

## Research Letters

### Nevirapine-associated Stevens-Johnson syndrome

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Patients infected with human immunodeficiency virus-1 (HIV-1) are at increased risk of developing severe mucocutaneous drug reactions. Although numerous medications have been associated with Stevens-Johnson syndrome (SJS) and toxic epidermal necrolysis (TEN) in HIV-infected patients,<sup>1</sup> sulphonamide drugs are the most common cause, with a combined prevalence of 0.8%.<sup>2</sup> We report a patient infected with HIV-1 who developed SJS in association with nevirapine (Viramune, Boehringer-Ingelheim Pharmaceuticals, Ridgefield, Connecticut). We also describe an additional 19 cases of nevirapine-associated SJS and TEN that have been reported to the US Food and Drug Administration since nevirapine's approval in June, 1996.

A 31-year-old man who was seropositive for HIV-1 was admitted to hospital with a generalised skin eruption accompanied by painful oral and ocular erosions that began 10 days after starting zidovudine 300 mg twice daily, lamivudine 150 mg twice daily, and 200 mg nevirapine per day. He was taking no other medications and had no history of drug allergies. On admission his temperature was 39.2°C. He had tender oral ulcers and haemorrhagic crusts on his lips (figure). Ophthalmological examination showed limbic subconjunctival haemorrhages and acute conjunctivitis with associated photophobia; however, instillation of fluorescein showed no corneal erosions. There were tender, erythematous, target-like lesions on his trunk, with iris and target lesions on his palms and soles. The anogenital region was spared. Laboratory evaluation showed a CD4-cell count of 506/ $\mu$ L; a leucocyte count of  $4.3 \times 10^3$ / $\mu$ L with 6% eosinophils; packed cell volume of 49%, and platelets of  $272 \times 10^3$ / $\mu$ L. Urinalysis and serum chemistries were normal. Rapid plasma reagin test for syphilis was negative. Multiple viral cultures and direct immunofluorescence tests with an antibody marker for herpes simplex virus and cytomegalovirus from labial erosions were negative. Blood and urine cultures were negative. His chest radiograph was normal. Nevirapine, zidovudine, and lamivudine were discontinued and supportive care with intravenous hydration, parenteral nutrition, antihistamines, and analgesics was started. After 2 days in hospital, his lesions began to improve. After 12 days he was discharged home.



Patient's lips

Rechallenge with zidovudine, lamivudine, or nevirapine was not done. He has had no recurrence of lesions in more than 6 months of follow-up.

Identification of a single antiretroviral drug as the cause of a drug eruption in a patient infected with HIV-1 is often difficult because antiretroviral drugs are rarely used as monotherapy. Although our patient was not rechallenged with nevirapine, we believe that nevirapine was responsible for his SJS. Severe cutaneous hypersensitivity reactions to zidovudine are rare;<sup>1</sup> despite zidovudine's widespread use since its approval as the first antiretroviral drug in 1987, there is only one published report of zidovudine-induced TEN.<sup>3</sup> Similarly, there were no cases of SJS or TEN in more than 900 patients who received lamivudine in premarketing clinical trials (Rubin M, Glaxo Pharmaceuticals, personal communication), and we are unaware of any published reports of lamivudine-induced SJS or TEN since its introduction in 1995. Since the introduction of nevirapine in the USA in June, 1996, 20 cases of nevirapine-associated drug eruptions requiring hospital admission have been reported to the Food and Drug Administration. At least three deaths have occurred.

The major clinical toxicity of nevirapine is a rash, which has been reported in between 32% and 48% of patients.<sup>3,4</sup> Of 245 patients who received nevirapine in published clinical trials, about 8% developed severe rashes and 1% developed SJS.<sup>4,5</sup> Rashes were often accompanied by fever, usually began within 2 to 4 weeks after starting treatment, and typically resolved after stopping the drug. There was no difference in incidence of severe, life-threatening eruptions between patients initiated on a single 400 mg daily dose and patients who received a 2-week lead-in dose of 200 mg per day followed by 200 mg twice a day thereafter.<sup>5</sup>

The risk of severe mucocutaneous adverse reactions associated with nevirapine in HIV-1-infected people appears to be among the highest reported for any drug. Although use of a 2-week lead-in dose of 200 mg per day followed by 200 mg twice a day may reduce the overall risk of rash (information from Roxane Laboratories), with the increasing use of nevirapine the incidence of SJS among patients infected with the HIV-1 virus is likely to increase.

- 1 Bayard PJ, Berger TG, Jacobsen MA. Drug hypersensitivity reactions and human immunodeficiency virus disease. *J Acquir Immune Defic Syndr* 1992; 5: 237-57.
- 2 Caumes E, Saiag P, Picard C, et al. Sulfonamide-induced toxic epidermal necrolysis (TEN) and Stevens-Johnson syndrome (SJS) in AIDS patients: 12 cases. Presented at 1988 Fourth International Conference on AIDS, Stockholm, Sweden, June 15-16, 1988.
- 3 Murri R, Antinori A, Camilli G, Zannoni G, Patriarca G. Fatal toxic epidermolysis induced by zidovudine. *Clin Infect Dis* 1995; 23: 640-41.
- 4 Carr A, Vella S, DeJohn MD, et al. A controlled trial of nevirapine plus zidovudine versus zidovudine alone in p24 antigenaemic HIV-infected patients. *AIDS* 1996; 10: 635-41.
- 5 D'Aquila RT, Hughes MD, Johnson VA, et al. Nevirapine, zidovudine and didanosine compared with zidovudine and didanosine in patients with HIV-1 infection: randomized, double-blind, placebo-controlled trial. *Ann Intern Med* 1996; 124: 1019-30.

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