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Short Communication

Clinical Experience of Raltegravir with Abacavir/Lamivudine or Zidovudine/Lamivudine in HIV-Infected Korean Adults

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SUMMARY: The efficacy and safety of raltegravir (RAL) with tenofovir (TDF)/emtricitabine (FTC) have been well studied in human immunodeficiency virus (HIV)-infected patients. However, limited clinical data are available on the use of RAL with abacavir (ABC)/lamivudine (3TC) or zidovudine (ZDV)/3TC. We investigated HIV-1-infected Korean adults, including 13 antiretroviral-naïve patients and 15 antiretroviral-experienced patients, treated with RAL plus ABC/3TC or ZDV/3TC. Virological suppression was achieved in 12 of the 13 (92%) antiretroviral-naïve patients within 24 weeks and in all (100%) patients within 96 weeks. In 13 of the 15 treatment-experienced patients, ritonavir-boosted lopinavir (LPV/r) was replaced with RAL because of hyperlipidemia ($n = 11$) and diarrhea ($n = 2$). A significant decrease in median total cholesterol, low-density lipoprotein cholesterol, and triglyceride levels was observed in these patients ($P < 0.01$, each). No adverse event related to RAL was observed in any of the 28 patients. The RAL plus ABC/3TC or ZDV/3TC regimens were effective and safe in antiretroviral-naïve Korean HIV-infected patients, and replacing LPV/r with RAL significantly improved lipid abnormalities in patients previously treated with regimens including LPV/r.

Raltegravir (RAL) has been an important drug in the treatment of HIV infection since 2007 because of its efficacy, small number of toxic effects, and antiretroviral activity against viruses resistant to reverse transcriptase and protease inhibitors (PIs) (1,2). RAL, in combination with tenofovir (TDF) and emtricitabine (FTC), was recommended as the initial regimen for antiretroviral-naïve patients (3) based on the results of clinical trials (4–7). However, the efficacy of RAL plus abacavir (ABC)/lamivudine (3TC) or zidovudine (ZDV)/3TC in treatment-naïve patients is not well established, with preliminary data being available from a single clinical trial, which had a limited number of patients (8). In previous studies, RAL has been shown to have a minimal impact on the serum lipid profile (4–7). Moreover, replacing ritonavir-boosted lopinavir (LPV/r) with RAL was shown to be an effective strategy to reduce the hyperlipidemia associated with PIs (9). However, all these studies used TDF/FTC as a nucleoside reverse transcriptase inhibitor (NRTI) backbone and mainly studied Caucasian populations. Thus, no clinical data are available for Asian patients treated with ABC/3TC, although ABC/3TC is widely used in Asian patients because HLA-5701-related side effects of ABC are very rare in Asians (10). This study aimed to report the efficacy and safety of RAL plus ABC/3TC or ZDV/3TC regimens in treatment-naïve patients and to evaluate the change in the lipid profile after replacing PIs with RAL in treatment-experienced Korean HIV-1-infected patients.

HIV-1-infected patients treated with RAL plus ABC/3TC or ZDV/3TC regimens at Chonnam National University Hospital (Gwang-ju, Republic of Korea) from August 2010 to December 2012 were investigated. The clinical and laboratory data of the patients were retrospectively reviewed from August 2010 to February 2011, and prospectively collected from March 2011. The study protocol was approved by the institutional review board (IRB No. CNUH-2011-045). CD4-positive T cell counts were determined by flow cytometry using the FACSCalibur cytometer (Becton Dickinson, San Jose, Calif, USA), and HIV-1 RNA was measured using the standard sensitive Roche COBAS® AmpliPrep/COBAS® TaqMan® HIV-1 Test (version 2.0), which has a detection range of 48–10,000,000 copies/mL. Virological suppression was defined as <48 copies/mL of HIV-1 RNA. Virological rebound was defined as >200 copies/mL of HIV-1 RNA after virological suppression (3). Hypertriglyceridemia and hypercholesterolemia were defined as ≥ 150 mg/dL and ≥ 200 mg/dL, respectively, according to the National Cholesterol Education Program guidelines (11). Adverse events were considered to be drug related if judged by the investigator as definitely, probably, or possibly related to RAL and graded using the 2004 Division of AIDS toxicity grading scale (12). The CD4-positive T cell count, HIV-1 viral copies, and lipid levels were compared between baseline and follow-up using the Wilcoxon signed-rank test. All tests of significance were 2-tailed, and P values ≤ 0.05 were deemed to indicate statistical significance. Statistical analyses of the data were performed using the SPSS Statistics software (version 19.0; SPSS Inc., Chicago, Ill., USA).

The initial median plasma HIV-1 RNA burden was

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Table 1. Clinical characteristics of 13 antiretroviral-naïve patients initially treated with ABC/3TC or ZDV/3TC plus RAL

No.	Age/ gender	Comorbidity	Opportunistic diseases	NRTI backbone	Baseline HIV-1 RNA (copies/mL)	Virological suppression documented (weeks)	CD4 cells (cells/mm³)		
							Baseline	Follow-up	Follow-up (weeks)
1	32/M	FHC	PCP, CNS lymphoma	ZDV/ 3TC	96,600	8	34	41	24
2	34/F	HBV, GERD	HAND		20,200	17	77	147	39
3	52/M	DM			19,000	13	308	853	13
4	64/F	HBV			3,190,000	94	65	365	16
5	23/M				34,300	7	111	1,015	33
6	71/M	HCV			55,700	14	114	258	14
7	27/M				108,000	7	143	181	26
8	58/M	HCV		ABC/ 3TC	1,680	7	160	111	7
9	57/F				135,000	9	209	327	35
10	36/M		PCP		163,000	12	273	340	29
11	41/M				1,700	8	291	404	46
12	34/M				2,780	7	321	720	41
13	52/M				2,890	11	384	420	28

ABC, abacavir; 3TC, lamivudine; ZDV, zidovudine; RAL, raltegravir; NRTI, nucleoside reverse transcriptase inhibitor; FHC, familial hypokalemic paralysis; PCP, pneumocystis jiroveci pneumonia; CNS, central nervous system; HBV, hepatitis B virus coinfection; GERD, gastro-esophageal reflux disorder; HAND, HIV-associated neurocognitive disorder; DM, diabetes mellitus; HCV, hepatitis C virus coinfection.

Table 2. Clinical characteristics of 15 antiretroviral-experienced patients treated with ABC/3TC or ZDV/3TC plus RAL

No.	Age/gender	ART		Reasons for switching	Lipid-lowering agent
		NRTI backbone	Switched agent to RAL		
1	41/M	ZDV/3TC	LPV/r	Hyperlipidemia	Pravastatin
2	63/M			Hyperlipidemia	—
3	52/M			Hyperlipidemia	—
4	46/M			Hyperlipidemia	—
5	38/M			Hyperlipidemia	—
6	45/M			Hyperlipidemia	—
7	53/M			Hyperlipidemia	Pravastatin
8	41/M			Diarrhea	—
9	64/M	ABC/3TC	LPV/r	Hyperlipidemia	Pravastatin
10	49/M			Hyperlipidemia	Pravastatin
11	53/M			Hyperlipidemia	Pravastatin
12	48/M			Hyperlipidemia	—
13	28/M			Diarrhea	—
14	57/F	ZDV/3TC	EFV	Dizziness, Insomnia	—
15	30/M			Somnolence	—

ABC, abacavir; 3TC, lamivudine; ZDV, zidovudine; RAL, raltegravir; ART, antiretroviral therapy; NRTI, nucleoside reverse transcriptase inhibitor; LPV/r, ritonavir-boosted lopinavir; EFV, efavirenz.

4.5 $\log_{10}$ copies/mL, and the median CD4-positive T cell count was 160 cells/mm³ (interquartile range [IQR] 94 to 300 cells/mm³) in the 13 antiretroviral-naïve patients (Table 1). Ten patients received ABC/3TC/RAL, and 3 patients received ZDV/3TC/RAL. Virological suppression was achieved in 12 of the 13 (92%) patients within 24 weeks. Virological suppression was observed in 1 patient following 96 weeks of antiretroviral therapy. The median level of total cholesterol was 173 mg/dL (IQR 146 to 196 mg/dL) at baseline and changed to 206 mg/dL (IQR 167 to 211 mg/dL) after RAL therapy ($P = 0.06$). The median level of triglycerides was 233 mg/dL (IQR 135 to 422 mg/dL) at baseline, and changed to 188 mg/dL (IQR 136 to 252 mg/dL) after RAL therapy ($P = 0.02$). None of the 13 patients reported adverse events related to RAL.

Among the treatment-experienced patients, LPV/r was replaced with RAL because of hyperlipidemia ($n = 11$) and diarrhea ($n = 2$) (Table 2). A significant decrease in median total cholesterol, low-density lipoprotein (LDL) cholesterol, and triglyceride levels was observed in these patients ($P < 0.01$; Fig. 1). Five patients who had been treated with statins because of hyperlipidemia associated with antiretroviral therapy discontinued statin treatment following the replacement of LPV/r with RAL. Efavirenz (EFV) was switched to RAL because of dizziness, insomnia, and somnolence in 2 patients. Among the 15 antiretroviral-experienced patients, 1 (7%) patient experienced loss of virological suppression after LPV/r was replaced with RAL. Two

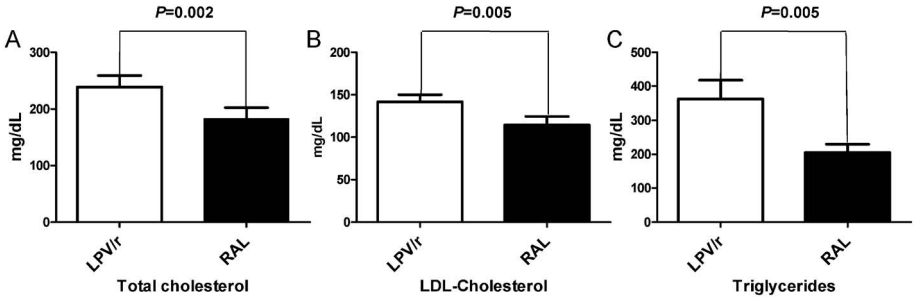

Fig. 1. Serum lipid profile changes in 13 patients following the replacement of LPV/r with RAL. (A) The median total cholesterol was 231 mg/dL (IQR 217 to 259 mg/dL) with LPV/r therapy and decreased to 185 mg/dL (IQR, 171 to 207 mg/dL) after RAL therapy ($P = 0.002$). (B) The median LDL cholesterol decreased from 141 mg/dL (IQR 117 to 160 mg/dL) to 120 mg/dL (IQR 85 to 143 mg/dL) after replacing LPV/r with RAL ($P = 0.005$). (C) The median triglycerides decreased from 342 mg/dL (IQR 256 to 406 mg/dL) to 201 mg/dL (IQR 135 to 254 mg/dL) after replacing LPV/r with RAL ($P = 0.005$). IQR, interquartile range; LDL, low-density lipoprotein; RAL, raltegravir; LPV/r, ritonavir-boosted lopinavir.

major NRTI resistance mutations (M41L, M184V) were detected in this patient; however, no non-nucleoside reverse transcriptase inhibitor (NNRTI) or PI mutations were detected. The median CD4-positeve T cell counts were 609 cells/mm^3 (IQR 266 to 864 cells/mm^3) before RAL therapy and 505 cells/mm^3 (IQR 314 to 838 cells/mm^3) after RAL therapy in these 15 patients ($P = 0.91$). No patient experienced any RAL-related adverse events.

As noted earlier, there has been only a single clinical study of RAL plus ABC/3TC in antiretroviral-naïve HIV-infected patients till date (8). This study showed a 100% success rate of viral suppression with 96 weeks of therapy in 32 Caucasians, 2 African Americans, and 1 American-Indian. In the present study, we report for the first time that RAL plus ABC/3TC or ZDV/3TC regimens were effective in 13 antiretroviral-naïve Asian patients. Previous studies also showed that replacing LPV/r with RAL was an effective strategy to reduce the hyperlipidemia associated with PIs in Caucasians treated with TDF/FTC as an NRTI backbone (9). In the present study, we showed that replacing LPV/r with RAL also significantly improved lipid abnormalities in Asian patients treated with ABC/3TC or ZDV/3TC as backbones.

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Conflict of interest None to declare.

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