Cutaneous adverse drug reaction in Human Immunodeficiency virus patient associated with antiviral therapy: A retrospective study

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Abstract

Drug hypersensitivity reactions specifically cutaenous adverse drug reaction (CADR) occur at higher rate in human immunodeficiency virus (HIV)-positive patients than general population and cause significant morbidity, in early era of antiretroviral therapy (ART), the incidence of skin rashes can reach 50% in HIV patients taking HIV medications. The purpose of this study is to evaluate the pattern of CADR in HIV patients associated with ART. A retrospective study took data from medical record CADR in HIV patients associated with ART at HIV ward, Dr. Soetomo General Hospital Surabaya, since January 2013 until December 2015. During the period of three years, there were 20 CADR patients in at HIV ward, Dr. Soetomo General Hospital Surabaya. The most common patient was male, with the highest age group of 25-44 years old, and the most clinical feature found were maculopapular rash, and *Steven Johnson Syndrome* (SJS). The most common antiviral therapy were nevirapine. The number of CADR in HIV patient associated with ART cases increased. The most clinical feature were maculopapular rash followed by SJS, only few cases of *toxic epidermal necrolysis*.

Introduction

Human immunodeficiency virus (HIV) is a lymphotropic human retrovirus, which is predominantly transmitted through sexual contact. Other important means of transmission include exposure to infected blood (including needles shared by injecting drug users and "skin popping") and transmission from an infected mother to her infant during pregnancy, delivery, or breastfeeding. The introduction of antiretroviral therapy (ART) has markedly altered the life expectancy and quality of life for many of the 33.4 million individuals worldwide infected with HIV. Cutaneous disorders occur in nearly every patient during the course of HIV disease, either as a result of acquired immunodeficiency or from treatment.[1]

Cutaneous adverse drug reaction (CADR) is the most common manifestation of drug hypersensitivity. Patients can present exanthema without systemic symptoms or drug hypersensitivity syndromes typically manifesting as an erythematous, maculopapular confluent rash with constitutional features (fever, rigors, myalgias, and arthralgias) in the presence or absence of internal organ involvement (hepatitis, pneumonitis, myocarditis, pericarditis, and nephritis). Stevens Johnson syndrome (SJS) or toxic epidermal necrolysis (TEN) develop in less than 0.5% of patients. A study by Coopman et al. which included 684 HIV-infected patients from The Harvard Community Health Plan's records showed that CADR accounted for 8.2% dermatologic diagnoses of HIV patients. The most common CADR is morbilliform rash. Others were urticaria, erythema multiforme, vasculitis, exfoliative dermatitis, and photodermatitis. Most of CADR in HIV patients are induced by cotrimoxazole. Antiretroviral medications have also been associated with CADR, ranging from mild exanthemas to life-threatening reactions, such as SJS or TEN.[2]

The incidence of adverse cutaneous drug eruptions is estimated to be as much as 100 times more common in individuals with untreated HIV disease compared to that in the general population, and may become more frequent with advancing immunodeficiency.[1-4] Although there have been case reports of nearly all antiretroviral drugs and drug hypersensitivity, the antiretroviral drugs most commonly associated with such syndromes include abacavir, a nucleoside analogue, the nonnucleoside reverse transcriptase inhibitors (NNRTIs; nevirapine, efavirenz, delavirdine, TMC-125, TMC-278), fosamprenavir, an HIV protease inhibitor and enfuvirtide (T-20), an HIV fusion inhibitor.[4]

Factors that have been associated with increased risk of drug eruptions include female gender, CD4+ T cell count <200/μL, CD8+ T cell count >460/μL, and a history of having had drug eruptions in the past.[1]

Diagnosis and management of drug hypersensitivity in HIV-infected patients is difficult because multiple medication regimens are used to treat patients. It is very challenging to determine which drugs cause the reactions.[2]

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Materials and Methods

We conducted a descriptive retrospective study using medical record of cutaneous adverse drug reaction in HIV patient associated with antiviral therapy since January until December 2015 at HIV ward in Dr. Soetomo General Hospital Surabaya. Participating practices provides information on patient demographics and characteristics (e.g age, sex, trigger factors), and medical diagnoses which are directly generated by the medical record.

Results

The observed patients encompassed 20 CADR associated with ART cases, of which 65% were male. The vast majority (85%) of patients were at the range of 25-44 years old, Among patients identified having CADR, 65% were identified as having maculopapular rash, 20% were diagnosed as *Steven Johnson Syndrome*, 5% were erythroderma and also TEN, with the onset maculopapular rash within 1-7 days (45%) and 7-14 days (20%), *Steven Johnson Syndrome* within 1-7 days (25%) and erythroderma also TEN were each within 1-

7days (5%) The most associated ART was nevirapine 45%. Distribution of subjects' characteristics can be seen in Table 1.

Discussion

In this study, the prevelance of CADR in HIV patients associated with ART were 20 (62.5%) of the total 32 CADR patients who are hospitalized in HIV Ward Dr. Soetomo General Hospital in January 2013 –December 2015. The total HIV /AIDS patient were 2168 patients. A study by Coopman et al. which included 684 HIV-infected patients from The Harvard Community Health Plan's records showed that CADR accounted for 8.2% dermatologic diagnoses of HIV patients.[2]

Table 1. Characterics of subjects with CADR in HIV patient associated with ART in HIV ward Dr. Soetomo General Hospital Surabaya since 2013-2015.

Characterictics	Total (%)
CADR	32
CADR associated with ART	20 (62.5)
Age category n (%)	
< 1	0 (0)
1 – 4	0 (0)
5 – 14	0 (0)
15 – 24	1 (5)
25 – 44	17 (85)
45 – 64	2 (10)
> 65	0 (0)
Diagnosis	
Maculopapular rash	13 (65)
Steven Johnson Syndrome (SJS)	5 (20)
Erythrodermi e.c drug eruption	1 (5)
Toxic Epidermal Necrolysis (TEN)	1 (5)
Onset	
Maculopapular rash	
1-7 days	9 (45)
7-14 days	4 (20)
Steven Johnson Syndrome (SJS)	
1-7 days	5 (25)
Eritrodermi e.c drug eruption	
1-7 days	1 (5)
Toxic Epidermal Necrolysis (TEN)	
1-7 days	1(5)
Antiretroviral therapy	
Maculopapular rash	
Nevirapine	9(45)
Zidovudine+Lamivudine	10(50)
Efavirenz	4(10)
Tenovofir	3(15)
Lamivudine	3(15)
Steven Johnson Syndrome	
Nevirapine	5(25)
Zidovudine+Lamivudine	4(20)
Lamivudin	1(5)
Tenofovir	1(5)
Erythrodermi e.c drug eruption	
Nevirapine	1(5)
Zidovudine+Lamivudine	1(5)
Toxic epidermal necrolysis	
Efavirenz	1(5)
Lamivudine	1(5)
Tenofovir	1(5)

Studies have reported to be more prevalent in middle-aged adults and female, as reported in Tatiparthi and Mamo journal, from a total of 233 HIV positive adult patients on HAART treatment, 141 were females, 211 (90.6%) aged between 15-49 years old.[5] In this retrospective study, 1 patient (5%) aged 15-24, 17 (85%) aged 25-44, followed by 2 patients (10%) aged 45-64.

Cutaneous drug eruptions including morbilliform rash, urticaria, hypersensitivity syndrome, SJS, and TEN are the most frequent side effects of the medication and may be seen in as many as 35% of patients.[6] Morbilliform eruptions are by far the most common manifestation, accounting for about 75%–95% of cases.[1] Based on this study, the most common diagnosis were maculopapular rash 65%, followed by *Steven Johnson Syndrome* 20%, Erythroderma caused by drug eruption and *Toxic Epidermal Necrolysis* each were 5%.

The most common ART associated with CADR were nevirapine in each diagnosis. There were 45% cases of Maculopapular rash, 25 % of SJS, and 5% erythroderma caused by drug eruption were associated with nevirapine. Drugs are the most common cause of SJS; more than 100 different agents have been reported to cause SJS. Nevirapine is the classic example of an HIV drug associated with SJS/TEN.[7] The present study found that antiretroviral drug nevirapine (NVP) was most commonly associated with CADRs in an outpatient setting. NVP was incriminated in 39 out of 69 (39/69, 56.12%) cases of MP rash and 5 out of 8 (5/8, 62.5%) cases of urticaria. All four cases of SJS, two cases of pustular rash and two cases of angioedema were attributed to NVP. NVP is the most commonly used non-nucleoside reverse transcriptase inhibitor (NNRTI) as a part of first-line ART. Besides NVP, other anti-retroviral drugs namely efavirenz, zidovudine, lamivudine and atazanavir were also suspected in CADRs especially MP rash in present study.[8]

Because the risk of severe CADR appears to be greatest within the first several weeks of treatment, standard recommendations are to start nevirapine at a half-dose (200 mg) for the first 2 weeks. Anto´n et al. (1999) compared this regimen to an even more gradual escalating schedule (100 mg _ 1 week, 200 mg _ 1 week, 300 mg _1 week, then full dose 400 g) and found that 8.5% of 166 patients on the standard schedule had to discontinue the medication due to rash compared with 2.1% of 97 patients using a more gradual taper. Tolerance induction with graded dosing of nevirapine in conjunction with antihistamines has also been successful in two of three patients who had previously failed treatment due to non-bullous cutaneous reactions.[6,9]

The diagnosis and treatment of drug hypersensitivity to antivirals, as per any drugs, is still largely based on clinical assessment of the specific syndrome involved. As per other drugs the presence of mild to moderate rash without systemic symptoms, internal organ or mucosal involvement is commonly associated with many antiviral drugs. Desensitization or graded re-introduction of drug has also been used to reintroduce an antiviral where the original reaction consisted of an isolated mild to moderate skin rash.[9,10,11]

Conclusions

Drug hypersensitivity is common for those living with HIV and its pathophysiology is complex and multifactorial. Early recognition and withdrawal of the drug is essential particularly in those with the more severe reactions. More studies are also needed to understand the mechanisms of antiretroviral hypersensitivity so that better strategies for prevention and treatment can be defined.The importance of this is emphasized by the fact that allergic reactions with anti-HIV drugs are not restricted to the older compounds, and will thus continue to be a clinical problem.

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