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Case report

CMV resistant to ganciclovir and maribavir in a heart-transplanted Patient: A case report

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ABSTRACT

Resistant/refractory Cytomegalovirus (CMV) infection is an important threat in the management of solid organ transplant recipients, often associated with poor outcomes. We describe the case of a heart-transplanted patient who developed primary CMV infection with fever and subsequent appearance of resistance to ganciclovir and maribavir during antiviral treatment, and with important toxicity due to foscarnet. The outcome was good with reduced-dose continuous infusion of foscarnet. Further research is needed to improve the management of difficult-to-treat CMV infection.

1. Introduction

Human cytomegalovirus (CMV) is one of the most common viruses causing infectious complications after solid organ transplantation (SOT). It may significantly affect allograft and recipient survival due to direct and indirect effects, including CMV disease, drug-related toxicities, bacterial and opportunistic superinfections, and graft rejection [1].

Maribavir (MBV) is a benzimidazole L-riboside inhibitor of the CMV UL97 kinase that has multiple activities important in viral replication and was recently approved for treatment of CMV infection refractory or resistant to standard therapy [2]. While valganciclovir (VAL) is often used as the first-line oral antiviral therapy in the treatment of CMV infection, MBV represents a promising oral alternative to second line nephrotoxic drugs such as foscarnet (FOS) and cidofovir (CID) [3] and avoids the hematologic toxicity of ganciclovir (GCV). In their phase 3 clinical trial of MBV therapy for refractory or resistant CMV infection, Chou et al. [2] found that baseline MBV resistance was rare, but post-treatment emergent MBV resistance mutations were detected in 26 % of patients randomized to MBV.

MBV resistance in patients treated for CMV infection is increasingly reported in real life experiences [3–7]; we add here the case of a patient developing GCV and MBV resistance during therapy for CMV infection. Treatment decisions were further complicated by

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FOS-related adverse events.

2. Case report

A 52-year-old male patient underwent heart transplantation on February 27th, 2024, for post-ischemic dilated cardiomyopathy. Immunosuppressive therapy included *anti*-T-lymphocyte globulin, steroids, tacrolimus, and mycophenolate mofetil as per protocol. Both donor and recipient were *anti*-CMV IgG negative; no *anti*-CMV prophylaxis was prescribed. The post-surgical course was complicated by bradycardia and third-degree atrioventricular block needing pacemaker implant. He also received two filtered units of red blood cells in March 2024.

While still hospitalized in the Cardiosurgery Unit, at the beginning of April 2024 the patient developed fever and CMV infection (see Fig. 1), with CMV viremia 290,222 IU/mL in whole blood (CMV Elite MGB, ElitechGroup SAS, 92800 Puteaux France). Concomitant physical examination was unremarkable. Therapy with GCV 5 mg/kg q12h was started on April 4th. During such therapy, the patient showed resistance to this drug: on April 17th' 2024 (T0), the CMV viremia was 1,554,430 IU/mL and the genotype resistance test yielded an A594E mutation in the UL97 gene, conferring resistance to GCV, although in heterozygosis with wild type virus (Sanger sequencing of overlapping amplicons derived from nested PCR, using primers described by Sahoo et al. [8] with slight modifications). No other antiviral resistance mutations to any other drugs were detected at this time on either the UL97 or UL54 gene. On April 18th the patient started FOS therapy 60 mg/kg q8h but developed a severe acute kidney disease requiring haemodialysis, with serum creatinine levels up to 8.9 mg/dL. FOS was stopped and MBV therapy was started on April 30th, at the dose of 400 mg q12h, with initial success on CMV viremia. The patient was discharged home on May 20th and followed-up in the Cardiosurgery outpatient clinic, continuing MBV oral therapy. On discharge, serum creatinine was 1.88 mg/dL and the immunosuppressive therapy included tacrolimus 3 mg q12h, mycophenolate mofetil 250 mg q12h, prednisone 15 mg q24h. However, in the following weeks a progressive increase in CMV DNA was noted, from 468 IU/mL on May 29th to 51,753 IU/mL on June 26th. The patient developed fever and was then admitted to our Infectious Diseases Unit at Spallanzani Hospital, Rome (Italy), on June 28th, 2024.

On admission the patient was in good general conditions, physical examination was unremarkable, body weight 70 Kg, and the blood tests showed: white blood cells (WBC) 5760/mmc (neutrophils 80 %), Hb 9 g/dL, platelets 166.000/mmc, creatinine 2.56 mg/dL, eGFR 33 mL/min (estimated by Cockcroft-Gault Formula), C-reactive protein 0.16 mg/dL, transaminase and bilirubin levels within normal limits, tacrolimus 5.1 ng/mL. CMV DNA in whole blood was 64,985 IU/mL (CMV Elite MGB, ElitechGroup SAS, 92800 Puteaux France).

FOS was started at a reduced dose in continuous infusion of 50 mg/kg/24h. On July 1st CMV viremia was 6933 IU/mL.

On July 4th, blood tests showed a sudden increase in transaminase levels (aspartate aminotransferase [AST] 127 U/L, alanine aminotransferase [ALT] 348 U/L), WBC were 3240/mmc, Hb 7.9 g/dL, CMV viremia was 12,934 IU/mL; after consultation with the transplantologists, FOS and micofenolate were stopped, and the prednisone dose was reduced from 15 to 10 mg/day. On July 6th, MBV 400 mg q12h was started; two days later, after a drop in transaminase levels (AST 27, ALT 152 U/L) and an improvement in renal function (creatinine 1.38 mg/dL), FOS 90 mg/kg/day continuous infusion was added. On the same day, CMV viremia was 516,629 IU/mL. CMV T-cells specific response was performed on July 8th stimulating PBMC from patient with a cocktail of CMV peptides (1ug/mL, pp65, IE1, IE2 from JPT Technologies) for 20 hours. After the incubation data were obtained following kit's instruction (Elispot Pro, Mabtech, USA). Results showed low production of Interferon-γ (60 spot forming cells or SFC/10^6 PBMC) corresponding to the presence of the detectable CMV DNA. A genotype resistance test was requested and performed on a blood sample stored on June 28th (T1). The results of Sanger sequencing were available on July 23rd and documented a T409M mutation in UL97 gene associated to MBV resistance; therefore, MBV was suspended from therapy. On July 25th, CMV viremia was 2077 IU/mL while on FOS monotherapy. In the following weeks, CMV viremia slowly lowered and was below the lower limit of quantification (<178 IU/mL) on September 9th. Subsequently, FOS was stopped and secondary prophylaxis with letermovir (LTV) 480 mg q24h was prescribed.

During his hospital stay, the patient underwent several instrumental exams looking for organ localizations of CMV disease. Chest X

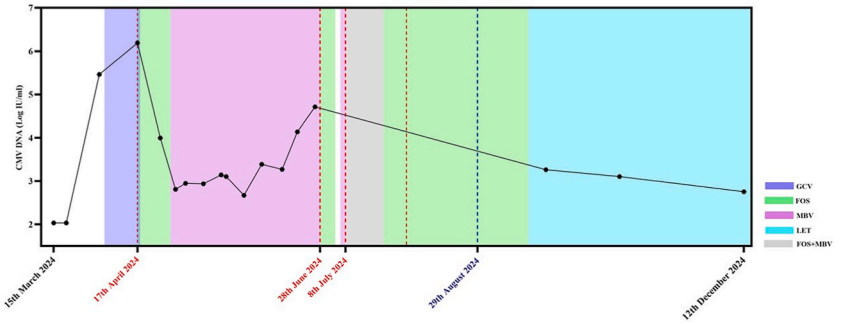

Fig. 1. Kinetic of CMV replication on whole blood during antiviral therapy.
Viral load is represented as a transformed $\log_{10}$ function. Date of resistance tests (T0, T1, T2 and T3) and of the administration of CMV-specific immunoglobulin (Cytomegatect) are reported on the diagram as vertical dotted lines (red and blue, respectively). On the right, the legend indicates the time periods of therapy with the different drugs represented with different colors.

ray and abdominal ultrasound were unremarkable. Ocular fundus examination detected no signs of chorioretinitis. Transthoracic echocardiography revealed minimal mitral and tricuspid regurgitation, ejection fraction 60 %. The esophagogastroduodenoscopy showed erosions and hyperemia at the gastric antral and duodenal levels: the immunohistochemical staining revealed the presence of CMV in antral and duodenal tissue. The colonoscopy did not find relevant changes, but the search for CMV DNA in colonic biopsy was positive by Real-time PCR. On August 29th the patient received CMV-specific immunoglobulin (Cytomegatect® 100 U/mL) at the dose of 1 mL/kg. He was eventually discharged in good general condition on September 19th, 2024, and followed-up in the Cardiosurgery outpatient clinic. On October 23rd, CMV specific T cells response resulted increased compared to that tested in July (1867 SFC/10^6 PBMC).

To better analyze the emergence of MBV resistance on blood and colonic biopsy, a parallel ultra-deep sequencing was performed starting from the first-round amplification of the UL97 and UL54 genes of the nested PCR already carried out to obtain amplicons that underwent Sanger sequencing. The samples analyzed were those collected at INMI ward admission on 28 June (T1) and at the moment of viremia peak on July 8th (T2) and on the colonic biopsy taken August 1st (T3) (see Fig. 1). NGS libraries were prepared and sequenced on the Ion Torrent Gene Studio S5 Prime Sequencer as per the manufacturer's instructions (Life Technologies, Carlsbad, CA, USA). Viral gene sequences were aligned to the AD169 CMV strain using BioEdit for Sanger data and for NGS data using a custom bioinformatics pipeline developed with the CLC Genomics Workbench software version version 24.0 (Qiagen, Hilden, Germany). The results of the comparison shown in Table 1 indicated that Sanger sequencing of UL97 (panel A) identified T409M in the first two plasma samples and H411L in the second plasma and subsequent biopsy. In contrast, NGS detected both T409M and H411L at all time points, with respective frequencies of 59.46 % and 34.80 % in the first plasma sample, 50.99 % and 42.29 % in the second plasma sample, and 56.00 % and 86.72 % in the biopsy. In addition, NGS identified polymorphisms N68D, S108N, and I244V in a region not covered by Sanger sequencing. While both methods detected at least one T409M, the most frequent MBV resistance mutation, NGS additionally always revealed H411L, a recently emerging variant also linked to MBV resistance [9]. UL54 polymorphisms with respect to the AD169 strain, shown in panel B, namely S655L, F669L, N685S, A885T, and N898D were consistently detected by both methods. No other mutations associated with other *anti*-CMV drugs administered to the patient were found, including the previously detected A594E that emerged under GCV.

3. Discussion

CMV infection remains a significant cause of morbidity and mortality in SOT recipients [10]. In this case both donor and recipient were *anti*-CMV IgG negative. Looking for an origin of the infection, we found that the patient received 2 two filtered units of red blood cells in the post-transplant period. The blood donors of these units had not been tested for CMV, but the units were filtered before transfusion. It is not possible to exclude a role of these blood transfusions in the origin of this CMV infection.

Refractory CMV infection refers to persistence of infection despite administration of appropriate antiviral treatment, consisting in an increase (of at least 1 log10) or in the persistence of CMV viremia in blood with less than 1 log10 reduction after two weeks of appropriate therapy. A resistant CMV infection is defined as the detection of a viral mutation conferring a reduced sensitivity to at least one *anti*-CMV drug [11]. The frequency of CMV resistance after GCV therapy in the SOT population is generally low (<5 %), although it seems to be higher (18 %) in lung recipients and in intestinal and multiorgan transplant recipients (31 %) [12]. According to a recent survey by the Working Group of the European Society for Organ Transplantation, an annual incidence of <1 % of GCV resistance was reported by 80 % of interviewed participants [13]. Likewise, baseline MBV resistance is rare. However, after treatment with MBV for refractory/resistant CMV infection, Chou and coll. described that 26 % of patients developed genotypic evidence of MBV resistance [2]. Emergence of resistance was found in 48 % of non-responders and in 86 % of patients who initially cleared CMV viremia but rebounded while still on MBV. MBV seems to have an intermediate genetic barrier to resistance compared to LTV (lower) and DNA polymerase inhibitors (higher) [13].

Our patient showed GCV resistance after an exactly 2-week course of therapy. According to Kotton et al. [12] antiviral drug

Table 1
Comparative analysis of Sanger sequencing and NGS in detecting resistance associated with MBV
Amino acid substitutions.

A: UL97 gene		
	Amino Acid Substitutions	
Time	Sanger	NGS (detection frequency)
T1	T409M	N68D (99,57 %), S108N (99, 46 %) I244V (99,47 %), T409M (59,46 %), H411L (34,80 %)
T2	T409M, H411L	N68D (99,84 %), S108N (99,21 %) I244V (99,90 %), T409M (50,99 %), H411L (42,29 %)
T3	H411L	S108N (100 %), T409M (56,00 %), H411L (86,72 %)
B: UL54 gene		
	Amino Acid Substitutions	
Time	Sanger	NGS (detection frequency)
T1	S655L, F669L, N685S, A885T, N898D	S655L (99,23 %), F669L (99,56 %), N685S (100 %), A885T (100 %), N898D (99,72 %)
T2	S655L, F669L, N685S, A885T, N898D	S655L (99,29 %), F669L (99,91 %), N685S (100 %), A885T (100 %), N898D (100 %)
T3	S655L, F669L, N685S, A885T, N898D	S655L (99,56 %), F669L (99,55 %), N685S (99,73 %), A885T (99,92 %), N898D (99,83 %)

resistance should be suspected in case of persistent or recurrent CMV viremia or disease during prolonged antiviral therapy, i.e. for GCV usually 6 or more weeks of cumulative drug exposure, including at least two weeks of ongoing full-dose therapy. By definition, refractory disease is after at least 2 weeks of full-dose antiviral therapy [14]: unfortunately, we do not have a baseline sample to test a possible baseline resistance to GCV; baseline resistance however is very rare in untreated patients and our patient did not receive *anti*-CMV drugs before starting GCV. The detected A594E mutation in CMV UL97 gene is described as relatively uncommon and conferring a low grade (2-5 x) increase in EC_{50} value compared to wild type [15]. In the case of CMV-resistant mutations in UL97 (or some codons in UL54) conferring resistance to GCV only, the switch to FOS could be considered [12]. FOS is a second line *anti*-CMV drug often prescribed in front of GCV/VAL resistance; recognized doses for normal renal function include 60 mg/kg q8h or 90 mg/kg q12h; unfortunately, its potential for renal toxicity and electrolyte disturbances is also well known [16]. A few days after the beginning of foscarnet therapy our patient started experiencing nausea, vomiting and acute renal injury and foscarnet had to be withdrawn on day 12 of therapy.

MBV was started on April 30th, when CMV viremia was not so high: 9901 IU/mL on April 26th and 645 IU/mL on May 2nd. Due to FOS toxicity, transition to oral MBV with a better safety profile is preferred, once the viral load has declined to low levels [1]. Higher baseline CMV viral loads have been reported among patients who experienced treatment failure or recurrence, when compared with patients for whom MBV treatment was successful [6]; however, a clear cut-off is not available.

After an initial good response with MBV, the CMV viremia increased and the patient experienced virologic failure due to onset of a T409M mutation in UL97 gene associated to MBV resistance. T409M is a mutation identified near the ATP-binding domain, conferring a–70-fold increase in MBV resistance and has been described in both real-world and clinical trial data as emerging within 2–3 months from start of treatment in the context of a high CMV viral load [5]. In our patient MBV resistance was detected after about 2 months of therapy.

After readmission, therapy decision was a dilemma. The patient had a CMV infection resistant to GCV/VAL, had a recent FOS-related acute kidney injury (AKI) and experienced a treatment failure while on MBV. The choice was to re-start FOS at a reduced dose and administered as continuous infusion with important hydration. The continuous infusion was chosen with the aim to avoid peak concentrations, in the light of the previous AKI occurred with intermittent infusion. A recent retrospective observational study by Domingo et al. comparing continuous vs intermittent infusion of FOS found similar efficacy in clearing the infection in both administration modalities with similar rates of adverse reactions [17]. The risk of a reduced dose was of course the onset of further resistances. On day 7 of treatment FOS was stopped after a sudden increase in transaminases levels; also, CMV infection itself could have led to the increase of hepatic enzymes, but the rapid drop in transaminases level after FOS (and micofenolate) withdrawal may suggest the hypothesis of a drug-related toxicity. An increase in transaminases level has been rarely described with FOS use [18]. Anyway, after the improvement of liver function tests, FOS was reintroduced at 90 mg/kg/day continuous infusion and was subsequently well tolerated and effective in treating this patient. During 15 days, our patient received both FOS and MBV (before the withdrawal of the latter drug due to resistance). The antiviral activity of MBV in combination with other drugs active against CMV was studied by Chou in Ref. [19], where MBV showed additive interactions with FOS, CID, LTV and GW275175X, strong antagonism with GCV, and strong synergy with rapamycin.

In addition to the antiviral treatment, the patient received a reduction in immunosuppressive therapy: micofenolate was stopped and the dose of prednisone was reduced from 15 to 10 mg/day; this may have contributed to the final clearance of CMV infection, as described in Ref. [20].

The new *anti*-CMV drugs recently introduced, presenting less toxicity than those currently used as first and second lines, have generated a certain enthusiasm regarding the treatment of complicated clinical situations. However, MBV and, even more so, LTV, the latter in addition to prophylaxis also used in some cases of rescue therapy, present a low genetic barrier with respect to the onset of resistance mutations. In the case series described by von Hoerschelmann et al. [21] interestingly two out of eight patients treated with LTV developed LTV resistance but simultaneously lost GCV resistance, allowing reintroduction of VAL and clearance of CMV: it seems that GCV resistance in some instances can be lost after withdrawal of the drug, maybe due to a reduced viral fitness induced by some resistance mutations; this could open the way to a possible reintroduction of GCV/VAL in complicated situations. The present data corroborate the risk associated with MBV monotherapy. In the future, as well established for HIV treatment, a possible strategy could be the use of combined regimens of these new drugs, as recently reported by Dickter and coll. [22]. Furthermore, this study underscores the enhanced sensitivity of NGS compared to Sanger sequencing in identifying resistance-associated mutations, with the ability to extend the analysis to entire resistance-related genes.

4. Conclusions

In conclusion, resistant/refractory CMV infection is an important threat in the management of SOT patients, often associated with poor outcomes. We have described the case of a heart-transplanted patient who developed primary CMV infection with subsequent appearance of resistance to GCV and MBV and with important toxicity due to FOS. The outcome was good with reduced-dose continuous infusion of FOS. Further research is needed to improve the management of difficult-to-treat CMV infection.

CRediT authorship contribution statement

Pierangelo Chinello: Writing – review & editing, Writing – original draft, Data curation, Conceptualization. **Isabella Abbate:** Writing – review & editing, Writing – original draft, Data curation, Conceptualization. **Samir Al Moghazi:** Writing – review & editing, Validation, Conceptualization. **Alessandro Capone:** Writing – review & editing, Supervision, Conceptualization. **Simone Topino:**

Writing – review & editing, Validation, Conceptualization. **Eleonora Cimini:** Writing – review & editing, Writing – original draft, Data curation, Conceptualization. **Fabio Sbaraglia:** Writing – review & editing, Data curation, Conceptualization. **Gabriella Rozera:** Data curation, Methodology, Writing – original draft. **Elisabetta Lazzari:** Data curation, Formal analysis, Methodology, Writing – original draft. **Martina Rueca:** Methodology, Writing – original draft. **Fabrizio Maggi:** Writing – review & editing, Supervision, Conceptualization. **Stefania Cicalini:** Writing – review & editing, Supervision, Conceptualization.

Ethics statement

Signed informed consent was obtained from the patient for publication of clinical data included in the manuscript; formal approval from the Institutional Ethical Committee is not required by Italian law for publication of case reports regarding patients cured in research Institutes. The study protocol conformed to the ethical guidelines of the 1975 Declaration of Helsinki.

Data availability statement

NGS data were submitted to Sequence Read Archive (SRA) of the National Center for Biotechnology Information (NCBI). Accession numbers: SAMN46015980, SAMN46015979, SAMN46015978, SAMN46015977, SAMN46015976 and SAMN46015975.

Declaration of competing interest

The authors declare that they have no known competing financial interests or personal relationships that could have appeared to influence the work reported in this paper.

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