Fanconi Syndrome and Osteomalacia Induced by Tenofovir

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ABSTRACT

Introduction: Tenofovir disoproxil fumarate (TDF), an antiviral nucleoside analog reverse transcriptase inhibitor, has been used for the treatment of HIV and HBV in the past decades. TDF nephrotoxicity has been reported and could lead to renal failure and Fanconi Syndrome (FS). **Case:** A 58-year-old female HBsAg carrier with TDF treatment since 2013 presented with osteomalacia. She had glucosuria, albuminuria, vitamin D insufficiency, hypophosphatemia, and occasional hypokalemia episodes. Laboratory results showed amino aciduria, which indicates renal tubulopathy. The diagnosis of Fanconi syndrome was confirmed. Withdrawal of TDF was followed by improvement. **Conclusion:** The acquired FS associated with TDF is reversible. The use of TDF-containing antiviral regimens should be followed by screening recommendations to detect early Fanconi syndrome.

Keywords: Fanconi syndrome, osteomalacia, renal tubulopathy, tenofovir disoproxil fumarate.

ABSTRAK

Pendahuluan: *Tenofovir disoproxil fumarate* (TDF), sebuah antivirus *nucleoside analog reverse transcriptase inhibitor*, digunakan untuk pengobatan HIV dan Hepatitis B dalam beberapa dekade terakhir. Nefrotoksisitas yang disebabkan oleh TDF telah banyak dilaporkan dan dapat menyebabkan sindrom Fanconi/*Fanconi syndrome* (FS) dan gagal ginjal. **Kasus:** Seorang wanita HBsAg-*carrier* berusia 58 tahun dengan pengobatan TDF sejak tahun 2013 datang ke poliklinik dengan osteomalasia. Hasil laboratorium menunjukkan glukosuria, albuminuria, kekurangan vitamin D, hipofosfatemia, dan pasien mengalami episode hipokalemia. Hasil laboratorium menunjukkan aminoasiduria yang mengindikasikan tubulopati ginjal. Diagnosis sindrom Fanconi ditegakkan. Setelah berhenti mengonsumsi TDF, pasien mengalami perbaikan. **Simpulan:** FS terkait TDF bersifat reversibel. Penggunaan rejimen antivirus mengandung TDF harus diikuti dengan skrining untuk deteksi dini sindrom Fanconi. **Lissa Sabrina, Sidharta Salim. Sindrom Fanconi dan Osteomalasia Diinduksi *Tenofovir***

Kata Kunci: Sindrom Fanconi, osteomalasia, tubulopati ginjal, *tenofovir disproxil fumarate.*

INTRODUCTION

Renal rickets, glycosuria, and hypophosphatemia in several children were first described by Fanconi, a pediatrician, followed by de Toni and Debre, *et al.*[1] Fanconi syndrome (FS) is now described as a global abnormal function of the proximal tubule that leads to excessive urinary excretion of glucose, phosphate, amino acids, low molecular weight proteins (LMWPs), bicarbonate, uric acid, and other solutes normally reabsorbed by this nephron segment. These losses can lead to severe dehydration, electrolyte imbalances, metabolic acidosis, rickets, osteomalacia, and growth failure.[2]

Numerous inherited or acquired disorders are associated with Fanconi syndrome. Hereditary conditions associated with FS are cystinosis, glycogen storage diseases, mitochondrial cytopathy, tyrosinemia, hereditary fructose intolerance, galactosemia, Wilson's disease, Dent's disease, and X-linked Lowe syndrome.[1]

Causes of acquired FS are varied; toxic side effects from therapeutic drugs are the most common cause; exposure to chemotherapies such as ifosfamide, cisplatin and carboplatin, azacytidine, and mercaptopurine; antiretroviral drugs specifically tenofovir, didanosine (ddI), cidofovir, and adefovir; and antibiotics such as aminoglycoside, and expired tetracycline changed to epitetracycline and anhydrotetracycline, which are toxic to proximal tubule. Poisoning may also lead to Fanconi syndrome. Multiple myeloma or monoclonal gammopathy of undetermined significance can also cause the condition. Fanconi syndrome can also be manifested as symptoms from certain autoimmune disorders. Other conditions associated with Fanconi syndrome are chronic glue sniffing, heavy alcohol abuse, prolonged exposure to heavy metals and occupational chemicals, severe vitamin D deficiency, and kidney transplantation.[3]

World Health Organization (WHO) guidelines for initial regimen HIV treatment recommends ART based on tenofovir disoproxil fumarate (TDF) or tenofovir alafenamide (TAF). TDF

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is also used to treat hepatitis B virus (HBV). Unfortunately, TDF may have several side effects that lead to renal dysfunction. The reported incidence of Fanconi syndrome in patients using TDF is 5.5/1000 person.[4] Typical findings in TDF-induced Fanconi syndrome are glucosuria without any previous history of diabetes mellitus, aminoaciduria, hypophosphatemia, and phosphaturia, as well as hyperchloremic metabolic acidosis due to excessive loss of bicarbonate.[5]

CASE

A 58-year-old female with chronic Hepatitis B came to the clinic in 2013, laboratory examination showed an abnormal liver function test, SGOT 116 U/L and SGPT 124 U/L, and HBeAg positive 75.13 IU/mL. The patient started taking antiviral telbivudine 600 mg once daily, but the HBeAg level kept rising in the next month's laboratory examination so adefovir dipivoxil 10 mg once daily was added. But no improvement was achieved, HBeAg was elevated to 150,126 IU/mL from two months prior. Telbivudine was replaced with tenofovir disoproxil 600 mg once daily. The combination of tenofovir and adefovir resulted in a reduction of HBeAg to 21,753 IU/mL and normal liver function after three years. In 2017, the patient came with severe lethargy and right coxalgia. She admitted to taking the herbal medicine Kianpi, with ginseng as the main ingredient, for 2 months. She believed it could alleviate her body weakness and improve her appetite. Kianpi contained dexamethasone.[6] Laboratory results showed elevated cortisol levels with a morning cortisol level of 21.46 mcg/dL (control 18) and an evening cortisol level of 11.64 mcg/dL (control 10). CT scan showed erosion of the right femur head.

She was diagnosed with iatrogenic Cushing syndrome, the erosion of the right femur head was thought to be caused by steroids. She still took adefovir 10 mg and tenofovir 600 mg once daily. HBeAg positive 19,896 IU/mL. Her urinalysis showed glucosuria 4+ and albuminuria 1+. Salmon calcitonin injection thrice a week, calcium carbonate 500 mg thrice daily, calcium phosphate 200 mg twice daily, vitamin D3 5,000 IU once daily, alendronate 70 mg once a week was given for her osteomalacia. Tenofovir and adefovir were still consumed regularly. She had several episodes of hypokalemia corrected with potassium infusion. Her kidney function deteriorated, and creatinine clearance was 37 mL/m, so the dosage of adefovir was reduced to once every two days (Tuesday, Thursday, and Saturday). She kept having glucosuria and albuminuria. Dipyridamole, an antiplatelet said to be effective in preventing glomerular lesions[7], was given in 3x50 mg dose and resulted in improvement of urine albumin. Tenofovir and adenovir were no longer prescribed because of deteriorated kidney function. Without our knowledge, the patient continues to take tenofovir.

After the pandemic's hiatus, the patient came to the outpatient clinic in 2022 with pain in her right leg after a minor accident, and difficulty to move due to generalized muscle weakness. A right tibia x-ray showed a thinned cortex, diminished trabeculation and a healed fracture with distal angulation. Laboratory examination showed glucosuria with normal blood sugar with no prior history of diabetes, low vitamin D3, and hypophosphatemia. This condition along with the history of antiviral medication aroused suspicion of Fanconi syndrome, possibly due to prolonged administration of tenofovir.

Tenovofir was withdrawn, and the patient subjectively felt better. She was given high-dose of 1,000 mg 25-OH-vitamin D divided into two doses of 500 mg each, potassium chloride 600 mg thrice daily, and calcium phosphate 1000 mg once daily. Urine examination showed elevated excretions of several unrelated amino acids with a non-specific pattern of generalized aminoaciduria indicating a renal tubulopathy. Diagnosis of Fanconi syndrome was confirmed. Her condition improved.

DISCUSSION

Tenofovir is a nucleoside reverse-transcriptase inhibitor (NRTI) based on acyclic nucleoside analogs. Tenofovir Disoproxil Fumarate (TDF) 300 mg daily has been used as a preferential treatment for HIV and HBV.[5] However, chronic TDF usage has serious side effects, especially bone and kidney toxicity.[5] Tenofovir is eliminated by active tubular secretion and also by passive glomerular filtration; circulating plasma tenofovir may damage the proximal tubule which could lead to renal impairment and Fanconi Syndrome.[8] In Fanconi Syndrome, the defect only occurs in tubular proximal which can be classified as renal tubular acidosis. While renal failure means that the renal system cannot function properly.[8] Fanconi syndrome mainly causes malfunction of bone formation, dehydration, and muscle weakness while renal failure usually causes fatigue, fluid retention, and high blood pressure.

A cohort study by Medland, *et al*, concluded that the FS incidence is 1 in every 1000 patients taking TDF per year and increased approximately five-fold when consumed together with ritonavir. They also found that several hypothesis risk factors for chronic kidney disease (CKD) (diabetes, age, hypertension, hyperlipidemia, chronic hepatitis B or C co-infection, pre-treatment renal function), degree of prior immunosuppression or virological suppression were not related to the development of FS. Fanconi Syndrome occurs relatively late in TDF exposure.[9]

Guideline of the European Association for the Study of the Liver (EASL) urges all patients starting TDF treatment should be tested for serum creatinine levels before taking tenofovir and assess the baseline renal risk as well as factors such as decompensated cirrhosis, creatinine clearance <60 mL/min, uncontrolled hypertension and diabetes mellitus, proteinuria, concomitant nephrotoxic drugs, and organ transplantation.[10]

Medland, *et al*, described that one in 1000 patients taking TDF per year will develop Fanconi Syndrome. They also observed that the incidence is increased approximately five-fold when TDF is co-administered with ritonavir. The risk factors for Fanconi syndrome are chronic kidney disease (such as chronic diabetes, age, hypertension, hyperlipidemia, chronic hepatitis B or C co-infection, and pre-treatment renal function).[4]

Even though the correlation between TDF and the mechanism of bone density loss remains unclear, it has been suggested that TDF phosphonate molecules could impact osteoclast and osteoblast function by altering their gene expression.[5] And Fanconi syndrome with hypocalcemia and hypophosphatemia, may worsen the osteomalacia state.[5]

Grant, *et al*, found that patients treated with TDF showed greater BMD loss and increased

bone turnover compared to non-TDF users. Besides, though rare, TDF can cause acquired Fanconi syndrome which is a proximal tubular dysfunction, marked by wasting phosphate that would lead to hypophosphatemia and therefore osteomalacia and muscle weakness.[11]

Even without obvious risk factors, nephrotoxicity developing into Fanconi syndrome may happen in TDF treatment and may be observed at variable times after starting the therapy; hence it is important to periodically monitor all patients taking TDF-containing antiviral regimen, with possible immediate TDF withdrawal and change to an effective alternating agent.[5]

CONCLUSION

Diagnosis of TDF-induced Fanconi syndrome is based on the findings of glucosuria, aminoaciduria, and phosphaturia, as well as hypophosphatemia. If left untreated, hypophosphatemia would lead to osteomalacia. Acquired Fanconi syndrome might be treatable and reversed so careful observations are mandatory.

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