Clinical Pediatrics: Open Access

Wai LT et al, Clin Pediatr OA 2016, 1:3
DOI: 10.4172/2572-0775.1000105

Research Article Open Access

Antiretroviral-therapy-related Hepatotoxicity in HIV-infected Children in Integrated HIV-care Clinic, Mandalay Children's Hospital, Myanmar

Wai Lin Tun*, **Khaing KW and Tin M**

***Corresponding author:** Wai Lin Tun, MD, Department of Pediatrics, University of Medicine, Mandalay, Myanmar, Tel: +6594475793; E-mail: wailintun.kowai@gmail.com

Received date: December 13, 2015; **Accepted date:** March 18, 2016; **Published date:** March 26, 2016

Abstract

Objectives: To determine the prevalence and severity of antiretroviral-therapy-related hepatotoxicity in HIV-infected children in the local population and to relate hepatotoxicity with patient characteristics such as age, gender, baseline aminotransferase levels, clinical stages and immunologic categories at the initiation of antiretroviral therapy (ART) and types of ART, in the Integrated HIV-care Clinic, Mandalay Children's Hospital, Myanmar.

Method: This study was performed on 68 HIV-infected children in 2010. They were followed up for 8 weeks from the start of ART. Serum ALT and AST levels were measured before the initiation of ART, and then again at 2 weeks, 4 weeks and 8 weeks from the start of ART. The severity of hepatotoxicity was determined by the highest level of ALT or AST during the first eight weeks. Patients with documented pre-existing liver diseases or Hepatitis B virus or Hepatitis C virus co-infections, those who were currently on anti-tuberculous drugs, and those with grade 2, 3, 4 liver enzyme elevations at baseline, were excluded.

Result: Out of 68 patients, 18 patients (26.5%) suffered some degree of hepatotoxicity. Most patients (16 patients) had mild hepatotoxicity. Severe hepatotoxicity (grade 3 or 4) was observed in 2 patients. Hepatotoxicity was found to be more common in patients with normal baseline liver enzyme levels than those with elevated baseline liver enzyme levels (P = 0.035). No statistically significant relation was found between the occurrence or severity of hepatotoxicity and patients' other characteristics such as age, gender, WHO clinical stages, immunologic categories and types of ART.

Conclusion: Although hepatotoxicity was frequently observed in children who were newly started on ART, most cases were of mild degree (grade 1 or 2 hepatotoxicity). The occurrence or severity of hepatotoxicity was not attributable to patient characteristics except baseline liver enzyme levels.

Introduction

Hepatotoxicity is a significant problem in patients on ART. It occurs in approximately 6% to 30% of patients [1]. Adverse drug effects such as hepatotoxicity may negatively affect adherence to ART and the goal of successful management of HIV. There have been a number of international studies on ART-related hepatotoxicity in children. However, there has been no data that would reflect or represent our population in this regard. In Myanmar, according to UNAIDS's estimation, there were 210,000 people living with HIV in 2014, of which 11,000 were children under 14 years of age, and 10,000 death (all age groups) per year due to AIDS [2]. Due to increasing community awareness and expanding medical services, more and more Myanmar children are receiving ART. As of 2016, about 6000 children in Myanmar are receiving ART from both the public and private sectors. In this study, we tried to look into the hepatic side effects of ART in our specific population.

Objectives

The general objective of this study is to study ART-related hepatotoxicity in HIV-infected children in Integrated HIV-care Clinic (IHC) of Mandalay Children's Hospital (MCH), Myanmar.

The specific objectives are to determine the incidence and severity of ART-related hepatotoxicity in HIV- infected children, to find out the possible relation between hepatotoxicity and patient characteristics such as age, gender, baseline aminotransferase levels, WHO clinical stages and immunologic categories at the initiation of ART and types of ART [3].

Methodology

This study is a non-randomized prospective observational study which was performed over a period of 12 months starting from 1st January, 2010 to 31st December, 2010. The sample size was 68 patients with equal numbers of male and female patients. All children who were newly started on ART of any regime were included in the study after taking written informed consent from the caregivers. We included children with normal levels of liver enzymes as well as those with grade 1 liver enzyme elevations at baseline. We excluded patients with documented pre-existing liver diseases or Hepatitis B virus or Hepatitis C virus co-infections, those who were currently on anti-tuberculous drugs, and those with grade 2, 3, 4 liver enzyme elevations at baseline.

Before starting ART, the following tests were done; liver function tests (LFTs) including serum alanine aminotransferase (ALT) and aspartate aminotransferase (AST), hepatitis B surface antigen (HBs antigen), anti-hepatitis C virus antibody (anti-HCV antibody) and

CD4 count. LFTs were rechecked at 2 weeks, 4 weeks and 8 weeks after initiation of ART.

Operational definitions

ALT levels up to 40 IU/L and AST levels up to 37 IU/L are defined as normal.

The grades of hepatoxicity are defined as shown in Table 1. Grade 1 and 2 are classified as mild hepatotoxicity and grade 3 and 4 as severe hepatotoxicity [1,4].

Hepatotoxicity	With normal baseline LFT	With abnormal baseline LFT
Grade 1	1.1-4.9 times ULN (upper limit of normal)	1.25-2.5 times of baseline level
Grade 2	5-9.9 times ULN	2.6-3.4 times of baseline level
Grade 3	10-15 times ULN	≥3.5 times of baseline level
Grade 4	>15 times ULN	≥5 times of baseline level

Table 1: Grades of Hepatotoxicity.

Results

We included the equal numbers of male and female patients. We also stratified the patients into 3 age groups as shown in the Table 2. Most patients had mildly transaminitis before ART initiation. The vast majority of patients had clinical stage 3 diseases and severe immune suppression. Most of them received a combination of stavudine/lamivudine/nevirapine.

Patient Characteristics		Number	Percentage
Gender	Male	34	50%
	Female	34	50%
Age	12 to 35 months	10	14.70%
	35 to 59 months	10	14.70%
	More than 5 years	48	70.60%
Baseline LFT	Normal	20	29.40%
	Grade 1 elevation (1.1-4.9 times ULN)	48	70.60%
WHO Clinical Stage	1	1	1.50%
	2	9	13.2
	3	56	82.3
	4	2	3%
Immunologic categories	No significant immune suppression	2	3%
	Mild immune suppression	1	1.50%
	Advanced immune suppression	14	20.50%
	Severe immune suppression	51	75%
Types of ART	stavudine/lamivudine/nevirapine	34	50%
	zidovudine/lamivudine/nevirapine	19	28%
	zidovudine/lamivudine/efavirenz	9	13.20%
	stavudine/lamivudine/efavirenz	6	8.80%

Table 2: Patient characteristics.

(d4T: stavudine, 3TC: lamivudine, NVP: nevirapine, AZT: zidovudine, EFV: efavirenz).

Hepatotoxicity was observed in 18 patients (26.5%). Most of them (16 patients, 88.9%) had only mild hepatotoxicity. Two patients (11.1%) were found to have severe hepatotoxicity (grade 3 and 4 respectively). No patient needed discontinuation of ART due to hepatotoxicity. Even the two patients with severe hepatotoxicity were asymptomatic and later recheck LFTs showed return of ALT and AST levels to normal levels or to baseline levels.

We also tried to find out whether there was any relation between patient characteristics and the occurrence or severity of hepatotoxicity. In our data analysis, we used one of the stratified groups as a reference group for other groups to compare to; e.g. normal baseline LFT, WHO clinical stage 1 and no immune suppression (Table 3). We used D4T/3TC/EFV as the reference regime because no hepatotoxicity was observed in patients who received this regime.

Patient characteristics		Relation to occurrence of hepatotoxicity			Relation to severity of hepatotoxicity		
		P-value	OR	95% CI	P-value	OR	95% CI
Gender (female compared to male)		0.597	1.3	0.449-4.135	0.889	0.789	0.018-34.48
Age	12 - 35 months	0.318	0.429	0.007-27.09	0.778	0.167	0.001-23.11
	35 - 59 months	0.318	0.429	0.007-27.09	0.375	0.5	0.005-49.56

	> 5 years	0.255	0.333	0.006-17.73	0.115	0.091	0.001-7.569
Baseline LFTs (grade 1 elevation compared to normal)		0.035	0.288	0.089-0.917	0.754	1.603	0.016-10.98
WHO Clinical Stage (stage 2, 3 and 4 compared to stage 1)	2	0.946	0.873	0.015-51.25	0.375	0.5	0.005-49.56
	3	0.786	0.61	0.012-30.14	0.094	0.071	0.001-5.897
	4	0.625	0.5	0.005-49.56	0.5	1	0.004-255.5
Immune suppression (other categories compared to no significant suppression)	Mild	0.641	3.651	0.035-381.4	0.4	2	0.011-357.2
	Advanced	0.75	0.577	0.013-25.84	0.776	0.516	0.007-38.27
	Severe	0.491	0.316	0.008-12.97	0.457	0.201	0.003-13.93
Types of ART (other regimes compared to D4T/3TC/EFV regime)	D4T/3TC/NVP	0.305	3.811	0.387-125.1	0.227	0.25	0.004-16.92
	AZT/3TC/NVP	0.403	3.268	0.282-116.7	0.846	0.1	0.001-13.16
	AZT/3TC/EFV	0.321	4.445	0.293-180.8	0.778	0.166	0.001-23.11

Table 3: Relation between patient characteristics and frequency and severity of hepatotoxicity.

Only the baseline liver enzyme levels were found to have a statistically significant relation with the occurrence of hepatotoxicity. No factor was found to be associated with the severity of hepatotoxicity.

Discussion

In this study, hepatotoxicity was observed in 26.47% of patients, which was much higher than that observed in a study performed in the United States of America by Baylor et al. (2.7%) [5]. On the other hand, a study performed in Spain reported an incidence rate of 20% [6]. The difference in incidence rates is likely due to differences in study population. In India, a country with similar demographics to ours, an identical incidence rate of 27% was reported [7].

Regarding the severity, most patients had only mild hepatotoxicity. Two patients suffered severe hepatotoxicity (grade 3 and grade 4 respectively). Both patients were asymptomatic with no vomiting, abdominal pain, rash or jaundice. So, ARTs were continued with close follow-up which showed the normalization of liver enzyme levels 4 weeks after initiation of ART). No patient needed dose adjustment or cessation of ARTs due to hepatotoxicity. These findings are similar to what Gil et al. found out in their study [1].

We found out that apart from baseline liver enzyme levels, the other patient characteristics did not have any statistically significant relation with the occurrence or the severity of hepatotoxicity.

Before the initiation of ART, 20 patients (29.41%) had normal baseline liver enzyme levels, and 48 patients (70.59%) had grade 1 elevation of liver enzymes. After initiation of ART, 9 patients with normal baseline LFTs (45%) and 9 patients with abnormal baseline LFTs (18.75%) showed biochemical evidence hepatotoxicity. Therefore, patients with normal baseline LFTs were found to be more likely to have hepatotoxicity than those with abnormal baseline values. This finding is statistically significant with P value of 0.035. This finding is similar to that observed by Sanne et al. [8]. In their study, they concluded that lower AST level < 75 IU/L was an independent risk factor for subsequent development of hepatotoxicity. Moreover, in our study, interestingly, 70.59% of patients had abnormal LFTs before ART, but after the initiation of ART, only 26.47% had abnormal values. A similar finding was noted by Pryce et al. [9] who stated that elevations of bilirubin, AST and ALT prior to commencing ART could be due to the severity of HIV disease, and these elevations did not necessarily lead to hepatotoxicity after the initiation of ART. Since HIV is a hepatotrophic virus, the improvement of liver functions after the initiation of ART could be due to reduced viral loads which we did not measure in our study.

We did not find any relation between types of ART and hepatotoxicity. There was also no significant difference between regimes containing nevirapine and those not containing nevirapine. These finding was contrary to those sited in literature [10-12] which reported a particular relation of nevirapine and hepatotoxicity. However, in a study performed by Baylor et al. [5], they found that 21 out of 779 patients suffered hepatotoxicity but only one case could be attributed to nevirapine.

Limitations

This study has a number of limitations. Firstly, the sample size was too small to give conclusive results. As regards to hepatotoxicity, the patients were monitored only for 8 wks. This time interval theoretically allows the detection of hepatotoxicity caused by metabolic host-mediated injury or hypersensitivity reactions. However, the effect of mitochondrial toxicity could have gone undetected because it usually presents on prolonged exposure. Although patients taking anti-tuberculous drugs were excluded, patients who took other drugs with potential hepatotoxicity such as cotrimoxazole or systemic antifungal drugs were not excluded. Consequently, confounding effects of those medications could not be excluded.

Conclusion and Recommendation

According to our small study's findings, ART seemed to be safe in children as regards to hepatic side effects. Most of the hepatic side effects were asymptomatic liver enzymes elevations. Larger studies are needed to provide more conclusive answers. In this study, the pubertal stages of the adolescent patients were not assessed, and we cannot provide information on possible effects of puberty on the side effect

profile of ART. Future studies with particular attention on pubertal stages would be useful.

References

1. Gil ACM, Lorenzetti R, Mendes GB, Morcillo AM, Dalbo AA, et al. (2007) Hepatotoxicity in HIV-infected Children and Adolescents on Antiretroviral Therapy. Sao Paulo Med J 125: 205-209.
2. UNAIDS (2016) UNAIDS Country Profile: Myanmar.
3. WHO Antiretroviral Therapy for HIV Infection in Infants and Children: Towards Universal Access: Executive Summary of Recommendations. (2010) Geneva, Switzerland.
4. Sulkowski MS, Thomas DL, Chaisson RE, Moore RD (2000) Hepatotoxicity Associated with Antiretroviral Therapy in Adults Infected with Human Immunodeficiency Virus and the Role of Hepatitis C or B Virus Infection. JAM A 283: 74-80.
5. Baylor M, Ayime O, Truffa M, Denson A, Johann LR (2005) Hepatotoxicity Associated with Nevirapine Use in HIV-infected Children. 12th Conference on Retroviruses and Opportunistic Infections, Boston, Massachusetts, the United States of America, abstract no. 776.
6. Ena J, Amador C, Benito C, Fenoll V, Pasquau F (2003) Risk and Determinants of Developing Severe Liver Toxicity during Therapy with Nevirapine- and Efavirenz-containing Regimens in HIV-infected Patients. Int J STD AIDS 14: 776-781.
7. Kumarasamy N, Vallabhaneni SJ, Cecelia AJ, Yepthomi T, Balakrishnan P, et al. (2006) Reasons for Modification of Generic Highly Active Antiretroviral Therapeutic Regimens among Patients in Southern India. Journal of AIDS 41: 53-58.
8. Sanne I, Marin HM, Hinkle J, Bartlett JA, Lederman MM, et al. (2005) Severe Hepatotoxicity Associated with Nevirapine Use in HIV-infected Subjects. J of Infect Dis 191: 825-829.
9. Pryce C, Pierre RB, Steel-Ducan J, Evans-Gilbert T, Palmar P, et al. (2008) Safety of Antiretroviral Drug Therapy in Jamaican Children with HIV/AIDS. West Indian Med J 57: 238-245.
10. Medrano J, Barreiro P, Tuma P, Vispo E, Labarga P, et al. (2008) Risk for Immune-Mediated Liver Reactions by Nevirapine Revisited. AIDS Rev 10: 110-115.
11. Bjornsson E, Olsson R (2006) Suspected Drug-induced Liver Fatalities reported to the WHO Database. Dig Liver Dis 38: 33-38
12. Schieferstein C, Buhk T (2006) Management of Side Effects. In: C Hoffmann, JK Rockstroh and BS Kamps (eds). HIV Medicine. Flying Publisher 281-284.