Role of Efavirenz in HIV-infected Patients with Preceding Nevirapine-related Skin Rash

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ABSTRACT

In the resource-limited countries, nevirapine (NVP)-based highly active antiretroviral therapy (HAART) has been widely used due to its availability and antiviral efficacy. Skin reaction is the most frequently observed adverse event from NVP. Both NVP and efavirenz (EFV) are in the same class of non-nucleoside reverse transcriptase inhibitor (NNRTI), and they also can cause skin rash and hypersensitivity reaction. To date, the previous clinical data may support the safety of subsequent use of efavirenz and encourage the physicians to use efavirenz in HIV-infected patients who had preceding nevirapine-associated skin rash. This review outlines the clinical safety data regarding use of EFV in HIV-infected patients who had preceding NVP-associated rash. (J Infect Dis Antimicrob Agents 2007;24:89-93.)

INTRODUCTION

Highly active antiretroviral therapy (HAART) has been widely used for the treatment of in patients with advanced HIV infection, and has been successful in achieving immune restoration and thus reducing morbidity and mortality.1-3 Common initial HAART regimens consist of two nucleoside reverse transcriptase inhibitors (NRTIs), combined with either a boosted protease inhibitor (PI) or a non-nucleoside reverse transcriptase inhibitor (NNRTI). The three currently available NNRTIs (nevirapine, efavirenz, and delavirdine) were introduced between 1996 and 1998. The choice between an NNRTI and a boosted PI remains largely a matter of opinion, but more clinical data favor NNRTI-based regimens.

The current treatment guidelines for HIV-1-infected adults recommend the use of efavirenz in combination with zidovudine (ZDV) or tenofovir disoproxil fumarate (TDF) together with lamivudine (3TC) or emtricitabine (FTC) as one of the preferred first-line antiretroviral regimens.4 However, the options of the initial HAART regimen should always be adapted to the individual situation with respect to compliance, concurrent opportunistic infections, concomitant

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medications, accessibility, expense, and the needs of the patients. During the last few years, the first-line NNRTI-bases regimens have become increasingly popular, compared to PI-based regimens. NNRTIs are favored not only because of good clinical efficacy, but also because of lower pill burden, once-daily dosing with no restrictions regarding food intake, and avoidance of the perceived toxicity of PI-based regimens. All these factors contribute to better adherence to HAART, which is necessary for a sustained antiretroviral effect of treatment. Nevertheless, a single mutation of NNRTI drug may lead to cross-class resistance.

The NNRTIs that are currently available in Thailand are efavirenz and nevirapine. As mentioned earlier, efavirenz is the preferred NNRTI for an initial regimen. However, efavirenz is not a drug that is well tolerated by all patients, and the adverse reactions need to be carefully discussed to every patient before initiating this drug. Nevirapine is an NNRTI that has been shown to have high antiretroviral efficacy. However, the 2006 US DHHS guidelines for the use of antiretroviral agents in HIV-infected adults and adolescents still recommended two NRTIs plus nevirapine as an alternative regimen for the treatment of adults with HIV-1 infection. Nevirapine has been compared with efavirenz in the 2NN study, and was shown to be of comparable efficacy. In resource-limited countries, nevirapine-based HAART regimen has been widely used because it is more readily available and affordable than other regimens. In Thailand, the Government Pharmaceutical Organization (GPO) has produced a new formulation of antiretroviral drugs i.e., a fixed-dose combination of 30-mg or 40-mg stavudine (d4T), 150-mg 3TC, and 200-mg nevirapine (GPO-VIR S); and a fixed-dose combination of 250-mg ZDV, 150-mg 3TC, and 200-mg nevirapine (GPO-VIR Z) which have been available on the market since 2002 and 2006, respectively. These generic combinations are components of the universal antiretroviral treatment coverage program in Thailand. Most of Thai HIV-infected patients can access to HAART.

Regarding adverse reactions, skin rash is the most frequently observed adverse event associated with nevirapine, manifesting as diffuse maculopapular or erythematous rash with or without constitutional symptoms. The risk of rash of any severity is greatest within the first six weeks of treatment. Generally, the rash is mild and transient. However, more severe rash including extensive maculopapular rash, serum sickness-like reaction, hypersensitivity syndrome, Steven-Johnson syndrome (SJS), and toxic epidermal necrolysis have been reported. In addition, the severity of rash is not reduced by the co-administration of steroids, which should be avoided.

Nevirapine shows autoinduction of cytochrome P450 isoenzymes, resulting in a decrease in the terminal half-life in plasma from 45 hours following a single dose to 24-30 hours with multiple dosing. To account for this phenomenon, an initial reduced dose in the first two weeks of treatment before escalation to 400 mg/day is recommended. The recommended dose of nevirapine 200 mg once daily for 14 days prior to escalation to 200 mg twice daily has been shown to reduce the frequency of rash. Although this recommendation has been strictly followed, the overall frequency of rash ranges from 9 percent to 32 percent. The incidence of nevirapine-associated skin reactions among Thai patients ranges from 6 percent to 21 percent. The main adverse reaction, besides cutaneous manifestations, is hepatotoxicity. It usually occurs within the first month of nevirapine initiation. A recent data has shown a 12-fold higher incidence of serious hepatic events in women with CD4 cell counts of >250 cells/mm³ and in men with CD4 cell counts of >400 cells/mm³.
For the management of nevirapine-associated skin reactions, a mild skin reaction without mucous membrane involvement or development of transaminase elevation can be treated with antihistamine. If this skin rash occurs during the first two weeks of initiation, the dose should not be increased until the rash has resolved completely. Nevirapine should be discontinued if severe rash occurs as well as if other systemic symptoms occur such as fever, conjunctivitis, myalgia, arthralgia, and malaise. Due to nevirapine long half-life of approximately 24-30 hours, the two NRTIs of the nevirapine-based HAART regimen should be continued after nevirapine discontinuation. It usually takes 7-14 days for nevirapine to be completely eliminated from the human body.

A commonly known major disadvantage of the currently available NNRTIs is the low genetic barrier for the development of drug-resistant viral variants. Certain single amino-acid mutations in the NNRTI-binding region can cause a high level of drug resistance, such as K103N, Y181C, and Y188L. Cross-resistance between the currently licensed NNRTIs is extensive. A single mutation in the HIV-1 genome can increase the 50-percent inhibitory concentration (IC50) by up to 100-fold. The inter-patient variability of nevirapine clearance should be another concern. This is attributable to the variation of half-life of this drug and may be difficult to predict individually. It’s well established that a single-dose nevirapine is a highly cost-effective strategy to reduce perinatal HIV-1 transmission. However, its major disadvantage is the selection of nevirapine resistance in 20 percent to 30 percent of women. Muro and colleagues reported that most women who received a single 200-mg nevirapine dose still had detectable plasma concentrations of nevirapine after more than two weeks. Thus, the purpose of tail-off management is to prevent occurrence of single amino-acid mutations that may limit the efficacy of subsequent NNRTI drug. However, the future clinical study should be conducted to confirm the benefit of these techniques.

Another concern is a that whether there is cross-toxicity between nevirapine and efavirenz in HIV-infected patients because both drugs belong to the NNRTI class and act similarly. Their molecular structure may not be related as nevirapine is a member of the dipyridodiazepinone class while efavirenz is a member of trifluoroderviate class. In a resource-limited setting, patients can not afford the PI-based regimen due to its high cost. Thus, efavirenz-based HAART, which is more affordable, is an alternative regimen in HIV-infected patients with preceding nevirapine-associated skin rash. Although a hypersensitivity reaction can develop with both nevirapine and efavirenz, there have been no clinical data on the risk of cross-toxicity between these two drugs.

We reviewed the literature from Medline database that reported the safety and tolerability of efavirenz in patients with preceding nevirapine-associated skin rash. However, there is a scarcity of clinical data in this area. Clarke and colleagues reported a small cohort of eight patients (four men and four women) with a mean CD4 cell count of 143 cells/mm³. A mean age was 45.7 years. Seven of eight patients had a history of antiretroviral treatment, with all seven having received multiple NRTIs and PIs. None of the patients had previously received an NNRTI. Six of the eight patients discontinued nevirapine due to skin rash of grade III, and the others due to liver toxicity. A mean duration of nevirapine treatment before a development of adverse reactions was 14.6 days. All patients had a washout period of seven to ten days before reinstitution of efavirenz-based HAART regimens. All eight patients in this cohort were successfully switched from nevirapine to efavirenz.
treatment without recurrence of skin reactions. Soriano and colleagues reported seven of eight patients with nevirapine-associated skin rash could successfully switch from nevirapine to efavirenz treatment.\(^{18}\) However, this report did not describe the details regarding a washout period before switching to efavirenz. In the study by Podzamczer and colleagues, the authors described two HIV-infected patients who were able to tolerate efavirenz after having developed a severe hypersensitivity reaction due to nevirapine.\(^{19}\)

The latest study was conducted in Thai patients.\(^{20}\) This retrospective cohort study was conducted in 122 HIV-infected patients diagnosed with nevirapine-associated rash and subsequently received efavirenz. All patients were followed-up for three months after receiving efavirenz. Possible risk factors were compared between those who had (group A) and did not have (group B) rash from efavirenz. Regarding preceding nevirapine-associated rash, 46 of the 122 (37.7\%) patients had developed skin rash of level III. Of these 46 patients, 8 (6.6\%) had developed nevirapine-associated Steven-Johnson syndrome. Of the 122 patients, 10 (8.2\%) developed rash from efavirenz and all needed efavirenz discontinuation. Baseline characteristics between group A (10 patients) and group B (112 patients) were similar. Median (IQR) time from nevirapine discontinuation to efavirenz initiation was 12 (9-21) days in group A and 11 (7-21) days in group B (p = 0.765). None of the possible risk factors investigated were associated with a subsequent development of efavirenz-associated skin rash. The overall incidence of efavirenz associated skin rash was 8.2 percent, and was relatively low when compared to a previous study conducted in Thai HIV-infected patients with higher CD4 cell counts who had no history of preceding nevirapine-associated skin rash.\(^{7}\) The high incidence of NNRTI-related skin rash has been reported in females with high CD4 cell counts.\(^{7,21}\) Although the majority of skin reactions from efavirenz in this study was erythematous rash and was classified mild, the attending physicians decided to discontinue efavirenz.

As described above, all of these data may support the safety of subsequent use of efavirenz and encourage the physicians to use efavirenz in HIV-infected patients with preceding nevirapine-associated skin rash. Efavirenz is more easily accessible than PIs in developing countries including Thailand. The application of a pharmacogenetic approach to antiretroviral drug therapy represents a significant challenge, such as drug-drug interactions and variability of drug metabolism within each individual. A better understanding of host genetic factors and adverse drug reactions would be helpful. To date, a pharmacogenomic study in this area is still lacking. The future clinical utility of pharmacogenomic testing in HIV management should be emphasized. In addition, a further study to determine immunologic and genetic factors associated with rash is needed.

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