

Long-term safety and efficacy of nevirapine tolerance induction

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Summary

Background The most frequent side-effects due to nevirapine (Viramune®), the first non-nucleoside HIV reverse transcriptase inhibitor introduced for clinical use, are cutaneous hypersensitivity reactions. In non-serious cases, tolerance induction can be proposed.

Objective Describe the long-term safety and efficacy of tolerance induction to nevirapine.

Methods Six HIV-infected patients started a tolerance 1 to 2 months after an episode of nevirapine hypersensitivity. Increasing doses of nevirapine (2.5, 10, 25, 100, 250 and 750 µg and 2.5, 5, 10, 25, 50 and 100 mg) were given orally at half-hour intervals under strict medical surveillance and patients were followed up regularly.

Results All but two of the patients tolerated this induction well. One had a mild and transient reaction on day 1; nevirapine was not stopped. One had a moderate to severe reaction one month later; nevirapine was stopped and he recovered fully. All other patients have been taking nevirapine for more than 3 months without any adverse reaction.

Conclusion Therefore, when no alternatives are available in severely ill and hypersensitive HIV-infected patients, tolerance induction is a possible therapeutic option.

Keywords drug hypersensitivity, nevirapine, tolerance induction

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Introduction

Reverse transcriptase inhibitors (RTIs) are critical drugs in combination therapy for HIV-infected patients, and nevirapine (Viramune®) was the first non-nucleoside RTI introduced for clinical use [1], available in the USA since 1996 and in Europe since 1998. The first 2 months of treatment is critical for the occurrence of cutaneous and hepatic toxicities. Anti-HIV drugs are often responsible for allergic reactions, mainly cutaneous reactions, which are sometimes very severe. Among these drugs, nevirapine is responsible for 'rashes' of any severity in 35% of the treatments (350 patients treated in one meta-analysis vs. 19% in 308 controls) [2]. In rare cases, these cutaneous reactions can be serious, including drug hypersensitivity syndrome or DRESS [3], toxic epidermal necrolysis and Stevens–Johnson syndrome [4]. Very often, fear of these reactions leads to the cessation of this treatment and it has to be changed to another antiretroviral agent.

In a first paper [5] we described three cases of nevirapine-induced cutaneous hypersensitivity reactions with two successful tolerance inductions. We now describe six new cases, with five successful tolerance inductions, and can give the long-term results on efficacy and safety of these cases.

Report of cases

Patient hypersensitivity reactions and skin testing

Six HIV-infected patients (four women and two men, aged from 39 to 66 years) were treated with nevirapine 200 to 400 mg daily. They were also treated for more than 6 months with other antiretroviral agents but were not taking any other drugs, including sulphonamides (Table 1). The patients had no personal history of atopic diseases and no history of hypersensitivity reactions to any drug. Ten to 26 days after starting nevirapine, a generalized cutaneous maculopapular eruption or erythrodermia occurred, associated with high fever (39.5 °C) in two patients, and localized angio-oedema (to the lips) or general malaise in two patients. Liver enzymes remained normal in all patients. Nevirapine was withdrawn and antihistamines were started, which led to the disappearance of the cutaneous reactions within 5 days. Patients 1 and 2 also took 40 mg of prednisolone for 3 days. Other anti-HIV treatments were maintained. No test challenge was attempted. Skin prick tests (through one drop of the 50 mg/5 mL drinkable suspension of nevirapine) were negative in all patients.

Tolerance induction procedure and follow-up

Tolerance induction was started 1 to 2 months after nevirapine was stopped. No pre-medication was administered. Twelve doses were prepared from the 50 mg/5 mL drinkable suspension 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

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Table 1. Patient characteristics and description of hypersensitivity reaction

Patients	Sex	(yr)	CDC stage	Treatment*	CD4 ⁺ count†	Viral load (copies/mL)	Onset‡ (day)	Symptoms§
1	M	40	A2	NVP ₄₀₀ , 3TC ₃₀₀ , AZT ₆₀₀	335	Undetectable	26	MPE, F, Oed
2	F	44	A2	NVP ₂₀₀ , 3TC ₃₀₀ , AZT ₆₀₀	401	36303	14	MPE
3	M	51	A2	NVP ₂₀₀ , d4T ₆₀ , Saquinavir ₁₈₀₀ , Nelfinavir ₂₅₀₀	409	3500	13	MPE
4	F	66	A2	NVP ₄₀₀ , d4T ₆₀ , 3TC ₃₀₀	267	629	13	MPE
5	F	52	B2	NVP ₂₀₀ , 3TC ₃₀₀ , Abacavir ₆₀₀	350	1000	12	E, F, M
6	F	42	A1	NVP ₂₀₀ , 3TC ₃₀₀ , AZT ₆₀₀	905	300	10	MPE

*NVP = nevirapine; 3TC = lamivudine; AZT = zidovudine; d4T = stavudine; subscript doses are in mg daily. †Per cubic millimetre at time of tolerance induction. ‡Time elapsed from the start of the treatment and the beginning of the hypersensitivity reaction. §MPE = maculopapular eruption; F = high fever; Oed = angio-oedema; E = erythrodermia; M = malaise.

under strict medical surveillance. Total duration of the tolerance induction was 5.5 h.

All patients but one tolerated this induction well on the first day. Patient 6 had a mild, transient maculopapular eruption with pruritus and chills without fever on the same day (late evening) that disappeared completely with one 10 mg tablet of cetirizine. Nevirapine was not stopped. All patients but one tolerated this induction well for the first month. Patient 3 presented 1 month later with vomiting and sickness associated with a moderate hepatic cytolysis (liver transaminases increased up to around 200 U/mL). Nevirapine was stopped and he recovered fully. Patients 2 and 4 took the nevirapine, respectively, during 3 and 7 months without any sign of drug allergy, and then the treatment was stopped because of an increase of their viral load. Patients 1, 5 and 6 have been taking nevirapine without any adverse reaction, respectively, for 16, 8 and 9 months.

Discussion

The therapeutic options for HIV disease include several drugs. It is now recognized that these drugs are more effective in a combination of at least three of them. Nevirapine was the first non-nucleoside reverse transcriptase inhibitor (RTI) to be introduced for clinical use anywhere in the world. It has a rapid and potent anti-HIV activity [6]. Nevirapine has a different mechanism of action from that of nucleoside analogues and protease inhibitors. It inhibits selectively, according to a non-competitive mechanism, the reverse transcriptase of HIV1, but not that of HIV2 [6]. It has a widespread tissue penetration including the central nervous system. Also there is no cross-resistance and no cross-reactivity with nucleoside RTIs. It can be administered with nucleoside RTIs and/or protease inhibitors. Therefore, nevirapine has become an important 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]. The majority of the cutaneous reactions arise during the first 30 days of therapy and are mild to moderate, but 6% to 7% of patients permanently discontinue the drug. Toxic epidermal necrolysis and Stevens Johnson syndrome may also occur rarely [4], and a warning (from the Food and Drug Administration) is enclosed in the approved product inset. Moreover, a continuous

pharmacovigilant surveillance system is running. Stopping the drug is mandatory for serious reactions, including skin blistering, and large mucosal and organ involvements. However, milder reactions also frequently lead to the cessation of the drug, although these hypersensitivity reactions are frequent in HIV-infected patients [7]. The withdrawal of a major drug may also be deleterious for the treatment of HIV infection. Therefore, tolerance inductions have been tried successfully in these patients.

Tolerance induction is a way of forcing the tolerance of a drug in hypersensitive patients. Although very controversial in non-IgE-dependent reactions, it is a possible therapeutic option when no alternatives are available in severely ill patients. The cutaneous eruptions sometimes observed during this reaction are most of the time mild [8] but could be serious [9]. The first few weeks after induction appear to be crucial (for the recurrence of hypersensitivity reactions) and no further reactions have been observed after 1 month in our expertise of more than 100 tolerance inductions in HIV-infected patients hypersensitive to cotrimoxazole [8], nevirapine [5] and nelfinavir [10]. Considering the above, we now suggest that during a non-serious cutaneous reaction resembling a drug hypersensitivity and resistant to a few days of an anti-allergic treatment, the suspected culprit drug should be stopped and tolerance induction planned as early as 1 month later, if no satisfactory alternative drugs exist.

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