Acute renal failure and Fanconi syndrome due to deferasirox

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Abstract
Deferasirox is the first oral iron chelator and, as such, is widely used for the treatment of chronic iron overload. However, recent data from large studies confirmed the renal toxicity of deferasirox. We report a case of Fanconi syndrome associated with acute renal failure in a patient receiving deferasirox. In particular, new insights regarding the pathophysiology of the renal disease due to this treatment are discussed. This case highlights the importance of a careful monitoring of kidney function, markers of proximal tubulopathy and ferritinaemia in patients receiving deferasirox.

Keywords: deferasirox; Fanconi syndrome; iatrogenic disease; kidney failure

Background
Deferasirox (Exjade®, Novartis, Switzerland) is a recently approved iron chelator, used for the treatment of chronic iron overload [1]. To date, deferasirox is the only once-daily oral iron chelator available. Phase II and Phase III studies reported mild increases in serum creatinine, generally within the upper limit of normal, concluding to renal safety. Post-marketing cases of renal disease have recently been described in patients treated with deferasirox, sometimes with a fatal outcome. The incidence rate of these adverse events remains to be established, which raises important questions regarding the safety of this drug. Here, we report a case of Fanconi syndrome (FS) with decreased kidney function in a patient treated with deferasirox for non-hereditary haemochromatosis.

Case report
A 77-year-old Caucasian man was admitted to our Nephrology Department in February 2009 for asthenia, anorexia and severe hypokalaemia.

In 2001, hyperferritinaemia related to non-hereditary haemochromatosis was diagnosed, initially treated with bleeding and ursodesoxycholic acid. Because of an unsuccessful evolution, deferasirox was initiated 1 month before the admission (1500 mg/day). Medical history recorded mild hypertension for over 20 years. No pre-existing malignancy or immunological disorder was reported. The anamnesis revealed no unusual risk of exposure to heavy metals or environmental toxic agents. Ongoing medications included irbesartan 150 mg/day, hydrochlorothiazide 12.5 mg/day and ursodesoxycholic acid.

As asthenia and anorexia, associated with constipation and epigastralgia, appeared 15 days before admission. Laboratory examinations prescribed by the general practitioner showed an increase in serum creatinine and profound hypokalaemia (2.1 mmol/L). Table 1 lists the standard laboratory tests performed during the 5-day hospitalization. At admission, the patient presented with renal failure [Modification of Diet in Renal Disease (MDRD) estimated glomerular filtration rate (eGFR) = 34 mL/min/1.73 m²]. Tubular maximum for phosphate reabsorption (TmPi/GFR) was reduced, whereas fractional excretion of uric acid was increased. Normoglycaemic glycosuria was evidenced, and urine chromatography analysis revealed abnormal aminoaciduria composed of neutral and acidic amino acids. A serum protein electrophoresis excluded a monoclonal gammopathy, a classical aetiology of acquired FS in elderly patients.

Deferasirox was stopped on admission. Initial treatment included parenteral potassium, magnesium and phosphate supplementation for 2 days, relayed by oral supplementation. Kalaemia and phosphataemia normalized, and serum creatinine progressively decreased within 5 days, allowing discharge. One month later, the oral potassium and phosphate supplementation were stopped without recurrence of hypokalaemia or hypophosphataemia.

Discussion
Iron chelation therapy is essential for the treatment of iron overload related to haemochromatosis or repeated blood transfusions for chronic anaemia, including β-thalassaemia, sickle cell disease and myelodysplastic syndromes. Until recently, desferrioxamine was the only iron-chelating treatment available, but requirement of subcutaneous delivery
Acute renal failure and Fanconi syndrome due to deferasirox

Deferasirox is a once-daily oral iron chelator approved by the Food and Drug Administration (FDA) in 2005. It is a tridentate iron chelator, which has a high affinity and selectivity for Fe³⁺. Deferasirox is primarily metabolized by glucuronidation, with subsequent biliary excretion. Renal excretion is low (~8%). In the first Phase II and III studies, mild, non-progressive increases in serum creatinine, generally within the upper limit of normal, occurred in approximately one-third of the patients. These data were confirmed by two recent and large prospective studies, which assessed the renal safety profile of different doses of deferasirox in various types of anaemias [2,3]. Additionally, a clinical study (Study NCT00395629) is currently evaluating the renal safety profile of different doses of deferasirox in patients with hereditary haemochromatosis.

Post-marketing cases of renal diseases have recently been reported in patients treated with deferasirox. In 2008, Brosnahan et al. described a case of reversible acute interstitial nephritis due to deferasirox [4]. A dialysis patient with hypocalcaemia related to deferasirox was reported by Yusuf et al., with normalization of serum calcium concentration after discontinuation of deferasirox [5]. In 2009, Rafat et al. described a case of FS with acute renal failure in a 78-year-old patient treated by deferasirox for a sideroblastic anaemia [6]. Finally, Even-Or et al. described two other cases of reversible FS associated with deferasirox [7].

Here, we report a novel case of acquired FS related to deferasirox, resulting in hypophosphataemia, hypokalaemia, glycosuria, aminoaciduria, and abnormal wasting of uric acid and bicarbonate, associated with an acute decrease in kidney function. The patient did not receive other drugs known to induce FS, and there was no clinical or biological argument for a monoclonal gammopathy, in particular multiple myeloma. The normalization of biochemistry results after discontinuation of deferasirox is a strong argument for the drug's imputability. Nephrosclerosis related to incipient hypertensive kidney disease may have increased deferasirox toxicity in our patient. Renal biopsy was not performed because of the reversible nature of the findings.

No conclusive pathogenetic explanation to deferasirox-related serum creatinine increase and proximal tubulopathy has yet been demonstrated. Gattermann et al. reported that a greater velocity of iron removal was associated with elevated serum creatinine levels, and hypothesized that this may be related to haemodynamic modifications [8]. Papasotiriou et al. demonstrated the correlations between renal and cardiac biomarkers and ferritinaemia, and consequently suggested that renal haemodynamics may be modified by indirect consequences of the reduced iron burden [9]. Interestingly, we also noticed a prompt decrease in ferritinaemia in our patient, from 1519 to 376 µg/L within 2 months. Moreover, he was treated by irbesartan, which might have aggravated intrarenal haemodynamic alterations. Chronic toxicity studies in normal rats and marmoset monkeys treated by deferasirox showed vacuolization of proximal tubular epithelial cells and an increase in biomarkers of kidney injury, particularly in animals without iron overload [10]. Additionally, in a long-term oral toxicity study in monkeys, kidney iron content was reduced up to ~40%. Consequently, alterations related to the functional impairment of iron-bound proteins in proximal tubular cells may also be discussed. Lastly, deferasirox could also increase iron absorption and cause decompartmentalization of chelated iron in various organs, especially the kidneys, resulting in renal damage. To explain the nephrotoxic potential of deferasirox, Hider suggested that deferasirox is able to enter cells owing to its lipophilicity, but may not readily efflux because it forms a highly charged (3+) complex with iron [11].

Although further studies are necessary to understand the pathophysiological mechanisms of tubular toxicity related to deferasirox, the present report adds to the evidence for the nephrotoxic potential of this medication.
Successful management of recurrent pregnancy-related thrombotic thrombocytopenia purpura in a renal transplant recipient

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Abstract

Thrombotic thrombocytopenic purpura (TTP) is a rare but potentially devastating complication of pregnancy. We report the first documented case of a successful treatment of recurrent TTP complicating pregnancy in a renal transplant patient.

Keywords: ADAMTS-13; pregnancy; renal transplant; thrombotic thrombocytopenic purpura

In 2003, a 31-year-old nulliparous patient, with end-stage kidney disease secondary to chronic pyelonephritis, received a living-related transplant from her sister; immunosuppression was tacrolimus and mycophenolate mofetil (MMF). Graft function was excellent with a serum creatinine between 100 and 120 µmol/L. She subsequently requested preconception counselling. This included converting MMF to azathioprine 125 mg. She soon became pregnant. At the 22nd week of gestation, she presented with new-onset hypertension and proteinuria. Investigations showed haemolytic anaemia (Hb 7.7 g/dL, LDH 1047 U/L) and thrombocytopaenia (47 × 109/mL). Microangiopathic haemolytic anaemia (MAHA) was confirmed on the blood film. Liver enzymes were normal, but there was renal graft dysfunction (creatinine 145 µmol/L). The diagnoses of thrombotic thrombocytopenic purpura (TTP) and pre-eclampsia were made. Plasma exchange (PEX) was commenced using solvent-detergent virally inactivated fresh-frozen plasma (Octaplas) as replacement fluid. Tacrolimus and apheresis were continued. She was also commenced on deferasirox to deferasirox, this recent evidence demonstrates that careful monitoring of renal function and ferritinemia in patients receiving deferasirox is mandatory. This case illustrates the importance for nephrologists, haematologists and internists to be aware of potentially severe renal complications of this recently commercialized drug, in order to prevent progressive kidney disease.

Conflict of interest statement. None declared.

References


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