Clinical note
Bone scintigraphy and secondary osteomalacia due to nephrotoxicity in a chronic hepatitis B patient treated with tenofovir

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ABSTRACT
Tenofovir is a nucleotide analogue used for the treatment of chronic hepatitis B and HIV infection. The safety of tenofovir is high but it has been described that tenofovir produces tubular toxicity and Fanconi’s syndrome in some HIV-infected patients. To our knowledge this is the first documented case of bone involvement in Fanconi’s syndrome in a patient treated with tenofovir for chronic hepatitis B without HIV co-infection. Bone scintigraphy has proven to be very useful for the diagnosis of secondary osteomalacia. Normalization of the bone scan after the withdrawal of the drug and the decline in alkaline phosphatase and phosphate serum levels reinforce the cause-effect relationship.

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Osteomalacia secundaria a nefrotoxicidad en una paciente con hepatitis B tratada con tenofovir

RESUMEN
El tenofovir es un análogo de nucleótido que se utiliza para el tratamiento de la hepatitis B y la infección por VIH. La seguridad del fármaco es muy alta, pero se ha descrito que en algunos pacientes VIH produce toxicidad tubular y síndrome de Fanconi. En nuestro conocimiento este es el primer caso en el que se documenta afectación ósea en síndrome de Fanconi en una paciente tratada con tenofovir por hepatitis B. En este contexto la gammagrafía ósea ha resultado ser de gran utilidad para el diagnóstico de osteomalacia secundaria. La normalización de la gammagrafía ósea y de los valores séricos de fosfato y fosfatasa alcalina tras la retirada del fármaco refuerza la relación causa-efecto.

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Introduction
Tenofovir (TDF) is a nucleotide analogue that inhibits reverse transcriptase commonly used for the treatment of HIV infection and chronic hepatitis B. Although the safety of the drug is very high tubular toxicity and Fanconi syndrome have been described in patients with HIV infection treated with TDF. This is in our knowledge the first case of Fanconi syndrome and secondary osteomalacia due to the treatment with TDF for chronic hepatitis B.

Clinical note
A 49-year-old female patient diagnosed of HBsAg-negative chronic hepatitis B. In 2006 she began treatment with adefovir (ADV) for persistent elevation of transaminases and elevated serum HBV DNA (394,000 U/ml). She achieved good response with undetectability of HBV DNA level. Five years later she was switched to TDF. In January 2012 she began with widespread and diffuse bone pain mostly in thoracic region preventing her to develop a normal life. The bone pain was treated with non-steroidal anti-inflammatory drugs. At that time, the serum alkaline phosphatase (AP) was 438 U/L and phosphate value 1.7 mg/dl. A bone scintigraphy was required. It showed a diffuse uptake of the radiotracer in the whole skeleton with lack of visualization of kidneys and increase focal uptake in ribs, elbows, sacroiliacs, both hips, tarsus and skull (Fig. 1). With all these findings she was diagnosed of Fanconi syndrome with marked bone involvement secondary to TDF treatment. The drug was withdrawn and after a short period of time the symptoms disappeared. Three months later a new bone scan showed only a increased uptake in skull. At this time the serum AP level was 185 U/L and phosphate value had normalized (Fig. 2).

Discussion
It has been reported several cases of nephrotoxicity by TDF in HIV positive patients. Its prevalence seems to be near 0.5%. The most common disorder produced by this nucleotide analogue of adenosine is a proximal tubular dysfunction by intracellular accumulation of TDF. As a result of this alteration a great loss of phosphate occurs. The clinical picture courses like a partial or complete Fanconi syndrome that appears between 8 and 30 months after starting therapy. These clinical findings have been described mostly in HIV-infected patients since the association of the protease inhibitors with ritonavir increases plasma concentration and favours the risk of nephrotoxicity.1-3 There have been also described some cases of nephrotoxicity with bone involvement in chronic hepatitis B patients treated with adefovir,4 but to our knowledge this is the first case of...
Fig. 1. Bone scintigraphy of patient in treatment with TDF and bone pain. Diffuse increased uptake in the skeleton and especially in skull is observed. Poor visualization of renal silhouettes and multiple focal uptakes.

Fig. 2. Bone scans after withdrawal of TDF and its replacement by ETV. It persists a diffuse increase uptake in skull and a small focal uptake in costal region.
osteomalacia associated to nephrotoxicity appearing as an adverse event in a chronic hepatitis B patient treated with TDF without HIV coinfection. In addition, in our case the use of non-steroidal anti-inflammatory drugs for the treatment of bone pain can have enhanced the TDF nephrotoxic effect.5

The sensitivity of the scan to detect osteoblastic bone lesions makes this exploration especially indicated when bone involvement or an elevation of the AP levels occurs in patients treated with adenosine analogues. The characteristic findings in the scan are the usual that appears in metabolic pathology and consist in an increase in the uptake of the tracer in the whole skeleton with a diffuse uptake in the skull, and poor visualization of renal silhouettes.6 There are also multiple focal uptakes probably secondary to pathologic fractures in our patient.

The disappearance of the clinical findings, the decrease in serum values of AP and phosphate and the normalization of scintigraphic findings three months after withdrawal of the drug allows establish the relation cause–effect.

This case highlights the need to carefully monitor the tubular renal function in patients with chronic hepatitis B treated with TDF as it is already done in the population infected with HIV on treatment with this drug. In addition, it shows the usefulness of the scan in cases of insidious bone pains since this technique offers the possibility of exploring the entire body and has a great sensitivity to diagnose bone involvement.7

Conflicts of interest

The authors declare they have no conflicts of interest.

References