month course of high-dose prednisone.[16] A liver biopsy performed prior to prednisone administration showed central zonal cholestasis with bile canalicular plugs, mild portal tract eosinophilia and no hepatocyte necrosis. A 43-year-old female phlebotomist who received 2 weeks of a nevirapine-containing post-exposure prophylaxis regimen initially presented with fever, malaise and normal serum liver function tests. After continuation of the nevirapine-containing regimen for an additional week, grade 4 hepatotoxicity was noted and post-exposure prophylaxis was discontinued. One week later, she developed fulminant hepatic necrosis and coma and underwent liver transplantation 2 weeks after discontinuation of post-exposure prophylaxis.[16,45] Pathology review of the liver revealed extensive haemorrhagic central zonal necrosis, portal tract eosinophils and lymphocytes. In addition, five pregnant, antiretroviral-naive, HIV-infected women died following 4–5 weeks of nevirapine-containing antiretroviral regimens. Four of these women had baseline CD4 lymphocyte counts >250 cells/mm^3. In each of these cases, hepatitis progressed rapidly to death despite nevirapine discontinuation and close patient monitoring. Post-mortem liver biopsies for three of these women showed diffuse hepatic necrosis without steatosis or fibrosis. However, deaths occurring in women receiving nevirapine in combination with didanosine and stavudine were felt to be associated with lactic acidosis.[46] Finally, a study comparing 95 non-pregnant HIV-infected women with 58 pregnant HIV-infected women, both groups receiving long-term nevirapine, found that HIV-infected pregnant women are at greater risk ($p < 0.003$) for nevirapine-related hepatotoxicity than their non-pregnant counterparts.[47]

Qualitative Findings

Among pregnant HIV-infected women who received short- versus long-course nevirapine therapy for PMTCT, the incidence rates of grade 1–2 hepatotoxicity were 0.62% (95% CI 0.00, 1.50) and 7.04% (95% CI 5.30, 8.80), respectively. Rates of grade 3–4 hepatotoxicity were 0.2% (95% CI 0.10, 0.40) and 4.39% (95% CI 2.20, 6.50), respectively ($p < 0.001$ for each comparison).

No studies reported rates of grade 1 or 2 hepatotoxicity for neonates born to HIV-infected women who had received nevirapine therapy prior to delivery. For grade 3–4 hepatotoxicity, the incidence rate following short-course therapy for newborn infants was 0.79% (95% CI 0.46, 1.11) and 1.10% with long-course nevirapine therapy (95% CI 0.00, 2.34). These point estimates were

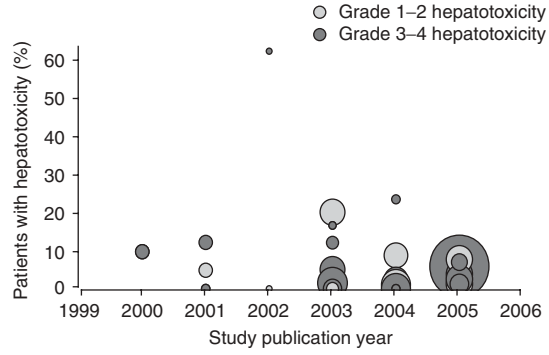

Fig. 2. Long-course nevirapine: patients with hepatotoxicity by study year as a function of study size.

Table IV. Nevirapine-related adverse drug reactions among non-HIV-infected patients who received pre-exposure prophylaxis (PrEP) or post-exposure prophylaxis (PEP)

Study	Population	No. of patients	No. of patients with AE of any kind [n (%)]	Other HIV medications	Onset of AE	Comments	Hepatic AE	
							grade 1–2 [n (%)]	grade 3–4 [n (%)]
4 d nevirapine 200 mg/d + 28 d NRTIs								
Rey et al.[38]	HCW and N/O	120	68 (57)	NRTIs, mainly zidovudine + lamivudine, 28 d	~3 d (range 2–28 d)	Elevated ALT values in five; rash on d 2 caused one patient to discontinue nevirapine	5 (4)	0 (0)
Livrozet et al.[39]	HCW and N/O	131	31 (24)	NRTIs for 28 d	2–14 d	No abnormal LFT results	0 (0)	0 (0)
Subtotal		**251**					**5 (2)**	**0 (0)**
4 wk nevirapine (200 mg/d for 2 wk and 200 mg twice daily for 2 wk) for PEP; 12 wk varying nevirapine for PrEP								
Puro et al.[40]	HCW and N/O	12	4 (33)	NRTIs	11–28 d	One patient with grade 2 ALT elevation also had rash	2 (17)	2 (17)
Johnson et al.[16]	HCW	8	5 (63)	Zidovudine + lamivudine	14 d (range 8–21 d)	Grade 4 ALT elevation in five cases: one HCW had fulminant hepatic necrosis requiring liver transplant; two patients had rash >50% of body	0 (0)	5 (63)
Bernasconi et al.[41]	N/O	16	12 (75)	NRTIs, mainly zidovudine + lamivudine	Not stated	AE resulted in one patient stopping and another changing therapy; specific events not cited	N/A	N/A
Benn et al.[42]	HCW and N/O	41	18 (44)	NRTIs, mainly stavudine + lamivudine	24–28 d	Five patients had drug-induced hepatitis: two with grade 4 ALT had rash (one with grade 3 rash was hospitalized)	2 (5)	5 (12)
Bennett CL, unpublished observations	Healthy volunteers	41	8 (20)	200–400 mg	6–15 d	Duration of use 2–4 wk	4 (10)	4 (10)
Jackson et al.[43]	Healthy volunteers	33	18 (55)	200 mg every other day	4–6 wk median	Four patients had severe increase in at least one LFT value and one had grade 4 toxicity (increase in two patients was thought to be a result of chemical or alcohol exposure)	0 (0)	4 (12)
Subtotal		**151**					**8 (5)**	**20 (13)**
Overall total		**402**					**13 (3)**	**20 (5)**

AE = adverse event; **HCW** = healthcare workers; **LFT** = liver function test; **N/A** = not applicable; **N/O** = non-occupational (community) exposure to HIV; **NRTIs** = non-nucleoside reverse transcriptase inhibitors.

not significantly different ($p < 0.72$). Among non-HIV-infected patients who received short- versus long-course nevirapine therapy for pre- or post-exposure HIV prophylaxis, the incidence of grade 1–2 hepatotoxicity was 1.99% (95% CI 0.30, 3.70) for short-course versus 5.30% (95% CI 1.70, 8.90) for long-course prophylaxis. For grade 3–4 hepatotoxicity, the rates were 0% for short-course (95% CI cannot be computed because of zero incidence) and 13.25% (95% CI 7.80, 18.70) for long-course prophylaxis ($p < 0.001$).

Nevirapine Dosage

While nevirapine hepatotoxicity may be dose related, it is not possible to state the dosages used in all the studies analysed (including whether or not the induction dose was used for the first 10–14 days as recommended) due to the heterogeneity of study reporting. Several studies, especially those reported in abstracts, did not provide the dose of nevirapine used, providing instead the various medication combinations used (without dosage) in each arm or study group, along with the list of adverse drug reactions and the efficacy results. Many of the studies that did not provide the dose of nevirapine, focused on the CD4 count stratification as a risk factor for the development of nevirapine-related hepatotoxicity (i.e. they reported nevirapine-related hepatotoxicity in the nevirapine-containing arm versus the non-nevirapine-containing arm and subsequently stratified by CD4 counts as all patients were receiving the same dose of nevirapine in that arm, but they were developing rates of hepatotoxicity at different rates depending on their CD4 count).

Discussion

Nevirapine is a potent non-nucleoside analogue inhibitor of HIV-1 reverse transcriptase. When used alone or in combination with nucleoside analogue reverse transcriptase inhibitors, rapid and significant reductions in HIV plasma viremia are observed. However, concerns exist over potential hepatotoxicity risks consequent to nevirapine use for HIV prophylaxis among non-HIV-infected individuals and neonates born to HIV-infected mothers. Our review revealed high rates of severe hepatotoxicity when nevirapine was administered for longer than 2–5 weeks to pregnant HIV-infected women receiving nevirapine-containing antiretroviral therapy for PMTCT, as well as for non-HIV-infected individuals who received post-exposure HIV prophylaxis. In contrast, few instances of hepatotoxicity were identified when ≤4 days of nevirapine-containing prophylaxis regimens were administered to HIV-infected pregnant women or non-HIV-infected individuals. In interpreting our findings, several factors should be considered.

Our study provides empirical data supporting observations that both HIV-infected women with CD4 lymphocyte counts >250 cells/mm^3 and HIV-infected individuals who receive ≥2weeks of nevirapine-based therapy are at high risk for severe drug-induced hepatic toxicity.[48] Lyons et al.[14] reported that one-quarter of HIV-infected women, 91% of whom were pregnant, developed severe hepatotoxicity shortly after initiation of nevirapine. A possible mechanism for this toxicity is an immune-mediated allergic response. Hypersensitivity reactions consisting of rash, peripheral eosinophilia, constitutional symptoms and hepatic dysfunction have been reported among nevirapine-treated HIV-infected individuals, typically within the first 2 months of treatment.[49-54] If the hypersensitivity reactions were mediated by CD4 lymphocytes, then this could account for the occurrence of hepatotoxicity among these individuals. Similar patterns of hypersensitivity have been seen in association with the use of other drugs, including co-trimoxazole. Drug-specific cytotoxic T cells have been identified in skin lesions associated with toxic epidermal necrolysis[55] and increased concentrations of the hydroxylamine metabolite of sulfamethoxazole have been found in the plasma of HIV patients treated with co-trimoxazole.[56]

Concerns over high rates of severe nevirapine-associated hepatotoxicity among HIV-infected women resulted in a 'black box' revision to the FDA-approved package insert for the drug in February 2004. The revised warning indicated that nevirapine-treated women with CD4 cell counts >250 cells/mm^3, including pregnant women, had a

12-fold greater risk of potentially fatal hepatotoxicity. The greatest risk occurred during the first few weeks of nevirapine treatment.[14] A unique clinical entity among nevirapine-treated patients in these clinical trials was rash-associated hepatotoxicity, suggestive of an immune-mediated phenomenon. Rash-associated hepatotoxicity occurred almost exclusively during the first 6 weeks of nevirapine treatment and was more likely in women with CD4 cell counts >250 cells/mm^3 and in men with CD4 cell counts >400 cells/mm^3.[56] The presence of a nevirapine-associated rash usually precedes evidence of liver damage and implies greater subsequent risk for the occurrence of hepatotoxicity.[57] Martin et al.[58] reported a greater risk of nevirapine-induced hypersensitivity among women with HLA-DRB1*01 and higher CD4+ T lymphocyte counts. The manufacturer's advisory recommended that liver function tests be monitored in any HIV-infected individual developing a skin rash while receiving nevirapine, particularly during the early weeks of therapy.[6]

The use of nevirapine-containing long-course post-exposure prophylaxis regimens was discontinued in the US in 2001 following reports of severe hepatotoxicity in five of eight non-HIV-infected Chicago healthcare workers who had received 8–30 days of a nevirapine-containing post-exposure prophylaxis regimen.[16] In contrast, few instances of hepatotoxicity followed administration of ≤4 days of nevirapine among 3031 pregnant women, 2801 infants or 251 non-HIV-infected adults who received nevirapine as pre- or post-exposure HIV prophylaxis. These findings have significant public healthcare implications.

In 2002, the manufacturer of nevirapine withdrew its FDA application seeking approval for prophylactic nevirapine use for prevention of mother-to-child perinatal HIV transmission in the US.[59] A senior NIH official raised concerns that single-dose nevirapine would be unsafe for use in the context of the HIVNET (HIV Network for Prevention Trials) 012 clinical trial, a study evaluating mother-to-child transmission in Uganda.[59] However, a follow-up NIH investigation of this trial in 2003 confirmed that administration of single-dose nevirapine to pregnant mothers and to newborns was safe and effective in PMTCT.[60] In 2005, the Institute of Medicine announced that their review also supported the HIVNET 012 clinical trial findings.[59]

The low incidence of hepatotoxicity during short-course nevirapine therapy supports this extremely low-cost and effective therapeutic alternative for PMTCT in resource-limited settings where full HAART is not possible for pregnant women with CD4 cell counts >250 cells/mm^3. Single-dose nevirapine remains the foundation of PMTCT programmes throughout resource-limited settings.[8] Another concern with this therapeutic intervention is the development of HIV viral resistance to nevirapine when given as single-dose therapy without combination antiretroviral therapy. However, recent data demonstrate that when single-dose nevirapine is used in combination with short-course nucleoside analogue reverse transcriptase inhibitors, such as zidovudine and, most recently, tenofovir plus emtricitabine, this risk may be minimized;[8,61] these new data indicate that the use of short-course nevirapine will continue to be an essential component of PMTCT.

The limitations of this review should be noted. Follow-up is often difficult and variable among non-HIV-infected individuals who receive post-exposure prophylaxis, limiting our ability to reliably estimate exposure-adjusted hepatotoxicity incidence rates in this setting. In addition, early trials failed to fully recognize the risk of nevirapine-related hepatotoxicity and often did not report the occurrence of grade 1–2 hepatotoxicity. Also, many data sources did not meet inclusion criteria. Similarly, concern has been raised over the likelihood of post-marketing reporting of adverse events in the US as well as the adequacy of clinical trial record keeping in resource-limited settings, as evidenced by the 15-month suspension of clinical trial research by the NIH in Uganda.

Conclusion

Nevirapine-associated hepatotoxicity remains a drug-related hazard for certain patient populations. The risk is greatest for those patients receiving nevirapine-containing antiretroviral therapy for more than 2 weeks, particularly for non-HIV-infected individuals or HIV-infected pregnant

women with CD4 cell counts >250 cells/mm^3. In contrast, the data presented demonstrate a relatively low rate of hepatotoxicity associated with short-course nevirapine therapy. When full HAART regimens are not available, single-dose nevirapine plus short-course nucleoside reverse transcriptase inhibitors to decrease the development of HIV viral resistance is an essential therapeutic option for PMTCT; these data support the safety of single-dose nevirapine in this setting.

Acknowledgements

No sources of funding were used to assist in the preparation of this study. Jorge Parada has been a consultant for Merck and Pfizer and is on the speaker's bureau for Pfizer. All other authors have no conflicts of interest that are directly relevant to the content of this study.

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