Cystic Fibrosis pulmonary disease is not a contra-indication to live-related renal transplantation

Sir,

A 26-year-old male cystic fibrosis (CF) patient (delta F508 homozygous) presented with symptoms of a pulmonary exacerbation and was treated with aminoglycosides. His CF was complicated by pancreatic insufficiency, CF-related diabetes, a previous orthotopic liver transplantation (1996) for CF related liver disease and CF bronchiectasis. On this occasion it was noted that his serum creatinine had risen from 102 to 180 mmol/l. His intravenous treatment was curtailed, but his serum creatinine continued to increase to 447 mmol/l and he presented in frank pulmonary oedema requiring emergency dialysis. His other risk factors for renal failure included CF-related diabetes and regular use of tacrolimus (2 mg once daily) prescribed for immunosuppressive therapy following his orthotopic liver transplantation. He subsequently developed chronic renal failure and was treated with regular haemodialysis. This had disastrous consequences on his general CF health and his quality of life. Over 3 months his weight diminished from 67 (dry weight) to 59 kg. His malnutrition was compounded by nausea resulting from uraemia and a fluid restriction that made dietary supplementation difficult. He required frequent treatments for pulmonary exacerbations which could only be treated with reduce dose mono-therapy such that his FEV1 measurement diminished by 11. His CF-related diabetes become very difficult to manage due to erratic eating habits and increased pulmonary exacerbations resulting in regular hypoglycaemic episodes. His HbA1C was measured at 8%. He also developed a uraemia cardiomyopathy resulting in a reduced left ventricular ejection fraction of 38%.

After a case conference with the renal physicians, CF physicians and transplant surgeons, he was listed for a live-related renal donor transplant. The transplantation was uncomplicated. The patient and graft have survived their first year and of note there have been no episodes of graft rejection since the transplant was performed. His most recent serum creatinine, taken 12 months since transplantation, is 90 mmol/l. His pulmonary function has improved from 55% predicted (1.95 l) to 65% predicted (2.9 l). He has regained the 6 kg lost during dialysis and his pulmonary exacerbation frequency has reduced from eight to two per annum. His HbA1C has also improved to 4.9% reflecting better diabetic control.

This case highlights the fact that moderate CF pulmonary disease is not a contra-indication to renal transplantation and, on the contrary, live-related renal transplantation may have widespread benefits in CF patients with dialysis dependent renal failure in terms of general well being and likely improvement in survival [1,2].

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Interaction between voriconazole and tacrolimus in a kidney-transplanted patient

Sir,

Infections are common life-threatening complications of long-term immunosuppressive therapy [1]. Among these, yeast infections are difficult to treat not only because of the context of immunosuppression, but also because of the pharmacokinetic properties of the antifungal agents, which inhibit the metabolism of calcineurin inhibitors, leading to an increase in the serum concentration and resulting in renal toxicity [2,3].

A 55-year-old male kidney transplant recipient was started on voriconazole for skin infection of the lower limbs due to *Pseudallescheria boydii*. End-stage renal failure secondary to medullary cystic kidney disease led to a cadaver renal transplantation 4 years earlier. His medical history also included severe bilateral peripheral vascular disease, ischaemic cardiomyopathy, arterial hypertension, chronic cholestasis of unknown aetiology (despite three hepatic biopsies) and hypercholesterolaemia. His treatment included tacrolimus 4 mg/day, prednisolone 7.5 mg/day, ciprofloxacin 1000 mg/day, cefadroxil 1000 mg/day, atenolol 2.5 mg od, furosemide 60 mg/day, lisinopril 20 mg/day, aspirin 160 mg/day, omeprazole 20 mg/day, pravastatin 20 mg/day, allopurinol 100 mg/day, dipyridamole 200 mg/day and molsidomine 16 mg/day.

Treatment with itraconazole was initiated 1 month before admission, concomitantly with a 50% reduction of the tacrolimus dosage (2 mg/day). Itraconazole was replaced by voriconazole after 1 month, because no clinical improvement had occurred. Upon start of oral voriconazole (4 mg/kg bid), tacrolimus trough level, previously stable and <12 ng/ml (aimed therapeutic interval: 5–12 ng/ml), increased markedly after 7 days (20 ng/dl after 10 days and 25 ng/dl after 17 days)
and was associated with an impairment of renal graft function (serum creatinine rising from 1.2 to 1.9 and 3.9 mg/dl after 10 and 17 days, respectively). The tacrolimus dosage was reduced further and was completely withdrawn over 3 days, ending with a dosage of 0.5 mg every other day, and then a gradual recovery of the previous renal function was seen.

Voriconazole (V-Fend®; Pfizer) is a new second-generation triazole antifungal agent that demonstrates excellent activity against a wide variety of yeasts and moulds. It is generally well tolerated and is effective against *Candida*, *Aspergillus* and unusual organisms, such as *Fusarium* and *P. boydii* [2,4]. The mechanism of action of voriconazole, similar to that of all azole agents, is inhibition of the action of cytochrome P-450 (CYP-450)-dependent 14α-lanosterol demethylation [2].

Because voriconazole is metabolized by the hepatic CYP-450 systems, drug interaction with calcineurin inhibitors occurs, resulting in increased serum concentration and sometimes leading to renal toxicity [3,5]. In this case, we present a case with a nephrotoxic effect of tacrolimus and voriconazole co-administration, despite a 50% reduction of tacrolimus. This severe interaction is clinically important and more pronounced than earlier described interactions with tacrolimus and other azole drugs. Perhaps, in this case, the interaction might have been aggravated by the chronic cholestasis our patient was suffering from.

Co-administration of calcineurin inhibitors with voriconazole is possible, though a reduction in the immunosuppressive drug dosage and a close monitoring of their trough levels have to be arranged [3,5]. Clinicians should be aware of this harmful drug interaction in order to avoid potential severe renal graft dysfunction, in particular in patients with chronic hepatopathy and cholestasis.

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