

Two Cases of Multidrug-Resistant Human Immunodeficiency Virus Infection Treated with Atazanavir and Lopinavir/Ritonavir Combination Therapy

The combination of atazanavir (ATV) and lopinavir/ritonavir (LPV/RTV) with nucleoside reverse transcriptase inhibitors (NRTI) has been used as a salvage regimen for human immunodeficiency virus (HIV)-positive patients. In this paper, we discuss two cases of HIV-positive patients who had long histories of virological failure following a heavy treatment of antiretroviral drugs, but then achieved virological suppression with double-boosted protease inhibitor (PI) regimens. In patients with multiple genotypic resistance to PIs and NRTIs, virological suppression can be achieved with a combination of ATV plus LPV/RTV with an NRTI backbone. The two cases in this report suggest that a combination of ATV plus LPV/RTV could be a useful salvage regimen for the subset of HIV-positive patients with limited treatment options.

Key Words : Double-Boosted Protease Inhibitor Therapy; Atazanavir; Lopinavir; Salvage Therapy; HIV Infections

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INTRODUCTION

The advent of highly active antiretroviral therapy (HAART) has substantially improved the prognosis of human immunodeficiency virus (HIV)-positive patients by reducing the incidence of opportunistic infections and HIV-related mortality (1). However, success rates outside clinical trial settings are limited by treatment failure due to medication non-adherence, drug toxicities, lack of drug potency and drug resistance (2). The use of low-dose ritonavir (RTV) as a pharmacokinetic enhancer of other protease inhibitors (PIs) has changed the management of HIV infection (3). Recently, triple PI regimens, including the combination of two active PIs with ritonavir as an enhancing agent, have been examined in treatment-experienced patients (4).

Although prospective comparative trials of single RTV-boosted PIs versus double-boosted PI combinations (e.g., lopinavir and ritonavir plus atazanavir) are lacking, the combinations of atazanavir (ATV), lopinavir/ritonavir (LPV/RTV), and NRTIs has been shown to be effective in antiretroviral-experienced and antiretroviral-naïve patients (4-6). In Korea, there are limited available treatment options because new agents such as enfuvirtide (T-20), tenofovir, darunavir (TMC-114), tipranavir and fosamprenavir are not available.

This report describes the use of double-boosted PI regimens to achieve virological suppression in HIV-positive patients who have a long history of virological failure in response to treatment with antiretroviral drugs.

CASE REPORT

Case 1

A 34-yr-old male presented as HIV-positive in 1999. His baseline CD4 cell count was 321 cells/ μ L and his viral load was 336,281 copies/mL.

The patient was treated for four months with lamivudine, zidovudine and indinavir starting in April 2001, but he voluntarily stopped the medication. He was admitted to the hospital because of perianal infection and syphilis in November 2003. His viral load was 765,000 copies/mL and his CD4 cell count was 2 cells/ μ L at that time. He was started on lamivudine, didanosine and indinavir with PCP/INH prophylaxis. In March 2004, his drug regimen was changed to lamivudine, stavudine and LPV/RTV because of nausea. In August 2004, his viral load was 255,000 copies/mL and we performed a drug resistance test to make a rational choice

for rescue therapy.

We performed viral genotypic resistance testing using polymerase chain reaction (PCR) amplification conditions based on the Stanford Center for AIDS Research laboratory protocol for sequencing protease and reverse transcriptase genes. Antiretroviral resistance interpretation was performed using the HIV Drug Resistance Database of Stanford University (<http://hivdb.stanford.edu>).

Genotypic resistance analysis showed that the virus was susceptible to all non-nucleoside reverse transcriptase inhibitors (NNRTI) and resistant to all PIs and nucleoside reverse transcriptase inhibitors (NRTI), except for zidovudine, stavudine and tenofovir. Genotypic analysis showed resistance-associated mutations both in the HIV reverse transcriptase gene (L74V, M184V, V35I, K122E, D123N, I135L, S162C, E194K, G196E, T200I, A272P, A288G, I293V, E297A, and E300D) and in the protease gene (M46I, I154V, V82A, L10V, L63A, and I15V). Based on these results, we changed the regimen to zidovudine, didanosine and efavirenz in November 2004. One month later, we changed zidovudine to lamivudine because of nausea. The patient then began LPV/RTV in March 2005. One year after beginning the LPV/RTV regimen, the patient's CD4 cell count was 181 cells/ μ L and his viral load was 289,000 copies/mL. Finally, a new regimen of lamivudine (150 mg twice daily), LPV/RTV (two tablets twice daily), atazanavir (300 mg/day) and abacavir (600 mg/day) resulted in virological success. The patient's CD4 cell count was 362/ μ L and his viral load was 41.5 copies/mL after six months of the new drug regimen. One year later, his CD4 count increased to 534/ μ L and virus was no longer detected.

Case 2

A 27-yr-old male patient presented with HIV infection in December 1998. His baseline CD4 count was 190 cells/ μ L and his viral load was 135,894 copies/mL. He was treated by HAART with zidovudine, lamivudine and indinavir for three years. In April 2002, he had suspected virological failure and poor adherence so the indinavir was replaced with efavirenz. Then, after the patient developed a rash, the efavirenz was replaced with Kaletra.

In September 2005, the patient was suspected to have virological failure and a genotypic resistance test was performed. The test showed mutations in the PI gene (L33F, M46I, I54V, V82A, L10V, I13V, K14R, I15V, K55R, R57K, Q58E, Q61H, I64V, and L76V) and in the RT gene (M41L, M184V, T215Y, T7R, K11R, K30R, D123E, I135T, G196E, F214L, D237N, V245T, R284K, A288S, I293V, and E300D). Genotypic resistance analysis showed that the virus was susceptible to all NNRTIs, and resistant to NRTIs and PIs. Based on this result, we changed his regimen to didanosine, abacavir and efavirenz in January 2006. In June 2006, he was diagnosed with Tbc lymphadenitis and he received treatment

with an antituberculosis agent. At that time, his CD4 count was 169 cells/ μ L and his viral load was 60,000 copies/mL. In October 2006, we changed his regimen to didanosine (400 mg/day), abacavir (600 mg/day), lamivudine (300 mg/day), atazanavir (300 mg/day) and LPV/RTV (2 tablets twice daily) due to virological failure. Six months later, his CD4 count was 204 cells/ μ L and his viral load was less than 40 copies/mL.

DISCUSSION

Ritonavir is a potent PI, but when prescribed at its recommended dose of 600 mg twice daily, it is not generally well-tolerated due to its adverse effects. When utilized in a low sub-therapeutic dose (100 or 200 mg), it acts as a pharmacoenhancer of indinavir, amprenavir, saquinavir, lopinavir, atazanavir and to a more limited extent, nelfinavir (7). Double-boosting, also referred to as a triple PI combination, is a term that describes the simultaneous use of two PIs with low-dose ritonavir (8).

Clinically, double-boosted PIs may serve multiple purposes: 1) salvage therapy for highly antiretroviral-experienced patients with limited treatment options due to extensive reverse transcriptase (RT) resistance and protease resistance (PR); 2) therapy for patients with retained PI activity, but limited RT inhibitor options because of toxicities or resistance; 3) initial therapy alone, thereby avoiding the potential mitochondrial toxicities of NRTIs or; 4) initial therapy alone, thereby avoiding agents with a low threshold to resistance, such as lamivudine, emtricitabine and the NNRTIs (6).

When RTV is used as a pharmacoenhancer, it increases the drug levels of the boosted drug that it is combined with in two ways: 1) inhibition of CYP3A4 in the gut wall and liver and 2) possible inhibition of p-glycoprotein preventing cellular drug efflux (5). The fixed combination of LPV and low-dose RTV (Kaletra) facilitates the simultaneous boosting of an additional PI.

However, the interaction between the various PIs is not as well characterized as the effect of ritonavir on the pharmacokinetics of PIs. Therefore, complex and unexpected interactions can occur and therapeutic drug monitoring is necessary to direct dosing and therapy. Administration of two PIs boosted with low RTV doses can produce complex drug interactions with unexpected results. Pharmacokinetic studies are required to ensure that therapeutic drug concentrations are being achieved in the plasma. A huge decrease in the concentration of both PIs has been described when LPV/RTV is administered with amprenavir or fosamprenavir (9-13). This unfavorable reaction does not occur when LPV/RTV is administered with saquinavir or when saquinavir and RTV are administered with ATV (14-17).

ATV appears to be a viable candidate to combine with LPV/RTV in double-PI regimens because of its low daily pill burden, modest CYP3A4 inhibition, different resistance

profiles and limited effects on lipid profiles. In a pharmacokinetic study, the combination of ATV and LPV/RTV provided high plasma concentrations of both PIs and was well tolerated despite the high plasma concentrations of both ATV and LPV (4).

Additionally, there are some data from non-comparative studies confirming the improved treatment outcomes from combinational PI therapy. Gilliam et al. suggested that the combination of ATV+LPV/RTV with an NRTI backbone could be considered for patients with multi-class resistance (extensive RT and PR mutations), including predicted phenotypic and/or genotypic resistance to ATV and/or LPV/RTV. In this study, 11 of 14 (79%) patients with 6 or more PR mutations achieved virological success. Multiple NRTI mutations were noted in 13 of 14 patients with 6 or more PR mutations. Despite predicted phenotypic resistance to ATV (6 patients) and LPV/RTV (7 patients), virological success was achieved in 4 of 6 (67%) and 4 of 7 (57%) patients, respectively. None of patients had phenotypic resistance to ATV and LPV/RTV simultaneously (6).

For the two cases in this study, there were long histories of virological failure and multiple genotypic and phenotypic resistances to PIs and NRTIs. However, virological suppression was achieved with a combination of ATV+LPV/RTV with an NRTI backbone. These cases support the hypothesis that the combination of ATV+LPV/RTV with NRTIs is tolerable and efficacious in PI-resistant patients.

Further studies are necessary to achieve clinical utility and specific indications for double-boosted PI therapy as a salvage therapy, especially in genotypic and phenotypic PI-resistant patients.

REFERENCES

- Palella FJ Jr, Delaney KM, Moorman AC, Loveless MO, Fuhrer J, Satten GA, Aschman DJ, Holmberg SD. *Declining morbidity and mortality among patients with advanced human immunodeficiency virus infection. HIV Outpatient Study Investigators. N Engl J Med* 1998; 338: 853-60.
- Loutfy MR, Walmsley SL. *Salvage antiretroviral therapy in HIV infection. Expert Opin Pharmacother* 2002; 3: 81-90.
- Gallant JE. *Protease-inhibitor boosting in the treatment-experienced patient. AIDS Rev* 2004; 6: 226-33.
- Ribera E, Azuaje C, Lopez RM, Diaz M, Feijoo M, Pou L, Crespo M, Curran A, Ocana I, Pahissa A. *Atazanavir and lopinavir/ritonavir: pharmacokinetics, safety and efficacy of a promising double-boosted protease inhibitor regimen. AIDS* 2006; 20: 1131-9.
- Boffito M, Maitland D, Samarasinghe Y, Pozniak A. *The pharmacokinetics of HIV protease inhibitor combinations. Curr Opin Infect Dis* 2005; 18: 1-7.
- Gilliam BL, Chan-Tack KM, Qaqish RB, Rode RA, Fantry LE, Redfield RR. *Successful treatment with atazanavir and lopinavir/ritonavir combination therapy in protease inhibitor-susceptible and protease inhibitor-resistant HIV-infected patients. AIDS Patient Care STDS* 2006; 20: 745-59.
- Moyle GJ, Back D. *Principles and practice of HIV-protease inhibitor pharmacoenhancement. HIV Med* 2001; 2: 105-13.
- Temesgen Z, Cainelli F, Poeschla EM, Vlahakis SA, Vento S. *Approach to salvage antiretroviral therapy in heavily antiretroviral-experienced HIV-positive adults. Lancet Infect Dis* 2006; 6: 496-507.
- De Luca A, Baldini F, Cingolani A, Di Giambenedetto S, Hoetelmanns RM, Cauda R. *Deep salvage with amprenavir and lopinavir/ritonavir: correlation of pharmacokinetics and drug resistance with pharmacodynamics. J Acquir Immune Defic Syndr* 2004; 35: 359-66.
- Taburet AM, Raguin G, Le Tiec C, Droz C, Barrail A, Vincent I, Morand-Joubert L, Chene G, Clavel F, Girard PM. *Interactions between amprenavir and the lopinavir-ritonavir combination in heavily pretreated patients infected with human immunodeficiency virus. Clin Pharmacol Ther* 2004; 75: 310-23.
- Kashuba AD, Tierney C, Downey GF, Acosta EP, Vergis EN, Klingman K, Mellors JW, Eshleman SH, Scott TR, Collier AC. *Combining fosamprenavir with lopinavir/ritonavir substantially reduces amprenavir and lopinavir exposure: ACTG protocol A5143 results. AIDS* 2005; 19: 145-52.
- Khanlou H, Graham E, Brill M, Farthing C. *Drug interaction between amprenavir and lopinavir/ritonavir in salvage therapy. AIDS* 2002; 16: 797-8.
- Mauss S, Scholten S, Wolf E, Berger F, Schmutz G, Jaeger H, Kurowski M, Rockstroh JK. *A prospective, controlled study assessing the effect of lopinavir on amprenavir concentrations boosted by ritonavir. HIV Med* 2004; 5: 15-7.
- Ribera E, Lopez RM, Diaz M, Pou L, Ruiz L, Falco V, Crespo M, Azuaje C, Ruiz I, Ocana I, Clotet B, Pahissa A. *Steady-state pharmacokinetics of a double-boosting regimen of saquinavir soft gel plus lopinavir plus minidose ritonavir in human immunodeficiency virus-infected adults. Antimicrob Agents Chemother* 2004; 48: 4256-62.
- Stephan C, Hentig N, Kourbeti I, Dauer B, Mosch M, Lutz T, Klauke S, Harder S, Kurowski M, Staszewski S. *Saquinavir drug exposure is not impaired by the boosted double protease inhibitor combination of lopinavir/ritonavir. AIDS* 2004; 18: 503-8.
- Boffito M, Kurowski M, Kruse G, Hill A, Benzie AA, Nelson MR, Moyle GJ, Gazzard BG, Pozniak AL. *Atazanavir enhances saquinavir hard-gel concentrations in a ritonavir-boosted once-daily regimen. AIDS* 2004; 18: 1291-7.
- Staszewski S, Babacan E, Stephan C, Haberl A, Carlebach A, Gute P, Klauke S, Hermschulte Y, Stuermer M, Dauer B; Frankfurt HIV Cohort. *The LOPSAQ study: 48 week analysis of a boosted double protease inhibitor regimen containing lopinavir/ritonavir plus saquinavir without additional antiretroviral therapy. J Antimicrob Chemother* 2006; 58: 1024-30.