Review

Journal of INTERNATIONAL MEDICAL RESEARCH

Journal of International Medical Research
48(10) 1–13

DOI: 10.1177/0300060520954713
journals.sagepub.com/home/imr
SAGE

Fanconi syndrome induced by adefovir dipivoxil: a case report and clinical review

Kaixin Song, Qi Yan, Yi Yang, Mengyue Lv, Yuting Chen, Yue Dai, Le Zhang, Yi Huang, Cuntai Zhang and Hongyu Gao

Abstract

More than 150 cases of Fanconi syndrome (FS) or hypophosphatemia osteomalacia induced by low-dose adefovir dipivoxil (ADV) have been reported since 2002, when ADV was introduced for the long-term treatment of hepatitis B virus (HBV) infection. Because the life expectancy of HBV-infected individuals has increased, the adverse effects of long-term treatment with antiviral therapies are increasingly observed, and nephrotoxicity is one of the most severe adverse effects of ADV. Therefore, the number of cases may be far higher than reported. Moreover, ADV-induced FS is often misdiagnosed or diagnosed long after it first develops. ADV-induced FS may seriously decrease patient quality of life and lead to bone fractures and even disability. Although progress has been made in the identification of biomarkers and treatments, few systematic clinical guidelines or clinical reviews for FS induced by ADV have been reported. In this study, we highlighted the recent progress toward understanding of FS induced by ADV, described a clinical case, and summarized the primary characteristics and laboratory findings of this disease.

Keywords

Fanconi syndrome, adefovir dipivoxil, nephrotoxicity, hepatitis B virus, hypophosphatemia, osteomalacia, antiviral therapy, adverse effects

Date received: 7 February 2020; accepted: 10 August 2020

Introduction

Fanconi syndrome (FS) is characterized by insufficient reabsorption activity in the proximal renal tubule, which excessively excretes many solutes into urine, consequently leading to symptoms such as aminoaciduria, low-molecular-weight

Department of Geriatrics, Tongji Hospital, Tongji Medical College, Huazhong University of Science and Technology, Wuhan, China

Corresponding author:
Hongyu Gao, Department of Geriatrics, Tongji Hospital, Tongji Medical College, Huazhong University of Science and Technology, No. 1095 Jiefang Road, Wuhan 430030, China.
Email: hygao@tjh.tjmu.edu.cn

albuminuria, glycosuria, hypophosphatemia, hyponatremia, hypokalemia, hypocalcemia, hypouricemia, reduced blood bicarbonate levels, and hyperchloremic metabolic acidosis.[1–4] FS was first reported by Lignae in 1924 and named after Fanconi in 1936.[5] FS has three types: genetic, idiopathic, and acquired.[6] The causes of acquired FS include multiple myeloma, amyloidosis, acute tubular necrosis, and bone tumors; however, drugs represent the most common cause, and the causative agents include aminoglycoside antibiotics, aristolochic acid, analgesics, expired tetracycline, contrast agents, ranitidine, streptozotocin, azathioprine, valproate anticonvulsants, cisplatin, 6-mercaptopurine, and antiviral drugs such as cidofovir, tenofovir, and adefovir esters.[7–9] In this study, we discuss FS induced by adefovir dipivoxil (ADV).

ADV is a nucleotide analog of adenosine monophosphate, and it is used in patients with treatment-naïve and lamivudine-resistant chronic hepatitis B virus (HBV) infection. Because of its effectiveness in suppressing HBV, ADV is used as the first-line treatment in developing countries, and it is also widely applied in primary hospitals.[10–12] Previous randomized control trials and cohort studies in Western countries indicated that the administration of 10 mg of ADV per day is not nephrotoxic in patients with HBV infection.[13–16] However, more than 150 cases of hypophosphatemia osteomalacia (HO) or FS induced by low-dose ADV have been reported since 2002, when ADV was first introduced for long-term HBV treatment.[17,18] As the life expectancy of HBV-infected individuals has increased, the long-term adverse effects of antiviral therapies have increasingly emerged,[19] and nephrotoxicity is one of the most severe adverse effects of ADV. Investigators[20] conducted a retrospective study of 687 HBV-infected patients who received long-term ADV treatment. Using a >20% decline in eGFR relative to baseline as the criterion, 10.5% of patients progressed to renal injury during a median of 27 months of treatment. Fontana[21] initiated a prospective study revealing that the 5-year rate of kidney injury in patients treated with ADV ranged 3% to 8%. Nevertheless, the toxic effects of ADV are not yet fully recognized by many physicians. This is because the clinical manifestations are not unique and the level of serum phosphorus is not routinely included in blood testing panels in most hospitals. Therefore, ADV-induced FS can easily be misdiagnosed, and it may seriously decrease the quality of life of patients and lead to bone fractures and even disability.[7,18] Therefore, more attention must be paid to FS induced by ADV.

Case report

A 58-year-old Chinese man who had received several prior misdiagnoses was referred to our hospital on 4 April 2018 with a 1-year history of lower extremity pain and walking difficulty. He had a history of hypertension, diabetes, chronic lamivudine-resistant HBV infection that had been treated with ADV for 10 years, cirrhosis, esophagus fundus ventricularis varication, and splenectomy. At the initial presentation, his vital signs were stable, and his blood pressure (BP) was 140/69 mmHg.

This patient additionally had symptomatic HO. Although his laboratory data (Table 1) were indicative of low-molecular-weight albuminuria, his rheumatic and immunity indices were normal, and BP and blood sugar levels were well controlled. Therefore, we excluded proteinuria induced by hypertension, diabetes, and rheumatic and immune diseases as diagnoses, and a tubulointerstitial injury was suspected. Although his blood sugar level was normal, glycosuria was detected (3+), and thus, renal glycosuria was suggested. The patient's phosphorus level was

Table 1. Laboratory data on admission.

Parameters	Results (Reference Range)
Blood cell count	
WBCs ($\times 10^9$/L)	4.7 (3.5–9.5)
RBCs ($\times 10^{12}$/L)	*3.52 (4.3–5.8)
Hemoglobin (g/L)	*120 (130–175)
Platelets ($\times 10^9$/L)	132 (125–350)
Urinalysis	
pH	6 (4.5–8)
Specific gravity	1.017 (1.010–1.025)
Glucose	*3+
Blood	*+
Creatinine (μmol/L)	5034 (3540–24,600)
Protein	*1+
RBCs (/μL)	1.3 (0–14)
WBCs (/μL)	5.1 (0–11)
β2-M (mg/L)	61.3 (0–0.3)
β2-M (%)	0
RBP (mg/L)	*41.4 (0–0.7)
RBP (%)	18.4
NAG (U/L)	9.2 (0–11.5)
Sodium (mEq/L)	ND
Potassium (mEq/L)	ND
Phosphate (mg/dL)	ND
Calcium (mg/dL)	ND
ACR (μg/mg)	*104.2 (<30)
Protein (mg/L)	*206 (≤150)
Others	
HBs-Ag (IU/mL)	*38.87 + (<0.05)
HBe-Ag (S/CO)	0.26 (<1.0)
HBe-Ab (S/CO)	1.07 (>1.0)
HBc-Ab (S/CO)	*9.61 (<1.0)
HBV viral load (IU/mL)	<MD
Biochemical data	
AST (U/L)	34 (≤40)
ALT (U/L)	32 (≤41)
ALP (U/L)	*254 (40–130)
γ-GT (U/L)	*99 (10–71)
BUN (mmol/L)	*8.04 (3.1–8.0)
Creatinine (μmol/L)	*127 (59–104)
HCO_3^- (mmol/L)	*18.6 (22–29)
Uric acid (μmol/L)	*121.3 (202.3–416.5)
eGFR (mL/minute/1.73 m^2)	*53.3 (>90)
Sodium (mmol/L)	140.7 (136–)
Potassium (mmol/L)	3.63 (3.5–5.1)
Chloride (mmol/L)	*111.1 (99–110)
Calcium (mmol/L)	*2.14 (2.15–2.5)
phosphate (mmol/L)	*0.45 (0.81–1.45)
pH	*7.3 (7.35–7.45)
BE (mmol/L)	* −8.7 (−3 to 3)
Albumin (g/L)	32.8 (35–52)
25-OH vitamin D (ng/mL)	37.6 (≥30)
M protein	NA
Blood sugar (mmol/L)	*6.89 (4.11–6.05)
HbA1c (%)	* 6.9 (4–6)
Intact PTH (pg/mL)	18.91 (15–65)
Anti-nuclear antibody	NA
Anti-SS-A antibody	NA
Anti-SS-B antibody	NA
RF (IU/mL)	<20 (<20)
Immunoglobulin A (g/L)	4.28 (0.82–4.53)
Immunoglobulin G (g/L)	14.5 (7.51–15.6)
Immunoglobulin M (g/L)	0.62 (0.46–3.04)
ESR (mm/L)	9 (0–15)

Abnormal values are indicated by asterisks (*).
WBC: white blood cell, RBC: red blood cell, β2-M: β2-microglobulin, RBP: retinol-binding protein, NAG: N-acetyl-β-D-glucosaminidase, ACR: albumin/creatinine ratio, HBs-Ag: hepatitis B surface antigen HBV: hepatitis B virus, HBe-Ag: hepatitis Be antigen, HBe-Ab: hepatitis Be antibody, HBc-Ab: hepatitis Bc antibody, MD: minimum detectability, AST: aspartate aminotransferase, ALT: alanine aminotransferase, ALP: alkaline phosphatase, γ-GT: γ-glutamyltransferase, BUN: blood urea nitrogen, PTH: parathyroid hormone, eGFR (based on CKD-EPI): estimated glomerular filtration rate, BE: base excess, HbA1c: glycated hemoglobin, RF: rheumatoid factor, ESR: erythrocyte sedimentation rate, ND: not detectable.

0.45 mmol/L, but his parathyroid hormone and 25(OH)D levels were normal. Considering his history of ADV treatment, the elevated phosphorus level might have resulted from ADV-induced reabsorption dysfunction in the proximal renal tubule. Arterial blood gas analysis and the patient's chloride level indicated hyperchloremic metabolic acidosis. Moreover, the patient exhibited elevated alkaline phosphatase (ALP) levels and depressed uric acid (UA) and HCO_3^- levels. Together with the changes on magnetic resonance imaging

(MRI) and bone scintigraphy (Figure 1), the patient was diagnosed with FS and HO induced by ADV.

ADV treatment was ceased, and the patient was switched to entecavir (ETV). Phosphate, calcium, and calcitriol were also added to the treatment regimen. Meanwhile, BP and blood glucose levels remained stable, indicating protection of the liver and kidneys. The patient's pain and mobility limitations were relieved significantly before his discharge from the hospital, and we reexamined the laboratory indices (Table 2), identifying improvements of glycosuria, kidney dysfunction, renal tubular injury, and phosphorus, HCO_3^-, UA, and chloride levels.

During follow-up conducted 1 year after discharge, the patient was walking normally, and laboratory examination (Table 3) indicated further improvement of various indices. The patient's ALP, chloride, and HCO_3^- levels had recovered, and his UA and phosphorus levels had further increased. Regarding renal function, the estimated glomerular filtration rate (eGFR) and levels of β2-microglobulin (β2-M) and retinol-binding protein (RBP) had improved. MRI revealed that the fractures of both the right medial tibial plateau (Figure 2a) and fibula head (Figure 2b) had healed, and bone scintigraphy demonstrated that multiple foci had also faded (Figure 2c). In addition, we recommended

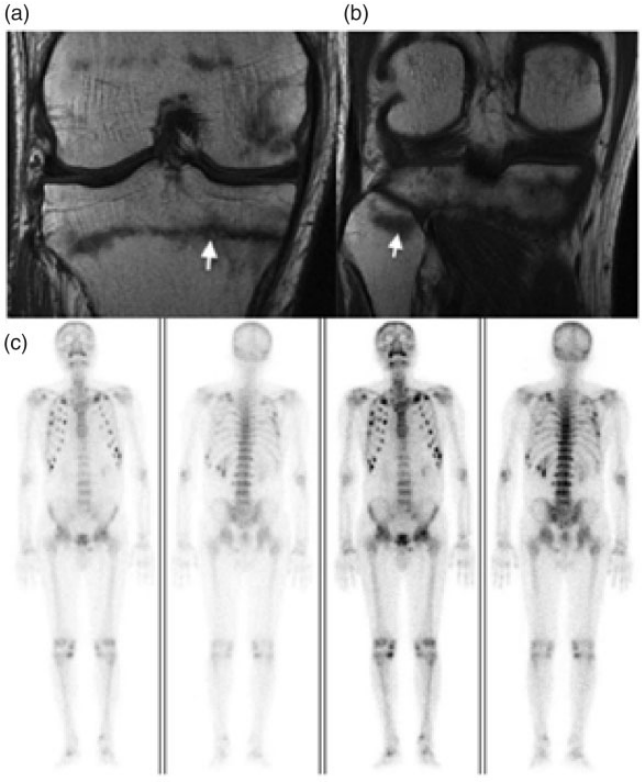

Figure 1. Radiographic changes. Magnetic resonance imaging of the right knee suggested fractures of the right medial tibial plateau (a) and fibula head (b). Bone scintigraphy uncovered multiple foci of increased radiotracer uptake in multiple bones and possible osteomalacia (c).

Table 2. Laboratory data on discharge.

Parameters	Results (Reference Range)
Urinalysis	
pH	7.5 (4.5–8)
Specific gravity	1.013 (1.010–1.025)
Glucose	*+
Protein	*1+
Blood	−
RBCs (/μL)	1 (0–14)
WBCs (/μL)	4 (0–11)
β2-M (mg/L)	52.4 (0–0.3)
Biochemical data	
Creatinine (μmol/L)	*107 (59–104)
Uric acid (μmol/L)	*117.9 (202.3–416.5)
HCO_3^- (mmol/L)	25.1 (22–29)
eGFR (mL/minute/1.73 m^2)	*65.6 (>90)
Potassium (mmol/L)	3.56 (3.5–5.1)
Chloride (mmol/L)	107.9 (99–110)
Calcium (mmol/L)	2.19 (2.15–2.5)
phosphate (mmol/L)	*0.63 (0.81–1.45)
Sodium (mmol/L)	141.3 (136–145)
Alkaline phosphatase (U/L)	*256 (40–130)

Abnormal values are indicated by asterisks (*).
WBC: white blood cell, RBC: red blood cell, β2-M: β2-microglobulin, eGFR: estimated glomerular filtration rate.

Table 3. Laboratory data after discharge.

Parameters	Results (Reference Range)
Blood cell count	
WBCs ($\times 10^9$/L)	4.30 (3.5–9.5)
RBCs ($\times 10^{12}$/L)	*3.92 (4.3–5.8)
Hemoglobin (g/L)	*114 (130–175)
Platelet ($\times 10^9$/L)	169 (125–350)
Urinalysis	
pH	6.5 (4.5–8)
Specific gravity	1.017 (1.010–1.025)
Glucose	*1+
Blood	−
Creatinine (μmol/L)	9592 (3540–24,600)
Protein	*1+
RBCs (/μL)	10.8 (0–14)
WBCs (/μL)	5.2 (0–11)
β2-M (mg/L)	*7.5 (0–0.3)
RBP (mg/L)	*8.25 (0–0.7)
NAG (U/L)	*32.7 (0–11.5)
ACR (μg/mg)	*104.7 (<30)
Protein (mg/L)	*671 (≤150)
Biochemical data	
AST (U/L)	38 (≤40)
ALT (U/L)	39 (≤41)
ALP (U/L)	115 (40–130)
γ-GT (U/L)	60 (10–71)
BUN (mmol/L)	5.00 (3.1–8.0)
Creatinine (μmol/L)	97 (59–104)
HCO_3^- (mmol/L)	25.3 (22–29)
Uric acid (μmol/L)	*155 (202.3–416.5)
eGFR (mL/minute/ 1.73 m^2)	*73.3 (>90)
Sodium (mmol/L)	138.9 (136–145)
Potassium (mmol/L)	3.73 (3.5–5.1)
Chloride (mmol/L)	103.5 (99–110)
Calcium (mmol/L)	2.22 (2.15–2.5)
Phosphate (mmol/L)	0.9 (0.81–1.45)
Albumin (g/L)	37 (35–52)
Blood sugar (mmol/L)	5.41 (4.11–6.05)
Others	
HBV DNA (copies/mL)	<500 (0–500)

Abnormal values are indicated by asterisks (*).
WBC: white blood cell, RBC: red blood cell, β2-M: β2-microglobulin, RBP: retinol-binding protein, NAG: N-acetyl-β-D-glucosaminidase, ACR: albumin/creatinine ratio, AST: aspartate aminotransferase, ALT: alanine aminotransferase, ALP: alkaline phosphatase, γ-GT: γ-glutamyltransferase, BUN: blood urea nitrogen, eGFR: estimated glomerular filtration rate.

a switch in treatment to tenofovir alafenamide (TAF), but further research is needed to clarify the efficacy of the drug against ADV-induced FS.

Review

Risk factors

Some descriptive studies identified male sex, decreased eGFR at the start of ADV treatment, hypertension, diabetes, cirrhosis, East Asian ethnicity, low body mass index, treatment with ADV for more than 24 months, residence in rural areas, and prior use of nephrotoxic drugs as risk factors for ADV-induced FS.[7,18,22,23] A study that focused on kidney tubular dysfunction induced by ADV identified a long treatment

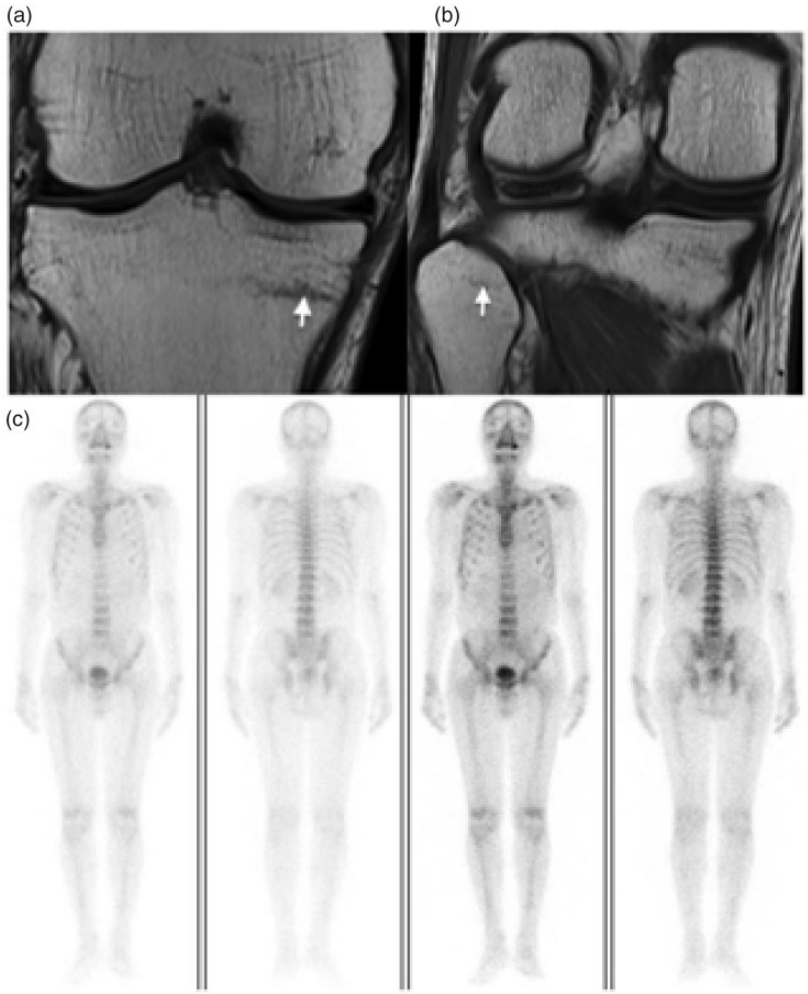

Figure 2. Radiographic changes after discharge. Magnetic resonance imaging of the (a) right medial tibial plateau and (b) fibula head. (c) Bone scintigraphy.

duration and older age at treatment initiation as risk factors via logistic regression analysis.[24] However, the number of cases was not sufficient, and further research and analysis are required.

Genetic predisposition characteristics

Some studies indicated that a single mutation of the ABCC2 gene in the C allele might decrease the activity of the drug transporter MRP2 and thus lead to nephrotoxicity and hypophosphatemia.[13,25]

Pathogenesis

Studies found that ADV is mainly excreted in urine,[26] and FS induced by the long-term administration of low-dose ADV may be related to the overexpression of OAT1 and suppression of MRP2, both of which are transporters. Activated OAT1 is localized on the basolateral membrane of the

proximal renal tubule, and it can accumulate ADV from blood. Conversely, MRP2 localizes on the apical membrane side depending on the ATP concentration in the proximal kidney tubule, which excretes ADV into urine. According to the aforementioned effects and changes of OAT1 and MRP2 expression, ADV may accumulate in proximal renal tubular cells.[13,25,27,28] By inhibiting HBV-DNA polymerase, ADV depresses mitochondrial DNA polymerase-r expression and induces cytochrome oxidase deficiency simultaneously; subsequently, the drug decreases mitochondrial function, alters cellular oxidation, causes mitochondrial swelling and distortion, and induces apoptosis of renal tubular epithelial cells.[13,25,27–30] Under these circumstances, the reabsorption ability of the proximal renal tubule is decreased because the high metabolic rate of proximal tubule cells and mitochondrial oxidative phosphorylation generate more than 95% of cellular ATP. Furthermore, Na^+/K^+ ATPase plays a crucial role in the resorption of chemicals, and its activity is also energy-dependent. Consequently, cellular ATP deficiency will lead to a decrease of Na^+/K^+ exchange and thereby reduce the Na^+-dependent reabsorption of phosphate and other solutes, and the excretion of phosphorus and other solutes will be increased.[31,32] Finally, electrolyte disturbance will appear, resulting in the subsequent development of FS and HO. Moreover, the elimination half-life of ADV is 7.5 hours, and it is prolonged by renal impairment, which will deteriorate renal function.[26]

In addition, fibroblast growth factor 23 (FGF23) has a significant role in regulating serum phosphate levels, and it is also a principal hormone regulating renal phosphate handling.[33] If serum FGF23 levels are high, patients will develop hypophosphatemia. However, several recent studies reported low FGF23 levels in patients with ADV-induced FS, suggesting the FGF23 may not cause hypophosphatemia in patients with drug-induced FS[33] and it may not be involved in the development of HO induced by ADV.[34]

Renal biopsy

Changes such as tubulointerstitial renal lesions, glomerular lesions, atrophy of proximal tubular epithelium, and dramatic vacuolization of epithelial cells with fading of the brush border can be found in ADV-induced FS.[29,35] According to previous studies, serum phosphate levels were depressed in patients with tubulointerstitial kidney lesions, implying a more severe condition.[29]

Clinical manifestation

The most common clinical manifestation of ADV-induced FS is HO, which is usually unspecific and associated with diffusive bone pain, mainly in the ribs, waist, and lower extremities. However, symptoms vary from mild signs, such as paresthesia, fatigue, and muscle weakness, to severe bone pain, walking difficulty, pathological fractures, disabling myopathy, and bone deformity.[29,35] Furthermore, according to prior research,[23] the apparent symptoms appear after a median of 30.5 months of ADV treatment. The main characteristics of 32 patients with ADV-induced FS, including eight patients in our institution and 24 published cases, are summarized in Table 4.[5,18,22,23,36–43]

Laboratory findings

The most frequent laboratory abnormalities are hypophosphatemia, elevated ALP levels, excessive urinary phosphate excretion, glycosuria, proteinuria, aminoaciduria, hypocalcemia, elevated urinary calcium excretion, hypokalemia, and metabolic acidosis. In addition, elevated serum creatinine levels have been described.[29]

Table 4. Main characteristics, laboratory findings, and treatment of 32 patients with ADV-induced FS*.

Parameters	Results
Age	51.7 ± 12.2
Male	24 (75.0%)
Clinical manifestation	
Bone pain	31 (96.8%)
Muscle weakness	12 (37.5%)
Mobility limitation	19 (59.4%)
Urinalysis	
Glucosuria	29 (90.6%)
Proteinuria	30 (93.8%)
24-hour phosphate (mmol)	28.4 ± 34.1
24-h calcium (mmol)	8.2 ± 4.3
β2-M (mg/L)	40.0 ± 33.2
Biochemical data	
Creatinine (μmol/L)	112.9 ± 44.5
eGFR (mL/min/1.73 m^2)	53.4 ± 16.4
Uric acid (μmol/L)	126.4 ± 31.9
Phosphate (mmol/L)	0.5 ± 0.1
Calcium (mmol/L)	2.2 ± 0.1
Potassium (mmol/L)	3.7 ± 0.4
Chloride (mmol/L)	110.9 ± 3.1
HCO_3^- (mmol/L)	19.7 ± 2.5
pH	7.3 ± 0.03
BE (mmol/L)	−5.7 ± 2.2
ALP (U/L)	451.9 ± 310.9
Treatment	
ADV termination	30 (93.8%)
Switch to other antiviral agents	20 (62.5%)
Phosphorus supplementation	23 (71.8%)
Calcium supplementation	12 (37.5%)
Calcitriol supplementation	17 (53.1%)

*Categorical variables were presented as frequencies and percentages. Continuous variables were expressed as the mean ± SD.
β2-M: β2-microglobulin, eGFR: estimated glomerular filtration rate, BE: base excess, ALP: alkaline phosphatase, ADV: adefovir dipivoxil.

Hypophosphatemia is defined by serum phosphate levels <0.8 mmol/L (2.5 mg/dL), and levels <0.32 mmol/L (1 mg/dL) indicate a severe condition.[44] Hypophosphatemia occurs after ADV treatment for 1 year in a time- and dose-dependent manner, and HO appears after 3 to 4 years of treatment.[35] eGFR is considered the best indicator of renal function in patients with chronic renal disease,[45] but some researchers consider eGFR and cystatin C (Cys-C) more sensitive indices of kidney function than serum creatinine in patients with ADV-induced FS. However, other studies describe eGFR as the best index.[7] Further research is needed to evaluate the utility of eGFR in assessing kidney function in patients with ADV-induced FS. A decline in eGFR is also present in ADV-induced FS.[46] Urine β2-M and RBP are biomarkers of kidney impairment during long-term ADV therapy in patients with chronic hepatitis B, and they indicate when treatment should be switched to other antiviral drugs. Urine RBP and β2-M abnormalities precede that of creatinine.[46] However, few studies have identified which marker among eGFR, Cys-C, RBP, and β2-M is most appropriate, and predicting renal injury before patients become symptomatic is critical. Some biomarkers of hepatic mitochondria impairment have been described, such as glutamate dehydrogenase, carbamoyl phosphate synthase-1, alanine aminotransferase-2, and ornithine carbamoyltransferase, but no kidney mitochondria-specific enzymes have been recognized to date. Thus, relevant biomarkers are needed to improve the diagnosis of ADV-induced kidney impairment and FS.[32] Some studies regarded the level of urinary mtDNA as a marker of mitochondrial injury in patients with kidney disease, but its utility should be further examined.[32] Several studies used cytochrome c as a biomarker of mitochondrial injury in the kidneys; however, it may be not suitable for the early discovery of ADV-induced kidney impairment, and its diagnostic utility may be limited.[47] In conclusion, the levels of serum electrolytes, especially phosphate, Cys-C, urine β2-M, and RBP, can be used to evaluate kidney impairment before the onset of symptoms, and the urinary

mtDNA level may emerge as a potential biomarker in the future.

Radiographic changes

Radiographic images reveal fractures, pseudofractures, vertebral biconcave changes, and physiological curvature loss of the spine, and fractures can occur at the ribs, neck of the femur, radius, and sacral bone. Bone scintigraphy may reveal multiple foci of increased radiotracer uptake at ankle joints, knee joints, the spine, and ribs.[29]

Diagnosis of ADV-induced FS

ADV-related FS can be diagnosed on the basis of proximal tubule dysfunction, including hypophosphatemia, glycosuria, and proteinuria after ADV treatment, and these findings exclude the possibility of FS induced by immune diseases, Wilson's disease, plasma cell disorders, and heavy metal poisoning.[29]

Differential diagnosis

ADV-induced FS is usually misdiagnosed as other diseases such as osteoporosis, ankylosing spondylitis, vertebral disc herniation, osteoarthropathy, bone tumors, degenerative diseases, chronic arthritis, and hematological disease.[22,29,35] Therefore, the aforementioned diseases must be eliminated before rendering a diagnosis, and when diagnosing those diseases, ADV-induced FS should be considered.

Treatment

A key factor in the treatment of ADV-induced FS is the timely cessation of therapy.[7] If changes of urine RBP or β2-M levels are confirmed, hypophosphatemia and increased creatinine levels are detected, or patients present with symptoms of HO, it is recommended to switch from ADV to other antiviral agents and add phosphate, calcium, and calcitriol as supplements.[29,46] According to the 2017 clinical guideline of HBV infection, it is not recommended to administer ADV, telbivudine, or lamivudine (LAM) to patients with chronic hepatitis B; however, for LAM-naïve patients, switching to TAF, ETV, or tenofovir disoproxil fumarate (TDF) can be considered. However, if patients are LAM-resistant, TAF or TDF are better options.[48] TAF has greater ability to target hepatocytes than TDF; thus, the distribution of TAF in other organs may be reduced, resulting in fewer side effects. Clinical trials indicated that TAF has fewer nephrotoxic and bone effects than TDF.[49,50] In such cases, the best option for LAM-resistant patients may be switching to TAF. In fact, most patients switch to ETV, but few studies have assessed the efficacy of TAF in the treatment of ADV-induced FS.[51] Therefore, further studies should be conducted.

Supplemental phosphorus also plays a crucial role in ADV-induced FS or HO. According to one study, phosphate levels were significantly elevated after 12 weeks of phosphate supplementation compared with the findings in the group without supplementation.[29] However, when administrating bisphosphonates intravenously, serum electrolyte disturbances and renal injury may occur;[32] moreover, bisphosphonates may influence bone mineralization. Hence, it is necessary to avoid the administration of bisphosphonates to supply phosphate.[18] Several potentially valuable therapies have been described. Denosumab, which is a monoclonal antibody, is used as to improve bone density in the treatment of osteoporosis. According to a case report, denosumab improves clinical manifestations of HO, which results from ADV-induced FS.[37] In addition, mitochondrial protection may be useful against ADV-induced FS and nephrotoxicity, and some chemicals such as

glycine, coenzyme Q10, L-carnitine, N-acetyl cysteine, carnosine, and taurine have nephroprotective effects. These chemicals have been studied in patients and different experimental models,[32] and they may be applied for prevention and treatment. In addition, transporter inhibitors may alleviate ADV-induced FS and nephrotoxicity, and thus, targeting different transporters in proximal renal tubules may represent a therapeutic strategy.[32]

Prognosis

According to earlier studies, it is generally accepted that kidney injury induced by ADV is reversible,[13] and few pathological fractures require surgical stabilization.[52] However, some recent studies indicated that renal damage induced by ADV may be irreversible.[18,23,29,34] However, it may be not sufficient to evaluate renal function using only β2-M.[18] Thus, further comprehensive research using longer treatment periods and considering eGFR, β2-M, RBP, and other potential biomarkers is needed to clarify whether renal dysfunction induced by ADV is completely recoverable. Moreover, a study using a 6-month follow-up period found that patients with chronic kidney disease and tubule acidosis have a poor prognosis.[22]

Prevention

According to prior studies, even low-dose ADV can induce renal injury, resulting in a severe decline of quality of life, bone fractures, and disability. Therefore, for patients treated with ADV, especially those with risk factors, it is necessary to regularly monitor serum electrolytes, creatinine, eGFR, Cys-C, urine β2-M, and RBP and conduct routine urinalysis. Further, physicians must exercise caution when urine RBP or β2-M changes are confirmed, hypophosphatemia and increased creatinine levels are detected, or symptoms of HO appear. Conversely, when patients are resistant to LAM, it is recommended to cease ADV, switch to TAF, and provide supplementation with phosphate, calcium, and calcitriol.

Acknowledgements

We thank the patients for their involvement in this study.

Declaration of conflicting interest

The authors declare that there is no conflict of interest.

Ethics statement

The study was approved by the ethics committee of Tongji Hospital, Tongji Medical College, Huazhong University of Science and Technology. The patient provided written informed consent for the publication of this article.

Funding

The author(s) disclosed receipt of the following financial support for the research, authorship, and/or publication of this article: This work was supported by a grant from the National Natural Science Foundation of China (No. 81800603 to Yan Qi).

ORCID iD

Hongyu Gao https://orcid.org/0000-0002-7462-8883

References

1. Izzedine H, Launay-Vacher V, Isnard-Bagnis C, et al. Drug-induced Fanconi's syndrome. *Am J Kidney Dis* 2003; 41: 292–309.
2. Kleta R. Fanconi or not Fanconi? Lowe syndrome revisited. *Clin J Am Soc Nephrol* 2008; 3: 1244–1245.
3. Solano A, Lew SQ and Ing TS. Dent-Wrong disease and other rare causes of the Fanconi syndrome. *Clin Kidney J* 2014; 7: 344–347.
4. Mathew G and Knaus SJ. Acquired Fanconi's syndrome associated with

tenofovir therapy. *J Gen Intern Med* 2006; 21: C3–C5.
5. Lee YS, Kim BK, Lee HJ, et al. Pathologic Femoral Neck Fracture Due to Fanconi Syndrome Induced by Adefovir Dipivoxil Therapy for Hepatitis B. *Clin Orthop Surg* 2016; 8: 232–236.
6. Tsilchorozidou T and Yovos JG. Hypophosphataemic osteomalacia due to de Toni-Debre-Fanconi syndrome in a 19-year old girl. *Hormones (Athens)* 2005; 4: 171–176.
7. Lin Y, Pan F, Wang Y, et al. Adefovir dipivoxil-induced Fanconi syndrome and its predictive factors: A study of 28 cases. *Oncol Lett* 2017; 13: 307–314.
8. Clarke BL, Wynne AG, Wilson DM, et al. Osteomalacia associated with adult Fanconi's syndrome: clinical and diagnostic features. *Clin Endocrinol (Oxf)* 1995; 43: 479–490.
9. Gou M and Ma Z. Osteomalacia, renal Fanconi syndrome, and bone tumor. *J Int Med Res* 2018; 46: 3487–3490.
10. Lim SG, Marcellin P, Tassopoulos N, et al. Clinical trial: effects of adefovir dipivoxil therapy in Asian and Caucasian patients with chronic hepatitis B. *Aliment Pharmacol Ther* 2007; 26: 1419–1428.
11. Minde Z, Yimin M, Guangbi Y, et al. Five years of treatment with adefovir dipivoxil in Chinese patients with HBeAg-positive chronic hepatitis B. *Liver Int* 2012; 32: 137–146.
12. Uteng M, Mahl A, Beckmann N, et al. Editor's Highlight: Comparative Renal Safety Assessment of the Hepatitis B Drugs, Adefovir, Tenofovir, Telbivudine and Entecavir in Rats. *Toxicol Sci* 2017; 155: 283–297.
13. Vigano M, Lampertico P and Colombo M. Drug safety evaluation of adefovir in HBV infection. *Expert Opin Drug Saf* 2011; 10: 809–818.
14. Marcellin P, Chang TT, Lim SG, et al. Adefovir dipivoxil for the treatment of hepatitis B e antigen-positive chronic hepatitis B. *N Engl J Med* 2003; 348: 808–816.
15. Hadziyannis SJ, Tassopoulos NC, Heathcote EJ, et al. Adefovir dipivoxil for the treatment of hepatitis B e antigen-negative chronic hepatitis B. *N Engl J Med* 2003; 348: 800–807.
16. Ha NB, Ha NB, Garcia RT, et al. Renal dysfunction in chronic hepatitis B patients treated with adefovir dipivoxil. *Hepatology* 2009; 50: 727–734.
17. Segovia MC, Chacra W and Gordon SC. Adefovir dipivoxil in chronic hepatitis B: history and current uses. *Expert Opin Pharmacother* 2012; 13: 245–254.
18. Qian YY, Dai ZJ, Ruan LY, et al. Low-dose adefovir dipivoxil-induced hypophosphatemia osteomalacia in five chronic hepatitis B virus-infected patients. Is low-dose adefovir dipivoxil-induced nephrotoxicity completely reversible? *Drug Des Devel Ther* 2019; 13: 1127–1133.
19. Koenig KF, Kalbermatter S, Menter T, et al. Recurrent bone fractures due to. tenofovir-induced renal phosphate wasting. *Scand J Infect Dis* 2014; 46: 221–224.
20. Kim YJ, Cho HC, Sinn DH, et al. Frequency and risk factors of renal. impairment during long-term adefovir dipivoxil treatment in chronic hepatitis B patients. *J Gastroenterol Hepatol* 2012; 27: 306–312.
21. Fontana RJ. Side Effects of Long-Term Oral Antiviral Therapy for Hepatitis B. *Hepatology* 2009; 49: S185–S195.
22. Li L, Wang SX, Wu HM, et al. Acquired hypophosphatemic osteomalacia is easily misdiagnosed or neglected by rheumatologists: A report of 9 cases. *Exp Ther Med* 2018; 15: 5389–5393.
23. Wu C, Zhang H, Qian Y, et al. Hypophosphatemic osteomalacia and renal. Fanconi syndrome induced by low-dose adefovir dipivoxil: a case report and literature review suggesting ethnic predisposition. *J Clin Pharm Ther* 2013; 38: 321–326.
24. Shimizu M, Furusyo N, Ikezaki H, et al. Predictors of kidney tubular. dysfunction induced by adefovir treatment for chronic hepatitis B. *World J Gastroenterol* 2015; 21: 2116–2123.
25. Vigano M, Lampertico P, Dongiovanni P, et al. A Drug Transporter Gene Polymorphism Predicts Renal Tubular Toxicity in Patients with Chronic Hepatitis B on Long-Term Adefovir and Lamivudine Combination. *J Hepatol* 2010; 52: S7.

26. Ho ES, Lin DC, Mendel DB, et al. Cytotoxicity of antiviral nucleotides adefovir and cidofovir is induced by the expression of human renal organic anion transporter 1. *J Am Soc Nephrol* 2000; 11: 383–393.
27. Tanji N, Tanji K, Kambham N, et al. Adefovir nephrotoxicity: Possible role of mitochondrial DNA depletion. *Hum Pathol* 2001; 32: 734–740.
28. Izzedine H, Launay-Vacher V and Deray G. Antiviral drug-induced nephrotoxicity. *Am J Kidney Dis* 2005; 45: 804–817.
29. Xu LJ, Jiang Y, Liao RX, et al. Low-dose adefovir dipivoxil may induce Fanconi syndrome: clinical characteristics and long-term follow-up for Chinese patients. *Antivir Ther* 2015; 20: 603–611.
30. Qi X, Wang JY, Chen L, et al. Impact of Nucleos(t)ide Analogue Combination Therapy on the Estimated Glomerular Filtration Rate in Patients With Chronic Hepatitis B. *Medicine (Baltimore)* 2015; 94: e646.
31. Girgis CM, Wong T, Ngu MC, et al. Hypophosphataemic Osteomalacia in Patients on Adefovir Dipivoxil. *J Clin Gastroenterol* 2011; 45: 468–473.
32. Heidari R. The footprints of mitochondrial impairment and cellular energy crisis in the pathogenesis of xenobiotics-induced nephrotoxicity, serum electrolytes imbalance, and Fanconi's syndrome: A comprehensive review. *Toxicology* 2019; 423: 1–31.
33. Park S, Kim WI, Cho DH, et al. Adefovir-induced Fanconi syndrome associated with osteomalacia. *Clin Mol Hepatol* 2018; 24: 339–344.
34. Koda R, Tsuchida M, Iino N, et al. Hypophosphatemic Osteomalacia Associated with Adefovir-induced Fanconi Syndrome Initially Diagnosed as Diabetic Kidney Disease and Vitamin D Deficiency. *Intern Med* 2019; 58: 821–825.
35. Chen N, Zhang JB, Zhang QJ, et al. Adefovir dipivoxil induced hypophosphatemic osteomalacia in chronic hepatitis B: a comparative study of Chinese and foreign case series. *BMC Pharmacol Toxicol* 2018; 19: 23.
36. Xiang Q, Liu ZY, Yu YY, et al. Osteomalacia and renal failure due to Fanconi syndrome caused by long-term low-dose Adefovir Dipivoxil: a case report. *BMC Pharmacol Toxicol* 2020; 21: 43.
37. Kunii T, Iijima T, Jojima T, et al. Denosumab improves clinical manifestations of hypophosphatemic osteomalacia by adefovir-induced Fanconi syndrome: a case report. *J Med Case Rep* 2019; 13: 99.
38. Koda R, Tsuchida M, Iino N, et al. A Case of Hypophosphatemic Osteomalacia Associated with Adefovir-induced Fanconi Syndrome Initially Diagnosed as Diabetic Kidney Disease and Vitamin D Deficiency. *Intern Med* 2018; 58: 821–825.
39. Li X, Shen M, Sun WJ, et al. Misdiagnosis of Bone Metastasis Cancer After Using Adefovir Dipivoxi in a Hepatitis B Patient with Fanconi Syndrome. *Indian J Hematol Blood Transfus* 2016; 32: 329–331.
40. Law ST, Li KK and Ho YY. Acquired Fanconi syndrome associated with prolonged adefovir dipivoxil therapy in a chronic hepatitis B patient. *Am J Ther* 2013; 20: e713–e716.
41. 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.
42. Takagi J, Morita H, Ito K, et al. Urinary beta-2 Microglobulin Levels Sensitively Altered in an Osteomalacia Patient Receiving Add-on Adefovir Dipivoxil Therapy for Hepatitis B Virus Infection. *Intern Med* 2016; 55: 1599–1603.
43. Jeong HJ, Lee JM, Lee TH, et al. Two Cases of Hypophosphatemic Osteomalacia After Long-term Low Dose Adefovir Therapy in Chronic Hepatitis B and Literature Review. *J Bone Metab* 2014; 21: 76–83.
44. Berkelhammer C and Bear RA. A clinical approach to common electrolyte problems: 3. Hypophosphatemia. *Can Med Assoc J* 1984; 130: 17–23.
45. Vassalotti JA, Centor R, Turner BJ, et al. National Kidney Foundation Kidney Disease Outcomes Quality I: Practical Approach to Detection and Management of Chronic Kidney Disease for the Primary

Care Clinician. *Am J Med* 2016; 129: 153–162.e7.
46. Jia HY, Ding F, Chen JY, et al. Early kidney injury during long-term adefovir dipivoxil therapy for chronic hepatitis B. *World J Gastroenterol* 2015; 21: 3657–3662.
47. Small DM and Gobe GC. Cytochrome c: potential as a noninvasive biomarker of drug-induced acute kidney injury. *Expert Opin Drug Metab Toxicol* 2012; 8: 655–664.
48. Liver EAS. EASL 2017 Clinical Practice Guidelines on the management of hepatitis B virus infection. *J Hepatol* 2017; 67: 370–398.
49. Buti M, Gane E and Seto WK. Tenofovir alafenamide versus tenofovir disoproxil fumarate for the treatment of patients with HBeAg-negative chronic hepatitis B virus infection: a randomised, double-blind, phase 3, non-inferiority trial. *Lancet Gastroenterol Hepatol* 2016; 1: E2.
50. Agarwal K, Fung S, Seto WK, et al. A phase 3 study comparing tenofovir alafenamide (TAF) to tenofovir disoproxil fumarate (TDF) in patients with HBeAg-positive, chronic hepatitis B (CHB): efficacy and safety results at week 96. *J Hepatol* 2017; 66: S478.
51. Garcia M, Le Moal G, Godet C, et al. First case report of renal improvement on tenofovir alafenamide in an HIV/hepatitis B virus-coinfected patient with adefovir-induced Fanconi's syndrome. *AIDS* 2016; 30: 1487–1488.
52. Moon NH, Shin WC, Do MU, et al. An Uncommon Case of Bilateral Pathologic Hip Fractures: Antiviral Drug-induced Osteomalacia in a Patient with Hepatitis B. *Hip Pelvis* 2018; 30: 109–114.