Original Article

Raltegravir and Abacavir/Lamivudine in Japanese Treatment-Naïve and Treatment-Experienced Patients with HIV Infection: a 48-Week Retrospective Pilot Analysis

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SUMMARY: Abacavir/lamivudine (ABC/3TC) is a nucleoside reverse transcriptase inhibitor used for treating human immunodeficiency viral (HIV) infections. Hypersensitivity reactions such as skin eruptions caused by ABC are well-known, but rarely occur in Asians. Raltegravir (RAL) is an integrase strand transfer inhibitor, that is now increasingly, used for treating HIV infections because it has few adverse effects. This retrospective analysis assessed the efficacy and safety of combined ABC/3TC and RAL in both treatment-naïve and -experienced Japanese patients with HIV infections. In all 11 treatment-naïve patients (100%), virological suppression to undetectable level was achieved. Liver transaminases, renal function, and serum lipid profiles showed no exacerbations up to 48 weeks of treatment. In 12 patients who were switched from previous regimens to ABC/3TC and RAL, HIV viral load was undetectable in 11 patients (91.6%), but remained detectable in 1 patient with poor adherence. Major reasons for switching regimens to ABC/3TC and RAL were hyperlipidemia and nausea. After switching, these adverse effects improved, and no new adverse effects were observed. Despite the small number of participants in this study, the results support the combination of ABC/3TC and RAL as a possible treatment choice in Japanese individuals with HIV-infection.

INTRODUCTION

Advances in antiretroviral therapy (ART) have increased the expected survival of patients with the human immunodeficiency virus (HIV) infection. The need for lifelong therapy with these agents indicates that physicians involved in the treatment patients with HIV infection must manage long-term adverse effects such as lipid metabolism abnormalities, renal dysfunction, and impaired bone metabolism. It is important to be aware of the differences in efficacy and adverse effects between the Asian and other populations. For example, abacavir/lamivudine (ABC/3TC), which is a combined nucleoside reverse transcriptase inhibitor (NRTI), is widely used in Asian patients with HIV infections because the human leukocyte antigen HLA-B*5701-related adverse effects of ABC are very rarely observed in Asians, especially those of Japanese descent (1,2). The antiviral effect of ABC/3TC is equivalent to that of tenofovir/emtricitabine (TDF/FTC) (3). According to the Japanese guideline, ABC/3TC and TDF/FTC are the primary recommended regimens for treatment-naïve patients with HIV infections (4). However, renal function declines more in tenofovir- than in abacavir-based antiretroviral therapy in treatment-naïve Japanese patients with HIV infection and having low body weight

(5).

Raltegravir (RAL) was recently designated as the primary recommended integrase strand transfer inhibitor in both the Japanese guideline and the U.S. Department of Health and Human Services (DHHS) guideline because of low frequency of adverse effects (4,6). The combination of ABC/3TC and RAL is used widely, but there are few reports on the efficacy of this combination. In particular, the efficacy and safety of ABC/3TC with RAL for Japanese patients have not been reported.

The purpose of this study was to investigate retrospectively the antiviral, immunological, and adverse effects among treatment-naïve and treatment-experienced Japanese patients with HIV-infections.

MATERIALS AND METHODS

Patients with HIV infections who were administered ABC/3TC and RAL at Juntendo University Hospital in Tokyo, Japan, from April 2009 to June 2012 were included in this retrospective investigation. The patients who began ART with ABC/3TC and RAL constituted the Naïve Group, and the patients who began ABC/3TC and RAL after discontinuation of another regimen constituted the Switched Group. Plasma hepatitis B surface antigen was confirmed to be negative before treatment. HIV viral load and CD4 T-cell counts were measured to analyze antiviral and immunological effects. In this study, virological suppression was defined as HIV-RNA <20 copies/mL. Alanine aminotransferase, total cholesterol, low-density lipoprotein cholesterol, triglycerides, estimated glomerular filtration rate, and urinary β_2 -microglobulin were also measured to monitor the adverse effects of ART on the liver, the kidney, and lipid metabolism. Laboratory data were collected at the

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starting or switching time (week 0), 12, 24, and 48 weeks later by retrospective chart review. Information about any skin eruptions or cardiovascular diseases was collected during the 48 week period. For patient in the Switched Group, previous regimens and reasons for changing from previous regimens to new combinations were extracted from the medical chart. After the regimen was switched to ABC/3TC and RAL, improvement or resolution of the reasons for changing regimens was noted for the 48 week period after regimen change.

All data were collected retrospectively by chart review, and no interventions with drugs or tests were added for this study. Physicians selected antiretroviral therapy based on their individual clinical assessment of each patient without any regard to this study.

RESULTS

A total of 11 patients (10 men and 1 woman) with a median age of 39 (range, 23–63) years were enrolled in the Naïve Group (Table 1). All patients (100%) showed an undetectable viral load at 48 weeks, which was indicative of successful treatment (Table 2 and Fig. 1). CD4-cell counts of all patients increased after starting treatment (Table 2 and Fig. 2). No liver enzyme elevations, dyslipidemias, decreased renal function, or other adverse events were observed in these patients (Table 3 and Fig. 3). No hypersensitivity reactive skin eruptions or cardiovascular diseases were observed in this group up to 48 weeks after the initiation of ART.

Table 1. Baseline patient demographics

Characteristic	Naïve Group (n = 11)		Switched Group (n = 12)	
	Range		Range	
Median age (yr)	39	23–63	44	31–68
Sex (man : woman)	10 : 1		8 : 4	
Median HIV viral load (copies/mL)	360,000	6,900–63,000	UD ¹⁾	UD–130,000 ²⁾
Median CD4 T-cell count (cells/mm ³)	274	12–395	567	147–1,441

¹⁾: Undetectable (<20 copies/mL).

²⁾: HIV-RNA was detected only in one case.

Fig. 1. HIV viral load of the Naïve Group. All of 11 patients (100%) showed undetectable viral load at 48 weeks. One patient was excluded at 24 weeks because of a transfer to a different hospital. Virological suppression was defined as <20 copies/mL of HIV-RNA.

A total of 12 patients (8 men and 4 women) with a mean age of 44 (range 31–68) years were enrolled in the

Table 2. Antiviral and immunological effects of ABC/3TC and RAL in the Naïve Group¹⁾

Case No.	Age	Sex ²⁾	HIV viral load (copies/mL)		CD4 T-cell count (cells/mm ³)	
			0 week	48 weeks	0 week	48 weeks
1	46	W	630,000	UD ³⁾	46	141
2	60	M	430,000	UD	395	629
3	39	M	370,000	UD	274	748
4	28	M	150,000	UD	319	584
5	39	M	120,000	UD	294	785
6	55	M	36,000	UD	27	252
7	63	M	17,000	UD	12	216
8	23	M	15,000	UD	337	433
9	35	M	14,000	UD	98	269
10	30	M	11,000	UD	160	376
11	39	M	6,900	UD	330	439

¹⁾: ABC, abacavir; 3TC, lamivudine; RAL, raltegravir.

²⁾: M, man; W, woman.

³⁾: Undetectable (<20 copies/mL).

Fig. 2. Median and range of CD4-lymphocyte counts of the Naïve Group. The median CD4-lymphocyte count increased after starting treatment with abacavir/lamivudine (ABC/3TC) and raltegravir (RAL).

Switched Group (Table 1). Patient profiles are shown in Table 4. At the time of switching, 1 patient had a detectable viral load; the other 11 patients achieved an undetectable viral load with their previous ART regimens. Major reasons for switching the ART to the new combination were hyperlipidemia (5 patients) and nausea (2 patients); other reasons are shown in Table 4. The patient with a detectable viral load when the ART regimen was switched from ABC/3TC and ritonavir-boosted fosamprenavir (case 1 in Table 4) experienced dizziness. The regimen was switched to ABC/3TC and RAL. An undetectable viral load was not achieved at 48 weeks after switching ART, but the viral load did show a remarkable decline at 48 weeks, from 1.3×10^5 copies/mL to 2.5×10^2 copies/mL. The CD4-lymphocyte count of case 1 also improved from 147/mm³ to 422/mm³. The other 11 patients all maintained undetectable viral loads and high CD4 counts, and their adverse effects that led to changing ART regimens had

Fig. 4. Median CD4 lymphocyte counts of the Switched Group. All patients maintained high CD4 T-cell count after switching regimen to abacavir/lamivudine (ABC/3TC) and raltegravir (RAL).

Fig. 3. Changes in laboratory data of the Naïve Group. No liver enzyme elevations or decreasing renal function are seen. Serum lipids remain stable.

ALT, alanine aminotransferase; T-Chol, total cholesterol; TG, triglycerides; LDL-C, low-density lipoprotein cholesterol; eGFR, estimated glomerular filtration rate; U-β₂MG, urinary β₂-microglobulin.

Table 3. Laboratory data of the Naïve and Switched Groups

Characteristic ¹⁾	Naïve Group, median (range)		Switched Group, median (range)	
	0 week	48 weeks	0 week	48 weeks
ALT (U/L)	20 (12–192)	28 (10–123)	23 (6–540)	21 (14–48)
T-Chol (mg/dL)	146 (119–192)	160 (111–224)	211 (146–337)	193 (153–237)
LDL-C (mg/dL)	165 (65–378)	116 (44–334)	176 (79–1,452)	130 (57–216)
TG (mg/dL)	74 (64–121)	94 (44–155)	132 (85–245)	101 (88–131)
eGFR (mL/min/1.73 m ²)	90.9 (19.3–124.9)	97.5 (66.5–128.3)	83.7 (50–132.8)	83.5 (58.2–100.4)
U-β ₂ MG (μg/L)	571 (133–4,057)	67.5 (7–332)	85.5 (29–2,272)	71.5 (4–221)

¹⁾: ALT, alanine aminotransferase; T-Chol, total cholesterol; LDL-C, low-density lipoprotein cholesterol; TG, triglycerides; eGFR, estimated glomerular filtration rate; U-β₂MG, urinary β₂-microglobulin.

Table 4. Previous regimen, antiviral effect, and immunological effect of ABC/3TC and RAL in the Switched Group

Case No.	Age	Sex ¹⁾	Previous regimen ²⁾	Reason for switching regimen	HIV viral load (copies/mL)		CD4 T-cell count (cells/mm ³)	
					0 week	48 weeks	0 week	48 weeks
1	44	W	ABC/3TC + FPV/r	Dizziness	130,000	250	147	422
2	31	M	ABC/3TC + FPV/r	Diarrhea	UD ³⁾	UD	532	445
3	39	M	ABC/3TC + EFV	Hyperlipidemia	UD	UD	671	798
4	59	M	ABC/3TC + EFV	Hyperlipidemia	UD	UD	547	714
5	45	M	TDF/FTC + LPV/r	Hyperlipidemia	UD	UD	601	423
6	68	M	TDF/FTC + LPV/r	Hyperlipidemia	UD	UD	377	561
7	33	W	ZDV/3TC + LPV/r	Nausea	UD	UD	1,441	1,224
8	52	M	ZDV/3TC + LPV/r	Nausea	UD	UD	586	448
9	40	W	ZDV/3TC + LPV/r	Renal dysfunction	UD	UD	1,218	1,400
10	44	M	ZDV/3TC + EFV	Nightmare	UD	UD	508	593
11	47	W	ZDV/3TC + NVP	Hyperlipidemia	UD	UD	994	534
12	40	M	d4T + 3TC + EFV	Insomnia	UD	UD	414	472

¹⁾ M, man; W, woman.

²⁾ ABC, abacavir; 3TC, lamivudine; FPV/r, fosamprenavir + ritonavir; EFV, efavirenz; TDF, tenofovir; FTC, emtricitabine; LPV/r, lopinavir + ritonavir; NVP, nevirapine; ZDV, zidovudine; d4T, stavudine.

³⁾ Undetectable (<20 copies/mL).

Fig. 5. Changes in laboratory data of the Switched Group. Liver enzyme abnormalities, hyperlipidemia, and renal dysfunction were improved.

ALT, alanine aminotransferase; T-Chol, total cholesterol; TG, triglycerides; LDL-C, low-density lipoprotein cholesterol; eGFR, estimated glomerular filtration rate; U-β₂MG, urinary β₂-microglobulin.

resolved (Table 4 and Fig. 4) with improved liver enzyme, lipid level, and renal function (Table 3 and Fig. 5). No hypersensitivity reactive skin eruptions or cardiovascular diseases were occurred during the 48-week observation period.

DISCUSSION

In the Naïve Group, virological treatment success was observed for all 11 patients without any adverse events up to 48 weeks of treatment, suggesting the efficacy and

safety of ABC/3TC and RAL among treatment-naïve patients. In particular, 5 patients with viral load >100,000 copies/mL were included in the present study, and all of them achieved successful viral load reduction and immunological recovery. In the DHHS guideline announced in 2013, ABC/3TC is recommended as an alternative NRTI drug for patients with HIV viral load >100,000 copies/mL, and TDF/FTC is recognized as being superior to ABC/3TC (6,7). However, the SHIELD trial showed that ABC/3TC gave good treatment results in patients with HIV viral

load >100,000 copies/mL (8). The HEAT study showed that the antiviral effect of ABC/3TC was not inferior to that of TDF/FTC (3). In a report comparing ABC/3TC with TDF/FTC in Japanese HIV-infected patients, ABC/3TC was found to be a safe and efficacious initial regimen for Japanese population (9). In the SHIELD trial, the number of cases was small to make any conclusions about the efficacy of ABC/3TC for the HIV-infected patients with viral loads >100,000 copies/mL; our study is the first report on the efficacy and safety of ABC/3TC for Japanese patients with high viral loads. Based on case 1 in the Switched Group, although the dizziness improved by switching regimens, the patient could not maintain adherence to the new combination. This patient was considered to have poor adherence from the start. The key to successful treatment with the ABC/3TC and RAL combination appears to be good adherence.

It is unknown as to whether ART guidelines from Western countries be applied directly to Japanese patients, despite differences in the physical constitution of Asians. Nishijima et al. studied the effects of ABC and TDF on renal dysfunction in Japanese patient with HIV infections (5). These investigators reported that renal function declined more in TDF-based ART than in ABC-based ART in low-body weight, treatment-naïve patients with HIV infection. Close monitoring of renal function was recommended for patients with low body weight treated with TDF, especially among those with a baseline body weight less than 60 kg. Therefore, TDF/FTC should be used cautiously in Japanese patient with low body weight. The present study showed normalization of renal function markers in both the Naïve and Switched Groups. Some antiretroviral drugs are also known to accelerate osteoporosis. In countries other than Japan, protease inhibitors (PIs) and TDF/FTC have been reported to decrease bone density compared with other types of antiretroviral drugs (10,11). Changes in bone density were not investigated in the present study, but the long-term effects of RAL and ABC/3TC on bone metabolism should be analyzed further among Japanese patients.

HLA-B*5701 is associated with hypersensitivity reaction skin eruptions by ABC/3TC. Although HLA-B*5701-positive patients with severe skin hypersensitivity reaction due to ABC have been reported among American and European patients, there have been few such reports in East Asia, especially in Japan (2). An investigation of Japanese and Taiwanese patients found that no HLA-B*5701-positive patients were identified among patients with suspected hypersensitivity reactions such as skin eruptions caused by ABC (2,12). Our study did not investigate HLA-B*5701 status in all patients, but no hypersensitivity reactions with skin eruptions occurred. Summarizing the results of previous reports and this study, the use of ABC/3TC rarely causes such skin reactions in Japanese patients. ABC was also reported to correlate with myocardial infarction, but another report showed no relationship between them (13,14). There is no consensus about the negative impact of ABC on cardiovascular diseases, and no cardiovascular events occurred in the present study.

RAL has an excellent antiviral effect and a low frequency of hyperlipidemia. Hyperlipidemia is a major

problem for HIV-infected patients because antiretroviral drugs, especially PIs, often cause hyperlipidemia. In addition, HIV infection itself is associated with hyperlipidemia (15). The combination of ABC/3TC and RAL improved lipid abnormalities in patients previously treated with ABC/3TC and ritonavir-boosted lopinavir (16). In the present study, the Naïve Group maintained stable serum lipid levels, and the Switched Group showed improvement of dyslipidemia. RAL is very useful in patients with HIV infection because it can be administered without concern for hyperlipidemia. The major adverse effects of RAL are headache, nausea, and liver transaminase elevation (7). In the present study, no such adverse effects were observed. The disadvantage of RAL is the necessity for a twice-daily regimen, which can decrease adherence and result in insufficient antiviral effect, as seen in case 1 of the Switched Group in this analysis.

This study had some limitations. The number of patients was small to reach definitive conclusions about the two groups, HLA-B*5701 was not investigated in all patients, and comparison of the cases with a control group could not be performed because this was a retrospective case series.

Despite these limitations, this study showed that the combination of ABC/3TC and RAL treatment was safe and had an excellent therapeutic effect, even in treatment-naïve patients with viral loads >100,000 copies/mL. Changing from other treatment regimens to this combination was also successful, but maintaining good adherence was deemed essential. Further research about the antiviral efficacy and long-term adverse effects of ABC/3TC and RAL in a larger number of Japanese patients with HIV-infections is necessary.

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