

Nevirapine-induced cutaneous hypersensitivity reactions and successful tolerance induction

Pascal Demoly, MD, PhD,^a Djamel Messaad, MD,^a Jacqueline Fabre, MD,^b Jacques Reynes, MD,^b and Jean Bousquet, MD, PhD^a Montpellier, France

HIV-infected patients frequently have hypersensitivity reactions (HS) to drugs, sometimes dramatically hampering management.¹ Reverse transcriptase inhibitors (RTIs) are critical drugs in combination therapy for these patients, and nevirapine (Viramune) was the first nonnucleoside RTI introduced for clinical use.² More than one third of the patients exposed to nevirapine have HS reactions that may lead to drug discontinuation.³ However, tolerance induction has not yet been reported. We describe 3 cases of cutaneous HS reactions induced by nevirapine, with 2 successful tolerance inductions.

REPORT OF CASES

Patient hypersensitivity reactions and skin testing

Three HIV-infected patients (2 women of 30 and 35 years and one 44 year-old man) were treated with nevirapine 200 to 400 mg daily. They were also treated for more than 6 months with other antiretroviral agents and were not taking any other drugs, including sulfonamides (Table 1). The patients had no personal history of atopic diseases and no history of HS reactions to any drug. Four to 30 days after starting nevirapine, a generalized cutaneous maculopapular eruption or urticaria, together with high fever or conjunctivitis and myalgia, developed. Nevirapine was withdrawn and antihistamines were started, which led to the disappearance of the cutaneous reaction within 4 days. Patient 2 also took 40 mg of prednisolone for 3 days. No test challenge was attempted. Skin test results (with one 200 mg tablet of nevirapine crushed and resuspended in 1 mL of normal saline solution) were negative.

Tolerance induction procedure

Tolerance induction was started 1 to 2 months after nevirapine was stopped. Twelve doses were prepared from a crushed 200-mg tablet of nevirapine (2.5, 10, 25, 100, 250, and 750 µg and 2.5, 5, 10, 25, 50, and 100 mg) and given orally at half-hour intervals under

Abbreviations used

HS: Hypersensitivity reactions
RTI: Reverse transcriptase inhibitor

strict surveillance. Patients 1 and 3 both had a mild, transient rash with pruritus on the same day (late evening) that disappeared completely with one 180-mg tablet of fexofenadine. After a follow-up period of 4 months, patients 1 and 2 are still taking nevirapine without any adverse reaction. Patient 2 had a generalized maculopapular eruption with fever after ingesting the fifth dose. Prednisolone and fexofenadine were prescribed and the graded challenge was restarted the following day with 100 µg of nevirapine. We could not increase the dose to more than 10 mg because of subsequent cutaneous reactions that resisted both prednisolone and antihistamine treatment; graded challenge was stopped the fourth day.

COMMENTS

More drugs are available to treat HIV disease and it is now recognized that these drugs are best used in combinations of at least 3 antiretroviral agents. Nevirapine has a different mechanism of action from that of nucleoside analogs and protease inhibitors: it has a widespread tissue penetration including the central nervous system. Also, there is no cross-resistance and no overlapping side effects. Thus nevirapine has become a crucial drug for HIV treatment. The most common adverse reactions after nevirapine treatment include cutaneous reactions and to a lesser extent elevated liver enzyme concentrations.² Patients are at greatest risk for a rash during the first 30 days of nevirapine exposure. Although the majority of rashes are mild to moderate, 6% are severe enough that the patients discontinue the drug permanently. Toxic epidermal necrolysis and Stevens-Johnson syndrome also occurred rarely,³ and a warning from the Food and Drug Administration is enclosed in the approved product insert. HS cutaneous reactions to other RTIs are half as frequent.² Nevirapine is primarily metabolized by cytochrome P450 CYP3A in the liver.² Whether this pathway could be involved in HS reactions, as they are for sulfonamides,¹ is unknown. The rashes that our patients had after tolerance induction, except for patient 2, were far mild and lasted for a shorter period of time than the original adverse reactions, strongly suggesting that simply continuing nevirapine with the addition of antihistamines, if patients are seen immediately, cannot be recommended. The culprit drug should rather be

From the Department of Maladies Respiratoires, Institut National de la Santé et de la Recherche Médicale U454-IFR3, Hôpital Arnaud de Villeneuve, and Centre Hospitalier Universitaire,^a and the Department of Maladies Infectieuses et Tropicales, Hôpital Guy de Chauliac, Centre Hospitalier Universitaire,^b Montpellier, France.

Received for publication Feb 12, 1999; revised Apr 29, 1999; accepted for publication Apr 29, 1999.

Reprint requests: Pascal Demoly, MD, PhD, Maladies Respiratoires, INSERM U454, Hôpital Arnaud de Villeneuve, Centre Hospitalier Universitaire, 34295 Montpellier Cedex 5, France.

J Allergy Clin Immunol 1999;104:504-5.

Copyright © 1999 by Mosby, Inc.

0091-6749/99 \$8.00 + 0 1/54/99647

TABLE I. Patient characteristics

Patients	Sex	Age (y)	CDC stage	Treatment	CD4+ count*	Viral load (copies/mL)	Hypersensitivity reaction	
							Time delay (d)	Symptoms
1	Female	30	B2	NVP ₂₀₀ , AZT ₆₀₀ , 3TC ₃₀₀	200	2400	10	MPE, F
2	Female	35	A1	NVP ₂₀₀ , AZT ₆₀₀ , ddC _{2,25}	626	Undetectable	4	Ur, M, F
3	Male	44	A2	NVP ₄₀₀ , ddI ₃₀₀ , 3TC ₃₀₀	487	2500	30	MPE, C

Superscript numbers indicate daily doses. CDC, Centers for Disease Control and Prevention; NVP, nevirapine; AZT, zidovudine; 3TC, lamivudine; MPE, maculopapular eruption; F, high fever; ddC, zalcitabine; Ur, urticaria; M, myalgia; ddI, didanosine; C, conjunctivitis.

*Per cubic millimeter at time of tolerance induction.

stopped and tolerance induction planed 1 to a few months later. Because glucocorticoids also induce CYP3A,⁴ they may have induced the metabolism of nevirapine in patient 2, leading to enhanced production of nevirapine-reactive metabolites and to recurrent eruptions and failure of tolerance induction. Whether the different clinical presentation of patient 2 (urticaria), as opposed to a history of maculopapular eruption in the other 2 patients might have influenced the outcome of the tolerance induction is also unknown.

Thus tolerance induction to nevirapine can help some HIV patients who are noncompliant or resistant to other antiretroviral agents and hypersensitive to this drug tolerate and carry on nevirapine treatment. Moreover, an

oral suspension form of nevirapine is now available, which will allow easier protocols.

REFERENCES

1. Carr A, Cooper DA, Penny R. Allergic manifestations of human immunodeficiency virus infection. *J Clin Immunol* 1991;11:52-64.
2. Harris M, Montaner JSG. Nevirapine. *HIV AIDS Curr Trends* 1997;3:6-8.
3. Warren KJ, Boxwell DE, Kim NY, Drolet BA. Nevirapine-associated Stevens Johnson syndrome. *Lancet* 1998;351:567.
4. Schuetz J, Schuetz E, Thottassery J, Guzelian P, Strom S, Sun D. Identification of a novel dexamethasone responsive enhancer in the human CYP3A5 gene and its activation in human and rat liver cells. *Mol Pharmacol* 1996;49:63-72.