We report the case of a liver transplant recipient, cytomegalovirus (CMV) donor-positive (D+), recipient-negative (R−), with primary multidrug-resistant CMV infection treated with a combination therapy of letermovir and (val)ganciclovir (Figure 1). This case illustrates the challenges of treating multidrug-resistant UL97 and UL54 positive CMV infections in solid organ transplant (SOT) recipients. Combination therapy with foscarnet and ganciclovir has been recommended in such cases, based on in vitro data and experts’ opinion.1 However, as illustrated in this case, available treatment options, particularly foscarnet, are associated with significant morbidities. Indeed, our patient developed esophageal (and genital) ulcers attributed to foscarnet, resulting in decreased oral intake and significant weight loss. Similarly, foscarnet-associated renal insufficiency has persisted after treatment discontinuation with his renal function never recuperating to his baseline. For the treatment of his infection and associated complications, the patient had to stay in the hospital for a total of 105 days, with severe debilitation and depression as a result. This further underlines the urgency for new, better tolerated therapeutic options for drug-resistant CMV. Two new CMV-active agents, maribavir and letermovir, have been recently developed for the treatment and prophylaxis of CMV, respectively.2 Both agents have activity against UL97- and UL54-mutated CMV. Maribavir, although on a fast-track status, has not yet been approved for the treatment of CMV infection by regulatory agencies. Letermovir was recently approved for prophylaxis of CMV in allogeneic hematopoietic cell transplant recipients.2 Since then, several groups have reported their experience with the off-label use of letermovir as salvage monotherapy or secondary prophylaxis for resistant and difficult to treat CMV infections in transplant recipients, with already raised concerns about efficacy and resistance development.3–8

This case report describes the introduction of letermovir in combination with (val)ganciclovir when low-grade viremia (at a log2) was achieved. Letermovir was not used alone because of lack of relevant data, including the appropriate therapeutic dose and because of its known low genetic barrier.2 Under this regimen, the patient had a slow but steady resolution of his clinical symptoms and complete virologic response. Whether ganciclovir was still active at this point, despite documented resistance mutations, remains unclear. Of note, combination maintenance therapy with letermovir was started when the CMV viral load was already too low and coincided with an immunologic response, as documented by a robust CMV IgG titer. Of note, CMV-specific cellular immune function was documented by a positive T-Track CMV assay (Lophius Biosciences, Germany) test as early as posttransplant day 132, suggesting that a combination of sufficient CMV-humoral and cellular immune function is required for the adequate control of this virus. Until more data and maribavir become available, this case suggests that letermovir could be considered as adjunct maintenance therapy combined with (val)ganciclovir for the treatment of drug-resistant CMV infection in high-risk SOT recipients with CMV viral

**References**

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loads <log3. Whether letermovir can be administered alone or in combination with (val)ganciclovir for the treatment of CMV infection to achieve optimal outcomes without the emergence of letermovir-resistant virus remains unclear. This case does not answer this very question. However, it may serve as the basis to stimulate the discussion within the Transplant Infectious Disease community for accelerated and targeted efforts that may definitively answer this question in the context of a prospective clinical trial.

REFERENCES