

Individualizing Treatment for CMV with UL97 del597-599 Mutation: Beyond Unusual Response to a Lower Ganciclovir Dose Increase

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ABSTRACT

Human cytomegalovirus (CMV) infection is the most prevalent infection affecting organ transplant recipients, and it is a cause of morbidity and mortality in patients undergoing kidney transplantation. The introduction of ganciclovir (GCV) for both prophylaxis and treatment has vastly improved patient outcomes. GCV resistance can be caused by mutations in the UL97 phosphotransferase gene or the UL54 polymerase gene. It occurs in 1 to 2% of kidney transplant recipients with CMV infection or disease. Antiviral resistance should be considered when increased viral loads and disease progression are observed despite the administration of adequate antiviral therapy. The degree of resistance varies depending on the type of mutation present. We report a patient with resistance to GCV due to a UL97 del597-599 mutation who, despite typically requiring an 8-fold increase in GCV dose, showed a significant decrease in viral load with just a double dose increase. However, the patient's overall clinical course remained complicated. Due to severe leukopenia, maribavir had to be started, with a good response. Nevertheless, he ultimately died due to indirect CMV-related complications. This case also highlights the complexity of transplant patients, who present multiple challenges ranging from infections to therapy management.

Descriptors: Cytomegalovirus Infection; Ganciclovir Resistance; UL97 Mutation; Maribavir.

Individualização do Tratamento contra CMV com Mutação UL97 del597-599: Além da Resposta Incomum a um Aumento Menor da Dose de Ganciclovir

RESUMO

A infecção pelo citomegalovírus humano (CMV) é a infecção mais prevalente que afeta os receptores de transplante de órgãos e é uma causa de morbidade e mortalidade em pacientes submetidos a transplante renal. A introdução do ganciclovir (GCV) para profilaxia e tratamento melhorou muito os resultados dos pacientes. A resistência ao GCV pode ser causada por mutações no gene da fosfotransferase UL97 ou no gene da polimerase UL54. Ela ocorre em 1 a 2% dos receptores de transplante renal com infecção ou doença por CMV. A resistência antiviral deve ser considerada quando se observa aumento da carga viral e progressão da doença, apesar da administração de terapia antiviral adequada. O grau de resistência varia de acordo com o tipo de mutação presente. Relatamos um paciente com resistência ao GCV devido a uma mutação UL97 del597-599 que, apesar de normalmente exigir um aumento de 8 vezes na dose de GCV, apresentou uma diminuição significativa na carga viral com apenas um aumento de duas vezes na dose. Entretanto, a evolução clínica geral do paciente permaneceu complicada. Devido à leucopenia grave, o Maribavir teve de ser iniciado, com uma boa resposta. No entanto, ele acabou morrendo devido a complicações indiretas relacionadas ao CMV. Esse caso também destaca a complexidade dos pacientes transplantados, que apresentam vários desafios, desde infecções até o gerenciamento da terapia.

Descritores: Infecção por Citomegalovírus; Resistência ao Ganciclovir; Mutação UL97; Maribavir.

INTRODUCTION

Human cytomegalovirus (CMV) is an important human pathogen. It is a member of the family *Orthoherpesviridae*, subfamily *Betaherpesvirinae*, and genus *Cytomegalovirus*.¹ Its prevalence, indicated by a positive IgG, varies markedly between different areas of the world, especially between developing countries (where in adults it can be close to 100%) and developed countries (approximately 40% at 20 years and 80% at 60 years).^{1,2} In a Finnish study, seroprevalence rates were 47% in people aged 10 to 12, 68% in people aged 15 to 35 and 81% in people aged 36 to 60.³ Likewise, in a study carried out in the United States, CMV seroprevalence increased from 36% in children aged 6 to 11 years to 91% in people aged over 80 years.⁴

Primary infections are typically asymptomatic and self-limited in immunocompetent individuals. However, infections in immunocompromised patients are associated with significant morbidity and mortality. CMV infection is the most prevalent infection affecting organ transplant recipients, and it is a cause of morbidity and mortality in patients undergoing kidney transplantation due to its direct and indirect effects on the graft and patient.^{5,6}

CMV prevention strategies have greatly reduced CMV disease and the impacts of CMV infection. The morbidity and mortality of CMV infection in solid organ transplantation have decreased since the first use of ganciclovir (GCV) for prevention and treatment.^{1,5,6} Currently, drugs used to treat CMV infection include valganciclovir, ganciclovir, foscarnet, cidofovir and more recently, maribavir.⁷

Cytomegalovirus resistance to antiviral drugs was initially reported in the laboratory in the 1980s, and these resistant isolates were later detected in immunocompromised hosts.⁸ CMV resistance to antiviral agents arises mainly due to mutations in the UL97 and UL54 genes. UL97 is a gene that encodes protein kinase, while UL54 encodes DNA polymerase. Resistance to GCV can be caused by mutations in the UL97 phosphotransferase gene or the UL54 polymerase gene, whereas resistance to foscarnet and cidofovir is caused only by mutations in the UL54 polymerase gene. Some cases of resistance to maribavir have also been reported related to mutations in the UL97 phosphotransferase gene.⁷

In approximately 90% of GCV-resistant cases, mutations in the UL97 phosphotransferase gene are responsible for the resistance, followed by UL54 mutations gene.^{1,9,10}

Antiviral resistance should be considered when increased viral loads and disease progression are observed despite the administration of adequate antiviral therapy. The different degrees of resistance varies depending on the type of mutation present.^{9,10}

In the management of CMV infection in transplant patients, highly resistant mutations like UL97 del597-599 pose significant challenges. This case report presents a patient with this mutation who, despite the typical need for an 8-fold increase in GCV dose, showed a significant decrease in viral load with just a double dose increase. However, the patient's overall clinical course remained complicated, and he ultimately died due to indirect CMV-related complications. This case underscores the importance of considering factors beyond viral load reduction when evaluating treatment efficacy in CMV infection.

CASE REPORT

We present the case of a 73-year-old Caucasian man, with a previous history of chronic kidney disease due to secondary segmental and focal glomerulosclerosis, who underwent hemodialysis between 2017 and 2022. His medical history also included arterial hypertension, hyperuricemia, past surgery for prostatic carcinoma (2011), and Guillain Barré syndrome. The patient underwent deceased-donor kidney transplantation in May 2022 at another institution. Induction therapies were unknown, but a positive donor and negative recipient CMV status (CMV D+/R-) was reported. His daily medication included tacrolimus (3 mg/day), mycophenolate mofetil (MMF) (500 mg/day), prednisolone (10 mg/day), and prophylactic valganciclovir (450 mg/day).

In May 2023, he was evaluated at our unit due to isolated fever peaks within the previous week. Analytically, his serum creatinine (SCr) was 2.2 mg/dL (baseline 1.8 mg/dL), leukocytes were $9.1 \times 10^9/L$, CMV viral load was 18,300 IU/mL, and c-reactive protein (CRP) was 1.65 mg/dL. CMV disease was assumed however, he refused hospitalization. MMF was reduced to 250 mg/day and he was medicated with anti-CMV immunoglobulin (Ig) (1 mg/kg), and valganciclovir 900 mg twice a day.

Five days later, he was brought to the emergency department with mental confusion and drowsiness. Additionally, *Klebsiella pneumoniae* was isolated in both blood and urine cultures and amoxicillin/clavulanic acid was initiated. Cranioencephalic magnetic resonance imaging and lumbar puncture were performed, excluding neurological involvement by CMV. MMF was stopped and GCV was started at a dose adjusted to renal function (1.25 mg/kg/day; GFR 18 mL/min/1.73 m²), with the dosage was subsequently adjusted for GFR changes (2.5 mg/kg/day; GFR 27 mL/min/1.73 m²). Despite treatment, the CMV viral load increased (maximum 90,800 IU/mL). Due to suspected resistance, CMV genotyping was requested, which confirmed the UL97 – del597-599 mutation for which the literature suggests an eight times higher

dosage.^{11,12} However, by the time knowledge of this resistance reached us, the patient had already shown a remarkable response to treatment with a viral load of 14,400 IU/mL at a dose of 2.5 mg/kg every 12 hours, lower than suggested in the literature. He was later discharged after 30 days of therapy with a CMV viral load of 559 IU/mL, CRP 1.3 mg/dL and renal function at baseline (Pcreat 1.5 mg/dL). At the time of discharge, therapy was changed to oral valganciclovir 900 mg twice a day. One month later, the CMV viral load was still decreasing (97 IU/mL), but it never went negative and leukopenia was constant, in spite of filgrastim courses. Two months later, the patient was readmitted due to *Escherichia coli* bacteremia. Additionally, he presented with severe leukopenia ($0.56 \times 10^9/L$), and filgrastim was reinitiated without response. CMV viral load increased to 628 IU/mL. Therapy was changed to maribavir 400 mg twice a day, after a special request under an early access program for this medication. At discharge, he had a decreasing but still positive viral load (395 IU/mL) and there was partial improvement in leukopenia ($2.01 \times 10^9/L$). Two weeks later, he was readmitted due to severe *Pneumocystis jirovecii* pneumonia. He remained on maribavir treatment, and CMV was undetectable after a month of this therapy. Despite the good response to maribavir, and the prompt initiation of antibiotic therapy with cotrimoxazole, the patient ended up dying from a mix of multiple complications – he developed acute kidney injury, acute upper gastrointestinal hemorrhage, worsened pneumonia, and bowel obstruction.

DISCUSSION

GCV resistance should be suspected when, despite treatment with an adequate dosage, the viral load remains persistently high or increases. Increased immunosuppression and lower prophylaxis dosages are also associated with an increased risk of resistance. GVC resistance occurs in 1 to 2% of kidney transplant recipients with CMV infection or disease and typically develops in CMV D+/R- patients.¹⁰

Genotype testing should be performed to identify specific resistance mutations when GCV-resistance is suspected. Common resistance mutations include those in the genes encoding UL97 phosphotransferase (which performs the initial phosphorylation of GCV and is required for its antiviral activity), and the viral DNA polymerase gene UL54. Mutations in UL97 are responsible for more than 90% of cases.¹¹

GCV resistance is a spectrum, with 2 to 10-fold increases in CMV inhibitory concentrations, depending on the resistance mechanism. Diagnostic mutations in the CMV UL97 kinase gene are used to determine the resistance level to GCV and other treatment options. Mutations in codons 460, 520, or 591 to 607 individually confer a 5 to 10-fold lower susceptibility to GCV, except for the C592G amino acid substitution, which results in a 3-fold decrease.^{11,12}

The UL97 deletion identified in this patient (del597-599) was described as highly resistant and associated with the need for an 8-fold higher dose of GVC.^{11,12} In this case, despite the identified deletion, a viral load decrease was achieved with “only” a doubling of the GCV dosage. Despite reducing the viral load, this medication may have contributed to the persistent leukopenia.

Both cidofovir and foscarnet should only be considered in life-threatening conditions, and in the absence of other alternative therapies, as renal toxicity is very common, particularly in kidney transplant recipients.⁹

Maribavir is the latest antiviral drug to treat CMV disease. It is an oral drug that inhibits UL97 phosphotransferase and stops viral maturation and egress. Maribavir is active against CMV with UL97 and UL54 mutations. Key advantages include a lack of bone marrow and kidney toxicity. It should be considered as an alternative in cases of resistance to GCV or in cases of bone marrow toxicity that prevent the use of the latter, as was the case with our patient.¹³

This case demonstrates an unusual response to GCV treatment, with a decrease in viral load despite a highly resistant mutation. It also highlights the complexity of CMV infection management in transplant patients. While the patient’s viral load decreased with GCV treatment, a sustained and significant clinical improvement was not observed. The patient continued to experience complications, including leukopenia, multiple serious infections and ultimately succumbed after multiple complications arising after the diagnosis of *P. jirovecii* pneumonia. This suggests that even partially controlled CMV infection can have detrimental indirect effects. The ongoing viral activity likely contributed to the patient’s persistent immunodepression, making him susceptible to further opportunistic infections.

CONCLUSION

This case highlights the complex interplay between CMV infection, antiviral therapy, and immunosuppression in transplant patients. Obtaining precise GCV resistance genotypes is crucial for determining the degree of antiviral efficacy impairment and defining the most effective dose. While the doubled dosage of GCV treatment unexpectedly achieved a significant reduction in viral load, it likely contributed to the patient’s persistent leukopenia, possibly due to the high dosage and underlying susceptibility.

A multifactorial etiology for the patient's leukopenia, potentially involving CMV, medications, and the overall immunosuppressed state may have been at play. The ongoing CMV activity, despite partial viral suppression, likely played a significant role in the patient's susceptibility to opportunistic infections. Earlier consideration of maribavir, an antiviral with a lower risk of bone marrow suppression, might have been beneficial in this case due to the presence of leukopenia. Finally, this case emphasizes the importance of tailoring treatment strategies to individual patient profiles and potential drug toxicities for optimal outcomes in transplant patients with CMV infection.

CONFLICT OF INTEREST

Nothing to declare.

AUTHOR'S CONTRIBUTION

Substantive scientific and intellectual contributions to the study: Piedade A; **Conception and design:** Piedade A; **Data analysis and interpretation:** Piedade A, Vidal H, Simões P; **Article writing:** Piedade A; **Critical revision:** Vieira MB, Chasqueira MJ, Caeiro F, Aires I, Paixão P, Jorge C; **Final approval:** Piedade A, Vieira MB, Chasqueira MJ, Caeiro F, Aires I, Paixão P, Jorge C.

DATA AVAILABILITY STATEMENT

All dataset were generated or analyzed in the current study.

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