CMI Clinical Management Issues

Case report

Adefovir dipivoxil-induced development of osteomalacia and Fanconi syndrome during the treatment of hepatitis B virus (HBV)-related cirrhosis

Orietta Staltari[1], Benedetto Caroleo[2], Andzelika Michniewicz[3], Giovambattista De Sarro[1,3], Franco Perticone[2], Luca Gallelli[1,3]

Abstract

Adefovir dipivoxil is a nucleotide analog reverse transcriptase inhibitor used to treat adult patients affected by HBeAg-positive and HBeAg-negative chronic hepatitis B and with clinical evidence of lamivudine-resistant hepatitis B virus (HBV). Adefovir administered at a dosage of 10 mg/day is generally well tolerated, even if renal toxicity, type Fanconi syndrome, was reported during long-term treatments.

We report a case of osteomalacia with Fanconi syndrome and pathologic fracture of the femur related to long-time (67 months) adefovir treatment (10 mg/day) in a patient with compensated hepatitis B virus (HBV) cirrhosis (Child 5A) and with a previous normal renal function (estimated Glomerular Filtration Rate before adefovir = 78.26 ml/min/1.73 m^2; during adefovir treatment = 57.38 ml/min/1.73 m^2). The patient was switched to entecavir at a dose of 1 mg/day, with both suppression of viremia and improvement of osteomalacia and Fanconi syndrome; the patient's follow-up is still ongoing after 22 months.

Keywords: Adefovir dipivoxil; Osteomalacia; Fanconi syndrome; HBV; Cirrhosis

Sviluppo di osteomalacia e di sindrome di Fanconi durante il trattamento con adefovir in un paziente affetto da cirrosi epatica HBV-correlata

CMI 2014; 8(4): 109-114

http://dx.doi.org/10.7175/cmi.v8i4.969

[1] Rete Regionale di informazione sul farmaco, Azienda Ospedaliera MaterDomini, Catanzaro, Italy
[2] Internal Medicine Operative Unit, Azienda Ospedaliera MaterDomini, Catanzaro, Italy
[3] Department of Health Science, University of Catanzaro and Operative Unit of Clinical Pharmacology and pharmacovigilance, Azienda Ospedaliera MaterDomini, Catanzaro, Italy

CASE REPORT

A 55-year-old man (height = 175 cm, weight = 68 kg, Body Mass Index = 22.2 kg/m^2) came to our observation in December 2012 due to the onset of bone pain, muscle cramps, and asthenia. Past history revealed that about 24 years before (1988) a chronic hepatitis B (anti-HBe positive) infection was diagnosed and 15 years later (2003) liver biopsy and endoscopy documented the presence of cirrhosis (Child 5A) with esophageal varices, respectively.

On 2005, a treatment with pegylated interferon (180 µg/week subcutaneously) was started (HBV-DNA = 10,000,000 IU/ml), but 18 months later (February 2007) for the persistence of high HBV-DNA levels (HBV-DNA = 352,000 IU/ml), pegylated-interferon was stopped and lamivudine (100 mg/day) was administered. During the follow-up, three months later (May 2007),

Why we describe this case

Notwithstanding adefovir is considered safe at the dosage of 10 mg/day, renal function must be carefully evaluated in order to prevent systemic disease and bone fracture. This case report could be useful in order to perform an appropriate prescription in HBV patients treated with adefovir and a risk of kidney or bone disease (e.g. patients taking non steroidal antinflammatory drugs, aminoglycosides, corticosteroids or menopausal women)

Corresponding author
Luca Gallelli
Department of Health Science, University of Catanzaro,
Viale Europa, 88100 Catanzaro and Operative Unit of Clinical Pharmacology and pharmacovigilance, Azienda Ospedaliera MaterDomini,
Via T Campanella 115, Catanzaro, Italy.
Tel +390961712322;
gallelli@unicz.it

Disclosure
The authors declare they have no competing financial interests concerning the topics of this article

Time	Test	Diagnosis or treatment
1988	Microbiology	HBV infection (anti-HBe positive)
2003	Liver biopsy and endoscopy	Cirrhosis (Child 5A) with esophageal varices F1
2005	HBV-DNA = 10,000,000 IU/ml	Pegylated interferon (180 µg/week)
February 2007	HBV-DNA = 352,000 IU/ml	Lamivudine (100 mg/day)
May 2007	HBV-DNA = 1025 IU/ml	Lamivudine (100 mg/day) + adefovir dipivoxil (10 mg/day)
July 2007	HBV-DNA < 200 IU/ml	Lamivudine (100 mg/day) + adefovir dipivoxil (10 mg/day)
February 2008	HBV-DNA = 3770 IU/ml	Entecavir (1 mg/day) + adefovir dipivoxil (10 mg/day)
May 2008	HBV-DNA undetectable	Entecavir (1 mg/day) + adefovir dipivoxil (10 mg/day)

Table I. *History of HBV infection and the related treatments*

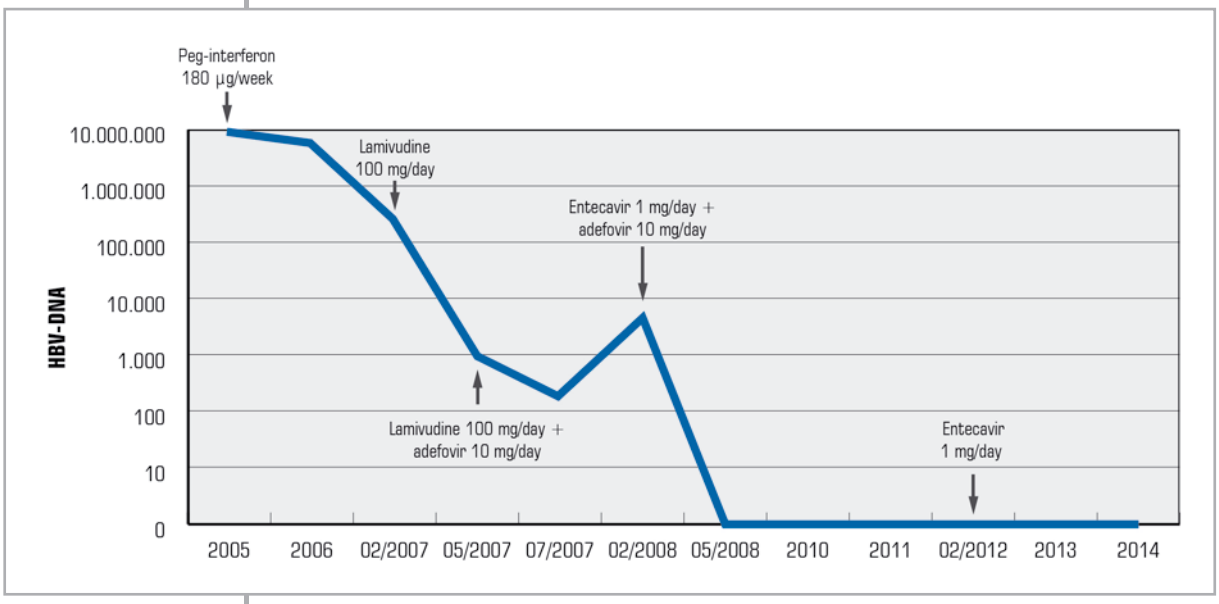

Figure 1. *Timetable of HBV-DNA levels during drug treatments*

the persistence of serum HBV-DNA levels (1025 IU/ml) was recorded, therefore adefovir (10 mg/day) was added, thus attaining a virological suppression in about 2 months (HBV-DNA < 200 IU/ml).

On February 2008, during the follow-up, an increase in serum HBV-DNA levels was detected (3770 IU/ml), lamivudine was stopped and entecavir (1 mg/day) was added with a complete suppression in three months (HBV-DNA undetectable). The history of HBV infection and the related treatments are reported in Table I, while Figure 1 shows the correlation between HBV-DNA levels and drug treatments.

On December 2010, biochemical evaluations revealed hypophosphoremia and glycosuria, without hyperglycemia (Table II).

On March 2011, the patient lamented muscular pain with walking difficulties and lower sensitivity in lower limbs and on February 2012, after an accidental fall occurred by sudden cramping pain of the left gastrocnemius, he reported a femoral neck fracture treated with arthroplasty. One week later, due to continuous muscular pain, he came to our observation as consultants. Clinical examination revealed an intense foot pain (visual analog pain scale, VAS = 8) with difficulty to extend the lower limbs and hyper-excitability of tendon reflexes. At the time of this observation, the patient used no other drugs, while pain was treated with local patch of fentanyl. Somesthetic potential, electromyography, computer tomography and magnetic resonance image of spin and hip failed to show any muscular or skeletal disease. Cervical, dorsal and lumbosacral spine X-ray showed extensive demineralization of the bones; dual-energy X-ray absorptiometry (DXA) at all sites confirmed a low bone max density (L1-L4 = 0.702 g/cm^2,

	Normal range	December 2010	February 2012	December 2014
Blood tests				
Phosphorus	2.7-4.5 mg/dl	2.1	0.9	3.2
Calcium	8.5-10.5 mg/dl	9.5	9.2	9.3
Glucose	70-100 mg/dl	92	90	90
Anion gap	8-16 mEq/l	11	11	11
Serum albumin	38-47 g/dl	41	42	42
pH	7.38-7.42	7.4	7.27	7.4
pO_2	80-100 mmHg	98	98	98
pCO_2	35-45 mmHg	40	20	40
Creatinine clearance	85-130 ml/min	95	62	95
eGFR	> 90 ml/min/1.73 m^2	78.26	57.38	87.08
Serum creatinine	0.7-1.2 mg/dl	1	1.3	0.9
Potassium	3.6-5 mEq/l	4	3.32	4.2
Phosphate	35-104 IU/l	98	202	99
Alkaline phosphatase	115-359 IU/l	340	1594	280
25-hydroxy-vitamin D	20-100 ng/ml	55	12	72
1-25-dihydroxy-vitamin D	25-66 ng/ml	48	19	52
Parathyroid hormone level	10-65 pg/ml	40	72	38
Serum-free T_4	0.7-1.5 ng/dl	1	0.95	0.96
TSH	0.1-4.5 µIU/ml	2.35	2.37	2.36
Urinalysis				
Proteins	< 150 mg/24h	0	4520	110
Phosphate	400-1300 mg/24h	795	1450	760
Uric acid	250-750 mg/24h	520	512	511
Calcium	93-248 mg/24h	120	375	115
Glucose	0 g/l	1	8.4	0
Potassium	30-120 mEq/24h	50	132	55

Table II. *Laboratory findings*

eGFR = estimated Glomerular Filtration Rate, using the Modification of Diet in Renal Disease study group formula; pCO_2 = partial pressure of carbon dioxide; pO_2 = partial pressure of oxygen; TSH = Thyroid-Stimulating Hormone

T-score = -4.2, Z-score = -3.3; left total hip = 0.423 g/cm^2, T-score = -4.2, Z-score = -3.3).

Arterial blood gas showed metabolic acidosis, while blood chemical evaluation revealed high levels of serum creatinine, phosphate, alkaline phosphatase and parathyroid hormone level, and low levels of creatinine clearance, phosphorus and potassium. Moreover, using a reversed phase (C18) high-performance liquid chromatography system (HPLC; UV detector 265 nm, limit of detection 1,5 ng/ml; intra-assay and inter-assay coefficients of variation for control = 8%), low levels of 25-hydroxy-vitamin D and of 1-25-dihydroxy-vitamin D were detected.

Anion gap, serum albumin, serum-free T_4 and TSH were within the normal ranges, while urinalysis showed high levels of proteins, glucose, potassium, calcium, and phosphate (see Table II).

The kidney biopsy showed diffuse and severe tubulointerstitial nephritis with dense lymphoplasmocyte infiltrates. The absence of nausea, diarrhea, abnormal stools, weight loss, and gas, after 1 week of diet with standard food, as well as immunoglobulin A anti-tissue transglutaminase antibody evaluation (for celiac disease) and hydrogen breath test (for lactose intolerance) excluded a malabsorption syndrome.

A diagnosis of Fanconi syndrome with hypophosphatemic osteomalacia was postulated and using the Naranjo probability scale [1] we documented a possible association between adefovir and proximal tubulopathy (score = 7). Adefovir was dismissed

Main questions a doctor should ask himself in this situation

- *Can the patient take this drug?*
- *Are there other drugs that could impair renal (e.g. non steroidal antinflammatory drugs, aminoglycosides) or bone function (e.g. corticosteroids)?*
- *Have I evaluated the development of muscular pain?*
- *Have I evaluated the kidney function and the values of vitamin D?*
- *Can I change adefovir with entecavir alone?*

(HBV-DNA < 200 IU/mL), bicarbonates (12 mEq/day) and vitamin D (100,000 UI/day for 7 days and then 800 UI/day) were added with an improvement of muscular pain in two months (VAS = 2); the inability to walk disappeared in about six months, with normalization of laboratory text.

On October 2014, the patient was in entecavir monotherapy, microbiology assay documented a suppression of HBV-DNA (< 200 IU/mL) and no side effects were recorded. A new follow-up performed on December 2014 revealed a significant improvement of both bone max density (DXA L1-L4 = 1.532 g/cm^2, T-score = 1.6, Z-score = 2.3; and left hip = 0.758 g/cm^2, T-score = -2.3, Z-score = -1.7) and biochemical assays (Table II).

DISCUSSION

Adefovir dipivoxil is a nucleotide analog reverse transcriptase inhibitor used to treat adult patients affected by HBeAg-positive and HBeAg-negative chronic hepatitis B and with clinical evidence of lamivudine-resistant hepatitis B virus (HBV) [2,3].

We report the development of tubules renal toxicity with osteomalacia and Fanconi syndrome during adefovir treatment.

Renal toxicity during the treatment with adefovir at the dosage of 30-120 mg/day is uncommon; and some papers revealed that adefovir administered at common dosage of 10 mg/day is well tolerated and does not cause alterations in creatinine clearance compared to placebo [4,5].

However, a long-time treatment can result in an increase in serum creatinine in about 6-8% of patients [6,7], or in the development of renal toxicity [8-15].

Kim and colleagues [16], evaluating retrospectively 687 chronic hepatitis B patients treated with adefovir alone (18.2%) or in combination with lamivudine (81.8%) for long-time periods (> 12 months) documented that about 10% developed renal toxicity after 27 months, which was mild in 77.8% of patients, moderate in 20.8%, and severe in one patient.

In agreement, Li et al. [17] reported a case of a patient that developed Fanconi syndrome and hypophosphatemic osteomalacia associated with muscular weakness 4 years after the beginning of adefovir.

In our case, renal disease became symptomatic 67 months after the beginning of adefovir, with the development of musculoskeletal pain and difficulty in walking. The nephrotoxicity of adefovir is characterized by a decrease in serum phosphate levels with a modest increase in serum creatinine, related to proximal renal tubules dysfunction, as documented through laboratory texts.

Respect to other papers [8-17] that reported the association between adefovir and renal-toxicity, in the present case, using HPLC, we documented low plasma levels of vitamin D responsible of femoral fractures after an accidental fall related to muscle cramps.

Previously, Tanaka and colleagues [18] reported a 62-year-old man that developed pathological femoral fractures due to osteomalacia after 5 years from the beginning of adefovir, without deficiency of vitamin D.

Moreover, the development of hypophosphatemic osteomalacia associated with tenofovir has been also reported [19-21] and its features are similar to those of hypophosphatemic osteomalacia documented in our patient.

Some Authors documented that proximal renal tubules dysfunction, reducing the absorption of amino acids, glucose, bicarbonate, and phosphate, and the synthesis of 1,25-diidroxy-vitamin D3, induces the development of hypophosphatemic osteomalacia and Fanconi syndrome. Low levels of vitamin D increase the risk of bone loss, muscle aches, cramps, and fatigue [22,23].

The dismission of adefovir and the treatment with vitamin D induced the improvement of symptoms with the normalization of laboratory findings.

Key points

- *Adefovir is effective and generally well tolerated at the dosage of 10 mg/day*
- *Even if unusual, the onset of renal toxicity may occur*
- *In presence of muscle pain, it is necessary to check the renal function and the level of vitamin D*
- *Renal function and vitamin D value must be carefully evaluated during the follow-up*
- *In the suspect of adefovir toxicity, it is advisable to replace it with another antiviral drug in agreement with guidelines*

In agreement with our previous paper [24-26], using the Naranjo score, we documented a probable association between adefovir and clinical symptoms.

Treatment with entecavir in monotherapy maintained the viremic suppression without the development of side effects.

In conclusion, in patients with chronic hepatitis B treated with adefovir, blood and urinary analysis should be carefully evaluated in order to prevent the development of serious adverse drug reaction. Moreover, as well reported by De Socio et al. [21] for tenofovir, in presence of osteomalacia-related to adefovir a multidisciplinary approach is important in order to perform a rapid diagnosis and a timely treatment.

REFERENCES

1. Naranjo CA, Busto U, Sellers EM, et al. A method for estimating the probability of adverse drug reactions. *Clin Pharmacol Ther* 1981; 30: 239-45; http://dx.doi.org/10.1038/clpt.1981.154
2. Peters MG, Hann HH, Martin P, et al. Adefovir dipivoxil alone or in combination with lamivudine in patients with lamivudine-resistant chronic hepatitis B. *Gastroenterology* 2004; 126: 91-101; http://dx.doi.org/10.1053/j.gastro.2003.10.051
3. Perrillo R, Hann HW, Mutimer D, et al. Adefovir dipivoxil added to ongoing lamivudine in chronic hepatitis B with YMDD mutant hepatitis B virus. *Gastroenterology* 2004; 126: 81-90; http://dx.doi.org/10.1053/j.gastro.2003.10.050
4. 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: 808-16; http://dx.doi.org/10.1056/NEJMoa020681
5. 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: 800-7; http://dx.doi.org/10.1056/NEJMoa021812
6. Marcellin P, Chang TT, Lim SGL, et al. Longterm efficacy and safety of adefovir dipivoxil for the treatment of hepatitis Be antigen positive chronic hepatitis B. *Hepatology* 2008; 48: 750-8; http://dx.doi.org/10.1002/hep.22414
7. 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: 1743-51; http://dx.doi.org/10.1053/j.gastro.2006.09.020
8. Ha NB, Garcia RT, Trinh HN, et al. Renal dysfunction in chronic hepatitis B patients treated with adefovir dipivoxil. *Hepatology* 2009; 50: 727-34; http://dx.doi.org/10.1002/hep.23044
9. Tamori A, Enomoto M, Kobayashi S, et al. Add-on combination therapy with adefovir dipivoxil induces renal impairment in patients with lamivudine-refractory hepatitis B virus. *J Viral Hepat* 2010; 17: 123-9; http://dx.doi.org/10.1111/j.1365-2893.2009.01160.x
10. 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: 389-93; http://dx.doi.org/10.5009/gnl.2010.4.3.389
11. Wong T, Girgis CM, Ngu MC, et al. Hypophosphatemic osteomalacia after low-dose adefovir dipivoxil therapy for hepatitis B. *J Clin Endocrinol Metab* 2010; 95: 479-80; http://dx.doi.org/10.1210/jc.2009-2051

12. Girgis CM, Wong T, Ngu MC, et al. Hypophosphataemic osteomalacia in patients on adefovir dipivoxil. *J Clin Gastroenterol* 2011; 45: 468-73; http://dx.doi.org/10.1097/MCG.0b013e3181e12ed3
13. Fabbriciani G, de Socio GV, Massarotti M, et al. Adefovir induced hypophosphatemic osteomalacia. *Scand J Infect Dis* 2011; 43: 990-2; http://dx.doi.org/10.3109/00365548.2011.581307
14. Shimohata H, Sakai S, Ogawa Y, et al. Osteomalacia due to Fanconi's syndrome and renal failure caused by long-term low-dose adefovir dipivoxil. *Clin Exp Nephrol* 2013; 17: 147-8; http://dx.doi.org/10.1007/s10157-012-0762-8
15. 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: 321-6; http://dx.doi.org/10.1111/jcpt.12050
16. 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: 306-12; http://dx.doi.org/10.1111/j.1440-1746.2011.06852.x
17. Li L, Dong GF, Zhang X, et al. Adefovir dipivoxil-induced Fanconi syndrome and hypophosphatemic osteomalacia associated with muscular weakness in a patient with chronic hepatitis B. *Nan Fang Yi Ke Da Xue Xue Bao* 2011; 31: 1956
18. Tanaka M, Setoguchi T, Ishidou Y, et al. Pathological femoral fractures due to osteomalacia associated with adefovir dipivoxil treatment for hepatitis B: a case report. *Diagnostic Pathol* 2012; 7: 108; http://dx.doi.org/10.1186/1746-1596-7-108
19. Mateo L, Holgado S, Mari-oso ML, et al. Hypophosphatemic osteomalacia induced by tenofovir in HIV-infected patients. *Clin Rheumatol* 2014 May 3 [Epub ahead of print]; http://dx.doi.org/10.1007/s10067-014-2627-x
20. Saidenberg-Kermanac'h N, Souabni L, Prendki V, et al. Normal plasma FGF23 levels kinetic in tenofovir-related hypophosphatemic osteomalacia in an HIV-infected patient with von Recklinghausen disease. *Joint Bone Spine* 2011; 78: 306-8; http://dx.doi.org/10.1016/j.jbspin.2010.11.007
21. De Socio GV, Fabbriciani G, Massarotti M, et al. Hypophosphatemic osteomalacia associated with tenofovir: a multidisciplinary approach is required. *Mediterr J Hematol Infect Dis* 2012; 4: e2012025; http://dx.doi.org/10.4084/mjhid.2012.025
22. Clarke BL, Wynne AG, Wilson DM, et al. Osteomalacia associated with adult Fanconi's syndrome: clinical and diagnostic features. *Clin Endocrinol* 1995; 43: 479-90; http://dx.doi.org/10.1111/j.1365-2265.1995.tb02621.x
23. Laing CM, Toye AM, Capasso G, et al. Renal tubular acidosis: developments in our understanding of the molecular basis. *Int J Biochem Cell Biol* 2005; 37: 1151-61; http://dx.doi.org/10.1016/j.biocel.2005.01.002
24. De Vuono A, Palleria C, Scicchitano F, et al. Skin rash during treatment with generic itraconazole. *J Pharmacol Pharmacother* 2014; 5: 158-60; http://dx.doi.org/10.4103/0976-500X.130086
25. Mumoli L, Gambardella A, Labate A, et al. Rosacea-like facial rash related to metformin administration in a young woman. *BMC Pharmacol Toxicol* 2014; 15: 3; http://dx.doi.org/10.1186/2050-6511-15-3
26. Caroleo B, Galasso O, Staltari O, et al. Muscular damage during telbivudine treatment in a chronic hepatitis B patient. *Muscles Ligaments Tendons J* 2011; 1: 57-60