Underdosing of Prophylactic Valganciclovir Due to Inaccurate Estimation of Glomerular Filtration Rate Leading to Severe Cytomegalovirus Disease in a Kidney Transplant Recipient

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Cytomegalovirus (CMV) is a frequent cause of morbidity and mortality in kidney transplant recipients (1). Therefore, chemoprophylaxis with (val)ganciclovir is recommended for all kidney transplant recipients at risk of CMV disease for at least 3 to 6 months after transplantation, especially in CMV-seronegative recipients with CMV-seropositive donors (2, 3). The dose of valganciclovir must be adjusted in patients with renal impairment, using the Cockcroft-Gault equation to estimate the glomerular filtration rate (GFR) (4). In clinical practice, however, the estimated GFR (eGFR) is commonly calculated with the modification of diet in renal disease (MDRD) equation instead (5), as it can easily be provided by the clinical laboratory. In a recent paper by Trevillyan et al., it was shown that dosing valganciclovir based on the eGFR as computed with the MDRD equation may lead to underdosing of valganciclovir in a substantial number of solid-organ transplant recipients (6). We fully agree with the authors that this may have major clinical implications, especially since viral load monitoring during prophylactic valganciclovir therapy is not routinely performed (4), due to the low antiviral resistance to the drug and high costs. If underdosing is not recognized, diagnosis and adequate treatment of CMV disease may be delayed, as illustrated by the case presented below.

A 43-year-old male with end-stage kidney disease due to polycystic kidney disease received a kidney transplantation from a living, unrelated donor in our center in April 2013. His postoperative course was unremarkable, and his posttransplant creatinine level was 145 $\mu\text{mol/liter}$ (eGFR, 46 ml/min, by the MDRD equation). The immunosuppressive regimen consisted of prednisone, mycophenolate mofetil, and tacrolimus. The donor was CMV IgG positive and the recipient CMV IgG negative; hence, chemoprophylaxis with valganciclovir was prescribed in an adjusted dose of 450 mg once daily based on the eGFR. He did not use concomitant drugs known to influence the metabolism of valganciclovir, and he always took the drug with his meal. Three months later, routine lab tests showed a marked thrombocytopenia, hemolysis, a slight deterioration of kidney function, and a high tacrolimus through level. Tacrolimus-related thrombotic microangiopathy was suspected, and tacrolimus was subsequently converted to sirolimus. When thrombocytopenia persisted, valganciclovir was temporarily withdrawn to evaluate the effect of this drug on thrombocyte level. A kidney biopsy could not be performed due to thrombocytopenia. Two weeks later, he was admitted with fever and dyspnea unresponsive to antibiotics. Blood tests revealed ongoing thrombocytopenia and hemolysis, increased liver enzymes, and mildly elevated inflammatory markers. Shortly thereafter, CMV disease was diagnosed (CMV load, >100,000 copies/ml). However, despite treatment with

valganciclovir at a therapeutic dose (450 mg orally twice daily, adjusted for renal function based on the eGFR), he did not improve, and the CMV load remained high. Underdosing of valganciclovir was suspected, and indeed, after the valganciclovir dose was increased (900 mg orally twice daily), the patient eventually fully recovered.

Afterwards, CMV load was assessed in a stored blood sample that had been routinely obtained for BK virus surveillance 1 month prior to disease onset, and it showed >100,000 copies/ml, indicating that CMV infection was already present during chemoprophylaxis with valganciclovir. Notably, the 24-h urine creatinine clearance was 65 ml/min, in this case much higher than the eGFR as estimated with the MDRD equation. The patient's creatinine clearance estimated with the Cockcroft-Gault equation was 74 ml/min.

Prophylactic valganciclovir does not guarantee full protection against CMV infection (3). It is conceivable that this is partly caused by underdosing of valganciclovir due to incorrect estimation of renal function. In the present case, CMV disease might have been prevented if valganciclovir dose adjustments were based on the Cockcroft-Gault equation instead of the MDRD equation. We suggest that in centers routinely using the MDRD equation to estimate GFR, a second estimate of renal function, such as the Cockcroft-Gault equation or 24-h urine creatinine clearance, should be used when dosing drugs dependent on renal clearance. In cases of large discrepancies, therapeutic drug monitoring could be considered.

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