

만성 B형 간염 환자에서 장기간의 Adefovir와 Tenofovir를 사용한 후 발생한 판코니증후군

¹울산대학교 의과대학 서울아산병원 내과, ²인제대학교 의과대학 일산백병원 내과

이현우¹ · 이준성² · 오세원² · 정주혁² · 박민용² · 김경아² · 송연한²

Fanconi Syndrome Associated with Long-term Adefovir and Subsequent Tenofovir Therapy for Chronic Hepatitis B Infection

Hyun Woo Lee¹, June Sung Lee², Se Won Oh², Joo Hyuk Jung², Min Yong Park², Kyung-Ah Kim², and Yeon Han Song²

¹Department of Internal Medicine, Asan Medical Center, Ulsan University College of Medicine, Seoul;

²Department of Internal Medicine, Ilsan Paik Hospital, Inje University College of Medicine, Goyang, Korea

Adefovir dipivoxil (ADV) and tenofovir disoproxil fumarate (TDF) are nucleotide analogues used to treat chronic hepatitis B (CHB) infection. Nephrotoxicity associated with the use of these medications causes Fanconi syndrome, a rare condition involving generalized dysfunction of the proximal renal tubule causing impaired reabsorption of glucose, uric acid, and phosphate. Fanconi syndrome has been previously reported in patients with human immunodeficiency virus (HIV) or HIV-CHB coinfection treated with other antiretroviral therapies. However, it is rarely reported in patients with CHB monoinfection. We observed a case of Fanconi syndrome in a 61-year-old woman with CHB monoinfection and a history of long-term ADV therapy (42 months), followed by TDF treatment for 9 months. She presented with ankle pain and a tingling sensation in both lower extremities. Laboratory tests revealed hypokalemia, hypocalcemia, hypophosphatemia, hypouricemia, proteinuria, and glycosuria. This case illustrates the importance of recognizing Fanconi syndrome associated with nucleotide analogue treatment and the need to carefully observe symptoms and monitor renal function in these patients. (Korean J Med 2016;91:174-178)

Keywords: Adefovir; Tenofovir; Fanconi syndrome

INTRODUCTION

Adefovir dipivoxil (ADV) and tenofovir disoproxil fumarate

(TDF) are acyclic nucleotide analogues of adenosine monophosphate and are used for the long-term treatment of chronic hepatitis B (CHB) infection. These medications inhibit viral rep-

Received: 2016. 3. 29

Revised: 2016. 6. 30

Accepted: 2016. 7. 7

Correspondence to June Sung Lee, M.D., Ph.D.

Department of Internal Medicine, Ilsan Paik Hospital, Inje University College of Medicine, 170 Juhwa-ro, Ilsanseo-gu, Goyang 10380, Korea

Tel: +82-31-910-7211, Fax: +82-31-910-7219, E-mail: jsleemd@paik.ac.kr

Copyright © 2016 The Korean Association of Internal Medicine

This is an Open Access article distributed under the terms of the Creative Commons Attribution Non-Commercial License (<http://creativecommons.org/licenses/by-nc/3.0/>) which permits unrestricted noncommercial use, distribution, and reproduction in any medium, provided the original work is properly cited.

lication by competing with deoxyadenosine triphosphate for binding to hepatitis B virus (HBV) DNA polymerase. The major route of elimination is through the kidney via glomerular filtration and tubular secretion. Nucleotide analogues effectively inhibit viral replication; however, although rare, long-term use is associated with renal toxicity. The most common renal toxicity is proximal renal tubular dysfunction, and Fanconi syndrome can occur in some cases. Fanconi syndrome has also been reported in patients undergoing other antiretroviral therapies for HIV or HIV-CHB coinfection, and is rarely reported in patients without HIV infection. Approximately 15% of patients with CHB monoinfection undergoing ADV and/or TDF therapy develop clinical features of proximal renal tubular dysfunction [1], but few develop Fanconi syndrome. Here, we report and discuss a case of Fanconi syndrome with osteomalacia in a CHB monoinfection patient after 42 months of ADV treatment, followed by 9 months of TDF therapy.

CASE REPORT

A 61-year-old female patient presented to our outpatient clinic with ankle pain and a tingling sensation in both lower extremities in November 2014. She was positive for CHB e-antigen and had been taking 10 mg ADV daily since September 2010. On ADV, the patient developed hepatitis B virological breakthrough, but restriction fragment mass polymorphism analysis revealed no mutation of rt181 or rt236. Because of the virological breakthrough, we stopped ADV treatment in March 2014 and switched to 300 mg TDF daily to treat her CHB infection. She had no known family history of renal disorder and no other health problems such as hypertension and diabetes mellitus.

A physical examination revealed diffuse tenderness over both ankles but normal bilateral muscle strength and movement. To investigate the tenderness over both ankles, we sequentially analyzed serial images taken during a previous skeletal survey. In October 2013, while still taking ADV, the patient developed mild myalgia in the lower extremities. The patient initially experienced persistent mild stiffness, which progressed to limited movement, even at rest. At this time, radiological tests were conducted in the rheumatology department. A whole-body bone

scan showed multifocal, incremental uptake in both ankles and knees (Fig. 1). Dual-energy X-ray absorptiometry (DEXA) showed decreased lumbar spine bone mineral density (BMD; 0.588 g/cm^2 ; T-score, -3.6) and a total hip BMD of 0.506 g/cm^2 (T-score, -3.0). X-rays of the same areas were normal. A serologic test revealed mild hypokalemia (3.3 mEq/L), hypouricemia (1.6 mg/dL), and an elevated alkaline phosphatase level (ALP; 496 U/L), with an increased bone fraction. Ionized calcium was normal (1.1 mmol/L). She had been taking calcium combined with vitamin D and risedronic acid. The severity of her ankle pain and the tingling sensation in both lower extremities increased and decreased over time.

At presentation, the patient had normal liver function, except a mildly increased ALP level, as assessed in laboratory tests done every 6 months, and well-controlled CHB with an 8-month TDF regimen. Her most recent liver ultrasound showed a slight-

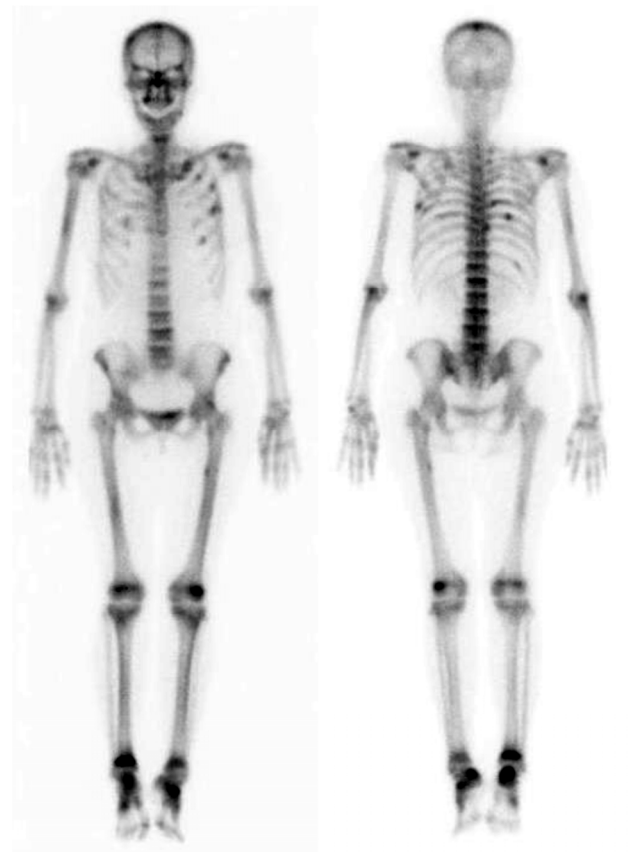


Figure 1. Technetium pertechnetate bone scan showing multifocal osteoblastic lesions involving the bilateral ribs, knee joints, and ankle joints.

ly coarse liver parenchymal pattern without splenomegaly or features of malignancy. Laboratory tests revealed a normal serum alpha-fetoprotein level (2.2 ng/mL; normal range, <7.0 ng/mL) and an HBV DNA viral load of 2.00×10^1 IU/mL. She had a normal creatinine level (0.94 mg/dL; normal range, 0.5-1.5 mg/dL), and her estimated glomerular filtration rate (eGFR) was 60.7 mL/min/1.73 m². She had mild hypokalemia (3.3 mEq/L; normal range, 3.5-5.1 mEq/L), low serum calcium (8.0 mg/dL; normal range, 8.8-10.6 mg/dL), phosphate (1.4 mg/mL; normal range, 2.6-4.8 mg/dL), and uric acid levels (1.5 mg/dL; normal range, 2.6-6.0 mg/dL), and an elevated ALP (148 U/L; normal range, 30-120 U/L) level. Urine studies revealed proteinuria (1+) and glycosuria (2+) in the absence of hyperglycemia. A 24-hour urinary study showed overt proteinuria (1.2 g/24 h); however, given a fraction of albumin of 174 mg/day, tubular proteinuria was considered. In addition, potassium excretion was elevated (54 mEq/day), despite the presence of serum hypokalemia. The phosphate level was also elevated (606 mg/day; normal range, 70-220 mg/day), and glucose excretion was up to 6944 mg/day (normal range, 500-1500 mg/day). A urinary electrophoresis and immunofixation test showed no significant pathologic findings.

Due to the presence of hypokalemia, increased potassium excretion, normoglycemia glycosuria, hypocalcemia, hypophosphatemia, hypouricemia, and proteinuria, acquired Fanconi syndrome was diagnosed. A follow-up skeletal DEXA survey also did not show significant changes compared to the previous study

(lumbar spine BMD; 0.676 g/cm², hip BMD; 0.595 g/cm²).

The patient was subsequently switched to 0.5 mg entecavir (ETV) daily in December 2014. A virological breakthrough developed while the patient was taking ETV; therefore, we ceased the CHB antiviral medication in July 2015. Supportive care, including oral potassium and phosphate supplementation, was provided until tubular recovery.

In March 2015, 3 months after ceasing TDF therapy, ALP was normalized (109 U/L), but hypokalemia (3.4 mEq/L), hypocalcemia (8.4 mg/dL), and hypouricemia (1.8 mg/dL) were still present. Hypophosphatemia was improved (2.7 mg/dL). Urinalysis still showed proteinuria (trace) and glycosuria (1+).

At the patient's last review in December 2015, 12 months after ceasing TDF therapy, there were no significant changes in laboratory findings and urinalysis results. Her symptoms gradually improved, and she no longer complained of ankle pain. Although she appeared to be recovering, the biochemical abnormalities had not fully normalized (Table 1).

DISCUSSION

We report a case of Fanconi syndrome with adverse effects in a patient with CHB treated with long-term ADV followed by TDF. In the absence of any drug history, besides the use of HBV antiviral agents, it was thought that prolonged ADV and TDF therapy were contributing to renal insufficiency. A renal

Table 1. Biochemical features and time course of a case of Fanconi syndrome with osteomalacia

	Rheumatology evaluation (On ADV)	Fanconi diagnosis (On TDF)	3 months after stopping TDF	12 months after stopping TDF	Reference range
Serum					
Creatinine, mg/dL	1.03	0.94	1.03	1.0	0.5-1.5
Potassium, mEq/L	3.3	3.3	3.4	3.5	3.5-5.1
Uric acid, mg/dL	1.6	1.5	1.8	1.9	2.6-6.0
Calcium, mg/dL	1.1 ^a	8.0	8.4	8.1	8.8-10.6
Phosphate, mg/dL	-	1.4	2.7	2.7	2.6-4.8
ALP, U/L	496	148	109	120	30-120
Urine					
Proteinuria	+	+	Trace	Trace	-
PCR	2.67	1.94	1.2	0.93	-
Glycosuria	+	++	+	+	-

ADV, adefovir dipivoxil; TDF, tenofovir disoproxil fumarate; ALP, alkaline phosphatase; PCR, protein to creatinine ratio.

^aIonized calcium.

biopsy was not performed because the patient had distinct clinical features and normal renal function.

In this case study, Fanconi syndrome, which is associated with the use of multiple medications and chemicals [2], was most likely drug-induced. Several drugs, including aminoglycosides, ifosfamide, cisplatin, streptozocin, mercaptopurine, tetracycline, and valproate, have been found to be associated with Fanconi syndrome [2].

ADV, at doses ranging from 60-120 mg/day, can cause nephrotoxicity when used as an adjuvant to antiretroviral therapy for HIV infection [3]. ADV does not appear to produce clinically significant nephrotoxicity at lower doses (10 mg/day for 48 weeks). A long-term (144 weeks) safety and efficacy study showed that only four patients (3%) had increased serum creatinine levels [4]. The more recently developed TDF therapy has been favored due to its excellent safety profile and, in particular, its lack of nephrotoxicity [5]. In patients with HIV treated with TDF, nephrotoxicity is uncommon and has been reported in only 1-2% of patients [6]. In CHB monoinfection, nephrotoxicity and decreased eGFR are less evident and TDF therapy is well tolerated. TDF at 300 mg daily is rarely associated with nephrotoxicity, at least when used for 1-2 years [7]. However, several case reports have described Fanconi syndrome with prolonged, low-dose ADV therapy [2] in HIV or CHB patients treated with TDF [8]. Therefore, ADV and TDF might be associated with rare instances of proximal renal tubular dysfunction, and nephrotoxicity can be affected by the treatment duration and dose.

The risk factors for this complication appear to be greater age and pre-existing renal function in HIV-infected patients [1,5], as well as comorbidities, concomitant use of nephrotoxic medication, and the use of some protease inhibitors. The combinations of nucleotide analogues with other drugs seem to enhance the otherwise low nephrotoxicity of the nucleotide analogue. In the present case, it was difficult to determine whether an adverse reaction was the result of one of the two drugs. Although Fanconi syndrome was diagnosed during TDF maintenance therapy, we cannot rule out the possibility of delayed diagnosis due to irregular laboratory monitoring. Prior to TDF therapy, the 42-month course of ADV therapy may have enhanced the low potential of TDF to cause nephrotoxicity, via intracellular accu-

mulation, and predisposed the patient to TDF-associated renal damage by synergistic nephrotoxicity.

The median time for renal dysfunction to resolve with high-dose ADV treatment was 15 weeks. Nephrotoxicity failed to resolve completely at 41 weeks after onset in 16% of patients. In TDF-based therapy, prolonged renal dysfunction has been found to last as long as 18 months [9]. A shorter duration of drug administration prior to discontinuation is associated with a greater likelihood of renal recovery. At the time of drug discontinuation, mild proteinuria was also a favorable indicator for eventual renal function recovery [10]. Despite the relatively short TDF maintenance period (9 months) in the present case, complete biochemical recovery was not achieved at 12 months after antiviral drug cessation, due to the 42-month course of ADV treatment. At the time of TDF discontinuation, severe proteinuria was likely to be associated with a poor prognosis. Therefore, a degree of renal dysfunction might persist and even be irreversible, after drug cessation.

Nucleotide analogues appear to cause Fanconi syndrome in a proportion of patients without obvious risk factors, and may be observed at varying times after therapy initiation. Therefore, patients with CHB who undergo prolonged nucleotide analogue treatment, even without symptoms, should be regularly monitored for levels of serum creatinine, electrolytes, phosphorus, uric acid, and calcium. Regular laboratory monitoring may lead to decreased morbidity and mortality associated with Fanconi syndrome, an easily reversible condition.

중심 단어: 아데포비어; 테노포비어; 판코니증후군

REFERENCES

1. Gara N, Zhao X, Collins MT, et al. Renal tubular dysfunction during long-term adefovir or tenofovir therapy in chronic hepatitis B. *Aliment Pharmacol Ther* 2012;35:1317-1325.
2. Jung YK, Yeon JE, Choi JH, et al. Fanconi's syndrome associated with prolonged adefovir dipivoxil therapy in a hepatitis B virus patient. *Gut Liver* 2010;4:389-393.
3. Kahn J, Lagakos S, Wulfsohn M, et al. Efficacy and safety of adefovir dipivoxil with antiretroviral therapy: a randomized controlled trial. *JAMA* 1999;282:2305-2312.
4. Hadziyannis SJ, Tassopoulos NC, Heathcote EJ, et al.

- Long-term therapy with adefovir dipivoxil for HBeAg-negative chronic hepatitis B for up to 5 years. *Gastroenterology* 2006;131:1743-1751.
5. Fernandez-Fernandez B, Montoya-Ferrer A, Sanz AB, et al. Tenofovir nephrotoxicity: 2011 update. *AIDS Res Treat* 2011;2011:354908.
 6. Hall AM, Hendry BM, Nitsch D, Connolly JO. Tenofovir-associated kidney toxicity in HIV-infected patients: a review of the evidence. *Am J Kidney Dis* 2011;57:773-780.
 7. Heathcote EJ, Marcellin P, Buti M, et al. Three-year efficacy and safety of tenofovir disoproxil fumarate treatment for chronic hepatitis B. *Gastroenterology* 2011;140:132-143.
 8. James CW, Steinhaus MC, Szabo S, Dressier RM. Tenofovir-related nephrotoxicity: case report and review of the literature. *Pharmacotherapy* 2004;24:415-418.
 9. Fisher EJ, Chaloner K, Cohn DL, et al. The safety and efficacy of adefovir dipivoxil in patients with advanced HIV disease: a randomized, placebo-controlled trial. *AIDS* 2001;15:1695-1700.
 10. Gupta SK, Anderson AM, Ebrahimi R, et al. Fanconi syndrome accompanied by renal function decline with tenofovir disoproxil fumarate: a prospective, case-control study of predictors and resolution in HIV-infected patients. *PLoS One* 2014;9:e92717.