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Case Report

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The Use of Letermovir for Ganciclovir-Resistant Cytomegalovirus in Kidney Transplant Recipients

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ABSTRACT

Resistant cytomegalovirus infection is a rising issue in kidney transplant recipients. Prolonged hospitalization, an increased burden for the patient, and worse outcomes are all potentiated by the use of highly toxic and poorly tolerated treatment options, which creates a growing need for investigation of safer alternatives. Letermovir represents a well-tolerated treatment option, and we present our experience in the treatment of 3 kidney transplant recipients with letermovir. Treatment outcomes were mixed; however, our results indicate the potential benefit of letermovir when used as step-down treatment and secondary prophylaxis.

Keywords: Kidney transplantation, letermovir, cytomegalovirus, treatment

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INTRODUCTION

Resistant cytomegalovirus (CMV) disease is a growing problem in kidney transplant recipients (KTRs). Prolonged hospitalization, use of medication with significant toxicity profiles, and effects of the infection itself pose risks for graft function and ultimately patient outcomes.[1,2] Resistant or refractory CMV disease is termed primarily for ganciclovir-resistant CMV; however, genotypic and phenotypic studies show evidence of the emergence of resistance to agents used as second-line or salvage treatments. Resistant or refractory CMV should be suspected in patients who display stable or progressive CMV viral loads or with persistent clinical symptoms despite adequate antiviral treatment for 2 weeks.[3] Medications used off-label for salvage treatment of resistant CMV infection or disease are selected for their different mechanisms of antiviral activity to avoid cross-resistance. Letermovir is not affected by viral mutations associated with first- or second-line treatment options, namely, ganciclovir and foscarnet.[4] As such, it is approved for use as primary prophylaxis of CMV in hematopoietic stem-cell transplant patients, while in kidney and other solid organ transplant recipients, it is used off-label as salvage treatment.[3] Recent reports focus on the use of letermovir as a step-down treatment, usually after initial treatment with ganciclovir and/or foscarnet.[5] In this case series of 3 KTRs with proven ganciclovir-resistant CMV infections, we describe our experience with letermovir for the treatment of resistant CMV. All the patients provided written informed consent.

CASE PRESENTATIONS

Case 1

A 59-year-old female KTR hospitalized after an evaluation at the post-transplant clinic revealed an increase in inflammatory parameters, a decrease in kidney function (baseline serum creatinine 170 µmol/L rose to 222 µmol/L), CMV viremia on CMV DNA polymerase chain reaction (PCR) (172 IU/mol) on plasma samples, and a urinalysis indicative of infection. She was suffering from

polycystic kidney disease and had received a kidney transplant from a deceased donor 9 years ago. Both the donor and the patient were seropositive for CMV prior to transplant. The patient was unable to take care of herself and required help with daily activities. Her comorbidities include metabolic disorder and prior pulmonary embolism. She was under follow-up for chronic graft failure due to secondary focal-segmental glomerulosclerosis. Two months before this presentation, she was hospitalized for necrotic changes of the dermis on the hands and histologically proven CMV colitis. During that hospitalization, molecular studies showed ganciclovir-resistant CMV and she was switched to foscarnet and CMV-specific immunoglobulin (CMV-IG). Two weeks after the foscarnet initiation, the patient became disoriented, which was attributed to foscarnet neurotoxicity; however, the viremia cleared. Immunosuppression was maintained by cyclosporine and prednisone, other medications included oxycodone, pregabalin, folic acid, repaglinide, allopurinol, and subcutaneous low-molecular-weight heparin (LMWH) due to earlier bilateral pulmonary embolism. On admission, she was disoriented, while the physical examination was unremarkable. Broad-spectrum antibiotics, LMWH, and oral letermovir 120 mg once daily were initiated, culture results were pending. After the urine culture came positive for Klebsiella *pneumoniae* OXA-48, the antibiotic therapy was de-escalated. Twenty-one days later, the viral loads increased (CMV DNA 1570 IU/mL), and letermovir was switched to foscarnet and CMV-IG, which lead to total viral clearance 3 weeks later. During the treatment course, kidney function stabilized (serum creatinine 105 µmol/L, proteinuria 0.64-1.2 g/L), inflammatory parameters decreased to within the reference range, and the patient's general state improved. She was discharged with oral letermovir for secondary prophylaxis 120 mg daily, and no viremia was detected on subsequent follow-ups up to 4 months later.

Case 2

A 45-year-old male was hospitalized after presenting with kidney failure manifested as oliguria and sudden 10 kg weight gain. He developed the end-stage kidney disease (ESKD) due to polycystic kidney disease and received an allograft from a deceased donor a year and a half prior to this presentation. Prior to transplantation, the recipient and the donor were CMV seronegative. His current medication includes mycophenolate mofetil (MMF), tacrolimus, prednisone, pantoprazole, amlodipine, folic acid, minoxidil, urapidil, moxonidine, torasemide, isosorbide mononitrate, calcium polystyrene sulfonate, sodium bicarbonate, and acetylsalicylic acid. The evaluation revealed a primary CMV infection (plasma CMV PCR DNA 1100 IU/mL). Cytomegalovirus-specific immunoglobulin was initiated, and valganciclovir was substituted with intravenous ganciclovir. This treatment regimen was maintained for 3 weeks and the viral loads decreased. The patient was discharged with oral valganciclovir. On follow-ups, the viremia persisted (387 IU/mol), and due to suspected ganciclovir resistance, letermovir was initiated. Soon thereafter, the viral load increased significantly (25700 IU/mol) and the patient developed worsening proteinuria. Workup showed no signs of graft rejection or CMV tissue-specific disease, and CMV resistance tests returned negative. He was managed as an outpatient with additional CMV-IG twice weekly; however, viral loads further increased and the patient was hospitalized. Cytom-egalovirus-specific immunoglobulin was administered 3 times weekly with daily intravenous ganciclovir, while mycophenolate mofetil was discontinued. Viremia persisted and resistance studies were repeated at a different laboratory where ganciclovir resistance was demonstrated; therefore, ganciclovir was substituted with foscarnet. After the first 7 days, the patient's kidney function declined which required foscarnet dose adjustments. After 3 weeks of foscarnet, the viral load decreased significantly and the patient was managed as an outpatient with oral letermovir and twice-weekly CMV-IG, and after 1 month of treatment, CMV DNA PCR was negative. The patient was treated with oral letermovir 240 mg daily for secondary prophylaxis. Four months later, he developed a low-copy viremia (<137 IU/mol) which persisted at this level to date.

MAIN POINTS

- Cytomegalovirus is considered the most important pathogen after kidney transplantation, and its resistance to treatment is an emerging problem.
- The main second-line treatment, foscarnet, is burdened by its side effect profile.
- Letermovir does not share mechanisms of effect with other antivirals used in cytomegalovirus treatment, making cross-resistance an unlikely issue.
- This case report shows mixed results in the use of oral letermovir as secondary prophylaxis, and it indicates letermovir may have the most benefit when used as step-down treatment after foscarnet use.

Case 3

Following a regular follow-up at the post-transplant kidney clinic, a 31-year-old male patient was admitted due to CMV viremia despite prophylactic treatment with oral valganciclovir. Due to ESKD caused by immunoglobulin A nephropathy, he underwent kidney transplantation from a deceased donor 6 months prior to this episode. Both the donor and the recipient were CMV seropositive prior to transplantation. Besides unilateral cryptorchidism in childhood, his other medical history was unremarkable. His graft function was decreased. Immunosuppression was maintained by tacrolimus, mycophenolate, and prednisone, other medications included valganciclovir and trimethoprim-sulfamethoxazole for prophylaxis and amlodipine, furosemide, and urapidil as needed. He was treated with intravenous ganciclovir and CMV-IG for 10 days and was discharged home with planned CMV-IG administrations as outpatient treatment and oral valganciclovir 2 × 450 mg daily. Mycophenolate dose was adjusted, and his graft function improved. On follow-ups, the viremia persisted (<137 IU/mol), and 1 month later oral letermovir 120 mg and 240 mg

interchangeably were initiated concurrently with 2× weekly CMV-IG. After 4 weeks, viremia was cleared, which allowed for CMV-IG to be ceased. Secondary prophylaxis was maintained by letermovir 120 mg daily. Ten months later, his CMV viral loads remained negative.

DISCUSSION

Three KTRs with different comorbidities and ganciclovir-resistant CMV infection treated with letermovir for treatment and/or secondary prophylaxis were presented (Table 1). In Case 1, the use of letermovir for in-hospital management of CMV disease failed to suppress viral loads and the use of alternative agents was required. However, letermovir was used for the successful maintenance of negative viral loads. In Case 2, in-hospital letermovir treatment similarly failed to suppress the viremia, requiring the use of foscarnet to reduce the viral load numbers. Upon release, the patient was switched to letermovir which successfully resulted in complete viral suppression 1 month later. However, letermovir secondary prophylaxis failed to maintain complete viral suppression as 4 months later the patient again presented with a low-copy viremia. In Case 3, the use of letermovir for low-copy viremia resulted in complete viral clearance and maintenance of negative CMV for over 10 months. In summary, in Cases 1 and 2, the in-hospital use of letermovir resulted in treatment failure and foscarnet was required for infection control. In Cases 2 and 3, letermovir was initiated during asymptomatic low-copy viremia and resulted in viral clearance. All patients received CMV-IG, and none exhibited any side effects attributable to letermovir treatment. All CMV PCR was performed on plasma samples using Cobas AmpliPrep/Cobas TaqMan CMV method.

A report published by Hofmann et al[6] displayed 2 KTRs treated with letermovir for secondary prophylaxis (240 mg 4 times daily) after viral load clearance with foscarnet. The patients displayed the progression of viremia and 1 patient developed genotypic resistance. Suboptimal dosing was considered the culprit for treatment failure in 1 case. A paper published by Turner et al[7] displayed the use of letermovir as salvage therapy for CMV retinitis in 4 solid organ transplant recipients. All patients showed clinical improvement; however, in 2 patients, genotypic resistance to letermovir developed and in 1, there was clinical evidence of resistance. Notably, they used higher doses of letermovir than we did in our patients (960 mg vs. 240 mg). Another case of use of letermovir as salvage treatment in a KTR failed to demonstrate viremia clearance, and a switch to another agent was warranted. Notably, the authors abstained from the use of foscarnet to avoid nephrotoxicity. Additionally, they did not identify genotypic resistance.[8] Equal to our findings, letermovir showed a favorable side effect profile as no patient developed any treatment-related side effects. An interesting study of letermovir and valganciclovir for step-down treatment after foscarnet was published by Rho et al.[5] They compared the onset CMV breakthrough or viral load increases in KTRs treated with valganciclovir alone versus valganciclovir and letermovir as a step-down treatment after foscarnet. The results of the study showed lower rates of a viral breakthrough in patients on combination treatment. The study was performed on a small sample, and further studies are required. Similar to their study, Cases 1 and 2 were put on oral outpatient prophylaxis after foscarnet treatment and viral load suppression or decrease. We used letermovir alone, and it was sufficient to prevent large viral load increases in both cases, although in Case 2, the patient did develop a low-copy viremia 4 months later. This may indicate that letermovir may have a substantial role in the step-down treatment and secondary prophylaxis, particularly after the use of foscarnet.

A major concern in letermovir use is its considerable drug interactions, primarily with immunosuppressive medication commonly used in KTRs. Letermovir is a CYP3A inhibitor, which implies the need for monitoring and dose adjustments of tacrolimus, as tacrolimus is metabolized by CYP3A.[8,9] The mechanism of interactions among cyclosporine and letermovir has not been fully elucidated; however, they likely involve inhibition of transporters required for hepatic uptake of letermovir.[9] Due to this effect,

Table 1. Overview of the Cases with Respect to Letermovir Secondary Prophylaxis

Age, sex	Clinical Aspect	Treatment Prior to Letermovir Prophylaxis	CMV Load at Start of Letermovir	Time from Prophylaxis to Rebound Viremia	Rebound Viremia Management	Outcome
59, F	Reactivation of resistant CMV	Ganciclovir, foscarnet, CMV-IG	173 IU/mL	n/a	n/a	CMV negative; letermovir prophylaxis
45, M	Primary infection	Valganciclovir, ganciclovir, CMV-IG	387 IU/mL	4 months	foscarnet	Low-copy viremia; letermovir prophylaxis
31, M	Reactivation	Valganciclovir, ganciclovir, CMV-IG	<137 IU/mL	n/a	n/a	CMV negative; letermovir prophylaxis

CMV-IG, cytomegalovirus-specific immunoglobulin.

letermovir dose reduction is necessary when used concurrently with cyclosporine. Mycophenolate mofetil and letermovir have no significant interactions.[10] Limitations of this study include the lack of available genotypic results, hindering the discussion regarding mechanisms of resistance. However, we considered the clinical course and documented ganciclovir resistance sufficient for the discussion and purposes of this paper.

In conclusion, we report mixed results for letermovir use for (val)ganciclovir-resistant CMV infection treatment or secondary prophylaxis in KTRs. Unfavorable side effect profiles of second-line and alternative agents indicate the need for the study and development of other treatment options. Good drug tolerance and no cross-resistance with other medication favor the use of letermovir; however, treatment failure pushes clinicians to revert to not only more potent but also more toxic agents. Inconsistent treatment outcomes with letermovir signal that it may have a role in selected patient groups; however, larger studies are needed to identify the patients who would benefit most from letermovir. Letermovir potentially has the most benefit when used as a step-down treatment after foscarnet use, as well as for the primary prophylaxis.

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