Successful treatment with 4-drug HAART that includes raltegravir in a treatment-naïve patient with advanced HIV/AIDS: a case report

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Citation

Abstract

Raltegravir has recently been FDA-approved for use in treatment-naïve HIV-infected adults. We describe a 41-year-old newly-diagnosed HIV-infected woman who presented to the outpatient HIV clinic with a history of 80-lbs weight loss and diarrhea. Baseline HIV-1 RNA and $CD4^+$ cell count were 3,593,000 copies/mL (6.56 $\log_{10}$) and 1 (0.5%) cells/mm^3, respectively. She was initiated on emtricitabine/tenofovir and lopinavir/ritonavir. On day 1 of HAART, the patient was admitted to the intensive care unit (ICU) with sepsis and pneumonia. Due the patient's poor prognosis, and extraordinarily high baseline HIV-1 RNA level, her HAART was intensified with raltegravir. After 10 days of HAART (7 days of RAL) the patient's HIV-1 RNA declined by 4.23 $\log_{10}$ copies/mL, to 213 copies/ml (2.33 $\log_{10}$), and $CD4^+$ cell count increased to 17 (4%) cells/mm^3. After a long hospitalization that was complicated by disseminated Mycobacterium avium complex (MAC) infection, Clostridium difficile colitis, and a CNS lesion, the patient was discharged to home. Upon follow-up in the outpatient clinic, 4 weeks after HAART initiation, patient's clinical status was stable; HIV-1 RNA declined to < 48 copies/mL and CD4 count was 11 (4%) cells/mm^3. Initial studies with raltegravir suggest a faster viral decay with this agent compared to other antiretrovirals. Intensification with raltegravir was performed in our case to achieve a faster HIV-1 RNA decline in a patient with AIDS-related complications and a poor prognosis. This approach may be useful in patients with advanced HIV/AIDS disease and high baseline HIV-1 RNA levels, although data from randomized controlled studies are needed.

INTRODUCTION

The prognosis of patients diagnosed with human immunodeficiency (HIV) has improved substantially since the introduction of highly active antiretroviral therapy (HAART).[1,2] Unfortunately, up to 21% of HIV infections in the United States remain undiagnosed[3] and up to 43% of individuals are diagnosed with HIV infection late in the course of their disease (CD4 cell count < 200 cells/mm^3).[4]

Standard HAART regimens for antiretroviral-naïve patients consist of 3 active antiretroviral agents: 2 nucleoside reverse transcriptase inhibitors (NRTIs) plus one non-nucleoside reverse transcriptase inhibitor (NNRTI), or 2 NRTIs plus a ritonavir-boosted protease inhibitor (PI).[5] Four active antiretroviral agents have not shown significant clinical benefit over this standard 3-drug approach.[6,7] Raltegravir is an integrase inhibitor that has recently been approved by the FDA for initial treatment of HIV infection. Initial data with this agent suggest that it is at least as effective as a standard efavirenz-containing regimens.[8,9] Initial studies have also shown significant HIV-1 viral decay in the initial stages of treatment with raltegravir.[10,11]

This case report describes a patient with newly-diagnosed HIV/AIDS, hospitalized with sepsis, pneumonia, and other AIDS-related complications, whose baseline HIV-1 RNA was 6.56 $\log_{10}$ copies/mL, and who experienced 4.23 $\log_{10}$ reduction in the HIV-1 RNA after 10 days of HAART (7 of which included raltegravir), and an undetectable HIV-1 RNA level after 4 weeks of therapy.

CASE REPORT

A 41-year-old Hispanic woman presented to the outpatient HIV clinic with newly-diagnosed HIV/AIDS and severe wasting syndrome. Patient's past medical history was significant for an 80-pound (36-kg) weight loss over the last year and a history of hospitalizations with pneumonias and diarrhea. Patient's medications on presentation included trimethoprim/sulfamethoxazole (TMP/SMX) for Pneumocystis jiroveci pneumonia (PCP) prophylaxis and fluconazole for oral candidiasis. Her social history did not

reveal any risk factors for HIV; she is married with two children. Her husband and children were reportedly healthy, although, they have not yet been tested for HIV. She denied any history of illicit drug, tobacco, or alcohol use.

Patient's vital signs on presentation were within normal limits. She appeared to have extreme wasting syndrome; her weight was 41-kg and height was 160 cm. Baseline laboratory evaluation was significant for advanced HIV/AIDS disease and abnormal liver function tests (LFTs): HIV-1 RNA level, 3,593,000 (6.56 $\log_{10}$) copies/mL; CD4 cell count, 1 cells/mm^3 (CD4 percent, 0.5%); alkaline phosphatase (AP), 352 IU/L (reference range, 25-150 IU/L); aspartate aminotransferase (AST), 87 IU/L (reference range, 0-40 IU/L); alanine aminotransferase (ALT), 40 IU/L (reference range, 0-40 IU/L); albumin 1.4 g/dL (reference range, 3.5-5.5 g/dL). Other pertinent laboratory findings included a serum creatinine (SCr) of 0.6 mg/dL, negative hepatitis A, B, and C serologies, Toxoplasma gondii Ab IgG <6.5 IU/mL (negative), Cytomegalovirus (CMV) Ab IgG 18.6 IU/mL (positive).

Standard HAART consisting of co-formulated emtricitabine/tenofovir (FTC/TDF) and lopinavir/ritonavir (LPV/r) was initiated, and the patient was counseled regarding the possible risks and side effects of HAART. Given her advanced HIV disease, significant time was spent counseling the patient regarding the signs and symptoms of immune reconstitution inflammatory syndrome (IRIS). Upon returning home with her medications, the patient collapsed and was taken to the emergency department.

She was admitted to the intensive care unit (ICU) with initial diagnoses of sepsis and pneumonia. A bronchoscopy was performed, and the bronchial alveolar lavage (BAL) cultures remained negative for the first 2 weeks of hospitalization. A chest x-ray on admission showed multifocal hazy pulmonary infiltrates in the right upper and lower lobes and in the left lower lobe. A MRI scan of the brain revealed a right posterior frontal 1.8-cm rounded lesion with surrounding vasogenic edema. Due to her unstable clinical status, the patient was not a candidate for a brain biopsy.

She was placed on pressor agents and broad-spectrum antimicrobials, including doripenem, vancomycin, azithromycin, high-dose intravenous TMP/SMX. Due to the CNS lesion seen on the MRI, empiric toxoplasmosis therapy was also initiated. The patient's sepsis resolved on day 3 of ICU stay. All blood cultures remained negative. After 2

weeks of hospitalization, Mycobacterium avium complex (MAC) was identified from the BAL cultures, and the patient was initiated on clarithromycin, ethambutol, and rifabutin. Patient's hospitalization was complicated by severe Clostridium difficile colitis, and recurrent MAC peritonitis. As her clinical status started to improve, all antimicrobials, except for the MAC therapy, were eventually discontinued.

Antiretrovirals were continued during the hospitalization. Due to patient's poor prognosis, concomitant AIDS-related complications, and extremely high HIV-1 RNA level, raltegravir 400 mg BID was initiated on day 2 of hospitalization. This "intensification" with raltegravir was performed with the goal of achieving a faster reduction in the HIV-1 RNA during this initial and critical phase of the patient's clinical course. On day 10 of hospitalization (day 10 of HAART; day 7 of raltegravir), patient's HIV-1 RNA level was reported as 213 (2.33 $\log_{10}$) copies/mL, indicating a 4.23 $\log_{10}$ decline from baseline; CD4$^+$ cell count increased to 17 (4%) cells/mm^3. The patient was discharged home after a 3-week-long hospitalization.

Upon follow-up in the outpatient HIV clinic, 4 weeks after HAART initiation, patient's clinical status was stable. Her HIV-1 RNA declined to < 48 copies/mL, and CD4 count was 11 (4%). Our plan is to discontinue raltegravir when the MAC infection resolves and the CD4$^+$ count increases to at least 100 cells/mm^3.

DISCUSSION

Our patient's late diagnosis of HIV/AIDS unfortunately mirrors that of many persons in the United States. To characterize late HIV testing, the Centers for Disease Control and Prevention (CDC) gathered data from 34 states (1996-2005) and determined that within 1 year of HIV diagnosis, 38.3% of patients were diagnosed with AIDS.[12] Late HIV testing causes significant morbidity and mortality to the patient, and can contribute to high rates of HIV transmission to others. In efforts to minimize late testing, the CDC launched the Advancing HIV Prevention initiative in 2003, recommending HIV testing as part of routine medical care and emphasizing the importance of early HIV testing.

Our patient's initial HAART consisted of the currently recommended 3-drug combination of two NRTIs (FTC/TDF) and a boosted PI (LPV/r). However, given her unstable clinical status in the ICU, concomitant AIDS-related complications, and the extremely elevated baseline

HIV-1 RNA level, we added raltegravir to her regimen. Although studies have not shown significant benefit of four- compared to three- drug HAART combinations in antiretroviral naïve individuals,[6,7] these trials did not examine the integrase inhibitor, raltegravir. In treatment experienced HIV-1-infected patients, this agent has demonstrated durable HIV-1 RNA suppression and increase in the CD4 cell counts,[13] and has been approved by the FDA to be used in this patient population (in combination with other antiretrovirals).

Most recently, raltegravir has been FDA-approved for use in treatment-naïve HIV-infected adults as well due to promising data with this agent in treatment-naïve HIV-1 infected patients. A phase II, randomized, multicenter, double-blind controlled study (n=198) comparing raltegravir to efavirenz (both in combination with lamivudine and tenofovir) found similar virologic and immunologic responses in the two treatment groups through week 48.[8] A phase III, double-blind, randomized, active control, non-inferiority study in 563 treatment-naïve patients, comparing raltegravir to efavirenz (both in combination with FTC/TDF), also found similar virologic efficacy in both groups. At week 48, 86% of patients in the raltegravir group achieved a HIV-1 RNA level <50 copies/mL, compared to 82% of patients in the efavirenz group ($\Box$ 4%; 95% CI, -2 to 10%; p<0.001 for noninferiority).[9] CD4 cell counts increased by 189 cells/mm^3 and by 163 cells/mm^3 in the raltegravir and efavirenz groups, respectively ($\Box$ 26; 95% CI, 4 to 47).[9]

Initial studies with raltegravir suggest that the HIV-1 viral decay with this drug may be significantly faster compared to other antiretrovirals. In the phase II study evaluating raltegravir to efavirenz in treatment-naïve patients, the proportion of patients achieving HIV-1 RNA level <50 copies/mL was greater in the raltegravir groups compared to the efavirenz group at weeks 2, 4, and 8.[8] It was also found that from day 15 through day 57, patients in the raltegravir arm were significantly more likely to have HIV-1 RNA <50 copies/mL compared to efavirenz-treated patients (p < 0.047).[11] Similarly, significantly shorter time to virologic response was seen in the raltegravir group compared to the efavirenz group in the treatment-naïve phase III study (P < .001).[9] An ongoing, 96-week, phase III, open-label, randomized trial in 209 treatment-naïve HIV-1-infected patients is evaluating antiviral efficacy of raltegravir plus LPV/r (NRTI-sparing) versus FTC/TDF plus LPV/r.[10] Interim results indicate that greater proportions of patients

had HIV-1 RNA levels <40 copies/mL at week 2, 4, and 8 when treated with raltegravir plus LPV/r compared to FTC/TDF plus LPV/r: 37.0% vs. 8.8% (week 2; p<0.001), 65.3% vs. 18.8% (week 4; p<0.001), 80.8% vs. 42.6% (week 8; p<0.001).[10]

Several studies have been performed to further characterize viral decay with raltegravir. The decay of HIV-1 RNA after initiation of antiretroviral therapy is biphasic.[14] The first phase occurs within the initial 2 weeks of treatment and represents the clearance of activated, virus-producing CD4+ lymphocytes.[14] The second phase viral decay is slower and represents the loss of chronically infected cells.[14] Raltegravir not only produced significantly greater HIV-1 viral decay in the first 2 weeks, but treatment with raltegravir also resulted in 70% lower HIV-1 RNA levels at initiation of second-phase decay compared to treatment with efavirenz (p<0.0001).[11] Mathematical modeling has been used to explore the reasons for rapid viral decay with raltegravir,[11,15,16] suggesting that the stage in the life cycle at which different drugs act (e.g., reverse transcriptase vs. integrase) affect the observed decay rates of viremia. These models suggest that drugs which block viral replication at late phases of the viral life cycle produce the fastest viral decay rates. It should be noted, however, that the viral decay of raltegravir has not yet been compared head-to-head with the viral decay of protease inhibitors in treatment-naïve HIV-infected persons.

The clinical relevance of rapid viral decay with raltegravir is currently being explored in various trials. Data have shown, however, that HIV-1 RNA levels after 4 and 8 weeks of therapy are indicative of treatment response at weeks 24 and 48, and are superior to pretreatment RNA levels as predictors of response to HAART.[17,18] Decreasing the HIV-1 RNA quickly may also minimize the development of antiretroviral resistance.[19]

These initial data regarding efficacy and viral decay with raltegravir, along with our patient's baseline HIV-1 RNA level of 3,593,000 copies/mL (6.56 log$_{10}$), prompted us to initiate raltegravir, with the main purpose of quickly decreasing the HIV-1 RNA during the patient's acute illness and her poor prognosis in the ICU. Raltegravir monotherapy results in a 2.2 log$_{10}$ HIV-1 RNA reduction.[8] Our patient, however, experienced a 4.23 log$_{10}$ decline in the HIV-1 RNA after 10 days of HAART (7 days of raltegravir), suggesting that raltegravir had additive effects with the boosted PI (LPV/r) and two NRTIs (FTC/TDF). Viral decay of

raltegravir, when combined with other antiretrovirals, has not yet been well-defined and is an interesting area for further investigation.

CONCLUSION

To our knowledge, this is the first case report describing short-term virologic and immunologic response in a HIV/AIDS patient initiated on a 4-drug combination HAART that includes the integrase inhibitor, raltegravir. Our patient's initial presentation with a CD4$^+$ count of 1 cells/mm^3 and a HIV-1 RNA of greater than 3 million copies/mL highlights the importance of implementing routine HIV testing by the public and private sectors, as currently recommended by the CDC. The approach of "intensifying" treatment with an integrase inhibitor for patients with very advanced HIV disease has not been studied in clinical trials, but may be useful in very select clinical settings. Risks of immune reconstitution should always be considered when evaluating the benefits of rapid HIV-1 RNA reduction. In addition, the clinical relevance of rapid viral decay with raltegravir has not yet been fully characterized in clinical trials. Multiple studies evaluating utilization of raltegravir with various antiretrovirals,[20-25] as well studies examining the viral decay of this drug,[26-30] are currently under way and will provide further valuable information regarding this agent and this new class of drugs.

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