Incidence and Risk Factors for Non-Nucleoside Reverse Transcriptase Inhibitors (NNRTI)-Related Rash in Thai Children with HIV Infection

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The present study evaluated the incidence and risk factors that correlated with the development of non-nucleoside reverse transcriptase inhibitor (NNRTI) related rash in 69 Thai children followed prospectively. The overall incidence of NNRTI-related rash was 16% (22% for NVP and 4% for EFV rash). The only significant predictive factor that correlated with the development of NNRTI-related rash in a multivariate logistic regression model was a CD4% decrease at week 12.

Keywords: *NNRTI, Rash, Children, NVP, EFV, HIV*

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Non-nucleoside reverse transcriptase inhibitor (NNRTI) based regimens using Nevirapine (NVP) are some of the most widely used first-line antiretroviral (ARV) regimens worldwide because of the availability of generic NVP. Rash is the most common side effect and cause of discontinuation from NVP. The NNRTI Efavirenz (EFV) can cause rash, but usually to a lesser extent. NVP causes rash in about 20% of adults, while rash from EFV is seen in about 10% of adults[1-5]. In a recent prospective study in Thai children, the incidence of rash from NVP and EFV was 23% and 7%, respectively[6].

The present study investigated the incidence and factors associated with the development of NNRTI-associated rash in children, which has not yet been well established. The variables chosen were based on reported risk factors for adults[1,7].

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Material and Method

Data was collected prospectively from ARV-naïve patients enrolled in two clinical trials (HIV-NAT 010 and HIV-NAT 015), from July 2001 to February 2005, at the HIV Netherlands Australia Thailand Research Collaboration Center (HIV-NAT) and Chulalongkorn University Hospital (Bangkok, Thailand) and Khon Kaen University (Khon Kaen, Thailand). Both studies were approved by the Institutional Review Board of Chulalongkorn and Khon Kaen University, and written informed consent was obtained from guardians. HIV-NAT -010 randomized 43 ARV-naïve children with CD4 15-25% to receive AZT/3TC/NVP either immediately or when CD4 count decreased to < 15%. HIV-NAT 015 prospectively followed 76 children who presented to the authors'. According to Thai National Treatment

Guidelines[8], ARV therapy was initiated when CD4 dropped below 20%. The regimen comprised AZT or d4T, 3TC, and NVP or EFV. Generic NRTI's and NVP were used, and one pediatric HIV specialist selected the NNRTI based on the most appropriate dosing using the available formulation of NVP (200mg pill) and EFV (200mg pill). Dosing of NVP and EFV was based on the US guidelines, except that a 200mg/m^2 NVP lead-in dose was used[9]. Data on demographics, BMI, Center for Disease Control and Prevention (CDC) clinical classification, rash occurrence and characteristics, and SGPT were collected prospectively at baseline, 2, 4, 8, 12, and 24 weeks. Due to resource limitations, CD4 counts were only measured at baseline, 12, and 24 weeks in all patients, and HIV RNA was measured at baseline and 24 weeks in 75% of patients. NNRTI was considered a cause of rash if it had at least a possible relationship to NNRTI. Severity was graded using the 2004 US National Institutes of Health Division of AIDS grading system.

Statistical analysis

Comparisons between the NVP and EFV users as well as comparisons between patients with and without NNRTI-related rash were done using the Wilcoxon rank sum test for continuous variables and the chi-square test or Fisher's exact test for categorical variables. Odds ratios for developing NNRTI-related rash were calculated using logistic regression models. A multivariate analysis was done using the variables that yielded a p value of less than 0.30 in the univariate analysis. Statistical analysis was performed using SAS, Version 8.2 (SAS Institute Inc., Cary, NC, USA).

Results

Baseline characteristics

Sixty-nine children who had begun treatment with at least 24 weeks of follow-up were included in the present analysis: twenty five children were from HIV-NAT 010 and 44 were from HIV-NAT 015. Of these, 48 were treated with NVP and 24 with EFV. Three patients initially treated with NVP were switched to EFV because of rash and were included in both the NVP and the EFV groups for analysis. There were approximately equal numbers of males and females, median age was 5 (Interquartile Range [IQR] 3-8) years, CDC clinical classification N (asymptomatic): A (mildly symptomatic): B (moderately symptomatic): C (severely symptomatic) were 1:31:21:16, median CD4 10% (256 cells/mm^3, IQR 3-17%), median HIV RNA 5.1 $\log_{10}$ copies/mL (IQR 4.7-5.3), and median SGPT 23 IU/L (IQR 15-45). Patients on EFV had more advanced HIV clinical disease (62% had CDC C while only 6% of NVP patients had CDC C, $p < 0.0001$), lower CD4% and counts [CD4 3.5% (47.5 cells/mm^3) vs. CD4 13% (477 cells/mm^3) in NVP patients, $p = 0.002$], and lower SGPT (SGPT 35 IU/L vs. 52 IU/L in NVP patients, $p = 0.006$).

Incidence and characteristics of NNRTI-associated rash

Of the 69 patients, 29 (42%) developed rash, but only 11 (16%) were from NNRTI. Two of 11 were Grade I, and nine were Grade II. No patients had Grade III or IV rashes. The median onset of NNRTI-related rash was 10 (IQR 9-12) days and the median duration was 6.5 (IQR 5-10) days. Of the 48 children taking NVP, 20 (42%) had rash, and 10 (21%) were from NVP; one was Grade I, and nine were Grade II. Four of the children with Grade II rash also experienced constitutional symptoms. The median onset of NVP-related rash was 10.5 (IQR 10-12) days and the median duration was 6 (IQR 5-10) days. Of the 24 children taking EFV, nine (38%) had rash, but only one (4%) was from EFV. This patient had rash from NVP and switched to EFV after the rash resolved. The subsequent rash from EFV was Grade I and occurred after 3 days. There were 18 patients with NNRTI-unrelated rash (6 from HIV-NAT 010; 12 from HIV-NAT 015).

Only patients with Grade II rash received treatment. Of these nine patients, one was treated with corticosteroids and the rest with antihistamines. All rashes resolved after treatment and only one of the 11 children developed another rash (non-drug-related impetigo). Of the 10 patients with NNRTI-related rash, one stopped ARV and left the study, three were switched from NVP to EFV, one was switched from NVP to Ritonavir, and six continued NVP. Of these patients, five had to interrupt NNRTI during rash for a median of 31 days (range 3 to 106 days). There were no hospitalizations or deaths from the rash.

Risk factors for NNRTI-related rash

Patients with and without NNRTI-related rash were compared to identify risk factors and correlations for rash development. The authors did not find differences in gender, age, BMI, baseline CD4% or count, or baseline SGPT level; however, patients with rash had a less advanced HIV clinical disease at baseline ($p = 0.04$).

Interestingly, the authors found that more of the children with rash showed a decrease in CD4% at week 12 compared to baseline. In univariate analysis,

a CD4% decrease at week 12 correlated with rash (p = 0.013, Table 1). Because it has been demonstrated that adult females with higher CD4 counts are at higher risk for rash[1], the authors assessed whether female children with higher CD percentages were also at higher risk compared to other groups. Indeed, female children with baseline CD4 count greater than 15% were at higher risk of developing rash (p = 0.03).

A second univariate analysis was done to identify risk factors for rash among the patients using NVP only. This analysis also showed CD4% decrease at week 12 to be correlated with rash (p = 0.019). An analysis of EFV users for risk factors was not done because only one EFV user had rash.

After adjusting for the effects of other variables in multivariate analysis, the only variable significantly associated with rash development was a decrease in CD4% at week 12 (p = 0.005, Table 1).

Discussion

In the present study population of HIV-infected Thai children, the overall incidence of NNRTI-related rash was 15% (29 of 69): Grade I, Grade II, Grade III, and Grade IV was 3%, 12%, 0%, and 0%, respectively. The incidence of rash from NVP was 22% (10 of 46) and from EFV was 4% (1 of 24). Univariate analysis showed a CD4% decrease at week 12 after initiating NNRTI correlated with NNRTI-related rash, and a sub-analysis of NVP users showed the same correlation. Univariate analysis also showed that females with baseline CD4 more than 15% were at higher risk of rash. However, the only significant correlate with development of NNRTI-related rash in a multivariate model, was a CD4% decrease at week 12.

NNRTI-related rash is differentiated from rash of other causes primarily by its onset. An NNRTI rash rarely occurs during the first week of initiation but

Table 1. Univariate and multivariate analyses of risk factors for NNRTI-related rash in children (n = 72)

Variable	NNRTI-related rash n (%)	Univariate OR (95% CI)	p	Multivariate OR (95% CI)	p
Gender					
Female	7 (10)	1.00		1.00	
Male	4 (6)	0.49 (0.13-1.83)	0.29	0.64 (0.08-5.38)	0.68
NNRTI					
EFV	1 (1)	1.00			
NVP	10 (14)	6.05 (0.73-50.42)	0.09	1.00	
BMI (kg/m^2)				5.72 (0.49-66.83)	0.11
< 15	4 (6)	1.00			
≥ 15	7 (10)	1.93 (0.51-7.28)	0.33		
Baseline CDC classification					
A or N	8 (11)	1.00		1.00	
B or C	3 (4)	0.28 (0.07-1.15)	0.08	0.72 (0.11-4.50)	0.72
CD4 % at baseline					
< 15	5 (7)	1.00			
≥ 15	6 (8)	2.4 (0.65-8.83)	0.19	1.00	
Percent CD4 response at week 12*				0.42 (0.03-6.38)	0.51
Increase from baseline	7 (10)	1.00			
Decrease from baseline	3 (4)	12.00 (1.70-84.69)†	0.013	1.00	
ALT response at week 2**				12.61 (1.43-111.54)	0.005
Increase from baseline	4 (6)	1.00			
Decrease from baseline	5 (7)	2.06 (0.5-8.6)	0.32		
Drug regimen					
AZT based	7 (10)	1.00			
Non-AZT based	4 (6)	0.77 (0.20-2.91)	0.69		
All Males or females with					
Baseline CD4 < 15%	6 (8)	1.00		1.00	
Baseline CD4 > 15% and female	5 (7)	4.82 (1.21-19.17)	0.03	3.57 (0.13-97.96)	0.44

* 1 missing value; ** 10 missing values

† Values in bold are significant at p < 0.05

rather between the first and third week. Similar to other drug hypersensitivity, it typically manifests as an erythematous, maculopapular, pruritic rash on the body and arms with or without constitutional symptoms such as fever, arthralgia, myalgia, and mucosal involvement. Diagnosis, therefore, can be challenging in children who are on multiple drugs[3].

A recent study in 107 Thai children with a median CD4 of 13% reported a similar incidence of rash to the present study: 16% overall incidence of Grade II NNRTI-related rash - 23% (14 of 61) in NVP and 7% (3 of 46) in EFV-treated children[6]. Because higher CD4 has been reported as a risk factor for NNRTI-related rash[1,7], the authors expected the presented NVP-treated children (median CD4 13%) in this present study to have a higher incidence of rash than the previously mentioned cohort; however, the incidence was the same. Two recent studies including one in Thais found that adult females with higher CD4 counts at the start of ARV treatment were at higher risk for NNRTI-related rash, which is also in line with the present findings. Proposed reasons for gender variation include differences in cytochrome P450 metabolism and/or hormonal effects; however, the latter is less likely in pre-pubertal children.

The authors' findings in both univariate and multivariate analyses that a decrease in CD4% at week 12 correlates with NNRTI-related rash contrasts with other studies[1,7]. An adult study found that a rise in CD4 count at week 4 was predictive of rash[1], which is supported by the generally accepted model of NNRTI-associated rash as a cell-mediated process that is more likely to manifest as a patient's CD4 rises. The authors' finding showing the opposite may be due to a large time gap between CD4 test (week 12) and the onset of rash (12 days) and the fact that the patients with rash had interruptions of ARV during this time; therefore, they had a shorter treatment time compared to those without rash.

There were several limitations to the present study. First, the sample size is small, especially for EFV patients; therefore, the results seen reflect the effect of NVP. Second, due to resource limitations, the important risk factors for rash, CD4% and HIV RNA, were not done frequently. Third, the patients included in this report came from two different studies in which one had strict CD4 inclusion criteria; therefore, the patients may not represent the general population. Lastly, the study is not randomized and the patients on EFV had a more advanced HIV disease, which may cause bias on evaluating the risk of EFV rash.

In conclusion, 16% of children experienced NNRTI-related rash. Females with baseline CD4 above 15% and children who had a decrease in CD4% at week 12 were at higher risk. There is a need to evaluate a larger population of NNRTI-treated children to better identify risk factors for rash.

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อุบัติการณ์และปัจจัยเสี่ยงของการเกิดผื่นจากยาต้านไวรัสเอ็นเอ็นอาร์ทีไอในเด็กไทยที่ติดเชื้อเอชไอวี

สุนิตา เวมูลา, สตีเฟน เคอร์, ชิษณุ พันธ์เจริญ, อาริดา ศิริพงศ์, ภพ โกศลารักษ์, จุฬาพรรณ อึ้งจะนิล, อาภา เชื่อมชัยตระกูล, จินตนา อินต๊ะเสน, ผกากรอง ลุมพิกานนท์, ประพันธ์ ภานุภาค, จินตนาถ อนันต์วรณิชย์

การศึกษานี้มีวัตถุประสงค์เพื่อหาอุบัติการณ์และปัจจัยเสี่ยงของการเกิดผื่นจากยากลุ่มเอ็นเอ็นอาร์ทีไอในเด็กไทย 69 คนที่ได้รับการติดตามไปข้างหน้า พบอุบัติการณ์การเกิดผื่นร้อยละ 15 โดยที่เป็นผื่นจากยาเนวิราปีนร้อยละ 22 และจากยาเอฟาไวเรนซ์ร้อยละ 4 ปัจจัยที่สัมพันธ์กับการเกิดผื่นคือการลดลงของค่าเซลล์เม็ด เลือดขาว CD ร้อยละ 4 ณ สัปดาห์ที่ 12 หลังรับประทานยา