

## Rapid Communications

# Failure of a Short-Term Prednisone Regimen to Prevent Nevirapine-Associated Rash: A Double-Blind Placebo-Controlled Trial: The GESIDA 09/99 Study

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**Objectives:** Rash is the most frequent adverse event associated with nevirapine. The use of prednisone has been controversial in this setting. A double-blind placebo-controlled study was performed to evaluate its efficacy in nevirapine-induced rash prevention.

**Design:** Multicentered, randomized, double-blind, placebo-controlled clinical trial with prednisone (30 mg/day × 2 weeks). Inclusion criteria: HIV-1 infection; CD4 count >200 cells/mm<sup>3</sup>; plasma viral load (PVL) <5 log<sub>10</sub> copies/ml; nevirapine (200 mg/day × 2 weeks, followed by 200 mg twice daily) plus stavudine and didanosine. Clinical follow-up was performed at 15, 30, and 60 days and thereafter every 2 months.

**Results:** In all, 75 evaluable patients were enrolled (39 prednisone/36 placebo). Median baseline CD4<sup>+</sup> cell count was 390 cells/mm<sup>3</sup> and PVL, 20,200 copies/ml. Overall, nine cases of rash (12.5%) were detected, seven (18%) in the prednisone group and two (5.5%) in the placebo group (odds ratio [OR], 3.85; 95% confidence interval [CI], 0.65–29.3; *p* = .11). Incidence of moderate-to-severe rashes leading to nevirapine withdrawal was 13.5% (5 of 37) in the prednisone group and 3% (1 of 35) in the placebo group (*p* = .2). Median time to rash in both groups was 16 days. Adverse events that motivated withdrawal of therapy appeared in 6 patients from the prednisone group (15.4%) and 3 from the placebo group (8.3%) (*p* = .3).

**Conclusion:** Short-term prednisone administration does not prevent nevirapine rash, but might even increase its incidence.

**Key Words:** Nevirapine—Prednisone—Exanthema—Adverse drug reaction—Randomized trial—Double-blind method.

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Presented in part at the 40th Interscience Conference on Antimicrobial Agents and Chemotherapy (ICAAC), American Society for Microbiology, Toronto, Ontario, Canada, September 17–20, 2000 [Late breaker abstract L-15].

Manuscript received May 5, 2001; accepted June 28, 2001.

Nevirapine (NVP) is widely used for the treatment of HIV infection and its efficacy has been proved in several clinical trials (1,2). Initial trials found a 48% incidence of rash in patients receiving 400 mg daily (3,4). As NVP metabolism is self-induced, the current recommendation is to start with half dose for the first 2 weeks, and increase to full dose thereafter. However, despite this strat-

egy, rash continues to be the most frequent adverse event in HIV-1-infected patients who are receiving NVP. The incidence reported in different studies varies between 9% and 32% and is severe in 7% of patients (5). In fact, this is the leading cause of withdrawal from NVP therapy.

Drug hypersensitivity in HIV-infected patients is about 100 times more common than in the general population (6). Although its pathogenesis is unknown, suggested mechanisms include the degree of immunodeficiency or immune activation, the longer duration and higher doses of therapy, altered drug metabolism, and coexisting infections; several cytokines are probably involved (7). NVP can sometimes cause hepatotoxicity as part of a hypersensitivity reaction and, when compared with findings in controls, liver function abnormalities occur at a 7% excess among NVP recipients. Nevertheless, clinically significant liver function abnormalities with NVP and their association with hepatitis coinfection remain controversial issues (8,9).

Corticosteroid therapy has been tried so as to prevent this hypersensitivity reaction. The results of two observational studies and two open-label, randomized studies have shown contradictory results (10–13). Given that results from these studies are not clear, we designed a randomized, double-blind, placebo-controlled clinical trial to observe whether prednisone could prevent rash in HIV-1-infected patients receiving NVP.

**METHODS**

Multicenter, randomized, double-blind, placebo-controlled clinical trial. Inclusion criteria were adult patients with confirmed HIV-1 infection; CD4 cell count >200 cells/mm<sup>3</sup>; plasma viral load <5 log<sub>10</sub>/ml; and informed signed consent. All patients had to be naive to the three antiretroviral drugs in the study. Exclusion criteria included absolute neutrophil count < 1.0 × 10<sup>9</sup>/L; platelet count < 0.5 × 10<sup>12</sup>/L; hemoglobin level lower than 90 g/L; transaminase levels >3 times the upper limit of the normal range; diabetes mellitus, severe hypertension, and peptic ulcer disease. The treatment schedule was: prednisone (30 mg/d, 1 capsule for 15 days) or placebo (1 capsule for 15 days) combined with NVP (initial dose of 200 mg/d po for 14 days followed by 200 mg bid po) plus stavudine and didanosine (40/200 mg orally every 12 hours if weight ≥60 kg or 30/150 mg orally every 12 hours if weight <60 kg). Randomisation was performed at the coordinating center by center in blocks of 2 patients using a computer-generated sequence. Blinding with identical prednisone and placebo was used to maintain the double-blind nature of the trial. Blind codes were kept at the study site pharmacy and blinding was not broken during the study. The institutional review boards of the participating centers approved the protocol and the informed consent. Clinical follow-up was performed at baseline and at 15, 30, and 60 days and thereafter every 8 weeks until week 24.

**Study Definitions**

The primary outcome of interest was the occurrence of rash. All cutaneous eruptions were recorded. The following grading scheme was

used: grade I: erythema with(out) pruritus; grade II: a diffuse erythematous macular or maculopapular cutaneous eruption or dry desquamation with(out) pruritus or typical target lesions without blistering, vesicles, or ulcerations in the lesions; grade II B: urticaria; grade III: diffuse erythematous macular or maculopapular cutaneous eruption or moist desquamation with(out) pruritus together with any of the four physiologic findings possibly related to the drug (twofold increase above baseline alanine aminotransferase or aspartate aminotransferase; fever; blistering, vesiculation, or both of cutaneous eruptions; or any site of mucosal lesions); angioedema; exfoliative dermatitis; or diffuse rash and serum sickness-like reactions (fever, lymphadenopathy, edema, myalgia, arthralgia); diffuse cutaneous eruptions plus one of the following: cutaneous bullae with widespread sheet-like detachment of skin, Stevens-Johnson syndrome, two or more anatomically distinct sites of mucosal erosion or ulceration; and grade IV: toxic epidermal necrolysis. Depending on the level of transaminase increase, hepatotoxicity was defined as mild-to-moderate (<5 × baseline levels) or severe (≥5 × baseline levels).

**Statistics**

To calculate the sample size, we assumed that 20% of patients on NVP would develop a skin rash during the first 6 months of therapy, and that this figure would be less than 2% in the group that received prednisone. To test this hypothesis, we estimated that at least 35 evaluable patients at risk would be needed in each arm to detect a difference of 18%, if it existed, with 90% certainty and a 5% significance level. Ten percent of patients were expected to be lost for follow-up. The enrollment period for this study closed on April 30th, 2000.

The primary endpoint of the study was the effect of prednisone on the development of rash. Analysis was completed on an intent-to-treat basis. All patients with observations after initiation of the study were included. We assessed differences in proportions using the Fisher exact test.

**RESULTS**

Of the 78 patients enrolled, 3 failed to attend the first evaluation visit and were excluded from all analysis. Of the 75 evaluable patients, 39 received prednisone, and 36 received placebo. Baseline characteristics in both groups are shown in Table 1. Two patients were lost for follow-up, 1 in each group.

A summary of results is shown in Table 2. Nine rashes (12%) were detected, 8 in men (12.7%), 1 in a woman (8.3%); 7 in the prednisone group (17.9%) and 2 (5.6%) in the placebo group (*p* = .15; odds ratio [OR], 3.85; 95% confidence interval [CI], 0.65–29.3). Six patients (8%) withdrew from NVP therapy because of moderate or severe rashes, 5 in the prednisone group (12.8%) and 1 in the placebo group (2.8%) (*p* = .19). The median time to rash in both groups was 16 days (range 11–39) (Fig. 1). Total adverse events which motivated withdrawal of therapy appeared in 9 patients (12%); 6 in the prednisone group (15.4%) and 3 in the placebo group (8.3%). The incidence of hepatotoxicity was 7 cases

**TABLE 1.** Baseline characteristics. HIV-1-infected patients treated with nevirapine combined with stavudine and didanosine

|                                       | Prednisone<br>39 patients | Placebo<br>36 patients | <i>p</i><br>value |
|---------------------------------------|---------------------------|------------------------|-------------------|
| Male, <i>n</i> (%)                    | 32 (82.1)                 | 31 (86.1)              | .51               |
| Age, yr, mean (SD)                    | 36 (9.1)                  | 35.4 (6.4)             | .85               |
| IDU (%)                               | 20 (51.3)                 | 15 (41.7)              | .5                |
| Disease stage, <i>n</i> (%)           |                           |                        |                   |
| Group A                               | 23 (58.9)                 | 24 (66.6)              | .52               |
| Naive to treatment, <i>n</i> (%)      | 24 (61.5)                 | 19 (52.8)              | .45               |
| CD4 cell count, cells/mm <sup>3</sup> |                           |                        |                   |
| Mean (SD)                             | 413.7 (267)               | 408.8 (269)            | .9                |
| Median (percentile 25–75)             | 425 (241–482)             | 378 (219–497)          |                   |
| HIV-1 RNA, copies/ml                  |                           |                        |                   |
| Mean (SD)                             | 65,415 (21,588)           | 56,999 (23,689)        | .8                |
| Median (percentile 25–75)             | 27,621 (6,950–88,700)     | 11,050 (546–53,500)    |                   |

SD, standard deviation; IDU, injecting drug user.

(9.3%), 5 (12.8%) in the prednisone group, 2 (5.6%) in the placebo group.

The virologic and immunologic outcome at 6 months was: 26 (66.6%) patients in the prednisone group and 23 (63.6%) in the placebo group reached undetectable plasma viral load (<200 RNA HIV-1 copies/ml) ( $p = 0.9$ ); the median (range) increment of CD4 cell count was of 84 cells/mm<sup>3</sup> (range, 12–283) in the prednisone group and 154 cells/mm<sup>3</sup> (range, 25–298) in the placebo group ( $p = .09$ ).

## DISCUSSION

Several studies on the prevention of NVP-induced rash using corticosteroids have been developed. In one observational study, prednisone reduced the incidence of NVP-induced rash from 14% to 1.2% when given during

the 14-day induction phase (10). The results of the other observational study were in sharp contrast, reporting an incidence of 30% of NVP-induced rash in patients treated with prednisolone versus 9.5% in those without (11). Concerning the two open-label, randomized studies, Barreiro et al. (12) reported that a slower escalation of NVP dose with prednisone decreases the incidence of NVP-induced rash from 18.7% in the standard lead-in regimen to 7.7% in the slower escalating prednisone regimen. However, methodologic problems make results difficult to interpret, because the same patients are included in observational and randomized studies and in different arms in the randomized studies (13,14). Using a similar prednisone regimen, Montaner et al. (15) found a higher incidence of NVP-induced rash in the prednisone group than in the placebo group (36% vs. 18%,  $p < .05$ ).

From a practical point of view, the main conclusion of this clinical trial is that short-term prednisone administration does not prevent NVP-induced rash and may even increase its incidence. This is the first double-blind, placebo-controlled clinical trial designed to analyze whether prednisone could prevent rash in HIV-1-infected patients receiving NVP. This study design is the only way to control potential confounding variables that make it difficult to interpret the contradictory results of observational and some open randomized studies. Although our results show a clear trend with clinical relevance (17.9% vs. 5.6%,  $p = .15$ ), this clinical trial cannot demonstrate that prednisone increases rash incidence. This is because we assumed prednisone superiority over placebo and the sample size was calculated for unilateral tests. Conversely, the incidence of NVP-induced rash may be reduced using a higher dose or by prolonging exposure to prednisone. However, in our study, most rashes (5 of 7, 71%) in the prednisone group appeared during the first 2

**TABLE 2.** Adverse events judged by the investigators to be at least possibly related to drugs involved in the study

|                                      | Prednisone<br>39 patients | Placebo<br>36 patients | <i>p</i><br>value |
|--------------------------------------|---------------------------|------------------------|-------------------|
| Rash, <i>n</i> (%)                   |                           |                        |                   |
| Grade I                              | 1 (2.6)                   | 1 (2.8)                | —                 |
| Grade II A                           | 1 (2.6)                   | —                      | —                 |
| Grade II B                           | 3 (7.7)                   | 1 (2.8)                | —                 |
| Grade III                            | 2 (5.1)                   | —                      | —                 |
| Rash total                           | 7 (17.9)                  | 2 (5.6)                | .15               |
| Rash moderate–severe <sup>a</sup>    | 5 (12.8)                  | 1 (2.7)                | .2                |
| Hepatotoxicity total, <i>n</i> (%)   | 5 (12.8)                  | 2 (5.6)                | .4                |
| Mild–moderate                        | 3 (7.7)                   | 1 (2.8)                | —                 |
| Severe                               | 2 (5.1)                   | 1 (2.8)                | —                 |
| Constitutional symptoms <sup>b</sup> | 1 (2.6)                   | 4 (11.1)               | .18               |
| Gastrointestinal <sup>c</sup>        | 3 (7.7)                   | 4 (11.1)               | .7                |
| Any adverse event                    | 27 (73)                   | 25 (71)                | .9                |
| Withdrawal from therapy              | 6 (16)                    | 3 (9)                  | .6                |

<sup>a</sup> Rash grades IIB, III and IV.

<sup>b</sup> Fever, arthralgia, and myalgia.

<sup>c</sup> Nausea, vomiting, abdominal pain, and diarrhea.

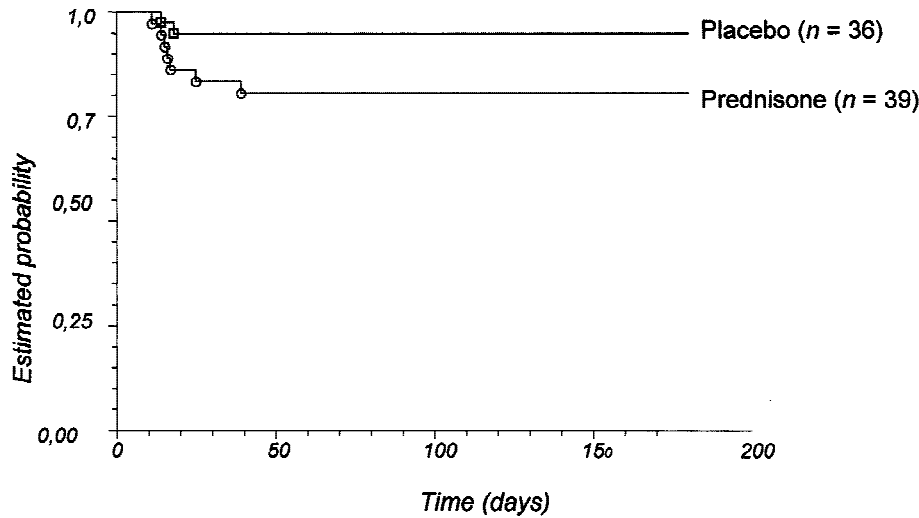


FIG. 1. Time to onset of rash by treatment group.

|            |    |    |    |    |    |
|------------|----|----|----|----|----|
| Placebo    | 36 | 36 | 35 | 35 | 35 |
| Prednisone | 39 | 37 | 36 | 36 | 36 |

weeks. In a recent retrospective study, Bersoff-Matcha et al. (16) found that women had up to a sevenfold higher risk of developing severe rash. Although the small number of patients recruited in our study sheds no light on this point, the proportion of women was similar in both groups (placebo and prednisone). Prednisone did not prevent liver toxicity, the total incidence of which was 9.3% (12.8% in the prednisone group and 5.5% in the placebo group,  $p =$  nonsignificant). The difference with respect to other studies, besides the double-blind design, is that ours had strict inclusion criteria with high homogeneity among patients with the same virologic and immunologic status and the same exposure to drugs. This adds strength to the validity of our results.

In conclusion, prednisone at the dosage and duration used in this study is ineffective in the prevention of NVP-induced rash. Given the potential harmful effect of prednisone in this setting, NVP has to be used with caution in HIV-1-infected patients who need corticosteroid therapy for other reasons.

### APPENDIX

Members of the GESIDA 09/99 Study Group: H. Knobel, A. González, and A. Guelar (Hospital del Mar, Barcelona); J. M. Miró, J. L. Blanco, E. Martínez, and J. M. Gatell (Hospital Clinic i Provincial, Barcelona); P. Domingo, J. M. Guardiola, M. A. Sanbeat, G. Gurgui, J. L. Barrio, and M. Fuster (Hospital San Pau, Barcelona); A. Rivero, J. M. Kindelán, J. Torre-Cisneros, R. Jurado, and E. Vidal (Hospital Reina Sofía, Córdoba); M. Márquez, J. Santos, and J. Ruiz (Hospital Virgen de la Victoria, Málaga); P. Barrufet and L. Force (Hospital de Mataró, Mataró), J. Sanz and J. De Miguel (Hospital Príncipe de Asturias, Madrid); V. Boix, E. Merino, and J. Portilla (Hospital General

de Alicante, Alicante); J. Locutura, J. F. Lorenzo, and C. Dueñas (Hospital General Yagüe, Burgos); D. Dalmau and X. Martínez Lacasa (Hospital Mutua de Terrasa, Barcelona); M. Cervantes, B. Font, and C. Frías (Hospital Parc Taulí, Sabadell); and V. De Miguel (Agencia de Ensayos Clínicos GESIDA/SEIMC, Madrid).

**Acknowledgments:** Supported by the Grupo de Estudio del Sida de la Sociedad Española de Enfermedades Infecciosas y Microbiología Clínica (GESIDA/SEIMC), by the National AIDS Plan Secretariat of The Spanish Ministry of Health and by Boehringer Ingelheim Laboratories.

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