Incidence and Risk Factors of Nevirapine-Associated Severe Hepatitis Among HIV-Infected Patients with CD4 Cell Counts Less than 250 Cells/µL

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Objectives: *To determine incidence and risk factors of nevirapine (NVP)-associated severe hepatitis that led to NVP discontinuation among HIV-infected patients with CD4 < 250 cells/µL.*
Material and Method: *A retrospective cohort study was conducted among antiretroviral-naive HIV-infected patients who had baseline CD4 < 250 cells/µL and were initiated NVP-based antiretroviral therapy (ART) between January 2003 and October 2005. All patients were categorized to group A: occurred clinical hepatitis and group B: did not occur clinical hepatitis. All were followed until 6 months after ART.*
Results: *There were 910 patients with a mean age of 35.4 years, 57% were males and median (IQR) CD4 cell count was 27 (9-80) cells/µL; contributing 5,006 person-months of observations. Ten (1.1%) patients were in group A and 900 (98.9%) patients were in group B. Incidence of clinical hepatitis was 2 per 1,000 person-months. Probabilities of clinical hepatitis at 0.5, 1, 2, 3 and 6 months after ART were 0.2%, 0.5%, 0.7%, 0.8% and 1.1%, respectively. By Cox regression analysis, baseline AST ≥ 1.5 times of upper limit was associated with higher incidence of clinical hepatitis (p = 0.019, HR = 5.83, 95% CI = 1.33-25.51).*
Conclusion: *Incidence of NVP-associated severe hepatitis that lead to NVP discontinuation among HIV-infected patients with baseline CD4 < 250 cells/µL is low. The higher baseline AST is also associated with a higher risk of severe hepatitis.*

Keywords: *HIV, Nevirapine, GPOvir, Hepatitis, Incidence, Risk factor*

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Elevated liver enzymes are common adverse events among HIV-infected patients who have been receiving highly active antiretroviral therapy (HAART). The incidence and severity depend on drug classes or agents, as well as on pre-existing liver dysfunction. The severity of hepatotoxicity ranges from mild to fatal liver failure. Currently, non-nucleoside reverse transcriptase inhibitor (NNRTI)-based HAART regimen is preferred as initial regimen because of its efficacy, tolerability, and lesser long-term toxicities[1-3]. Nevirapine (NVP) is an NNRTI that have shown effective antiretroviral efficacy[4-6]. Liver toxicity secondary to NVP is well recognized. Elevation of transaminase enzymes have been reported in HIV-infected patients receiving NVP. Severe hepatotoxicity and liver failure have been observed[7]. High rate of potentially fatal liver toxicity primarily occurs with initial therapy in women with high CD4 cell counts[8-11]. Furthermore, serious and fatal hepatotoxicity has been reported during post-exposure prophylaxis[12-15].

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In developing countries, NVP-based HAART has been widely used due to its availability. HIV-infected patients in these areas usually present late with low CD4 cell counts. The incidence and risk factors of NVP-associated severe hepatitis among the patients with advanced HIV disease have not been well described. The authors therefore conducted this retrospective cohort study to determine the incidence of NVP-associated severe hepatitis after initiation of ART that lead to NVP discontinuation and to determine risk factors that were related to the occurrence of NVP-associated severe hepatitis.

Material and Method

A retrospective cohort study was conducted among antiretroviral naïve HIV-infected patients who were initiated NVP-based ART between January 2003 and October 2005 at Bamrasnaradura Infectious Diseases Institute, Ministry of Public Health, Nonthaburi, Thailand. All patients received NVP 200-mg once-daily lead-in dose, prior to escalation to 200 mg twice daily by using separated pills. Inclusion criteria were as follows: (1) HIV-infected patients greater than 15 years of age, (2) Antiretroviral naive prior to initiation of NVP-based ART, (3) Baseline CD4 cell counts < 250 cells/μL, (4) Had received 2 weeks of NVP 200-mg once-daily lead-in dose prior to escalation to 200 mg twice daily, and (5) Had received ART at least two clinic visits. The authors excluded the patients who commenced ART from another hospital and subsequently transferred to our institute. Each patient was categorized into two groups according to whether or not they developed NVP-associated severe hepatitis: Group A developed NVP-associated severe hepatitis and Group B did not develop NVP-associated severe hepatitis. All patients were followed until 6 months after ART initiation. Possible risk factors includingdemographics, previous opportunistic infections (OIs), baseline CD4 cell counts, baseline plasma HIV-1 RNA and liver enzymes were studied and compared between those who had (group A) and did not have (group B) severe hepatitis from NVP. All patients were cared and followed every 6 to 12 weeks to monitor clinical response and adverse reactions as standard of care in our institute. The final decision regarding whether the relevant adverse events developed was determined by the attending investigator. In routine clinical practice, liver function test was not routinely and regularly monitored except in case of any clinical symptoms indicated or suspected.

The primary objective of the present study was to determine the incidence of NVP-associated severe hepatitis after initiation of ART that needed discontinuation of NVP. The secondary objectives were to define risk factors that related to occurrence of NVP-associated severe hepatitis; and probability of NVP-associated severe hepatitis in different baseline AST.

Median (interquatile range, IQR) and frequencies (%) were used to describe patients' characteristics in both groups, respectively. Chi-square and Mann-Whitney U tests were used to compare categorical and continuous variables between the two study groups. The Kaplan-Meier test was used to estimate the probability of NVP-associated severe hepatitis after ART and the median time to develop hepatitis. The patients were censored when they had hepatitis or discontinued the ART due to any causes. The patients who had been on drug holidays longer than 4 weeks were considered as lost to follow-up and were censored at the date of first lost to follow-up visit. The log-rank test was used to compare the median time to develop hepatitis between the two groups. The Cox proportional hazard model was used to determine the chance of developing clinical hepatitis after receiving treatment by adjusting for confounding factors, i.e. age, gender, body weight, previous cryptococcal infection, baseline CD4 cell counts and baseline aspatate aminotransferase (AST) enzyme. Age, body weight and baseline CD4 cell counts were examined as continuous variable. Baseline AST levels were transformed to dichotomous variables and tested. AST levels were categorized to equal or above 1.5 time vs. below 1.5 time of the upper limit of normal range. Gender and previous OIs were also examined as dichotomous variables. Statistical calculations were performed using SPSS program version 11.5 (SPSS Inc., Chicago, Illinois, USA). A two-sided p-value of less than 0.05 was considered statistically significant. The study was approved from the institute review board.

Results

A total of 910 patients met the inclusion criteria. The mean (± SD) age was 35.4 (± 7.7) years and 56.4% were males. The median (IQR) CD4 cell count was 27 (9-80) cells/μL. Of the 910 patients, 10 (1.1%) patients developed severe hepatitis and were categorized in group A; 900 (98.9%) patients were categorized in group B. This contributed 5,006 person-months of observations. The incidence of clinical hepatitis was 2 per 1,000 person-months. During the study period, 41 (4.5%), 16 (1.8%) and 13 (1.4%) patients had lost to follow-up, died, and were referred to another hospital, respectively. No patient died from hepatitis. The

patients' characteristics between the two groups were compared as shown in Table 1. There were no differences of baseline characteristics between the two groups ($p > 0.05$).

Regarding severity of NVP-associated hepatitis, 6 patients, 5 patients and 5 patients had elevated AST, alanine aminotransferase (ALT) and total bilirubin grade III and grade IV, respectively. The median (IQR) serum alkaline phosphatase (ALP) level, AST level, ALT level, and total bilirubin at time of hepatitis was 318 (165-601) mg/dl, 318 (165-601) U/L, 195 (81-493) U/L, and 6.3 (2.3-11.5) mg/dl, respectively. Two of 10 patients also developed constitutional symptoms and skin rash grade III whom diagnosed as having hypersensitivity reactions. The median (IQR) duration between initiation of NVP-based ART to discontinuation in these 10 patients was 43 (15-79) days. After NVP discontinuation, clinical symptoms and liver enzymes ultimately returned to baseline values and 9 patients could subsequently tolerate efavirenz-based ART. The remaining one patient was lost to follow-up after diagnosis of NVP-associated hepatitis. All patients continued to receive the same NRTI backbone, stavudine and lamivudine, after NVP discontinuation. When hepatitis occurred, none of the patients received corticosteroid. Of 10 patients who developed hepatitis, 2 patients had positive serology of hepatitis C virus (HCV) and 2 had positive serology of both hepatitis C virus and hepatitis B virus (HBV). None of these 10 patients died during the study period.

Of 910 patients, the probabilities of NVP-associated clinical hepatitis at 0.5, 1, 2, 3 and 6 months after ART were 0.2%, 0.5%, 0.7%, 0.8% and 1.1%, respectively. The probability of NVP-associated hepatitis after initiation of ART stratified by the level of AST is shown in Fig. 1. Patients with baseline AST > 1.5 time of normal range had a higher probability to have hepatitis (log rank test, $p = 0.004$). The results of Cox regression analysis of possible risk factors for NVP-associated severe hepatitis are shown in Table 2. The patients with baseline AST level $\geq$ 1.5 times of upper limit were six times more likely to develop hepatitis than those with baseline AST level < 1.5 times ($p = 0.016$).

Table 1. Baseline characteristics of patients between the two groups

Demographics	Group A (n = 10)	Group B (n = 900)	p-value
Age, years, mean ± SD	35.5 ± 8.5	35.4 ± 7.7	0.957
Male gender, number (%)	43 (55.8%)	479 (57.5%)	0.810
Weight, kgs, mean ± SD	52.7 ± 9.7	52.7 ± 10.5	1.000
History of previous major OIs	7 (70.0%)	426 (47.3%)	0.206
Baseline CD4 count, cells/μl, median (IQR)	25 (9-82)	27 (9-81)	0.755
Baseline CD4 percentage, median (IQR)	2 (1-7)	3 (1-7)	0.687
Baseline plasma HIV RNA, copies/mL, median (IQR)	116,000 (33,650-367,500)	281,500 (113,500-611,500)	0.133
Baseline plasma log HIV RNA	5.0 (4.5-5.5)	5.5 (5.0-5.8)	0.130
ALP, mg/dL median (IQR)	125 (86-165)	97 (70-150)	0.422
ALT, U/L, median (IQR)	37 (20-43)	27 (17-46)	0.660
AST, U/L, median (IQR)	83 (25-145)	33 (25-51)	0.107

Table 2. Cox regression of possible factors for NVP-associated hepatitis

Risk factors	HR	95% Cl	p-value
Elevated baseline AST (1.5 times of upper limit)	5.830	1.333-25.510	0.019
Gender	1.518	0.344-6.706	0.582
Baseline CD4 cell counts	0.996	0.980-1.012	0.610
Body weight	1.009	0.934-1.091	0.814
Age	0.997	0.908-1.095	0.955

HR = Odds ratio, CI = Confidence interval

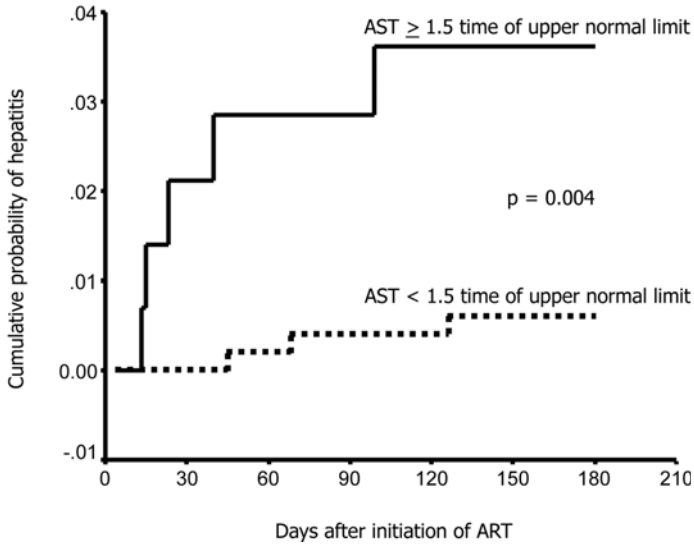

Fig. 1 Probability of NVP-associated clinical hepatitis stratified by baseline AST levels

Discussion

Liver toxicity is an important complication among HIV-infected patients who receive NVP-based ART. This drug can increase potential for liver toxicity through either hypersensitivity reaction during the early period of ART or dose-dependent effect[16]. The overall incidence of NVP-associated severe hepatitis observed in the present study was 1.1%. The previous study demonstrated that clinical hepatitis occurs in 1% of NVP-treated patients in the patients with higher baseline CD4 cell counts[17]. Asymptomatic hepatitis has been shown to occur in 8% to 28% of patients[18]. NVP-associated hepatotoxicity usually occurs within the first 2 weeks to 5 months after initiation of this agent[15, 17]. Therefore, the authors followed the patients until 6 months after commenced ART. Almost all of the patients who had hepatitis in this cohort developed hepatitis within the first three months of ART. In the present study, two of 10 patients developed hepatic hypersensitivity reactions which accompanied by rash, eosinophilia and constitutional symptoms. This syndrome typically appears within the first 2 months of treatment[19-21].

In addition, the previous studies demonstrated that woman with higher CD4 cell counts appear to be at a highest risk for hepatic events. A 12-fold higher incidence of symptomatic events was seen in woman with CD4 cell counts of > 250 cells/μL at the time of nevirapine initiation when compared with woman with CD4 cell counts of ≤250 cells/μL (11.0% vs. 0.9%). An increased risk was also seen in men with baseline CD4 cell counts > 400 cells/μL when compared with baseline CD4 cell counts ≤400 cells/μL (6.3% vs. 1.2%)[8-11]. The other established risk factors for symptomatic hepatic adverse events include elevated pretreated AST value and HBV and/or HCV co-infection. Herein, the result showed that HIV-infected patients with baseline AST level ≥ 1.5 times of upper limit had six times more likely to develop severe hepatitis than those with baseline AST level < 1.5 times of upper limit. However, the authors could not identify that "gender" and "increment of baseline CD4 cell counts" are risk factors of NVP-associated among patients with CD4 cell count of less than 250 cells/μL in the present study. This corresponds to the previous reports[11,22]. Gender is a risk factor only among patients who had a higher number of CD4 cell counts as mentioned above.

Geel et al demonstrated that trough plasma NVP level was elevated in patients concurrently received NVP and fluconazole 200 mg/day[23]. This is a reason that why the authors added the factor of concurrent receiving fluconazole in the multivariate analysis. However, the authors did not find the correlation of hepatitis and concurrent receiving fluconazole that correspond to the previous study[24]. The reason is that the markedly lower number of CD4 cell counts in the present study.

The previous study demonstrated that nucleoside reverse transcriptase inhibitors (NRTI) might cause a syndrome of hepatic steatosis and lactic acidosis as a manifestation of mitochondrial toxicity[25]. In the present study, all patients received a backbone of stavudine and lamivudine. Nevertheless, all of the patients continued to receive stavudine and lamivudine after discontinuation of NVP. Clinical symptoms and biochemical abnormalities returned to baseline after discontinuation of NVP. This evidence supports that a backbone NRTI, especially stavudine, unlikely to be the causative drugs of hepatitis.

The limitation of the present study is the nature of retrospective study that patients' clinical status may be underreported. Firstly, identification of the definitive drugs that respond to hepatitis may be difficult by clinical diagnosis alone. Meanwhile many drugs are metabolized via the same pathway, which may have additional potential effect. Nonetheless, abnormal biochemical parameters returned to normal after discontinuation of NVP for a while. Secondly, some patients may have co-infection with HBV or HCV. Most of the presented patients were not routinely tested for HBsAg and antibody to HCV. Therefore, the authors lack these factors in the multivariate analysis. However, the authors' previous study showed that the prevalence of HBV or HCV co-infection with HIV were about 9% and 8% in Thai HIV-infected patients[26]. Thus, the present study showed the high incidence of HCV and HBV co-infection in the patients who developed severe hepatitis. Thirdly, most patients had not been checked liver enzymes during the first few weeks after ART and had not been regularly monitored liver function test. So, the number of patients who performed liver function test and the incidences of asymptomatic elevated liver enzymes at each different time point could not be demonstrated. Fourthly, AST level is analyzed in the multivariate analysis instead of ALT level because the results of ALT levels were assessed in only two-third of the patients. Lastly, the majority of patients in the present study had relatively low CD4 cell counts. Thus, the present results may not be applicable for the patients who had higher CD4 cell counts. Further studies to determine immunologic and genetic factors associated with hepatitis are needed[27,28].

In summary, HIV-infected patients with baseline CD4 < 250 cells/μL had incidences of NVP-associated severe hepatitis that lead to NVP discontinuation approximately 1.1%. Almost all of the patients developed adverse events within the first three months after ART. The number of baseline CD4 cell counts and gender are not associated with the high incidence of hepatitis in advanced HIV-infected patients but the higher baseline AST is associated with a higher risk of clinical hepatitis. Even in the resource-limited situations, the frequent monitoring of transaminase enzyme should be closely monitored in the first few weeks of NVP-based ART especially in high risk patients.

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อุบัติการณ์และปัจจัยเสี่ยงของการเกิดตับอักเสบจากยาเนวิราพีนในผู้ป่วยเอชไอวีที่มีเม็ดเลือดขาวซีดีสี่น้อยกว่า 250 เซลล์ต่อไมโครลิตร

วีรวัฒน์ มโนสุทธิ, สมนึก สังฆานุภาพ, สมสิทธิ์ ตันสุภสวัสดิกุล, สุทัศน์ โชตนะพันธ์, วิโรจน์ หมั่นคติธรรม, สุกัญญา ฉิมสุนทร, ชยนันท์ สิทธิบุศย์, วิศัลย์ มูลศาสตร์, อัจฉรา เชาวะวณิช

จุดประสงค์: *เพื่อศึกษาอุบัติการณ์และปัจจัยเสี่ยงของการเกิดตับอักเสบรุนแรงที่มีความสัมพันธ์กับยาเนวิราพีน และจำเป็นต้องมีการหยุดใช้ยาดังกล่าวในผู้ป่วยเอชไอวีที่มีเม็ดเลือดขาวซีดีสี่น้อยกว่า 250 เซลล์ต่อไมโครลิตร*

วัสดุและวิธีการ: *เป็นการศึกษาแบบย้อนหลังในกลุ่มผู้ป่วยเอชไอวีที่ยังไม่เคยได้รับยาต้านไวรัสมาก่อน มีเม็ดเลือดขาวซีดีสี่น้อยกว่า 250 เซลล์ต่อไมโครลิตร และได้มีการเริ่มรับยาต้านไวรัสที่มีเนวิราพีนเป็นส่วนประกอบ ระหว่างเดือนมกราคม พ.ศ. 2546 ถึงเดือนตุลาคม พ.ศ. 2548 ผู้ป่วยทุกรายจะถูกแบ่งเป็น 2 กลุ่มดังนี้ กลุ่มเอเป็นผู้ป่วยที่เกิดภาวะตับอักเสบทางคลินิก และกลุ่มบีไม่เกิดภาวะตับอักเสบทางคลินิก โดยที่ทุกรายจะได้รับการติดตามเป็นเวลา 6 เดือนหลังเริ่มยาต้านไวรัส*

ผลการศึกษา: *มีจำนวนผู้ป่วยทั้งหมด 910 ราย มีอายุเฉลี่ย 35.4 ปี และเป็นเพศชายร้อยละ 57 มีค่ามัธยฐานปริมาณเม็ดเลือดขาวซีดีสี่เท่ากับ 27 เซลล์ต่อไมโครลิตร คิดเป็นระยะเวลาการติดตามผู้ป่วย 5,006 บุคคล-เดือน แบ่งเป็นผู้ป่วยกลุ่มเอ 10 ราย (ร้อยละ 1.1) และกลุ่มบี 900 ราย (ร้อยละ 98.9) พบว่าอุบัติการณ์การเกิดตับอักเสบทางคลินิกคิดเป็น 2 รายต่อ 1000 บุคคล-เดือน ความน่าจะเป็นของการเกิดตับอักเสบทางคลินิก ณ เดือนที่ 0.5, 1, 2, 3 และ 6 หลังเริ่มยาต้านไวรัส คิดเป็นร้อยละ 0.2, 0.5, 0.7, 0.8 และ 1.1 ตามลำดับ โดยการวิเคราะห์แบบ Cox regression พบว่าค่าเอนไซม์เอเอสที ก่อนเริ่มยาที่มากกว่าหรือเท่ากับ 1.5 เท่าของค่าปกติสูงสุด มีความสัมพันธ์กับอุบัติการณ์การเกิดตับอักเสบทางคลินิกสูงขึ้น (ค่าพีเท่ากับ 0.019)*

สรุป: *พบว่าอุบัติการณ์การเกิดตับอักเสบรุนแรงจากยาเนวิราพีนที่นำไปสู่การหยุดใช้ยาดังกล่าวอยู่ในเกณฑ์ต่ำในผู้ป่วยเอชไอวีที่มีค่าเม็ดเลือดขาวซีดีสี่น้อยกว่า 250 เซลล์ต่อไมโครลิตร ค่าพื้นฐานเอนไซม์เอเอสทีที่สูงสัมพันธ์กับความเสี่ยงต่อการเกิดตับอักเสบรุนแรงจากยาเนวิราพีน*