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# Single Nucleotide Polymorphisms in *ABCC2* Associate With Tenofovir-Induced Kidney Tubular Dysfunction in Japanese Patients With HIV-1 Infection: A Pharmacogenetic Study

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***Background.*** Tenofovir is a widely used antiretroviral drug although it can cause kidney tubular dysfunction (KTD). The aim of this study was to determine the association between polymorphisms in genes encoding drug transporters and KTD in Japanese patients treated with tenofovir.

***Methods.*** The association between tenofovir-induced KTD and 14 single nucleotide polymorphisms (SNPs) in the *ABCC2*, *ABCC4*, *ABCC10*, *SCL22A6*, and *ABCB1* genes was investigated in 190 Japanese patients. KTD was diagnosed by the presence of at least 3 abnormalities in the following parameters: fractional tubular resorption of phosphate, fractional excretion of uric acid, urinary β2-microglobulin, urinary α1-microglobulin, and urinary N-acetyl-β-D-glucosaminidase. Genotyping was performed by allelic discrimination using TaqMan 5′-nuclease assays with standard protocols. Associations between genotypes and KTD were tested by univariate and multivariate logistic regression analyses.

***Results.*** KTD was diagnosed in 19 of the 190 (10%) patients. Univariate and multivariate analyses showed a significant association between KTD and genotype CC at position −24 CC (adjusted odds ratio [OR], 20.08; 95% confidence interval [CI], 1.711–235.7; $P = .017$) and genotype AA at position 1249 (adjusted OR, 16.21; 95% CI, 1.630–161.1; $P = .017$) of *ABCC2*. Multivariate analysis showed higher adjusted OR for patients with both homozygotes (adjusted OR, 38.44; 95% CI, 2.051–720.4; $P = .015$). *ABCC2* haplotype −24T and 1249G was a protective haplotype for KTD (OR, 0.098; 95% CI, .002–.603; $P = .003$

***Conclusions.*** This is the first study of our knowledge to identify the association between SNPs in *ABCC2* and tenofovir-induced KTD in an Asian population. Close monitoring of renal function is warranted in tenofovir-treated patients with these SNPs.

Tenofovir disoproxil fumarate (TDF), a prodrug of tenofovir, is a nucleotide reverse transcriptase inhibitor widely used for the treatment of human immunodeficiency virus type 1 (HIV-1) infection and hepatitis B infection [1–4]. Tenofovir is excreted by a combination of glomerular filtration and active tubular secretion. Although the nephrotoxicity of tenofovir is regarded mild and tolerable [5–7], several cases of tenofovir-induced nephrogenic diabetes insipidus, Fanconi syndrome, and acute renal failure have been reported, and prognosis of renal function with long-term tenofovir use remains unknown [8–10].

The mechanism of tenofovir-induced kidney damage is not fully understood. However, mitochondrial damage in the proximal renal tubular cells was observed in patients with prominent tenofovir-induced kidney tubular dysfunction (KTD) [11, 12].

Received 20 May 2012; accepted 24 August 2012; electronically published 5 September 2012.

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**Clinical Infectious Diseases 2012;55(11):1558–67**

DOI: 10.1093/cid/cis772

Because the characteristics and severity of tenofovir-induced KTD vary widely among individuals, the role of host genetics has drawn a particular attention. Single nucleotide polymorphisms (SNPs) in transporter proteins of renal tubular cells have been investigated to elucidate their roles in tenofovir-induced KTD [13–15].

Tenofovir enters kidney tubular cells through the basolateral membrane and is transported mainly by organic anion transporter (OAT) 1 and, to a lesser extent, OAT 3, encoded by genes *SLC22A6* and *SLC22A8*, respectively [16]. Tenofovir is excreted into the urine at the apical membrane by 2 transporters on the luminal membrane; multidrug resistance protein (MRP) 4 and MRP 2, encoded by the adenosine triphosphate–binding cassette (ABC) genes *ABCC4* and *ABCC2*, respectively [17, 18]. Although the role of MRP4 in transporting tenofovir has been well established, that of MRP 2 remains controversial [19, 20]. Recently, MRP 7, encoded by *ABCC10* gene, was also reported to take part in the excretion of tenofovir [21]. P-glycoprotein is a membrane protein expressed on the cells of renal proximal tubule, intestine, and hepatocytes. Encoded by *ABCB1* gene, P-glycoprotein transports TDF, the prodrug of tenofovir. SNPs on *ABCB1* might alter the expression of P-glycoprotein and thus affect exposure of tenofovir [22–24].

Previous studies reported inconsistent findings on the association of the SNPs of the transporter protein on tenofovir-induced KTD [13–15]. Several pathological processes could induce KTD, such as active infection, inflammation, diabetic nephropathy, concurrent use of nephrotoxic drugs, and preexisting renal impairment, and thus it is difficult to evaluate KTD induced exclusively by tenofovir [25]. Moreover, drug interaction with other antiretrovirals, especially ritonavir-boosted protease inhibitors, modifies tenofovir clearance and thus the severity of tenofovir-induced KTD [26, 27]. Previous studies examined patients treated with various antiretroviral combinations, which might also contribute to the inconsistent findings. Thus, the effect of SNPs on tenofovir-induced KTD remains to be clarified and isolated from other abovementioned conventional risk factors for KTD [15, 28]. Of note, the population investigated in previous studies on the role of SNPs in tenofovir-induced KTD was mostly whites, and patients of other genetic background have hardly been examined.

Based on the above background, the present study was designed to elucidate the association between polymorphisms in genes encoding drug transporters in renal tubular cells and tenofovir-induced KTD, in a setting designed to exclude other predisposing or intervening factors: the inclusion of Japanese patients with HIV infection on the same antiretroviral combination with suppressed HIV-1 viral load, and free of preexisting renal impairment, major comorbidities, and active infections.

## METHODS

### Ethics Statement

This study was approved by the Human Genetics Research Ethics Committee of the National Center for Global Health and Medicine, Tokyo, Japan. Each patient included in this study provided a written informed consent for genetic testing and publication of clinical data for research purposes. The study was conducted according to the principles expressed in the Declaration of Helsinki.

### Study Design

We performed a single-center cohort study to cross-sectionally elucidate the association between SNPs in genes encoding renal tubular transporters in Japanese patients with HIV infection and tenofovir-induced KTD.

### Study Subjects

The study included consecutive Japanese patients with HIV infection, aged >17 years, with HIV-1 viral load <200 copies/mL, and on at least 4-week treatment with once-daily ritonavir (100 mg)–boosted darunavir (800 mg) plus fixed dose tenofovir (300 mg)/emtricitabine (200 mg), seen at our clinic between 1 October 2011 and 31 March 2012. The exclusion criteria were (1) active infection, (2) malignancy, (3) diabetes mellitus, defined by the use of anti-diabetic agents or fasting plasma glucose >126 mg/dL or plasma glucose >200 mg/dL on two different days, (4) alanine aminotransferase 2.5 times more than the upper limit of normal, (5) estimated glomerular filtration rate (eGFR) calculated by Cockcroft-Gault equation of <50 mL/minutes [creatinine clearance = [(140 − age) × weight (kg)]/(serum creatinine × 72)(×0.85 for females)] [29], and (6) patients without consent to the study.

### Measurements

Blood and spot urine samples were collected either on the day of enrollment or on the next visit, together with body weight measurement. The blood samples were used to measure serum creatinine, serum uric acid, serum phosphate, CD4 count, and C-reactive protein, whereas urine samples were used to measure phosphate, uric acid, creatinine, β2-microglobulin (β2M), α1-microglobulin (α1M), and N-acetyl-β-D-glucosaminidase (NAG). The values of β2M, α1M, and NAG measured in the urine samples were expressed relative to urinary creatinine of 1 g/L (/g Cr).

Urinary concentrations of β2M and α1M were measured with latex aggregation assay kits (β2M: BMG-Latex X1 "Seiken"; Denka Seiken Co, Niigata, Japan; α1M: Eiken α1M-III; Eiken Chemical Co, Tokyo, Japan), and those of NAG by colorimetric assay of enzyme activity with 6-methyl-2-pyridyl-N-acetyl-1-thio-β-D-glucosaminide as substrate (Nittobo Medical Co, Tokyo).

### Definition of Renal Proximal Tubular Dysfunction

KTD was defined as the presence of at least 3 abnormalities in the following 5 parameters: fractional tubular resorption of phosphate {1 − [(urine phosphate × serum creatinine)/(urine creatinine × serum phosphate)]} × 100 of <82%, fractional excretion of uric acid {[(urine uric acid × serum creatinine)/(urine creatinine × serum uric acid)] × 100)} of >15%, β2-microglobulinuria (β2M > 1000 μg/g Cr), α1-microglobulinuria (α1M > 16.6 mg/g Cr), and high-NAG level in urine (NAG > 5.93 U/g Cr). The above cutoff levels were selected on the basis of data reported previously by various investigators [15, 30, 31].

The potential risk factors for KTD were determined according to previous studies and collected together with the basic demographics from the medical records [6, 27, 32, 33]. They included age, sex, body weight, and presence or absence of other medical conditions (concurrent use of nephrotoxic drugs such as ganciclovir, sulfamethoxazole/trimethoprim, and nonsteroidal antiinflammatory agents, coinfection with hepatitis B, defined by positive hepatitis B surface antigen, coinfection with hepatitis C, defined by positive HCV viral load, hypertension, defined by current treatment with antihypertensive agents or 2 successive measurements of systolic blood pressure >140 mmHg or diastolic blood pressure >90 mmHg at the clinic, dyslipidemia, defined by current treatment with lipid-lowering agents or 2 successive measurements of either low-density lipoprotein cholesterol >140 mg/dL, high-density lipoprotein cholesterol <40 mg/dL, total cholesterol >240 mg/dL, triglyceride >500 mg/dL. At our clinic, blood pressure and body weight are measured every visit. We used the data on or closest to and preceding the day of blood/urine sample collection by no more than 180 days.

### Genetic Polymorphisms

SNPs in genes encoding tubular transporters were selected on the basis of their functional significance, findings of previously published reports, and/or reported minor-allele frequencies >5% in the Japanese [13–15, 21, 28]. The allele frequency data for the Japanese were obtained from the Japanese Single Nucleotide Polymorphisms (JSNP) database [34]. The 14 SNPs selected were (1) *ABCC2* (encodes MRP2) −24C → T (in the promoter; rs717620); 1249G → A (Val417Ile; rs2273697); 2366C → T (Ser789Phe; rs56220353); 2934G → A (Ser978Ser; rs3740070), (2) *ABCC4* (encodes MRP4) 559G → T (Gly187Trp; rs11568658); 912G → T (Lys304Asn; rs2274407); 2269G → A (Glu757Lys; rs3765534); 3348A → G (Lys1116Lys; rs1751034); 4135T → G [in the 3′ untranslated region (UTR); (rs3742106)]; 4976T → C (3′ UTR; rs1059751), (3) *ABCC10* (encodes MRP10) 526G → A (intron; rs9349256); 2759T → C (Ile920Thr; rs2125739), (4) *SLC22A6* (encodes OAT1) 180C → T (Asn60Asn; rs11568630), and (5) *ABCB1* (encodes P-glycoprotein) 2677T → A/G (A:Ser893Thr, G:Ser893Ala; rs2032582).

### Pharmacogenetic Analyses

Genomic DNA was extracted from peripheral-blood leukocytes using the protocol described in the sheet enclosed with the QIAamp DNA MiniKit (Qiagen, Valencia, California). All genotyping was performed by allelic discrimination using TaqMan 5′-nuclease assays with standard protocols (TaqMan SNP Genotyping Assays; Applied Biosystems, Foster City, California). The primer and probe sequences are available on request.

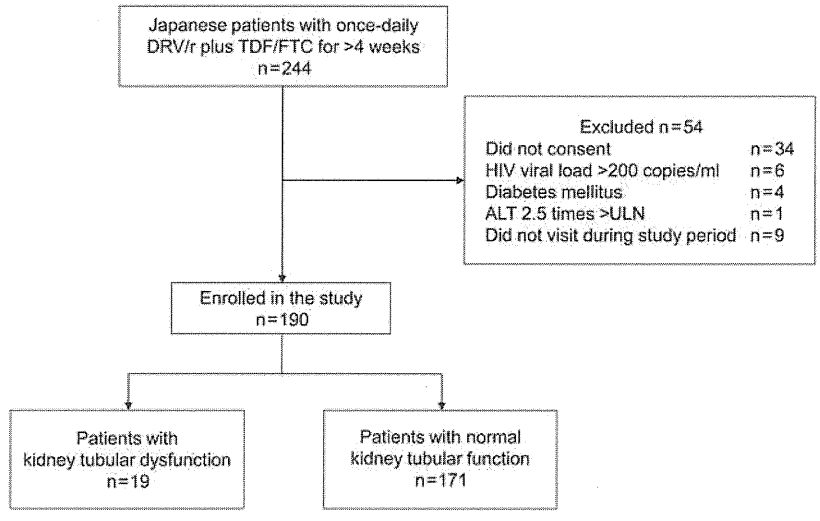


**Figure 1.** Patient enrollment. Abbreviations: ALT, alanine transaminase; DRV/r, ritonavir-boosted darunavir; HIV, human immunodeficiency virus; TDF/FTC, tenofovir/emtricitabine; ULN, upper limit of normal.

### Statistical Analysis

Baseline characteristics were compared between patients with KTD and without tubular dysfunction by the Student *t* test for continuous variables and by either the $\chi^2$ test or Fisher exact test for categorical variables. Statistical comparisons for genotype frequencies between 2 groups were made by use of $2 \times 3$ table Fisher exact test ($2 \times 6$ table for rs2032582). Associations between genotypes and KTD were tested by univariate and multivariate logistic regression analyses. The impact of other variables was estimated with univariate analysis, and those with $P < .20$ were incorporated into multivariate analysis, in addition to the basic demographics such as age and sex. Statistical significance was defined at 2-sided *P* value < .05. We used odds ratios (ORs) and 95% confidence intervals (95% CIs) to estimate the impact of each variable on KTD. The Haploview software was used to test Hardy-Weinberg equilibrium and *ABCC2* and *ABCC4* haplotype analysis. All other statistical analyses were performed with the Statistical Package for Social Sciences ver. 17.0 (SPSS, Chicago, Illinois).

## RESULTS

A total of 190 patients who provided blood and urine samples and satisfied the inclusion and exclusion criteria were enrolled in the study (Figure 1). KTD was diagnosed in 19 of the 190 patients (10%). The baseline characteristics and laboratory data for patients with and without KTD are listed in Table 1. Patients with KTD were older ($P < .001$), had smaller body weight ($P = .006$) and lower eGFR ($P = .003$), and were more likely to be hypertensive than patients with normal tubular function ($P = .088$). The median duration of tenofovir therapy was 71.5 weeks (interquartile range [IQR]: 36.8–109.2 weeks) for the entire study population, which was not different between the 2 groups ($P = .888$).

**Table 1. Characteristics of Patients With and Without Kidney Tubular Dysfunction**

| | Patients With KTD (n = 19) | Patients With Normal Tubular Function (n = 171) | *P* Value |
|---|---|---|---|
| Variables for kidney tubular markers | | | |
| Urinary β2M (μg/g Cr)[a] | 3066 (2247–10068) | 209.2 (114.2–536.2) | <.001 |
| Urinary α1M (mg/g Cr)[a] | 26.5 (19.8–37.4) | 7.95 (5.02–11.9) | <.001 |
| Urinary NAG (U/g Cr)[a] | 9 (6.2–14.3) | 3.74 (2.84–4.95) | <.001 |
| Fractional tubular resorption of phosphate[a] | 83.9 (81.7–92) | 91.9 (88.8–94.4) | <.001 |
| Fractional excretion of uric acid[a] | 9.7 (8.1–12.4) | 6.4 (5.0–9.0) | <.001 |
| Contribution of each parameter to KTD | | | |
| Urinary β2M > 1000 μg/g Cr, No. (%) | 19 (100) | 21 (12.3) | <.001 |
| Urinary α1M > 16.6 mg/g Cr, No. (%) | 18 (94.7) | 17 (9.9) | <.001 |
| Urinary NAG >5.93 U/g Cr, No. (%) | 17 (89.5) | 23 (13.5) | <.001 |
| Fractional tubular resorption of phosphate <82%, No. (%) | 5 (26.3) | 2 (1.2) | <.001 |
| Fractional excretion of uric acid >15%, No. (%) | 2 (10.5) | 4 (2.3) | .112 |
| Characteristics | | | |
| Sex (male), No. (%) | 18 (94.7) | 166 (97.1) | .473 |
| Age[a] | 60 (41–62) | 38 (32–42) | <.001 |
| Route of transmission (homosexual contact), No. (%) | 16 (84.2) | 153 (89.5) | .528 |
| Weight (kg)[a] | 56 (53.5–66.5) | 67.2 (58.1–75) | .006 |
| Estimated glomerular filtration rate (mL/minutes/1.73 $m^2$)[a] | 75.5 (62.8–93.5) | 87.7 (77.5–98) | .003 |
| Serum creatinine (mg/dL)[a] | 0.85 (0.68–0.96) | 0.80 (0.73–0.88) | .168 |
| CD4 cell count (μL)[a] | 380 (194–501) | 379 (275–533) | .261 |
| Serum phosphate (mg/dL)[a] | 3.4 (2.7–3.7) | 3.2 (2.9–3.6) | .815 |
| Serum uric acid (mg/dL)[a] | 4.7 (4.2–5.7) | 5.6 (4.8–6.4) | .080 |
| Nephrotoxic drug, No. (%) | 2 (10.5) | 12 (7.0) | .420 |
| Hepatitis C, No. (%) | 0 (0) | 3 (1.8) | .728 |
| Hepatitis B, No. (%) | 2 (10.5) | 24 (14) | .501 |
| Dyslipidemia, No. (%) | 4 (21.1) | 54 (31.6) | .253 |
| Hypertension, No. (%) | 8 (42.1) | 42 (24.6) | .088 |
| C-reactive protein (mg/dL)[a] | 0.07 (0.03–0.28) | 0.07 (0.03–0.16) | .277 |
| Duration of treatment with TDF (weeks)[a] | 60.3 (17.7–115.4) | 73.3 (37.7–109.1) | .888 |

Abbreviations: KTD, kidney tubular dysfunction; NAG, N-acetyl-β-D-glucosaminidase; TDF, tenofovir disoproxil fumarate.

[a] Median (interquartile range).

**Table 2. Genotype Frequencies at *ABCC2, ABCC4, ABCC10, SLC22A6,* and *ABCB1* in Patients With and Without Kidney Tubular Dysfunction**

| Genotype | Amino Acid | Patients With KTD (n = 19) | Patients With Normal Tubular Function (n = 171) | *P* Value[a] |
|---|---|---|---|---|
| *ABCC2* (MRP2) | | | | |
| −24 C → T, rs717620 | | | | |
| C/C | | 18 (94.7) | 108 (63.2) | |
| C/T | | 1 (5.3) | 52 (30.4) | .018 |
| T/T | | 0 (0) | 11 (6.4) | |
| 1249 G → A, rs2273697 | Val417Ile | | | |
| G/G | | 11 (57.9) | 133 (77.8) | |
| A/G | | 5 (26.3) | 34 (19.9) | .017 |
| A/A | | 3 (15.8) | 4 (2.3) | |
| 2366 C → T, rs56220353 | Ser789Phe | | | |
| C/C | | 19 (100) | 167 (97.7) | |
| C/T | | 0 (0) | 3 (1.8) | 1.000 |
| T/T | | 0 (0) | 1 (0.6) | |
| 2934 G → A, rs3740070 | Ser978Ser | | | |
| G/G | | 18 (94.7) | 159 (93.0) | |
| G/A | | 1 (5.3) | 11 (6.4) | 1.000 |
| A/A | | 0 (0) | 1 (0.6) | |
| *ABCC4* (MRP4) | | | | |
| 559 G → T, rs11568658 | Gly187Trp | | | |
| G/G | | 13 (68.4) | 133 (77.8) | |
| G/T | | 4 (21.1) | 34 (19.9) | .126 |
| T/T | | 2 (10.5) | 4 (2.3) | |
| 912G → T, rs2274407 | | | | |
| G/G | | 13 (68.4) | 102 (59.6) | |
| T/G | | 6 (31.6) | 52 (30.4) | .461 |
| T/T | | 0 (0) | 17 (9.9) | |
| 2269 G → A, rs3765534 | Glu757Lys | | | |
| G/G | | 15 (78.9) | 129 (75.4) | |
| G/A | | 2 (10.5) | 35 (20.5) | .241 |
| A/A | | 2 (10.5) | 7 (4.1) | |
| 3348 A → G, rs1751034 | Lys1116Lys | | | |
| A/A | | 13 (68.4) | 98 (57.3) | |
| A/G | | 3 (15.8) | 58 (33.9) | .185 |
| G/G | | 3 (15.8) | 15 (8.8) | |
| 4135 T → G, rs3742106 | | | | |
| T/T | | 6 (31.6) | 46 (26.9) | |
| T/G | | 7 (36.8) | 79 (46.2) | .707 |
| G/G | | 6 (31.6) | 46 (26.9) | |
| 4976T → C, rs1059751 | | | | |
| T/T | | 6 (31.6) | 46 (26.9) | |
| T/C | | 5 (26.3) | 86 (50.3) | .090 |
| C/C | | 8 (42.1) | 39 (22.8) | |
| *ABCC10* (MRP7) | | | | |
| 526G → A, rs9349256 | | | | |
| G/G | | 4 (21.1) | 32 (18.7) | |
| A/G | | 9 (47.4) | 65 (38) | .569 |
| A/A | | 6 (31.6) | 74 (43.3) | |

*Table 2 continued.*

| Genotype | Amino Acid | Patients With KTD (n = 19) | Patients With Normal Tubular Function (n = 171) | *P* Value[a] |
|---|---|---|---|---|
| 2759T → C, rs2125739 | Ile920Thr | | | |
| T/T | | 15 (71.4) | 131 (77.5) | |
| T/C | | 6 (28.6) | 31 (18.3) | .488 |
| C/C | | 0 (0) | 7 (4.1) | |
| *SLC22A6* (OAT1) | | | | |
| 180C → T, rs11568630 | | | | |
| C/C | | 18 (94.7) | 164 (95.9) | |
| C/T | | 1 (5.3) | 7 (4.1) | .577 |
| T/T | | 0 (0) | 0 (0) | |
| *ABCB1* (P-glycoprotein) | | | | |
| 2677T → A/G, rs2032582 | A:Ser893Thr<br>G:Ser893Ala | | | |
| T/T | | 0 (0) | 47 (27.5) | |
| T/A | | 3 (15.8) | 14 (8.2) | |
| G/G | | 4 (21.1) | 36 (21.1) | .002 |
| G/T | | 8 (42.1) | 46 (26.9) | |
| G/A | | 1 (5.3) | 24 (14) | |
| A/A | | 3 (15.8) | 4 (2.3) | |

Abbreviation: KTD, kidney tubular dysfunction.

[a] By Fisher exact test.

Table 2 summarizes the distribution of genotypes at the *ABCC2*, *ABCC4*, *ABCC10*, *SLC22A11*, and *ABCB1* genes in the 2 groups. All polymorphisms were in Hardy-Weinberg equilibrium with a cutoff *P* value of .001. In single SNP analysis, a higher percentage of patients with KTD were found among genotype CC at position −24 and genotype AA at position 1249 of *ABCC2*, compared to patients with other genotypes (−24 CC; 14.3% [in 18 of 126 patients] vs 1.6% [in 1 of 64 patients]; $P = .004$; 1249 AA; 42.9% [in 3 of 7 patients] vs 8.7% [in 16 of 183 patients]; $P = .023$), respectively. The percentage of patients with KTD was also higher among genotype AA at position 2677 of *ABCB1*, compared to patients with other genotypes (2677 AA; 42.9% [in 3 of 7 patients] vs. 8.7% [in 16 of 183 patients]; $P = .023$). KTD was marginally associated with genotype AA at position 559 and genotype GG at position 4976 of *ABCC4* ($P = .112$, and .090, respectively).

### Association of Genotypes with KTD

Univariate analysis showed a significant association between KTD and patients with genotype CC at position −24 (OR, = 10.50; 95% CI, 1.369–80.55; $P = .024$) and patients with genotype AA at position 1249 (OR, 7.828; 95% CI, 1.609–38.10; $P = .011$) of *ABCC2* (Table 3). The risk for KTD was higher in patients with both genotype CC at position −24 and genotype AA at position 1249 (OR, 31.88; 95% CI, 3.131–324.5; $P = .003$). Genotype AA at position 2677 of *ABCB1* was also significantly associated with KTD (OR, 7.828; 95% CI, 1.609–38.10; $P = .011$). Furthermore, old age (per 1 year, OR, 1.165; 95% CI, 1.100–1.233; $P < .001$), low body weight (per 1 kg decrement, OR, 1.076; 95% CI, 1.021–1.135; $P = .007$), and low eGFR (per 1 mL/minutes/1.73 $m^2$ decrement, OR, 1.052; 95% CI, 1.016–1.090; $P = .004$) were also associated with KTD.

Multivariate analysis identified genotype CC at position −24 and genotype AA at position 1249 of *ABCC2* as independent risks for KTD after adjustment for sex, age, weight, eGFR, and hypertension (adjusted OR, = 20.08; 95% CI, 1.711–235.7; $P = .017$; adjusted OR, 16.21; 95% CI, 1.630–161.1; $P = .017$), respectively (Table 4). Patients with both of the abovementioned two homozygotes showed higher adjusted OR in multivariate analysis (adjusted OR, 38.44; 95% CI, 2.051–720.4; $P = .015$; Table 4). On the other hand, genotype AA at position 2677 of *ABCB1* was not significantly associated with KTD in multivariate analysis adjusted for the abovementioned variables (adjusted OR, 1.686; 95%CI, .163–17.43; $P = .661$).

### Association of Haplotypes at ABCC2 and ABCC4 with KTD

Haplotype construction was performed with the 4 identified SNPs with $P < .10$ in univariate analysis: *ABCC2*, −24 C → T, 1249 G → A; *ABCC4*, 559 G → T, 4976T → C (Table 4). Haplotypes with frequency of >1% were analyzed. *ABCC2* haplotype CA was significantly associated with TDF-induced KTD (OR, 2.910; 95% CI, 1.295–6.221; $P = .011$), whereas *ABCC2* haplotype TG was a protective haplotype (OR, 0.098; 95% CI, .002–.603; $P = .003$). *ABCC4* haplotype TT was marginally

**Table 3. Univariate Analysis of Risks for Kidney Tubular Dysfunction in Patients With HIV Infection Treated With Tenofovir**

| Characteristic | OR | 95% CI | *P* Value |
|---|---|---|---|
| Female sex | 1.844 | .204–16.67 | .586 |
| Age per 1 year | 1.165 | 1.100–1.233 | <.001 |
| Weight per 1 kg decrement | 1.076 | 1.021–1.135 | .007 |
| CD4 count per 1/μL decrement | 1.002 | .999–1.004 | .261 |
| Baseline eGFR per 1 mL/minutes/1.73 $m^2$ decrement | 1.052 | 1.016–1.090 | .004 |
| Concurrent use of nephrotoxic drugs | 1.559 | .322–7.555 | .581 |
| Hepatitis B | 0.721 | .156–3.319 | .674 |
| C-reactive protein per 1 mg/dL | 1.551 | .689–3.494 | .289 |
| Hypertension | 2.234 | .843–5.922 | .106 |
| Dyslipidemia | 0.578 | .183–1.823 | .349 |
| Duration of treatment with tenofovir disoproxil fumarate (weeks) | 0.999 | .992–1.007 | .888 |
| *ABCC2* | | | |
| −24 CC | 10.50 | 1.369–80.55 | .024 |
| 1249 AA | 7.828 | 1.609–38.10 | .011 |
| −24 CC plus 1249 AA | 31.88 | 3.131–324.5 | .003 |
| 2934 GG | 1.358 | .167–11.07 | .775 |
| *ABCC4* | | | |
| 559 TT | 4.912 | .837–28.81 | .078 |
| 912 TT | 1.466 | .531–4.042 | .460 |
| 2269 AA | 2.756 | .530–14.34 | .228 |
| 3348 GG | 1.950 | .510–7.463 | .329 |
| 4135 GG | 1.254 | .450–3.494 | .665 |
| 4976 CC | 2.462 | .925–6.547 | .071 |
| *ABCC10* | | | |
| 526 GG | 1.158 | .360–3.725 | .805 |
| 2759 TT | 0.619 | .220–1.738 | .363 |
| *ABCB1* | | | |
| 2677 AA | 7.828 | 1.609–38.10 | .011 |

Abbreviations: CI, confidence interval; eGFR: estimated glomerular filtration rate; HIV, human immunodeficiency virus; OR, odds ratio.

[a] Due to low prevalence of minor alleles, rs56220353, rs11568630, and rs2274407 were not included in this analysis.

**Table 4. Multivariate Analysis for the Risk of Tenofovir-Induced Kidney Tubular Dysfunction With Homozygotes at −24 and 1249 of *ABCC2* in Patients With HIV Infection**

| *ABCC2* | Adjusted OR | 95% CI | *P* Value |
|---|---|---|---|
| Homozygote at −24 CC | 20.08 | 1.711–235.7 | .017 |
| Homozygote at 1249 AA | 16.21 | 1.630–161.1 | .017 |
| Homozygotes at −24 CC plus 1249 AA | 38.44 | 2.051–720.4 | .015 |

Each variable was adjusted for sex, age, weight, estimated glomerular filtration rate, and hypertension.

Abbreviations: CI, confidence interval; OR, odds ratio.

associated with tenofovir-induced KTD (OR, 2.497; 95% CI, .902–6.949; $P = .077$).

## DISCUSSION

The present study demonstrated that genotype CC at position −24 and genotype AA at position 1249 of *ABCC2* gene are associated with tenofovir-induced KTD in Japanese patients with HIV-1 infection. The effect of SNPs was more evident in patients with both −24 CC and 1249 AA homozygotes than in those with either homozygote only. The findings of this study resolve long-term controversy over the role of genetic polymorphisms in tenofovir-induced KTD and confirm the effect of the SNPs in *ABCC2* gene in tenofovir-induced KTD.

CA haplotype (−24C, 1249A) of *ABCC2* was associated with tenofovir-induced KTD, whereas TG was a protective haplotype (Table 5). Izzedine et al [13] reported the role of CATC haplotype (−24C, 1249A, 3563T, 3972C) of *ABCC2* in KTD. However, 3563T did not play such role in this haplotype analysis, because the prevalence of 3563T is 0% in the Japanese, according to the HapMap data, and haplotype with only −24C plus 1249A still exhibited its effect on tenofovir-induced KTD (Table 5; www.hapmap.org). The reported association between tenofovir-induced KTD and 526G and 2759C of *ABCC10* described by Pushpakom et al [21] was also not reproduced in this study. Furthermore, SNPs in *ABCC4*, *SLC22A6*, and *ABCB1* investigated in the present study did not show a significant association with tenofovir-induced KTD (Table 3).

Three main aspects of our study are important. First, this is the first study to our knowledge that elucidated the effect of SNPs on tenofovir-induced KTD conducted in a country other than European countries or the United States. Our study examined Japanese patients of genetic background different from patients of previous studies, which consisted mostly of whites. While SNPs −24C and 1249A of *ABCC2* have been speculated to correlate with tenofovir-induced KTD in previous studies, the present study confirmed that these SNPs are risk factors for tenofovir-induced KTD in nonwhites.

The result that the SNPs in *ABCC2* are a risk for tenofovir-induced KTD can also be applied to patients with other genetic backgrounds who host SNPs −24C and 1249A. Notably, the impact of SNPs on tenofovir-induced KTD might be more significant in Africans and Indians than in Japanese or whites, considering that the allele frequencies of −24C and 1249A are higher in these population according to the HapMap data (−24C; Africans 96.9%, Indians 92.6%, Japanese 80.8%, whites 81.9%, 1249A; Africans 21.7%, Indians 30.7%, Japanese 8.9%, whites 23.7%; www.hapmap.org).

Second, the study was designed to evaluate the exclusive effect of SNPs on tenofovir-induced KTD by excluding

**Table 5. Association Between Haplotype in *ABCC2* and *ABCC4* and Kidney Tubular Dysfunction**

| | | Allele/Haplotype Frequency, % | | | |
|---|---|---|---|---|---|
| SNP Marker/Haplotype | Allele | KTD Group (n = 19) | Control Group (n = 171) | OR (95% CI)[a] | *P* Value |
| *ABCC2* | | | | | |
| −24 C → T | C | 97.4 | 78.4 | 10.22 (1.658–419.8) | .003 |
| 1249 G → A | A | 28.9 | 12.3 | 2.91 (1.345–6.296) | .011 |
| *ABCC2* haplotype | CA | 28.9 | 12.3 | 2.91 (1.295–6.221) | .011 |
| | TG | 2.6 | 21.6 | 0.098 (.002–.603) | .003 |
| *ABCC4* | | | | | |
| 559 G → T | T | 21.1 | 12.3 | 1.905 (.705–4.614) | .213 |
| 4976 T → C | T | 48 | 55.3 | 0.746 (.375–1.470) | .399 |
| *ABCC4* haplotype | | | | | |
| TT | TT | 17.6 | 7.9 | 2.497 (.902–6.949) | .077 |

Abbreviations: CI, confidence interval; KTD, kidney tubular dysfunction; OR, odds ratio; SNP, single-nucleotide polymorphism.

[a] ORs and *P* values are for comparisons of allele/haplotype frequencies between the kidney tubular dysfunction and control groups.

possible predisposing factors for KTD, for example, active infection, malignancies, diabetes mellitus, and preexisting renal impairment, which are known risks for KTD [35]. Patients who showed no HIV-1 viral suppression were also excluded. Furthermore, the enrolled patients were Japanese only, and this helped to examine a study population with comparatively similar genetic background. The study population was also on the same antiretroviral regimen (ritonavir-boosted darunavir plus tenofovir/emtricitabine), and this also helped to evaluate more precisely the effect of SNPs, because plasma concentration of tenofovir is affected by concomitant antiretrovirals and the delta change in plasma tenofovir concentration likely differs in the presence of each concomitant drug [26].

Third, SNPs were examined in 190 patients in this study. To our knowledge, the number of enrolled patients is the largest among the studies that have so far examined the effect of SNPs on tenofovir-induced KTD. Thus, this feature provided the study a higher statistical power than previous studies.

Why are polymorphisms in *ABCC2* a risk for tenofovir-induced KTD, even though it is controversial whether MRP2 plays a role in the excretion of tenofovir via the luminal membrane? [18, 20] The exact mechanism has not been determined yet, but we speculate 2 hypotheses. First, there might be unknown endogenous substances that influence tenofovir nephrotoxicity in renal tubular cells, and SNPs in *ABCC2* modulate the function or transportation of such substances [15]. Second, MRP2 may indeed take part in transporting tenofovir, because various substances including methotrexate are reported to be a substrate of MRP2, and *ABCC2* mutation alters excretion of those substances [36, 37]. Further studies are warranted to elucidate the exact mechanism of these SNPs on tenofovir-induced KTD. Furthermore, the impact of these SNPs on KTD with long-term TDF use needs to be evaluated in prospective studies.

Several limitations need to be acknowledged. First, not all polymorphisms in genes of the targeted transporter proteins were examined. Thus, we might have missed other important SNPs on the function of tenofovir transportation. There might be other unknown transporter proteins for tenofovir excretion in the kidney that contribute to susceptibility to tenofovir-induced KTD as well. Second, the diagnostic criteria for TDF-induced KTD are not uniformly established in the field and are different in the published studies. The criteria applied in this study are not entirely similar to the ones used in previous studies that examined the role of SNPs in tenofovir-induced KTD. However, by excluding other predisposing factors for KTD and enrolling a large number of patients, this study succeeded in providing a clear-cut association between SNPs and tenofovir-induced KTD.

In conclusion, the present study demonstrated that SNPs in *ABCC2* associate with tenofovir-induced KTD in Japanese patients, in a setting that excluded other predisposing factors. Assessment of renal tubular function is more cumbersome and costly to monitor than serum creatinine. However, monitoring tubular function is clinically important, because undetected long-term tubular dysfunction might lead to premature osteopenia due to phosphate wasting and accelerated progression of renal dysfunction. Close monitoring of tubular function is warranted in patients with *ABCC2* −24C and 1249A under TDF treatment.

## Notes

***Acknowledgments.*** The authors thank Ryo Yamada, Takuro Shimbo, Fumihiko Hinoshita, Yoshimi Kikuchi, Katsuji Teruya, Kunihisa Tsukada, Junko Tanuma, Hirohisa Yazaki, Haruhito Honda, Ei Kinai, Koji

Watanabe, Takahiro Aoki, Daisuke Mizushima, Yohei Hamada, Michiyo Ishisaka, Mikiko Ogata, Mai Nakamura, Akiko Nakano, Fumihide Kanaya, and all other staff at the AIDS Clinical Center for their help in completion of this study.

***Financial support.*** This work was supported by a Grant-in-Aid for AIDS research from the Japanese Ministry of Health, Labour, and Welfare (H23-AIDS-001), and the Global Center of Excellence Program (Global Education and Research Center Aiming at the Control of AIDS) from the Japanese Ministry of Education, Science, Sports, and Culture.

***Potential conflicts of interest.*** S. O. has received honorariums and research grants from MSD K.K., Abbott Japan, Janssen Pharmaceutical K.K., Pfizer, and Roche Diagnostics K.K.; has received honorariums from Astellas Pharmaceutical K.K., Bristol-Myers K.K., Daiichisankyo, Dainippon Sumitomo Pharma, GlaxoSmithKline, K.K., Taisho Toyama Pharmaceutical, Torii Pharmaceutical, and ViiV Healthcare. H. G. has received honorariums from MSD K.K., Abbott Japan, Janssen Pharmaceutical K.K., Torii Pharmaceutical, Roche Diagnostics K.K., and ViiV Healthcare. The remaining authors declare no conflict of interest.

All authors have submitted the ICMJE Form for Disclosure of Potential Conflicts of Interest. Conflicts that the editors consider relevant to the content of the manuscript have been disclosed.

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INTERNAL MEDICINE

□ CASE REPORT □

# Drug-Induced Acute Interstitial Nephritis Mimicking Acute Tubular Necrosis after Initiation of Tenofovir-Containing Antiretroviral Therapy in Patient with HIV-1 Infection

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## Abstract

We describe a case of 68-year-old Japanese man with HIV-1 infection who developed acute kidney injury with prominent tubular dysfunction immediately after starting tenofovir-containing antiretroviral therapy. Antiretroviral therapy was discontinued in two weeks but renal function, as well as tubular function, did not shown full recovery even at a 3-year follow-up examination. Acute tubular necrosis, a rare but well-known side effect of tenofovir, was suspected, but kidney biopsy confirmed interstitial nephritis. It is important to distinguish drug-induced interstitial nephritis from acute tubular necrosis, because early steroid administration can improve renal dysfunction caused by acute interstitial nephritis.

**Key words:** tenofovir, acute interstitial nephritis, acute tubular necrosis, acute kidney injury, HIV infection, kidney biopsy

**(Intern Med 51: 2469-2471, 2012)**
**(DOI: 10.2169/internalmedicine.51.7766)**

## Introduction

Renal proximal tubular dysfunction is a well-known side effect of tenofovir (1, 2). Although rare, it sometimes leads to acute tubular necrosis (ATN) and results in acute kidney injury (AKI) (1, 3). Drug-induced acute interstitial nephritis has a similar clinical presentation to ATN, but has different etiology and management (4, 5). Here we report a case of tenofovir-induced acute interstitial nephritis (AIN) which mimicked ATN after initiation of tenofovir-containing antiretroviral therapy (ART).

## Case Report

A 68-year-old Japanese man with history of hypertension and diabetes mellitus was diagnosed with HIV infection and pneumocystis pneumonia (PCP). The latter was treated with sulfamethoxazole/trimethoprim plus prednisolone for three weeks, and the patient was referred to our hospital. Reactivation of PCP occurred and he was again treated with sulfamethoxazole/trimethoprim for three weeks. After completion of PCP treatment, sulfamethoxazole/trimethoprim was replaced with atovaquone for secondary prophylaxis, and one month later ART was started with tenofovir/emtricitabine plus lopinavir/ritonavir (baseline CD4 count 39/μL, HIV viral load 990,000 copies/mL). Baseline renal function tests were within the normal range (serum creatinine 0.53 mg/dL, blood urea nitrogen 8.7 mg/dL) with urine β2 microglobulin (β2MG) of 2,327 μg/L. The concurrent drugs were atovaquone (which was switched to prophylactic dose of sulfamethoxazole/trimethoprim on ART day 2), azithro-

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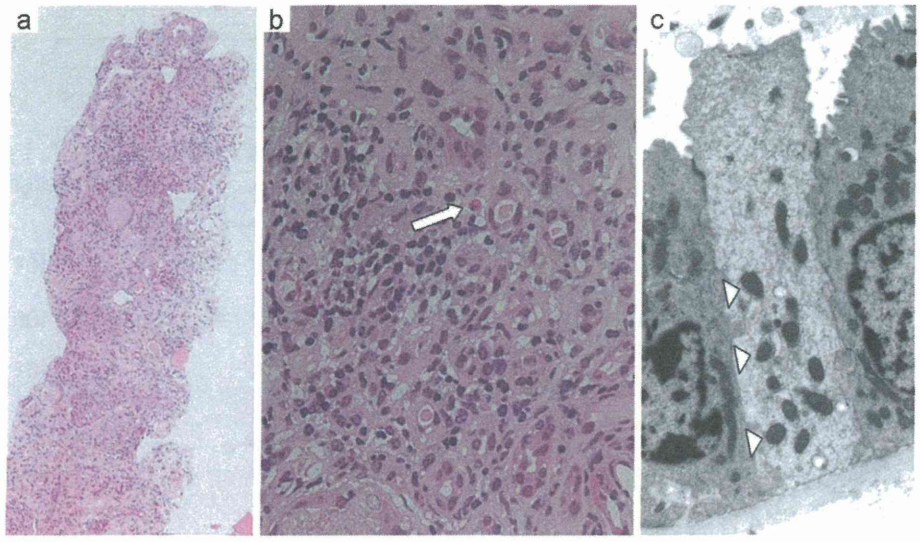


**Figure 1. The microscopic findings in the renal biopsy specimen. (a) Diffuse interstitial inflammation with histologically normal glomeruli (Hematoxylin and Eosin (H&E) staining, ×10). (b) Prominent interstitial inflammatory infiltrates characterized by lymphocytes, plasma cells, and focal eosinophils (white arrow) (H&E staining, ×400). (c) Electron microscopic examination showed mitochondria normal in size and morphology in proximal tubular epithelial cells (white arrow heads) (×5,000).**

mycin 1,200 mg/week, and olmesartan. No concurrent nonsteroidal anti-inflammatory drug was used.

Serum creatinine started to rise and on ART day 14, it reached 2.66 mg/dL with β2MG of 321,400 μg/L. No fever or rashes were observed, but prominent eosinophilia was noted (18.6% of leukocytes, 4,400/μL). Urine dipstick test showed proteinuria +3, occult blood +2, and glycosuria +1, together with renal tubular epithelial cells and granular casts in urine. Serum potassium, sodium, and phosphate levels were within the normal ranges. Serum IgE was high (1,040 IU/mL), and serum antinuclear antibodies, antineutrophil cytoplasm antibody, and cryoglobulin were negative. Renal ultrasonography was also negative for specific findings.

ART and the other concurrent medications, with the exception of azithromycin, were discontinued on that day. Hydration with central venous catheter was started. At 21 days after commencement of ART, serum creatinine reached a peak level of 5.39 mg/dL, though renal function started subsequently to improve slowly. At 32 days after discontinuation of ART, ART with darunavir/ritonavir plus raltegravir was provided (serum creatinine 2.59 mg/dL). The patient was discharged 44 days after re-commencement of ART with a CD4 count of 247/μL, and HIV viral load of 2,700 copies/mL. Within 3 months after discharge, HIV viral load was suppressed to <50 copies/mL with a CD4 count of 316/μL.

Five months after the episode, renal biopsy was performed (serum creatinine 1.76 mg/dL, β2MG 15,677 μg/L). Examination of the specimen showed interstitial infiltration of lymphocytes, plasma cells, and a few eosinophils. There was no vacuolation in tubular cells and the brush border was intact. The glomeruli were histologically normal (Fig. 1a, b). Immunofluorescence study was negative for IgG, IgM, IgA, C1q, C3, C4, or fibrinogen. Electron microscopic examination demonstrated no abnormalities in the mitochondria of tubular cells (Fig. 1c). The final diagnosis was drug-induced AIN. Serum creatinine and β2MG were still elevated three years later at 1.47 mg/dL and 25,718 μg/L, respectively.

## Discussion

We described a case of tenofovir-induced AIN, which clinically mimicked ATN, after commencement of tenofovir-containing ART. Although the causative drugs were discontinued in two weeks, renal function did not show full recovery and the patient developed chronic kidney disease (Fig. 2). Tenofovir was highly likely the causative drug, because sulfamethoxazole/trimethoprim, the other drug which was used just before the occurrence of AIN, had been intermittently used for more than two months before the introduction of ART without any complications. To our knowledge, this is the fourth reported case of tenofovir-induced AIN, in addition to the three cases reported by Schmid et al. (6). Nevertheless, it is difficult to entirely role out the involvement of sulfamethoxazole/trimethoprim in occurrence of this AIN case. A combination effect of TDF and sulfamethoxazole/trimethoprim might have played a role.

It is difficult to diagnose interstitial nephritis based on clinical and laboratory findings only, and renal biopsy is required for a definitive diagnosis (4, 5). Only 5 to 10% of patients present with the classic triad of AIN symptoms: fever, rash, and eosinophilia (4, 5). However, renal biopsy is not performed in many cases with tenofovir-induced renal dysfunction, and thus, a considerable number of tenofovir-

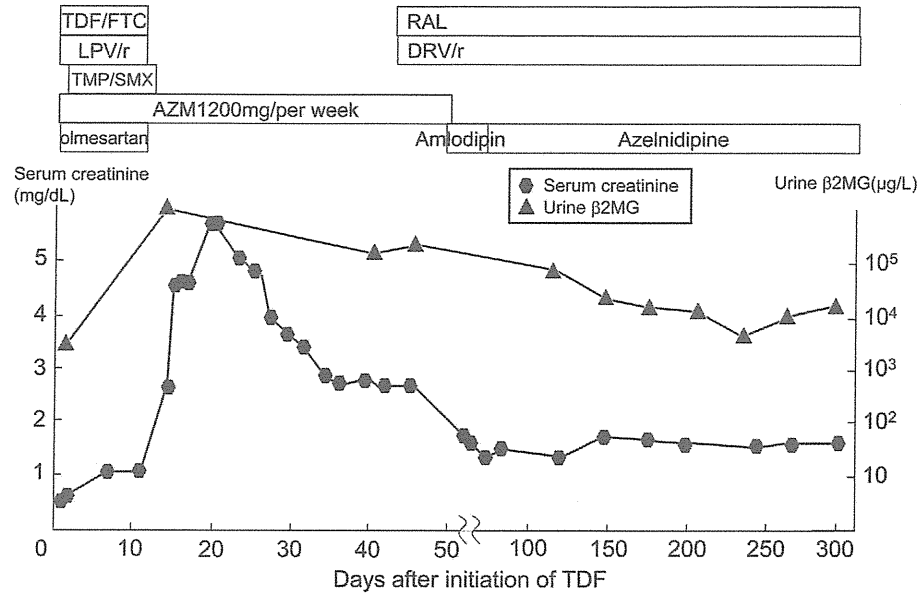


**Figure 2. The clinical course of the patient. TDF/FTC: tenofovir/emtricitabine, LPV/r: ritonavir-boosted lopinavir, RAL: raltegravir, DRV/r: ritonavir-boosted darunavir, TMP/SMX: trimethoprim/sulfamethoxazole, AZM: azithromycin, β2MG: β2 microglobulin**

induced AIN may have been misdiagnosed. Although a prominent eosinophilia and hyper-IgE (1,040 IU/mL) was noted for this case, these laboratory findings are commonly observed in patients with HIV-1 infection (7, 8). It is therefore difficult to dignose AIN solely based on these laboratory findings in patients with HIV infection.

The pathomechanism of tenofovir-induced ATN is considered to be mitochondrial toxicity in proximal tubular cells (9, 10). In contrast, interstitial nephritis occurs as an allergic response triggered by exposure to a drug (4, 5). It is important to distinguish AIN from ATN, because early steroid administration can improve the recovery of renal function in AIN (4, 5).

AIN should always be included in the differential diagnosis in a patient with AKI and prominent renal tubular damage following the introduction of tenofovir. In addition to prompt discontinuation of tenofovir, renal biopsy followed subsequently with steroid therapy at an early stage could produce a favorable renal outcome.

**Author's disclosure of potential Conflicts of Interest (COI).**
Oka S: Honoraria, Abbott Japan Co.; Research funding, MSD K. K..

**Acknowledgement**

The authors thank Makoto Mochizuki for the histopathological examination, and all the clinical staff at the AIDS Clinical Center for their excellent work.

All authors contributed to the concept, design, and writing of this submission.

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J Infect Chemother
DOI 10.1007/s10156-012-0464-x

CASE REPORT

# Long-term control of CMV retinitis in a patient with idiopathic CD4$^+$ T lymphocytopenia

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Received: 5 June 2012 / Accepted: 1 August 2012


**Abstract** Cytomegalovirus (CMV) retinitis with idiopathic CD4$^+$ T lymphocytopenia (ICL) is rare and difficult to control. We report a first case for long-term control of CMV retinitis with ICL using interleukin-2 (IL-2) therapy and succeeded in discontinuation of anti-CMV therapy. A 49-year-old Japanese woman was diagnosed with ICL based on low CD4$^+$ count (72/μl), negative for HIV-1 and -2 antibodies, and absence of any defined immunodeficiency diseases or immunosuppressive therapy. PCR test of the aqueous humor in the right eye was suggestive of CMV retinitis. She was treated with systemic ganciclovir, but after several relapses of CMV retinitis, rhegmatogenous retinal detachment appeared in the right eye and she became blind in that eye. Three years later, she developed CMV retinitis in the left eye. Although she received systemic and focal anti-CMV treatments, the retinitis showed no improvement. Finally, retinal detachment occurred, and she underwent vitrectomy. IL-2 was injected to increase CD4$^+$ counts. Because of hyperpyrexia, blepharedema, central scotoma, and color anomaly, we changed to low-dose IL-2 therapy with no side effects. Finally, we succeeded in increasing the CD4$^+$ count to more than 200/μl after discontinuation of low-dose IL-2 therapy. CMV retinitis never recurred after discontinuation of anti-CMV therapy, with good visual acuity of 20/20 in the left eye. She developed blindness of the first affected right eye, whereas the visual acuity of the left eye remains excellent more than 12 years after the onset of CMV retinitis through the combined use of anti-CMV therapy, IL-2 therapy, and vitrectomy.

**Keywords** Cytomegalovirus retinitis · CD4$^+$ T lymphocytopenia · IL-2 · Vitrectomy

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## Introduction

Idiopathic CD4$^+$ T lymphocytopenia (ICL) was first reported in 1992 as a new disease entity [1, 2]. The syndrome encompasses patients with (1) absolute CD4$^+$ T lymphocyte (CD4$^+$) counts less than 300/μl or less than 20 % of total T cells on more than one occasion, (2) no evidence of human immunodeficiency virus (HIV)-1 or -2 infection, and (3) absence of any defined immunodeficiency diseases or treatment that lowers CD4$^+$ counts.

Opportunistic infections similar to those associated with HIV infection are often encountered in patients with ICL. However, only a few patients with ICL complicated by cytomegalovirus (CMV) retinitis have been reported [3–5]. In this report, we describe a case of CMV retinitis in both eyes in a patient with ICL; vision was completely lost in

Published online: 31 August 2012

one eye, whereas good vision was successfully maintained in the other eye by anti-CMV therapy, IL-2 therapy, and vitrectomy.

## Case report

A 49-year-old Japanese woman visited her family physician in 1994 with visual field impairment in the right eye. She had no special family history, and reported having herpes zoster infection when 40 years old. Fundus examination of the right eye showed hemorrhagic retinitis with exudates in the inferior aspect of the optic disc, and polymerase chain reaction (PCR) test of the aqueous humor from the anterior chamber was suggestive of CMV retinitis. Leukocyte count was 5,290/μl, with a total lymphocyte count of 332/μl (5.6 %). Both $CD4^+$ and $CD8^+$ T lymphocyte ($CD8^+$) counts were low, at 91/μl (27.6 %) and 72/μl (21.8 %), respectively. Antibodies for HIV-1 and -2 were negative. Her general condition was satisfactory except for CMV retinitis; the patient had no other diseases such as cancer and was taking any immunosuppressant. Based on the foregoing findings, the final diagnosis was ICL.

The patient was treated with systemic ganciclovir but experienced several relapses of CMV retinitis. Rhegmatogenous retinal detachment appeared in the right eye in 1997. Retinal detachment surgery (retinal backing, encircling, and cryopexy) was successful with reattachment of the retina. However, CMV retinitis recurred in the right eye, which resulted in blindness in 1997.

Three years later, she developed CMV retinitis in the left eye. Although she received systemic and focal anti-CMV treatments (systemic ganciclovir, vitreous injection of ganciclovir and foscarnet, and replacement of the vitreous ganciclovir implant), the retinitis showed no improvement but rather gradual extension. Accordingly, she was referred to the National Center for Global Health and Medicine in September 2001. The main clinical course after the first visit is shown in Fig. 1. At arrival, she had already developed phthisis bulbi of the right eye. The visual acuity of the left eye was 20/20, and no inflammatory cells were detected in the anterior chamber. The ganciclovir implant was seen in the inferotemporal vitreous; however, CMV retinitis with granular border was noted in the inferotemporal retina. No other general abnormal findings were evident except for blood tests: leukocyte count of white cells 3,010/μl, total lymphocyte count 400/μl, $CD4^+$ count 164/μl, and $CD8^+$ count 43/μl. Intravenous injection of cidofovir resulted in significant improvement of CMV retinitis, but the condition recurred after 4 months. Finally, retinal detachment occurred in the left eye (Fig. 2). She underwent vitrectomy in April 2002 and the retina was reattached. During this period, she also developed a subcutaneous cryptococcus abscess in the left thigh. The abscess had disappeared subsequent to surgical

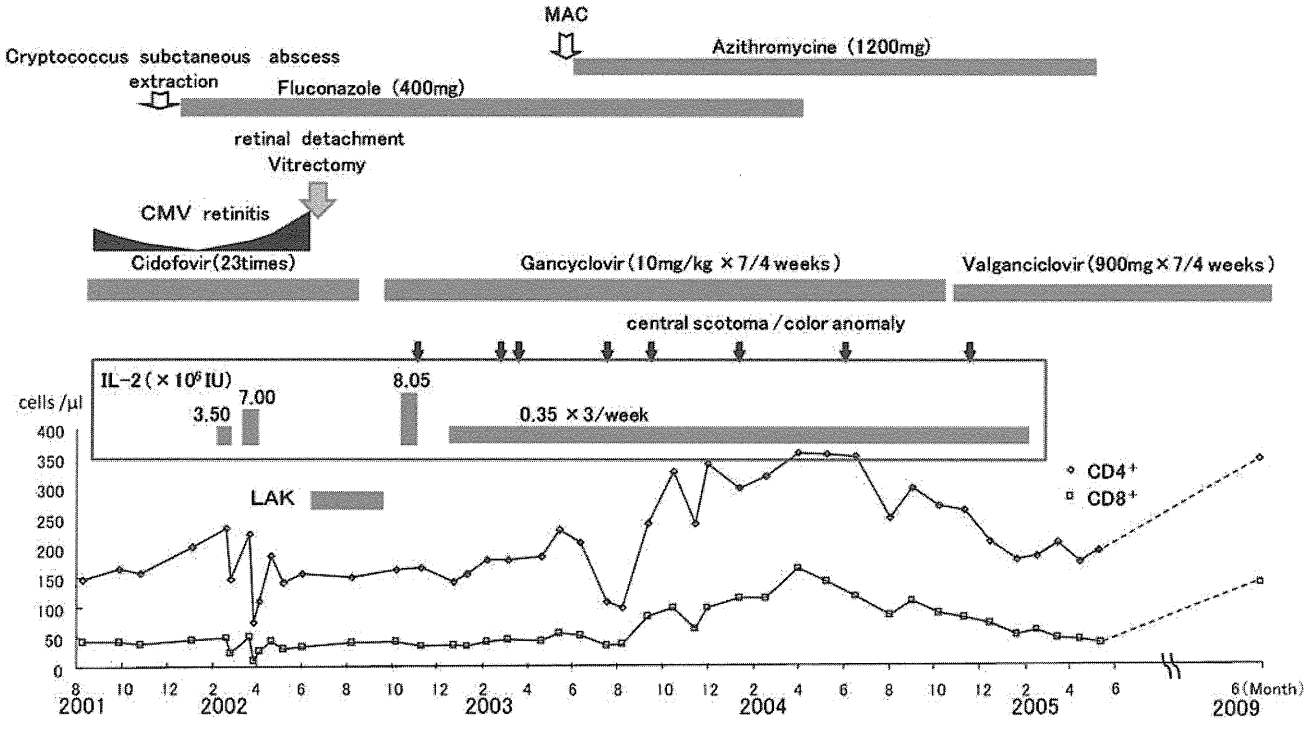


**Fig. 1** Clinical course

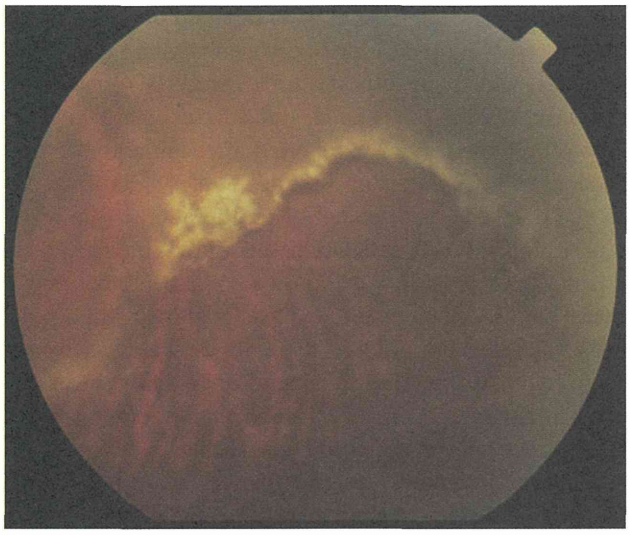

**Fig. 2** Retinal detachment in the left eye: the retina under the white granular border is already healed of cytomegalovirus (CMV) retinitis with tight atrophic adhesion. The peripheral healthy retina over the border is progressing toward retinal detachment

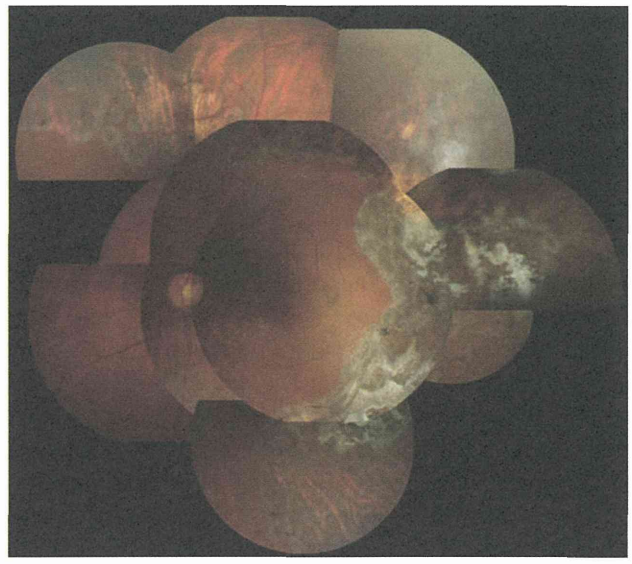

**Fig. 3** Retina reattached after vitrectomy: the optic nerve and macula are intact. The atrophic retina after CMV retiniti presents outside the arcade vessel with laser scar and proliferative epiretinal membrane. There is no relapse of CMV retinitis after vitrectomy

extraction and oral fluconazole (400 mg) by April 2004. According to ethics standard, the institutional review board permitted starting interleukin-2 (IL-2) therapy to increase the immune level. Subcutaneous IL-2 injection was started with written patient's informed consent in February 2002 (the first dose was 350,000 IU × 2 for 5 days, total 3,500,000 IU; and the second dose was 700,000 IU × 2 for 5 days, total 7,000,000 IU) to increase $CD4^+$ count, but the count decreased further to 37/μl. To improve the immune status, lymphokine activated killer cells (LAK) therapy was adopted four times from June to August 2002. However, clinical improvement was not observed, and $CD4^+$ count hovered around 40–50/μl. Therefore, a third dose of IL-2 (1,050,000 IU × 2 for 5 days) was scheduled in November 2002. Four days after subcutaneous injection, she developed hyperpyrexia, blepharedema, central scotoma, and color anomaly. Accordingly, we provided a decreased dose of IL-2 for 700,000 IU on the last day (total dose of 8,050,000 IU) and stopped the therapy. The Goldmann perimeter did not show central scotoma, but a pseudo-isochromatic plate showed color deficiency. Because the complications of central scotoma and color deficiency disappeared several days after each IL-2 injection, we restarted low-dose IL-2 (350,000 IU three times a week) in February 2005.

*Mycobacterium avium* complex (MAC) infection was suspected based on the findings of chest computed tomography and gastric juice culture positive for the acid-fast bacteria in June 2003. Prophylactic treatment with azithromycin (1,200 mg/day) was continued until June 2005 and successfully discontinued. In terms of anti-CMV treatment, intravenous ganciclovir (480 mg/day) was administered from September 2002 instead of cidofovir injection (total 23 times), and the dose was adjusted according to the severity of bone marrow suppression, together with IL-2 therapy. With the gradual increase in $CD4^+$ count, we were able to change the anti-CMV therapy from intravenous ganciclovir to oral valganciclovir (900 mg/day) in December 2004, and tapered the dose of valganciclovir (1,800 mg × 7 days/month). The $CD4^+$ count has been above 200/μl without IL-2 therapy since 2005. Valganciclovir was discontinued in June 2009.

Since the vitrectomy in 2002, CMV retinitis has not recurred (Fig. 3), and the patient continued to have good visual acuity of 20/20 in the left eye when tested in the last follow-up examination in January 2012.

## Discussion

Many ICL cases with various opportunistic infections similar to those of acquired immunodeficiency syndrome (AIDS) patients have been reported since 1989. However, this disease is not well known in the field of ophthalmology because few cases of CMV retinitis have been reported. In this case, the patient was diagnosed with ICL based on low $CD4^+$ count (< 300/μl), negativity for HIV, and absence of any defined immunodeficiency diseases or immunosuppressive therapy.

The etiology of ICL is not clear at present. However, the following mechanisms have been proposed. (1) Viral infection: Guputa et al. [6] reported the presence of

retroviral particles and found a human intracisternal A-type retroviral particle. These reports suggest that a virus other than HIV is involved in ICL. (2) Autoimmune disease. (3) Apoptotic depletion of $CD4^+$ cells associated with over-expression of Fas and Fas-ligand. The pathophysiology of ICL is thought to involve reduced cell-mediated immunity subsequent to low $CD4^+$ count. Therefore, the main complications associated with ICL are opportunistic infections and malignancies. Thus, this case developed CMV retinitis, subcutaneous cryptococcus infection, and MAC infection.

Bone marrow transplantation is the ultimate treatment for ICL. However, our patient had already suffered CMV retinitis, and we considered it was difficult to justify further suppression of the immune system before transplantation. The main treatment for ICL is designed to treat opportunistic infection or malignancy. Additionally IL-2 has stimulatory effects on T cells, leading to an increase in $CD4^+$ count; therefore, successful treatment of ICL with IL-2 has been reported [7–11]. The initial dose varies (38,000–600,000 IU/day, or 50,000 IU/$m^2$ weekly), and clinical response appears after approximately 5–6 months. Many side effects, mostly IL-2 dose dependent, have been reported, including hyperpyrexia, edema caused by blood vessel hyperpermeability, renal and hepatic dysfunction, and mental disorders. Our patient complained of central scotoma and color deficiency, as well as hyperpyrexia and blepharedema, which have not been reported in the past. We decided not to discontinue IL-2 therapy but to use low-dose IL-2. Finally, we succeeded in increasing the $CD4^+$ count without complications. The etiology of central scotoma and color anomaly remains unknown, but we presume they are related to hyperpermeability of blood vessels adjacent to the optic nerve, which resulted in reversible damage of the optic nerve.

It is thought there are two subtypes of ICL in terms of presence or absence of $CD8^+$ T lymphocytopenia, and low $CD8^+$ count at diagnosis represents a subset of ICL with a worse prognosis and increased risk for a serious opportunistic infection or death [12]. Although this case showed a low $CD8^+$ count, the left eye has maintained good visual acuity of 20/20 for more than 12 years from the onset of CMV retinitis.

What are the reasons for success and the mechanism of the longitudinal remission in the left eye? One can presume that the long-term use of anti-CMV therapy played a role; we used anti-CMV therapy for more than 15 years from the onset of ICL, and continued the use of low-dose valganciclovir for 7 years after the remission of CMV retinitis in the left eye to prevent its recurrence. The availability of oral anti-CMV therapy (valganciclovir) made it possible to use the drug over such a long term.

What about IL-2 therapy? The $CD4^+$ count greatly decreased in the induction period of IL-2 therapy in this case. Moreover, Zonios et al. [13] reported one-fifth of the patients resolving their lymphocytopenia within 3 years of diagnosis, which suggests the time course is spontaneous remission. On the other hand, transient decrease in IL-2-responsive lymphocytes is reported after initiation of IL-2 infusion [13]. Cunningham-Rundles et al. [7] have described the delayed enhancement of proliferation is the result of new clonal T cell populations permitted to emerge and expand. IL-2 is also well known to expand peripheral natural killer cell numbers and eosinophilia. Although a single case does not provide definitive answers, adjunctive therapy with IL-2 could trigger not quantitative but functional immune recovery of $CD4^+$ over the long term and allowed discontinuation of anti-CMV therapy.

Finally, vitrectomy was performed to repair retinal detachment. Vitrectomy has been thought to be effective for inflammatory activity and adjunctive medical therapy [14]. In this case, the assumption is that vitrectomy plays a role in the mechanical removal of CMV and inflammatory cytokines, and facilitates diffusion of anti-CMV drugs in the vitreous, which prevents the recurrence of CMV retinitis.

ICL is still an uncommon disease, especially for ophthalmologists; however, precise diagnosis and early treatment can facilitate longitudinal remission of opportunistic infection.

**Conflict of interest** None of the authors has conflict of interest with the submission.

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Eur J Clin Microbiol Infect Dis
DOI 10.1007/s10096-012-1754-z

ARTICLE

# A double-blind comparative study of the safety and efficacy of caspofungin versus micafungin in the treatment of candidiasis and aspergillosis

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Received: 26 June 2012 / Accepted: 19 September 2012


**Abstract** The safety and efficacy profile of caspofungin and micafungin in Japanese patients with fungal infections were directly compared in this prospective, randomized, double-blind study. The proportion of patients who developed significant drug-related adverse event(s) (defined as a serious drug-related adverse event or a drug-related adverse event leading to study therapy discontinuation) was compared in 120 patients [caspofungin 50 mg, or 50 mg following a 70-mg loading dose on Day 1 (hereinafter, 70/50 mg) group: 60 patients; micafungin 150 mg: 60 patients]. The overall response rate was primarily evaluated in the per-protocol set (PPS) population. The proportion of patients who developed significant drug-related adverse events was 5.0 % (3/60) in the caspofungin group and 10.0 % (6/60) in the micafungin group [95 % confidence interval (CI) for the difference: −15.9 %, 5.2 %]. The favorable overall response in the PPS population for patients with esophageal candidiasis, invasive candidiasis, and chronic pulmonary aspergillosis including aspergilloma was 100.0 % (6/6), 100.0 % (3/3), and 46.7 % (14/30) in the caspofungin group, and 83.3 % (5/6), 100.0 % (1/1), and 42.4 % (14/33) in the micafungin group, respectively. In Japanese patients with *Candida* or *Aspergillus* infections, there was no statistical difference in the safety between caspofungin and micafungin. Consistent with other data on these two agents, the efficacy of caspofungin and micafungin was similar.

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Published online: 03 October 2012