Adefovir dipivoxil-induced Fanconi syndrome and its predictive factors: A study of 28 cases

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Abstract. The aim of the present study was to identify monitoring and prevention measures as well as predictive factors for early detection of renal toxicity associated with long-term administration of adefovir dipivoxil in order to avoid progression to Fanconi syndrome. Clinical data of 28 patients with Fanconi syndrome caused by long-term administration of adefovir dipivoxil for the treatment of chronic hepatitis B virus (HBV) infection were collected pre-and post-administration for analysis. Patients presented with fatigue, progressive systemic pain in multiple bones and joints, as well as difficulty in walking and pathological fractures in a number of severe cases. Laboratory examinations revealed hypophosphatemia, elevated serum cystatin C (Cys-C), elevated serum creatinine (SCr), reduced glomerular filtration rate (GFR), positive urinary protein, erythrocytes and glucose, as well as osteoporosis. In consequence, adefovir dipivoxil administration was stopped, and patients received concentrated divitamins, sodium phosphate syrup and calcitriol. Symptoms and abnormalities in laboratory examinations were significantly improved in all patients after 2-6 months. Therefore, serum phosphate, SCr, routine urine parameters, Cys-C and GFR should be monitored regularly in chronic HBV patients treated with adefovir dipivoxil. The following factors were identified as predictive of kidney damage and Fanconi syndrome: Age ≥40 years, living in rural areas, previous renal toxicity, estimated GFR (eGFR) <90 ml/min/1.73 m^2, hypertension, diabetes, cirrhosis and duration of adefovir dipivoxil treatment exceeding 24 months. The present results indicate that timely termination of adefovir dipivoxil treatment and replacement with other antiviral agents is critical once renal impairment appears, and that it is necessary to change to other antiviral agents and prolong the interval of administration according to the eGFR level.

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Introduction

Antiviral drugs are key to the treatment of chronic hepatitis B virus (HBV) infection (1). Standard antiviral treatment should be administered as long as the indications and conditions allow (2). Nucleoside analogs ar e one of the two major classes of antiviral drugs (3). Compared with other nucleoside analogs, adefovir dipivoxil is characterized by low cost, low drug resistance and absence of cross-resistance, and has been applied widely in developing countries (4,5). However, renal toxicity is the most common adverse reaction associated with adefovir dipivoxil, and it has been reported to cause Fanconi syndrome (6-8), which is often misdiagnosed due to a dearth of knowledge among the majority of clinicians (9). In addition, some common manifestations of Fanconi syndrome, including systemic bone pain, osteoporosis and spontaneous fracture, are easily misdiagnosed as osteoarthrosis, osteoporosis and bone tumors in the early stages (9,10).

In the present study, an analysis of the possible predictive factors for kidney damage in 28 patients with Fanconi syndrome caused by long-term administration of adefovir dipivoxil is reported, alongside possible predictive factors for kidney damage in the clinic, and monitoring and prevention measures for early detection of renal toxicity and Fanconi syndrome are proposed.

Patients and methods

Patients. Patients at Mengchao Hepatobiliary Hospital of Fujian Medical University (Fuzhou, China) between May 2014

and February 2015 who were suffering from kidney damage and manifestations of Fanconi syndrome caused by long-term administration of adefovir dipivoxil (10 mg/day) for the treatment of chronic HBV infection were included in the present study. Of these patients (27 men and 1 woman), 19 cases were from rural areas and 9 cases were from urban areas. The age of patients at the start of adefovir dipivoxil administration ranged from 28 to 69 years.

The hepatitis B surface antigen (HBsAg)-positive status history ranged from 1 to 46 years, and 20 cases had a family history of HBsAg-positive status. There were 14 cases of chronic hepatitis B, 10 cases of compensatory hepatitis B-associated cirrhosis, 3 cases of decompensatory hepatitis B-associated cirrhosis and 1 case of hepatic failure. The HBV-DNA levels ranged from $2.0x10^3$ to $8.6x10^9$ IU/ml. In addition, 19 cases were positive for hepatitis B envelope antigen (HBeAg).

In total, 6 cases were accompanied by type 2 diabetes, 6 cases were accompanied by hypertension and 3 cases were accompanied by both diseases. Furthermore, 7 cases had previously received lamivudine and presented resistance; among these, 4 cases were changed to antiviral treatment with a combination of lamivudine (GlaxoSmithkline Pharmaceuticals, Co., Ltd., Suzhou, China) and adefovir dipivoxil (Chia Tai Tianqing Pharmaceutical Group Co., Ltd., Nanjing, China), while 3 cases were changed to antiviral treatment with a combination of entecavir (Sino-American Shanghai Squibb Pharmaceuticals Ltd., Shanghai, China) and adefovir dipivoxil. One case presented resistance against entecavir and was changed to antiviral treatment with a combination of entecavir and adefovir dipivoxil. In total, 2 cases did not respond to adefovir dipivoxil treatment and were changed to antiviral treatment with a combination of lamivudine and adefovir dipivoxil. Patients had normal renal function, blood electrolytes and routine urine examinations prior to administration of adefovir dipivoxil (Table I).

The present study was approved by the Medical Ethics Committee of Fuzhou Infectious Disease Hospital (Fuzhou, China). Informed consent was obtained from the 28 patients. All data were used with permission of the patients and published anonymously.

Table I. Baseline characterization of 28 Fanconi syndrome cases.

Variables	Baseline characterization (n=28)	Reference value
Age, years	45.5 (17.0)	
Gender, %		
Male	96.4	
Female	3.6	
$HbsAg^+$ family history, %		
With	71.4	
Without	28.6	
$HbsAg^+$ duration, years	14.7±12.2	
Biochemical level		
ALB, g/l	4.25±4.16	(34.00-54.00)
GLB, g/l	32.5 (6.0)	(20.0-40.0)
TBIL, μmol/l	21.23±8.40	(3.00-25.00)
DBIL, μmol/l	6.0±5.9	(0.0-8.6)
ALT, U/l	98.3±98.6	(9.0-50.0)
AST, U/l	87±99	(15-40)
GGT, U/l	54.9±36.6	(10.0-60.0)
log_{10} HBV-DNA, IU/ml	5.9 (1.6)	
HBeAg, %		
Positive	58.3	
Negative	41.7	

Age, GLB and log_{10}HBV-DNA are shown as median (interquartile range). The remaining data are presented as the mean ± standard deviation or percentage. ALB, albumin; GLB, globulin; TBIL, total bilirubin; DBIL, direct bilirubin; ALT, alanine aminotransferase; AST, aspartate aminotransferase; GGT, γ-glutamyl transpeptidase; HBV, hepatitis B virus; HBeAg, hepatitis B envelope antigen; HbsAg, hepatitis B surface antigen.

Histopathological and immunohistochemical assessment. Fresh renal biopsy samples were fixed in 4% paraformaldehyde at room temperature for 24 h, and then gradually dehydrated using ethanol and embedded in paraffin. The paraffin blocks were subsequently sectioned (5-μm) and stained with Mason's Trichrome and periodic acid-Schiff staining kit (Beijing Solarbio Science & Technology Co., Ltd., Beijing, China) or hematoxylin and eosin (Nanjing Jiancheng Bioengineering Institute, Nanjing, China), according to the manufacturer's protocol. To further assess the degree of renal tubular damage, the accumulation of complement component 3 (C3) in the renal tubule was detected using an anti-C3 monoclonal antibody (1:100 dilution; cat. no. ab11871; Abcam, Cambridge, MA, USA) at 4˚C overnight. After several rinses with PBS, the tissue sections were incubated with horseradish peroxidase-conjugated secondary antibody (1/1 dilution; cat. no. PV9003; ZSGB-BIO, Beijing, China) at room temperature for 1 h. Finally, the renal sections were stained with diaminobenzidine (Beijing Solarbio Science & Technology Co., Ltd.) and hematoxylin. Subsequently, double-blind evaluation of hepatic steatosis was performed by two expert pathologists. The histopathological examination was performed using an inverted phase-contrast microscope.

Results

Clinical manifestations. Of the 28 cases, 15 presented clinically with progressive fatigue and multiple joint pain; 11 cases manifested differing degrees of difficulty in walking; and 3 cases had pathological fractures. The time from medication to presentation of the symptoms described ranged from 16 to 100 months [mean ± standard deviation (SD), 54.80±25.64 months]. Pain was reported predominantly in the ankle, knee, hip, and lumbosacral and hypochondriac areas. Initially, pain was reported in one to two areas, and gradually progressed to systemic multiple joint pain with prolonged medication time. The pain was aggravated by adefovir dipivoxil loading, and progressed to disability in walking and pathological fractures. A total of 2 cases presented acroanesthesia, while 1 case presented a 2-cm decrease in height and

Table II. Main symptoms or serum/urine examinations of 28 Fanconi syndrome cases.

Main symptoms or serum/urine examinations	No. of positive cases	Percentage	Total no. of cases
Joint pain	15	53.6	28
Disability in walking	11	39.3	28
Pathological fractures	3	10.7	28
Osteoporosis	7	100.0	7
Hypokalemia	11	39.3	28
Hypocalcemia	2	7.1	28
Hypophosphatemia	23	82.1	28
Blood urea nitrogen upregulated	2	7.1	28
Serum creatinine upregulated	15	53.6	28
Cystatin C upregulated	15	93.8	16
Alkaline phosphatase upregulated	14	50.0	28
Urinary protein positive	19	73.1	26
Urinary glucose positive	13	50.0	26
Urinary erythrocytes positive	18	69.2	26

an 8-kg reduction in body weight. All the patients had normal sensation, muscular strength and muscular tension (Table II).

Laboratory examinations. All 28 cases exhibited changes in the results of routine urine examinations, serum phosphorus and renal function to varying degrees, and the time from the start of treatment to the presence of the described chemical abnormalities ranged from 16 to 106 months (mean ± SD, 53.64±25.09 months). In total, 22 cases presented with hypophosphatemia, with serum phosphorus levels in the range of 0.36-0.82 μmol/l (normal range, 0.90-1.62 μmol/l); 11 cases presented with hypokalemia, with serum potassium levels in the range of 2.92-3.44 mmol/l (normal range, 3.50-5.30 mmol/l); 14 cases presented with increased serum alkaline phosphatase in the range of 127-481 U/l (normal range, 45-125 U/l); and only 2 cases presented with hypocalcemia, with calcium levels of 1.66 and 2.07 mmol/l, respectively (normal range, 2.08-2.60 mmol/l). Among the 16 cases tested for cystatin C (Cys-C), the levels of Cys-C were increased in 15 cases, with values ranging from 1.06-1.49 mg/l (normal range, 0.00-1.03 mg/l). In addition, 2 cases presented with elevated blood urea nitrogen (BUN), with values of 8.9 and 9.2 mmol/l, respectively (normal range, 2.9-8.2 mmol/l), while 15 cases presented increased serum creatinine (SCr), with values ranging from 119-188 μmol/l (normal range, 53-115 μmol/l).

Urine routine examinations were performed in 26 cases, and urine pH in 1, 7 and 18 cases exhibited values that were <5.5, >6.5 and normal, respectively (normal pH range, 5.5-6.5). Specific gravity examinations revealed that 7, 2 and 17 cases presented with values that were <1.015, >1.025 and normal, respectively (normal range, 1.015-1.025). Urinary protein examinations revealed that 2, 17 and 7 cases presented with urinary protein levels that were ≥2 g/l, ≥1 g/l and normal (normal range, 0.04-0.99 g/l), respectively. Microalbuminuria was positive (≥0.56 g/l) in 19 cases, while urinary erythrocytes counts of ≥200 cells/μl, ≥80 cells/μl and ≥25 cells/μl were detected in 1, 7 and 10 cases, respectively. Urinary glucose levels of ≥28 mmol/l, ≥14 mmol/l and ≥5.6 mmol/l were detected in 7, 1 and 5 cases, respectively. A total of 7 cases underwent bone mineral density evaluation, and all returned osteoporosis. A renal pathological examination was conducted for 1 patient, and the results revealed diffuse mild mesangial cell proliferation accompanied by focal and segmental glomerulosclerosis (ischemic sclerosis), as well as mild renal tubular atrophy, interstitial fibrosis and atherosclerosis at two points (Table II). The microphotographs of a renal biopsy from one case are shown in Fig. 1.

Age distribution. The age of the patients ranged from 34-76 years, with the majority of patients aged between 40 and 59 years, accounting for 57.1% of the total cases (Table III).

Duration of adefovir dipivoxil treatment at first onset of symptoms or abnormal laboratory examinations and total administration duration. In the 28 cases, the time of the first onset of symptoms or laboratory examination abnormalities following administration of adefovir dipivoxil ranged from 16 to 106 months (mean ± SD, 53.64±25.09 months). Table IV reveals that only 5 cases had a duration of <24 months, accounting for 17.9% of all cases, while cases with a duration exceeding 24 months accounted for 82.1% of all cases, presenting a significant difference ($P<0.05$). The total time of administration ranged from 18-118 months, which was longer than the time from administration to the presence of abnormal laboratory examinations.

Estimated glomerular filtration rate (eGFR) at pre- and post-administration of adefovir dipivoxil in the 28 cases. The eGFR values at pre-and post-administration of adefovir dipivoxil were estimated in all patients using the Chronic Kidney Disease (CKD)-Epidemiology Collaboration formula (11,12). The eGFR values prior to the administration of adefovir dipivoxil ranged from 48.4-111.8 ml/min/1.73 m^2, among which, 9, 11 and 1 cases had eGFR values of >90 ml/min/1.73 m^2 [stage 1 CKD (CKD1)], 60-90 ml/min/1.73 m^2 [stage 2 CKD (CKD2)] and 30-60 ml/min/1.73 m^2 [stage 3 CKD (CKD3)], respectively. The baseline eGFR was not obtained in 7 cases.

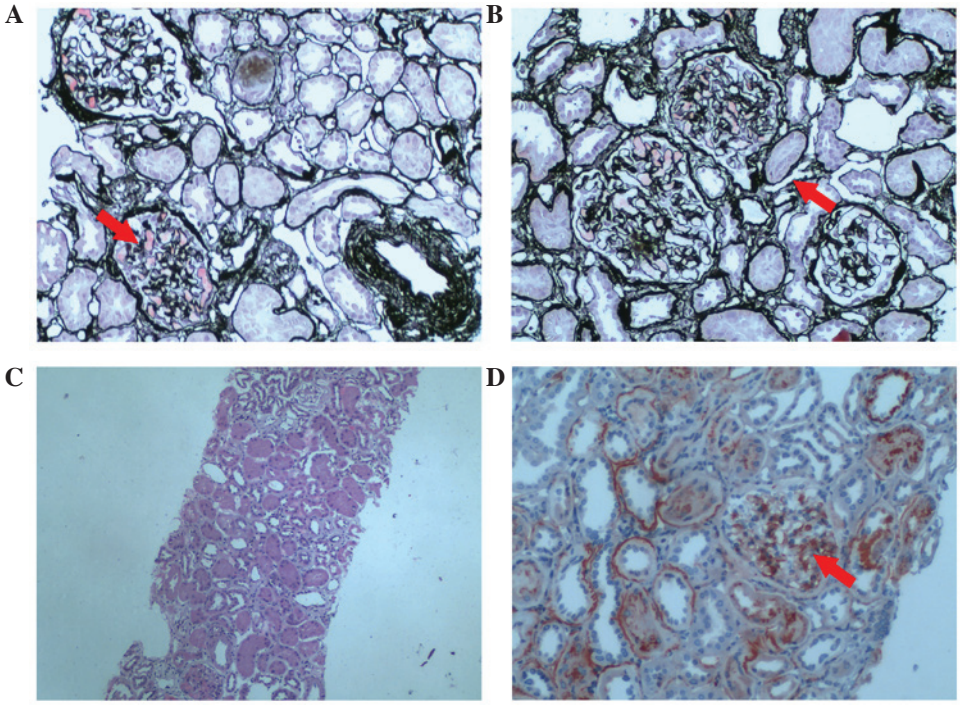

Figure 1. Microphotographs of a renal biopsy of a patient. (A) Masson's trichrome staining of a renal section. The red arrow indicates slight diffusive mesangial cell proliferation and focal/segmental ischemic glomerulosclerosis. Magnification, x200. (B) Masson's trichrome and periodic acid–Schiff staining of the section shown in (A). The red arrow indicates slight tubular atrophy and interstitial fibrosis, suggestive of arteriosclerosis grade 2. Magnification, x200. (C) Hematoxylin and eosin staining of the renal section. Magnification, x40. (D) Immunohistochemical straining of complement component 3. The arrowhead indicates immune complex deposition in the kidney. Magnification, x200.

The eGFR values at diagnosis of Fanconi syndrome ranged from 30-94 ml/min/1.73 m^2, and there were 2, 14 and 12 cases of CKD1, CKD2 and CKD3, respectively. Among the 12 cases of CKD3, the eGFR values preceding adefovir dipivoxil administration were determined in 9 cases, of which, 6 cases had an eGFR of <90 ml/min/1.73 m^2. The eGFR was reduced following adefovir dipivoxil administration in 17 patients, while it was elevated in 4 cases (Table V).

Outcome. Among the 28 patients, 1 case was changed to 0.5 mg/day entecavir, 1 case was changed to antiviral treatment with a combination of 0.5 mg/day entecavir and 300 mg/day tenofovir; 1 case was changed to 300 mg/day tenofovir, according to the Cr clearance rate; 1 case stopped antiviral treatment and received phosphate and calcium supplements; and patients with hypokalemia received potassium supplements. The follow-up duration ranged from 2-20 months. Patients with fatigue, joint pain and difficulty in walking experienced significant remission after 2-6 months, while patients with hypokalemia, hypophosphatemia and abnormalities in routine urine examinations and SCr were restored to normal levels after 1-4 months. A total of 5 patients with increased Cys-C were retested 5 months later, and the abnormalities remained, but with a mild reduction. Two months later, the eGFR values remained unchanged in 2 cases, while they were reduced in 4 cases and slightly elevated in 22 cases.

Discussion

Adefovir dipivoxil, which is a nucleotide analog with a single adenosine phosphate, exerts its antiviral effects by competing with the natural deoxyadenosine triphosphate substrate to terminate the extension of viral DNA chains (13). This drug has been used to treat human immunodeficiency virus infections in the early stages, with large doses associated with significant renal toxicity, including acute tubular necrosis and Fanconi syndrome (14), as well as mitochondrial abnormalities in the proximal renal tubular ultrastructure (15). Prospective studies have shown that the 5-year renal toxicity of adefovir dipivoxil ranges from 3-8% (16). Furthermore, adefovir dipivoxil-induced Fanconi syndrome has been reported (7,8).

Fanconi syndrome is characterized by proximal tubule transport dysfunction due to congenital or acquired factors, and is manifested as renal glucosuria, aminoaciduria, phosphaturia and renal tubular acidosis, thereby inducing a group of syndromes, including hypokalemic paralysis, hypophosphatemia and hypocalcemia osteopathy (osteoporosis and bone deformity) (10). This syndrome can be divided into hereditary, idiopathic and acquired categories (17). Acquired Fanconi syndrome occurs mainly in adults, and one of its main causes is treatment with various drugs, including aristolochic acid, analgesics, contrast agents, expired tetracycline, aminoglycoside antibiotics, azathioprine, 6-mercaptopurine, streptozotocin, cisplatin, ranitidine, valproate anticonvulsants, and antiviral drugs such as cidofovir, tenofovir and adefovir esters (18-26). Tenofovir-induced Fanconi syndrome is often accompanied by acute renal failure (27-35).

It is generally accepted that the mechanism of adefovir dipivoxil-induced liver damage is associated with the aggregation effects caused by the human renal organic anion transporter 1 (HOAT-1) on the drugs and by the toxicity of the drugs on the mitochondria (36). Several studies have reported

Table III. Age distribution of patients with Fanconi syndrome.

Age, years	No. of cases	Percentage
30-39	5	17.9
40-49	7	25.0
50-59	9	32.1
60-69	3	10.7
70-79	4	14.3

Table IV. Duration of adefovir dipivoxil treatment at first onset of symptoms or abnormal laboratory examinations.

Time range, months	No. of abnormal cases	Percentage
12-24	5	17.9
25-48	9	32.1
49-72	9	32.1
73-96	3	10.7
>97	2	7.1

Table V. eGFR values of patients at pre- and post-treatment with adefovir dipivoxil.

Case	Pre-treatment (ml/min/1.73 m^2)	Duration (months)	Post-treatment (ml/min/1.73 m^2)
1	79.0	48	30.0
2	76.0	108	36.0
3	75.0	78	42.0
4	48.4	60	43.0
5	NR	36	45.0
6	73.0	52	46.0
7	NR	100	46.0
8	69.0	73	53.0
9	95.0	106	53.0
10	NR	31	55.0
11	109.8	72	57.0
12	111.8	84	59.0
13	96.0	50	60.0
14	110.0	96	62.0
15	NR	96	63.0
16	89.0	78	63.0
17	NR	60	65.0
18	90.0	36	67.0
19	98.0	63	68.0
20	93.0	18	69.0
21	95.0	71	73.0
22	67.0	94	75.0
23	NR	27	78.1
24	107.3	70	80.0
25	NR	69	82.0
26	70.7	118	88.0
27	85.0	100	93.0
28	88.0	46	94.0

eGFR, estimated glomerular filtration rate; NR, no record.

that HOAT-1 has a strong affinity for adefovir dipivoxil, and that individuals who show high expression levels of HOAT-1 show a higher uptake of adefovir dipivoxil in the renal proximal tubule compared with individuals who show low expression of HOAT-1 or who are deficient (37,38); this was observed in cases with tenofovir-related kidney damage (39,40). Adefovir bisphosphonate, which is the effective metabolite of adefovir dipivoxil, tends to suppress the duplication of mitochondrial DNA, leading to mitochondrial DNA loss in the renal proximal tubule, thus affecting renal tubular reabsorption and secretion (36). Previous studies demonstrated that adefovir dipivoxil-induced proximal tubule damage tends to lead to Fanconi syndrome, which presents different degrees of hypophosphatemia, hypouricemia and combined dysfunction of the proximal renal tubule (41).

Patients with adefovir dipivoxil-induced Fanconi syndrome in the present study were characterized by a number of features. The male:female ratio was 27:1, with a significantly larger number of men affected than women. This may be due to the incidence of chronic hepatitis B, and consequently the number of cases treated with adefovir dipivoxil is significantly higher among males than females. Further studies are required to identify a correlation between kidney damage and Fanconi syndrome caused by adefovir dipivoxil with gender.

Furthermore, 57% of the patients in this group were aged between 40 and 59 years. Among the patients younger than 60 years, the incidence gradually increased with age. It is speculated that kidney damage caused by adefovir dipivoxil may be associated with age. Age >40 years may be a risk factor for kidney damage caused by adefovir dipivoxil; however, in the present study, the incidence decreased in the population older than 60 years. This may be associated with the fact that adefovir dipivoxil is suitable for the population aged between 18 and 65 years (1,42); consequently, a small number of patients aged >65 years are treated with adefovir dipivoxil. Among the patients in the current study, 19 cases came from rural areas and 9 cases came from urban areas. We speculate that this difference is associated with poor health consciousness, low follow-up probability and inferior medical conditions in rural areas compared with those in urban areas.

Among the 28 cases, 14 suffered from chronic hepatitis B and 14 suffered from hepatitis B-associated cirrhosis. Among the patients receiving adefovir dipivoxil, the proportion of patients with chronic hepatitis B was significantly greater than that among patients with hepatitis B-associated cirrhosis, suggesting that kidney damage and Fanconi syndrome are more likely to occur in patients with hepatitis B-associated cirrhosis following adefovir dipivoxil administration. Liver function remained normal upon receiving adefovir dipivoxil in 28 patients. Although it was mildly elevated in 2 cases, the HBV-DNA levels were normal in the remaining cases. The HBeAg-positive rate (58.30%) was not significantly different from the HBeAg-negative rate ($P>0.05$). It is not possible to determine the effects of liver function, HBeAg-positive status

or HBV-DNA levels on adefovir dipivoxil-induced kidney damage with only 28 cases; therefore, these effects require further investigations.

Among the 28 cases, 9 (32.1%) were accompanied by hypertension or type 2 diabetes, exhibiting a significantly higher prevalence than that in the population receiving adefovir dipivoxil. This is due to the fact that hypertension and type 2 diabetes may induce secondary liver damage, particularly among patients with poor control of blood pressure and glucose (43). Furthermore, antihypertensive and hypoglycemic drugs may increase liver burden and aggravate liver damage (44,45). In addition, liver damage is also a risk factor for hypertension, exhibiting an interaction effect (46). Therefore, patients with Fanconi syndrome accompanied by hypertension and type 2 diabetes may be subjected to a higher risk of liver damage when treated with adefovir dipivoxil compared with patients with Fanconi syndrome alone.

In total, 23 of the 28 patients had a total duration of adefovir dipivoxil treatment exceeding 24 months. Among 11 cases presenting progression to difficulty in walking, 9 had a total duration of adefovir dipivoxil treatment >24 months, and the symptoms were aggravated by prolonged duration of drug administration. Therefore, we speculate that duration of adefovir dipivoxil treatment >24 months is a predictive factor of liver damage and Fanconi syndrome. In certain patients, the total duration of adefovir dipivoxil treatment was longer than the period in which abnormalities were present, suggesting that these patients were not aware of having Fanconi syndrome and therefore continued receiving adefovir dipivoxil treatment. Among the 28 patients, 14 continued to receive adefovir dipivoxil following the appearance of joint pain, with a mean time of continued adefovir dipivoxil administration of 21.3 months. Prior to being diagnosed as Fanconi syndrome, these patients had visited a number of hospitals and medical departments and undergone multiple examinations, but had not obtained a distinct diagnosis or effective treatment; consequently, the joint pain was progressively aggravated. Of these patients, 11 had progressed to difficulty in walking when they visited the Mengchao Hepatobiliary Hospital of Fujian Medical University. Therefore, early detection of abnormalities in chemical examinations and early diagnosis are particularly important for timely alleviation of patients' pain. Since Fanconi syndrome is rare, numerous physicians are unfamiliar with its symptoms and signs, thus leading to delayed diagnosis and treatment (9). Therefore, improved knowledge of Fanconi syndrome is important, particularly for hepatologists.

Of the 28 cases,9 received combined antiviral drug treatment. Since nucleotide analogs, such as adefovir dipivoxil, are excreted by the kidney in their original form, combined antiviral drug treatment tends to increase the burden of the kidney (47,48). Further studies are required to investigate whether combined antiviral drug treatment increases the risk of renal dysfunction.

In the current group of patients, there were 12 cases of CKD3 at the point at which Fanconi syndrome was diagnosed. The eGFR was measured prior to adefovir dipivoxil administration in 9 cases, and was <90 ml/min/1.73 m^2 in 6 cases, suggesting that such patients are subjected to a greater risk of renal damage than patients with and eGFR of >90 ml/min/1.73 m^2. Thus, it is necessary to assess the renal function in patients prior to adefovir dipivoxil administration.

The National Kidney Foundation-Kidney Disease Outcomes Quality Initiative guidelines of chronic renal disease state that, while Cr alone is insufficient, GFR is widely accepted as the best index to assess renal function, wherein the GFR decrease is parallel to renal function damage in chronic renal disease (49). Among the 28 cases included in the present study, Cys-C detection was performed in 19 cases at diagnosis. The levels of Cys-C were elevated in 18 cases (range, 1.05-1.59 mg/l), among which, only 8 cases presented elevated SCr. In total, 26 of 28 cases had eGFR <90 ml/min/1.73 m^2, while 13 cases had eGFR <60 ml/min/1.73 m^2 at the time of Fanconi syndrome diagnosis, and only 15 cases presented increased SCr, suggesting that Cys-C and GFR are more sensitive measures of renal function than SCr (50), and that eGFR is the best index (51). Therefore, Cys-C and GFR accurately represent renal function.

All 28 patients discontinued adefovir dipivoxil when they were diagnosed as Fanconi syndrome, and subsequently received phosphorus and calcium supplementation. Significant remission in fatigue, joint pain, difficulty in walking and abnormalities in laboratory examinations were achieved after 2-6 months, indicating that the key to improvement is the timely termination of adefovir dipivoxil treatment.

A cross-sectional study involving 13,925 cases of kidney disease in China revealed that age, previous administration of nephrotoxic drugs, living in rural areas, history of cardiovascular disease, a high-density lipoprotein level <40 mg/dl and hypertension are independent risk factors for kidney function decline, while diabetes and abdominal obesity are associated risk factors for eGFR decline (52-55); this is consistent with the clinical characteristics of the patients in the present study. The population with chronic HBV infection presents a higher prevalence of, and susceptibility to, kidney disease than the general population (56). The prevalence of kidney disease increases gradually with the progression of liver disease, particularly in patients with decompensated hepatic cirrhosis (57). The eGFR significantly decreases with age in patients with hepatic cirrhosis (54,58), with an inverse correlation between baseline eGFR and risk of mortality in patients with hepatic cirrhosis (59). Additionally, renal impairment is a risk factor for mortality in patients with end-stage chronic hepatitis B (60,61). Therefore, it is of particular relevance to monitor renal function and to detect and correct renal dysfunction in patients with chronic HBV infection in a timely manner.

Adefovir dipivoxil has been used as an antiviral agent for ~10 years, and is extensively used in primary hospitals (62). Since the majority of physicians are not yet fully aware of the adverse reactions of adefovir dipivoxil, its use may seriously affect the quality of life of patients, even leading to bone fractures and disability, if treatment is not discontinued in a timely manner (16,63). Patients with chronic HBV infection may incur proximal renal tubule damage and acquired Fanconi syndrome upon receiving adefovir dipivoxil, and tenofovir may cause similar effects via the same mechanism (16,43,64). Therefore, prior to administering adefovir dipivoxil, it is necessary to assess renal function in patients. In addition to monitoring BUN and SCr, blood potassium, serum phosphorus, Cys-C, eGFR, urinary glucose, urinary protein, urine pH and other

indexes of renal tubular injury should be determined, with eGFR widely accepted as the best index for assessing renal function. Timely termination of adefovir dipivoxil treatment and replacement with other antiviral agents is critical once renal impairment appears. Furthermore, it is necessary to change to other antiviral agents and to prolong the interval of administration according to the eGFR level. Improvements in symptoms and chemical examination abnormalities were achieved in the majority of patients in the present study after 2-6 months.

In conclusion, the results of the present study indicated that being aged >40 years, living in rural areas, a history of nephrotoxic drug use, eGFR of <90 ml/min/1.73 m^2, hypertension, diabetes, cirrhosis and duration of adefovir dipivoxil treatment exceeding 24 months were predictive of kidney damage and Fanconi syndrome.

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