Lessons Learned From 2 Patients With Multidrug-Resistant HIV-1 Infection Successfully Treated With a Darunavir-Containing Antiretroviral Treatment Regimen

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The authors describe 2 patients with life-threatening multidrug-resistant HIV-1 infection who responded very well to a treatment regimen containing darunavir and enfuvirtide. They discuss the availability of several new treatment options such as darunavir, etravirine, integrase, and CCR5 inhibitors for patients with multidrug-resistant viruses.

Keywords: HIV; antiretroviral treatment; darunavir; resistance

Darunavir (Prezista™) is a next-generation HIV-1 protease inhibitor (PI), with potent antiviral activity against wild-type and most PI-resistant HIV-1-found inexperienced HIV-1-infected patients. The potency of darunavir against multidrug-resistant (MDR) viruses can be explained by its high affinity and binding properties to the HIV protease.[1] The elimination of darunavir in vivo is through the CYP3A4 enzyme, and darunavir itself is an inhibitor of the CYP3A4 enzyme.[1,2] Different studies[2-5] demonstrated a significant viral load response for persons with MDR HIV-1 treated with darunavir.

Darunavir must be co-administered with low-dose ritonavir (100 mg BID), which raises the bioavailability level of darunavir from 37% to 82%.[2] Darunavir was recently approved in the United States by the FDA, has been also approved in other countries, and is expected to be approved in Europe soon. In the meantime, an expanded access program for the drug has been implemented.

Case History 1

A 42-year-old Hispanic man of South American origin and living in the Netherlands was diagnosed to be HIV-seropositive in 1995. At that time, he presented with Kaposi's sarcoma lesions on the skin. He was followed up in an HIV treatment center in the Netherlands. He was initially treated with chemotherapy and zidovudine, zalcitabine, and saquinavir. Subsequently, he was switched to numerous other antiretroviral (ARV) regimens because of treatment failure. He had been exposed to all ARVs available in the Netherlands, including tipranavir, but he was still naive to enfuvirtide. In May 2003, genotypic resistance testing (VIRCO, Mechelen, Belgium) showed the following primary reverse transcriptase mutations: M41L, D67N, K70R, V75M, V118I, M184V, Y188L, H208Y, L210W, R211K, T215Y, K219Q, and G333E. It also showed the following protease inhibitor mutations: L10F, L33F, M46I, I54V, A71V, G 73S, V77I, I84V, and L90M. In August 2005, he presented with severe watery chronic diarrhea, weakness, and weight loss. He suffered also from polyneuropathy. His therapy was switched to only zidovudine and lamivudine as a salvage treatment. His viral load was >1.000.000 copies/ml, and his CD4 lymphocyte count was 30 cells/μl. He was transferred to our HIV clinic at the Institute of Tropical Medicine (ITM), Antwerp, Belgium, to be enrolled in an open darunavir trial for patients with MDR HIV infection. On December 2, 2005, he was enrolled in the trial and the following treatment was started: zidovudine 300 mg BID, lamivudine 300 mg QD, enfuvirtide 90 mg sc BID, ritonavir 100 mg BID, tenofovir 245 mg QD, and darunavir 600 mg BID. His physical condition improved gradually. After 8 weeks, his appetite had normalized and his diarrhea had stopped. His body weight increased from 51 to 71 kg in 9 months. His viral load dropped dramatically

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from >1.000.000 copies/ml before the treatment to undetectable levels (<50 copies/ml) 5 months after the start of the treatment. On October 10, 2006, he was without physical complaints and was again professionally active. His CD4 lymphocyte count was 232 cells/μl, and his viral load remained undetectable. The darunavir regimen was always well tolerated and did not result in significant drug-associated adverse events so far. Darunavir is now also available in the Netherlands. Therefore, the patient was transferred back to the clinic where he was followed initially.

Case History 2

A 37-year-old Caucasian man was diagnosed as HIV seropositive in 1995. Initially he was followed up at the ITM HIV treatment center in Antwerp, Belgium. In 1996, he was initially treated with zidovudine monotherapy. In 1997, he developed Kaposi's sarcoma lesions in his mouth and was treated for *Pneumocystis jirovecii* pneumonia. In March 1997, he was started on a treatment with zidovudine, zalcitabine, and saquinavir. Subsequently, he was switched to numerous other ARV regimens because of treatment failure or side effects. In 2003, for personal reasons he moved to Spain. He had been exposed to all ARV available at that time in Belgium and he had developed genotypic and phenotypic resistance to all of them. On November 28, 2005, he was hospitalized in the intensive care unit of a Spanish hospital with a *P jirovecii* pneumonia, severe watery diarrhea, nausea, and weight loss. Moreover, he had Kaposi's sarcoma lesions on the skin and in the mouth and anal condyloma. Modified acid-fast stains of stool and sputa revealed the presence of *Cryptosporidium sp.* December 2005, genotypic resistance testing (Trugene HIV-1, Bayer HealthCare, Tarrytown, NY) showed the following relevant reverse transcriptase mutations: M41L, E44D, D67N, K103N, V210W, and T215Y. It also showed the following relevant protease mutations: L10I, K20I, M36I, G48V, L63P, A71T, V82A, and I84V. On January 15, 2006, treatment with enfuvirtide 90 mg/d sc BID, lamivudine 300 mg QD, abacavir 300 mg BID, ritonavir 200 mg BID, and tipranavir 500 mg BID was started. This therapy, however, proved to be ineffective, as his viral load remained >1.000.000 copies/ml after 4 weeks. His CD4 lymphocyte count was now 115 cells/μl. His diarrhea remained unresponsive to treatment despite courses with paromomycin, nitazoxanide, lopermide, laudanum, and sandoglobulin. As a consequence, he developed severe cachexia. Since the ITM HIV treatment center was involved in an open darunavir trial for patients with MDR HIV infection, we suggested transferring the patient to Belgium. Initially this was considered not to be feasible because of the critical clinical condition of the patient. Parenteral nutrition was started. The patient's condition slightly improved, and a few days later (February 14, 2006), he was transferred to Belgium, where he was admitted at the ITM hospitalization unit at University Hospital in Antwerp. On admission, he was extremely cachectic, weak, and unable to walk. After discussion with the sponsor and despite the presence of an uncontrolled *Cryptosporidium* infection—a current active opportunistic infection was defined as an exclusion criteria—approval for study entry was obtained. The new ARV regimen included enfuvirtide 90 mg sc BID, lamivudine 300 mg QD, tenofovir 245 mg QD, and darunavir 600 mg BID administered with ritonavir 100 mg BID. As a result, after 2 weeks (April 3, 2006), his viral load had decreased to 447 copies/ml and became undetectable (<50 copies/ml) on June 7, 2006. His diarrhea resolved within the first month of the darunavir treatment. His weight increased from 48 to 55.5 kg in 2 months. At discharge from the hospital on April 30, 2006, his condition was much better. On August 29, 2006, his CD4 lymphocyte count was 124 cells/μl and his viral load remained undetectable. The darunavir was always well tolerated, and no side effects were reported so far.

Discussion

The remarkable rapid improvement of the general condition of both patients when treated with a darunavir combination with at least one other ARV-sensitive agent illustrates the effectiveness of such treatment in patients with an MDR HIV-1 infection. The relatively rapid disappearance of the chronic diarrhea in both patients during darunavir therapy suggested that its cause was mainly of HIV origin (even in patient 2 who presented with a concomitant *Cryptosporidium sp* infection).

It is very likely that both patients described in this article would have died without these new life-saving drugs. Therefore, we should always carefully consider all potential treatment options (even "investigational" ones) in patients with an MDR HIV-1 infection before making a decision to start palliative treatment. Moreover, HIV treatment centers should cooperate to offer the best treatment option for patients with MDR HIV infections. This may include the transfer of a patient from one center to another. Our 2 patients benefited from an international collaboration between European treatment centers.

Certainly in the approval process of new drugs, the results of phase III trials are extremely important. However, for life-threatening diseases, such as HIV disease, drug approval processes can be considered

with phase II data (eg, this was done in the approval process of darunavir by the FDA). Even case reports of terminally ill patients who recover should be taken into account.

The availability of several new treatment options such as darunavir, etravirine, integrase, and CCR5 inhibitors for patients with MDR HIV infection will influence our ARV treatment strategies. It is hoped that in the near future, at least in the industrialized world, we will have treatment options for every patient, even in cases of an infection with an MDR HIV. This means that our goals of ARV treatment should be to get the viral load of all our patients below detectable levels and that the term *salvage treatment* will become obsolete. Another consequence is that today we should not, in second- or third-line ARV treatment, include too many drugs because we believe this is the last treatment option for the patients (including even drugs about which we are not sure whether they still have any viral activity). Some of these 4 or 5 drug regimens may increase the toxicity of the regimen without improving its efficacy. While proposing such regimens, we have to realize now that very soon effective third- and even a fourth-line ARV treatment regimens will become available.

Although these new drugs are a reason to be hopeful for controlling HIV resistance in industrialized countries, it is likely that this may be much more difficult to achieve in countries with limited resources where the cost of these new drugs may be too high. Therefore, these new drugs, although they are extremely welcome, may also increase again the gap between what is medically possible in developed and developing countries.

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