Delavirdine in Combination with Zidovudine in Treatment of Human Immunodeficiency Virus Type 1-Infected Patients: Evaluation of Efficacy and Emergence of Viral Resistance in a Randomized, Comparative Phase III Trial

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We compared the activity of delavirdine (DLV) plus zidovudine (AZT) (n = 300) with that of AZT (n = 297) against human immunodeficiency virus type 1 in a randomized, double-blind, placebo-controlled trial. DLV exerted a transient antiviral effect, and mutations for resistance to DLV were found in more than 90% of subjects at week 12. The K103N mutation, which confers nonnucleoside reverse transcriptase inhibitor cross-resistance, was found in 85% of the patients.

Delavirdine (DLV) is a bisheteroarylpiperazine and is one of the nonnucleoside reverse transcriptase inhibitors (NNRTIs). Protocol M/3331/0013B was a large multicenter, double-blind, placebo-controlled trial in which DLV plus zidovudine (AZT) therapy was compared with DLV placebo plus AZT therapy in patients with symptomatic human immunodeficiency virus (HIV) type 1 (HIV-1) infection and CD4 counts of <350/μl. The patients were nucleoside naive or were receiving AZT monotherapy at the start of the study. Between July 1994 and April 1996, 597 patients were enrolled at 67 centers in Europe and Australia. They were randomized at a 1:1 ratio between those who received 600 mg of AZT daily plus 300 mg of DLV three times daily (n = 300) or placebo three times daily (n = 297). Randomization was stratified by the patient’s CD4 count (<50 or 51 to 350/μl) and prior nucleoside exposure (naive or not). AZT was selected as the comparator drug because when the protocol was initiated it was the most widely used nucleoside for the treatment of HIV infection. The study dosage of DLV was increased to 400 mg three times daily by protocol amendment (21 February 1996) due to the observation that this dosage was associated with the maximal effect on surrogate markers for disease progression in other studies analyzed at that time. After the results of the Delta and ACTG 175 trials were reported (4, 7), amendment 3 (21 February 1996) stipulated that patients currently enrolled in the trial should be offered additional therapy with didanosine or with zalcitabine if they were unable to tolerate didanosine. The protocol and the informed consent forms were approved by the medical ethics committee or investigational review board of each clinical site. All patients gave written informed consent. Primary endpoints were death or a new AIDS-defining illness, or both.

A total of 597 patients were enrolled in the study: 297 patients in the AZT treatment group and 300 patients in the DLV-AZT treatment group. An average of 84.8% of the patients had previously received nucleoside therapy. At the baseline, the patients in the AZT and AZT-DLV groups had mean CD4-cell counts equal to 140 and 141 cells/μl, respectively, and mean HIV RNA levels of 5.10 and 5.03 log10 copies/ml, respectively. The study course was completed by 24.1% of the patients (26.6% in the AZT group and 21.7% in the DLV-AZT group). The remainder of the patients prematurely discontinued participation in the study because they reached a clinical endpoint (131 patients; 22%), because they experienced a medical event (124 patients; 21%), or for other reasons (198 patients; 33%). Of the patients who withdrew for other reasons, the most common reasons were personal request (123 patients), immunological deterioration (31 patients), loss to follow-up (18 patients), protocol noncompliance (9 patients), and investigator’s choice (5 patients).

Twenty-four deaths occurred, with 13 of those being in the AZT treatment arm and 11 being in the DLV-AZT treatment arm. Kaplan-Meier curves of intent-to-treat survival analysis showed no significant differences between treatment groups for all patients. None of the deaths were attributed to the study medication. By intent-to-treat analysis, there were fewer patients with AIDS-defining illnesses in the DLV-AZT group (64...
Our results show that there was a trend in the reduction of patients (81 patients) (P = 0.09). Significantly more opportunistic infections or deaths (P = 0.03) were reported for patients in the AZT group (69 patients) than for patients in the DLV-AZT group (48 patients). By on-treatment analysis, the DLV-AZT group also had significantly fewer patients (P = 0.032) with AIDS-defining illnesses (77 patients in the AZT group versus 56 patients in the DLV-AZT group). There was a statistically significant greater frequency of patients with at least one drug-related medical event in the DLV-AZT group than in the AZT group (52.5 versus 34.1%; P < 0.0001), and that was primarily due to an increased incidence of skin rash observed in the DLV-AZT group (36.5%) compared with that observed in the AZT group (15.5%). DLV was discontinued in 24.3% of patients with skin rash. Only two of the skin rashes (in patients in the DLV-AZT group) were serious, and both were reported as Grade 3.

Changes in HIV RNA levels from the baseline levels were significantly greater in the DLV-AZT group than in the AZT group at week 2 (P = 0.0001) and week 4 (P = 0.0017). Therefore, the viral load increased until week 8 for the DLV-AZT group and did not differ between the two groups from week 8 to week 84.

The results of genotypic analysis are depicted in Table 1. At the baseline, 64.3% of the patients in the AZT group and 68.4% of the patients in the DLV-AZT group had one to five mutations associated with AZT resistance. AZT resistance mutations at positions 215, 70, and 41 were the most common. At week 12, about two- to threefold more subjects in the AZT group than in the DLV-AZT group developed new AZT resistance mutations. At week 24, there was a similar overall frequency of new AZT resistance mutations between treatment groups. In the DLV-AZT group, development of the K103N mutation appeared in 85.2% of patients at week 12 as either a single mutation (60.9% of patients) or dual mutations (24.3% of patients) associated with P236L or, rarely, Y181C. The P236L mutation was observed in 28.7% of patients, usually as a dual mutation (23.5% of patients). The Y181C mutation was rarely seen. Few additional DLV resistance mutations occurred between week 12 and week 24. Thirteen percent of subjects with one or zero AZT resistance mutation developed dual resistance mutations at positions 103 and 236 and positions 103 and 181 by week 24, whereas 34% of patients with two or more AZT resistance mutations at the baseline developed these dual resistance mutations.

Our results show that there was a trend in the reduction of clinical progression in the DLV-AZT group, although there was no significant difference between the two treatment arms in the occurrence of death or a new AIDS-defining illness. The difference was significant when the analysis was limited to the occurrence of death or opportunistic infections. However, the majority of patients in this trial had previously been treated with AZT and had evidence of AZT resistance at the time of entry. Thus, this trial compared the addition of DLV monotherapy or no additional therapy to AZT therapy. A similar transient antiviral efficacy in heavily nucleoside-pretreated patients has been reported with nevirapine (1, 2).

The decrease in the antiviral activity of DLV-AZT was associated with the emergence of genotypically resistant virus in a high percentage of patients. In previous studies, resistance to DLV was found to occur rapidly in vitro and in vivo and to be associated in vivo with the loss of an antiviral effect (5, 8). We found that the occurrence of dual DLV mutations was more frequent when the number of AZT resistance mutations was two or more at the baseline. The association between AZT resistance at the baseline and a worse response to combination therapy with DLV has been reported previously (3). K103N was the predominant mutation, as recently reported from the ACTG 260 trial (5). This mutation confers cross-resistance to other available NNRTIs. The P236L mutation was rarely found as a single mutation. This could be related to the replication defect of this mutant relative to the replication efficiency of the K103N mutant that has been observed in vitro (6).

The present study showed that DLV had a transient antiviral effect when it was used in combination with AZT in AZT-pretreated patients. More recent trials have shown the potent antiviral activity of the triple combination AZT-lamivudine-DLV in drug-naive patients, demonstrating the therapeutic value of DLV, provided that the conditions of administration are more appropriate (S. Sargent, S. Green, M. Para, W. Freimuth, L. Wathen, L. Getchel, and C. Greenwald, 5th Conf. Retrovir. Opportunistic Infect., abstr. 699, 1998; R. Wood, D. A. Emini, G. Moyle, W. De Cian, A. Ingrosso, and C. Greenwald, 6th Conf. Retrovir. Opportunistic Infect., abstr. 624, 1999).

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APPENDIX
The M3331/013B Study Group participants were as follows: Australia, D. Cooper, J. Hoy, D. Shaw, and A. Street; Austria, E. Tschachler and N. Vetter; Belgium, N. Clumeck, J. Demonty, and B. Vandercam; Denmark, L. Mathiesen; Ireland, G. Sheehan; France, J. Auvergnat, E. Bouvet, G. Delzant, V. Joly, J. Kisterman, A. Lafeuill-

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