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Letter to the Editor

Ganciclovir-resistant cytomegalovirus infection in transplanted patients: utility of drug monitoring

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To the Editor

We read with great interest the paper by Kim et al. (1), recently published in *Transplant Infectious Disease*. The authors evaluated the clinical impact of ganciclovir (GCV)-resistant cytomegalovirus (CMV) infection caused by UL97 mutations in pediatric patients undergoing hematopoietic cell and solid organ transplantation.

Among 89 transplant recipients presenting CMV viremia, 7 subjects considered to be GCV-resistant were tested for UL97 mutations, detecting the presence of major mutations in 2 cases. The clinical course of these 2 patients was particularly severe, being characterized by a complicated CMV disease that required multiple-drug therapy and resulted, in 1 case, in death from disseminated CMV infection. Therefore, the authors concluded that evaluation of gene mutations should be considered when resistant CMV infection is suspected.

We agree with this suggestion, which is also in line with that recommended by International Consensus Guidelines released by the Transplantation Society (2), but we think that other aspects are also noteworthy. In their paper, the authors, when evaluating GCV-resistant patients, did not consider the possibility that drug treatment with GCV could have been insufficient, and no data on plasma GCV levels have been reported. In fact, it should be underlined that resistance of CMV to antiviral drugs, which in most cases has been attributed to viral mutations of UL97 and UL57 genes (3), may also be associated with the use of subtherapeutic levels of the drug, instead of a genetic CMV mutation (4).

Recently, we reported a case of an adult kidney transplant recipient who, early after transplantation, experienced a life-threatening systemic CMV infection, which was resistant to standard GCV therapy (5). The lack of responsiveness to the therapy, associated with the rising viral loads (up to 11,347,000 copies/mL) and progressive disease, led us to suspect the occurrence of a CMV resistance to GCV. So, we

tested for the presence of UL97 and UL57 viral variants, but we did not find any alteration.

Afterward, we measured plasma GCV levels and we found it at a very low concentration, even if the drug dosage was already higher than that recommended for her renal function. Then, we further increased the GCV dosage and decided to adjust the patient's dosing regimen on the basis of repeated measures of plasma drug concentrations. This approach was successful and, in the following days, clinical conditions progressively improved, while CMV titer decreased until DNA results were negative.

With this letter, we would emphasize that, facing the problem of GCV resistance, the possibility of inadequate treatment should be taken into consideration and, consequently, therapeutic drug monitoring (TDM) may be of help to guide clinical decisions, all the more so because suboptimal dosage of antivirals could constitute *per se* a risk factor for the development of GCV resistance. In fact, it has been demonstrated that a reduction in CMV-specific T-cell response, which provides a protection against CMV replication, in conjunction with episodes of low GCV levels, may be a first step toward selecting antiviral resistance, especially in patients with changing renal function (6).

Bearing in mind all these considerations, although the real impact of TDM in the management of CMV-infected patients has not been evaluated in large studies, we propose to include this strategy in the diagnostic workup of patients whose clinical response or CMV DNA levels do not improve despite therapy.

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