
Sex Differences in Nevirapine Rash

SIR—Bersoff-Matcha et al. [1] reported the interesting finding that women are more likely than men to develop nevirapine rash. We made a similar clinical observation in an Asian population.

We started to administer nevirapine to our patients in January 1998. We followed the recommended administration method: a lead-in period of 2 weeks at a dosage of 200 mg nevirapine daily. Soon after, we noticed and reported a high incidence of nevirapine-associated rash in our HIV-infected Chinese patients [2]. We have since reviewed the case records of all patients who received nevirapine, using inclusion criteria similar to those used by Bersoff-Matcha et al. [1]. From January 1998 to January 2001, a total of 31 patients have received nevirapine-containing antiretroviral therapy. Two nucleoside analogue reverse transcriptase inhibitors (azidothymidine, didanosine, lamivudine, or stavudine) formed the backbone of the regimen for each patient.

Eleven patients (35.5%) developed rash; only 1 showed improvement when treated with antihistamine, and the therapy had to be discontinued for the other patients. The mean time (± SD) to onset of rash was short: 20.9 ± 7.0 days (range, 10–32 days). In addition to rash, many patients had accompanying symptoms or disease: fever or chills (8 patients), lip inflammation (3), oral mucosal ulcers (1), lower limb edema (3), and cholestatis hepatitis (1). Nevirapine was considered the culprit because the rash and associated reactions of all patients subsided completely after withdrawal of the drug. The toxicity did not recur when the concurrent antiretrovirals were reintroduced later.

A breakdown of the sex of our series of patients showed that rash developed in a much higher proportion of women than men (table 1). The difference was statistically significant for severe rash, with an OR of 1.5 (95% CI, 1–138.9) by Fisher’s exact test. The small number of patients might have contributed to the lack of statistical significance for the incidence of any rash and the incidence of rash that required withdrawal of therapy, but a trend was still observed for both parameters. Of the 8 women patients, 7 were Chinese, 5 of whom had nevirapine rash. The 1 other woman patient was a non-Chinese Asian who developed cholestatic hepatitis without rash 28 days after commencement of nevirapine therapy, which required discontinuation of the drug; the patient subsequently recovered. Of the men, 5 of the 19 Chinese patients and 1 of the 4 patients of European ethnicity developed rash. Both of the patients with severe rash were Chinese.

Bersoff-Matcha and colleagues suggested that nevirapine remains the non-nucleoside reverse transcription inhibitor of choice for women of reproductive age in whom conception may occur [1]. Administration of a single dose of nevirapine to mothers (at the onset of labor) and newborn infants was well tolerated and was effective in reducing mother–to–child transmission of HIV, with minimal chance of rash [3]. However, when nevirapine-containing antiretroviral regimens are administered starting in the sec-

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ond or third trimester of pregnancy, there is a remarkably high risk of toxicity.

Our study confirms that women are more prone than men to develop severe nevirapine rash. If the antiretroviral therapy is stopped, the impact on fetal health and mother-to-child transmission is of concern. Although all patients in our study recovered completely, we felt that treatment with nevirapine would best be avoided for Chinese women infected with HIV, especially those who are pregnant.

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References


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Reply

Str—We appreciate the comments of Wong et al. [1] regarding their experience with nevirapine rash in Chinese women. Their report adds to the growing body of literature in support of our observation that nevirapine rash occurs more frequently among women than among men [2]. Although it is curious that there was a very high incidence of rash among both men and women in their small cohort of patients, we take issue with their conclusion that nevirapine treatment should be altogether avoided for Chinese women.

There are limited choices for antiretroviral therapy for pregnant women because many drugs and/or drug combinations have proven to be hazardous to the mother, the fetus, or both. Efavirenz must be avoided during pregnancy because of concerns over teratogenicity [3]. Indinavir may lead to hyperbilirubinemia in the newborn infant [4]. Didanosine and stavudine should not be used in combination during pregnancy, unless there is no other option, because of the risk of severe lactic acidosis in the mother [3].

Treatment with most antiretroviral agents and antiretroviral combinations, however, has not been studied sufficiently in pregnant women to provide evidence regarding its safety and effectiveness. To date, only zidovudine [5] and nevirapine [6] therapy have been extensively studied in pregnant women, and both have been shown to be highly effective in reducing HIV transmission to the fetus, with minimal risk of toxicity. Removing nevirapine from the antiretroviral armamentarium for Chinese women will require treatment with a protease inhibitor (PI) not only during pregnancy, but also for any woman who does not use definitive contraception. Recognized side effects have been associated with PI therapy, including diabetes and hyperlipidemia, and although neither of these side effects has been associated with nevirapine, both may contribute to adverse outcomes for the mother and the infant.

We reported that the risk of severe rash (grade 3 or 4) was 9% for our female patients and 1% for our male patients; 13% of the women and 3% of the men needed to stop therapy because of rash [2]. While we did not find a difference in the incidence of rash that was associated with race or ethnicity, we had only a small number of Asian patients. Wong et al. [1] had a much larger percentage of patients with severe rash, even among the men. Since the pathophysiology of and risks for nevirapine rash remain unknown, larger and more focused studies are needed to elucidate exactly what factors contribute to nevirapine rash.

In addition to the risk of cutaneous reactions, nevirapine-induced hepatitis and related hepatic events are important to consider when selecting and maintaining an antiretroviral regimen. Die-trich et al. [7] recently reported that, among 2705 nevirapine-exposed patents, those with CD4 counts of <350 cells/mm³ had a 2.9% attributable risk for hepatitis and related hepatic events, compared with 8.1% among nevirapine-exposed patients with CD4 counts of >350 cells/mm³. An analysis by sex and by pregnancy status was not reported. Until other antiretroviral agents are found that are both effective and safe for pregnant women and their fetuses, we advocate the continued use of nevirapine for all populations, including pregnant women of all races and ethnicities.

Table 1. Occurrence of rash with or without associated symptoms for women and men receiving nevirapine.

<table>
<thead>
<tr>
<th>Variable</th>
<th>Women (n = 8)</th>
<th>Men (n = 23)</th>
<th>OR (95% CI)</th>
<th>P</th>
</tr>
</thead>
<tbody>
<tr>
<td>Symptom(s), no. (%) of patients</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Any rash</td>
<td>5 (62.5)</td>
<td>6 (26.1)</td>
<td>4.7 (0.6–38.2)</td>
<td>.095</td>
</tr>
<tr>
<td>Severe rash with accompanying symptoms or disease*</td>
<td>4 (50)</td>
<td>2 (8.7)</td>
<td>1.5 (1–138.9)</td>
<td>.026</td>
</tr>
<tr>
<td>Rash leading to cessation of nevirapine therapy</td>
<td>5 (62.5)</td>
<td>5 (21.7)</td>
<td>6.0 (0.8–50)</td>
<td>.074</td>
</tr>
<tr>
<td>Days to onset of rash, mean SD</td>
<td>19 ± 7.2</td>
<td>22.5 ± 7.2</td>
<td>—</td>
<td>.442</td>
</tr>
</tbody>
</table>

* Presence of fever and oral ulcers, lip inflammation, lower limb edema, or hepatitis; fever occurring alone was not counted.

Wong et al. [1] regarding their experience with nevirapine rash in Chinese women.