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REVIEW

New Insights on CMV Management in Solid Organ Transplant Patients: Prevention, Treatment, and Management of Resistant/Refractory Disease

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ABSTRACT

Cytomegalovirus (CMV) infection can have both direct and indirect effects after solid-organ transplantation, with a significant impact on transplant outcomes. Prevention strategies decrease the risk of CMV disease, although CMV still occurs in up to 50% of high-risk patients. Ganciclovir (GCV) and valganciclovir (VGCV) are the main drugs currently used for preventing and treating CMV. Emerging data suggest that letermovir is as effective as VGCV with fewer hematological side effects. Refractory and resistant CMV also still occur in solid-organ-transplant patients. Maribavir has been shown to be effective and have less toxicity in the treatment of refractory and resistant CMV. In this review paper, we discuss prevention strategies, refractory and resistant CMV, and drug-related side effects and their impact, as well as optimal use of novel anti-CMV therapies.

Keywords: Organ transplantation; Prevention; Resistant CMV; Refractory CMV; Letermovir; Maribavir

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Key Summary Points

Prevention of CMV is crucial to avoid both direct and indirect effects and optimize transplant outcomes.

VGCV has been extremely effective in CMV prevention, although the side effect of leukopenia is common; a recent phase III trial comparing letermovir with VGCV shows similar efficacy with reduced myelotoxicity in those who received letermovir.

In solid-organ-transplant patients, patients experiencing neutropenia are at increased risk of acute rejection.

Resistant/refractory (R/R) CMV generally occurs relatively rarely but conveys significant morbidity and mortality. Careful diagnosis is important; whenever possible, sequencing should be done to confirm resistance mutations.

Standard treatment of R/R CMV had significant toxicity. Maribavir provides better efficacy and less toxicity.

INTRODUCTION

Cytomegalovirus (CMV) infection can be responsible for direct and indirect effects after solid-organ transplantation [1]. Direct effects include CMV syndrome and tissue-invasive organ disease, such as gastrointestinal CMV invasive disease in kidney transplant patients or CMV-induced hepatitis in liver transplant patients. In 1989, Robert H. Rubin evoked for the first time the indirect effects of CMV [2]. Indirect effects are independent of a high viral load and result in part from the effect of the virus on the host's immune response in the setting of long periods of low level of CMV replication. Several indirect effects are associated with CMV, including acute and chronic rejection, arteriosclerosis and cardiovascular disease, opportunistic infections, malignancies, and diabetes mellitus [1].

Despite prevention strategies that are now currently used after transplantation and that decrease the risk of CMV disease [3], CMV disease can still occur in up to 50% of high-risk solid-organ transplant (SOT) patients (CMV-seropositive donor/CMV-seronegative recipients, D+/R−) and 17% of CMV-seropositive recipients (R+) [4]. In a recent meta-analysis, several risk factors for CMV infection or disease were identified: D+/R− serological status, seropositive recipients, use of polyclonal antibodies for induction and/or mycophenolic acid and/or steroids, donors' and recipients' advanced age, and history of acute rejection [5]. In a nationwide retrospective French study, it has been shown that, despite preventive strategies, CMV infection after SOT is associated with an increased risk of acute rejection and graft failure, a higher mortality, and increased costs related to a higher number of inpatient days, number of hospital readmissions, and hospital costs [6].

This article is based on previously conducted studies and does not contain any new studies with human participants or animals performed by any of the authors.

Prevention of Cytomegalovirus Infection

There are two strategies for CMV prevention after SOT: universal prophylaxis and preemptive therapy [7]. Universal prophylaxis relies on giving antiviral therapy to all at-risk recipients (except D−/R−) for 3–12 months according to the type of transplantation and serological status [7]. For instance, 6 months of prophylaxis is recommended for D+/R− kidney transplant patients and for seropositive kidney-transplant patients given polyclonal antibodies induction therapy, while 3 months of prophylaxis is recommended kidney transplant patients not given T-cell-depleting agents. In liver-transplant patients, 3–6 months of prophylaxis can be given. Conversely, in lung transplant patients, a longer duration of prophylaxis is recommended (up to 1 year) [7]. Valganciclovir (VGCV) is usually used in this setting. In the early period

post-transplantation, intravenous ganciclovir (GCV) can be given for few days before it is replaced by oral VGCV. Prophylaxis is quite easy to implement. Very rare cases of early CMV replication/infection occur. Conversely, late CMV infection/disease after the end of prophylaxis is common.

A preemptive strategy relies on the weekly monitoring of CMV DNAemia and the initiation of antiviral therapy when the viral load is above a predetermined threshold. It requires more complicated logistics, which makes this strategy more difficult to implement in centers with a large number of transplantations. Early CMV replication/infection is common. VGCV is the most common antiviral used for treatment. Both strategies prevent CMV disease. However, the effect of preemptive therapy on CMV indirect effects is uncertain, including on preventing opportunistic infections [7]. In a recent survey that assessed prevention strategies from 224 transplant centers, it was shown that universal prophylaxis is used in 90% of centers in D+/R− SOT patients [8]. Kidney and heart-transplant patients are mostly treated for 6 months and lung-transplant patients are given 12 months prophylaxis, while 50% of liver-transplant patients were treated for 3 months and 50% for 6 months. Among CMV-seropositive patients, 50% of centers use a prophylaxis strategy while the others prefer a preemptive strategy [8]. In liver-transplant patients, preemptive therapy is preferred in seropositive patients. VGCV is the most anti-CMV drug used to prevent CMV after SOT. The main side effect reported by different centers is VGCV-induced myelotoxicity, which can lead to its discontinuation in at least 10% of patients [8].

Treatment of CMV Infection

The treatment of CMV infection in SOT patients relies mainly on oral VGCV (900 mg twice a day, renally adjusted) or intravenous GCV (5 mg/kg twice a day, renally adjusted). Intravenous GCV is recommended in case of sight- or life-threatening disease, very high viral load, or questionable gastrointestinal absorption. CMV DNAemia should be monitored weekly to detect refractory/resistant CMV. Treatment is recommended until resolution of clinical symptoms, and until obtaining virological clearance (or very low results with ultrasensitive testing) on one or two samples obtained at 1-week intervals. The minimum duration of therapy is 2 weeks [7]. In the real-life setting, this recommendation seems to be followed by the large majority of centers [8]. However, nearly 14% of centers add anti-CMV immunoglobulins to antiviral therapy in the following indications: primary CMV infection in D+/R− patients, in case of hypogammaglobulinemia (< 500 mg/dL), and in case of severe clinical manifestations such as pneumonia, enteritis, or severe leukopenia [8].

Neutropenia in Transplant-Patients

Neutropenia is frequently observed after solid-organ transplantation. It occurs in up to 30–40% of patients within the first year after transplantation [9–11]. It is mainly related to use of myelotoxic drugs such as polyclonal antibodies, mycophenolic acid, mammalian target of rapamycin inhibitors, VGCV, and trimethoprim/sulfamethoxazole.

In a recent study that included 572 adults who received a kidney transplant and were CMV mismatched or had a panel reactive antibody rate ≥ 80%, 208 (36.3%) participants had neutropenia that was defined as absolute neutrophil count < 1000 cells/μl. In a pediatric cohort of SOT patients, VGCV prophylaxis was associated with neutropenia [11]. In patients presenting with neutropenia, physicians are prompted to either decrease or stop VGCV, decrease or stop mycophenolic acid, stop trimethoprim/sulfamethoxazole, or use of granulocyte colony stimulating factors (G-CSF). In a cohort of 721 kidney-transplant patients, 31% developed at least one neutropenic episode within the first year after kidney transplantation [12]. Most neutropenia episodes were presumably drug related (71%) and managed by reduction/discontinuation of potentially responsible drugs [mycophenolic acid (MPA) 51%, VGCV 25%,

trimethoprim/sulfamethoxazole 19%]. Granulocyte colony-stimulating factor was used in 0.6% of patients [12]. The incidence of infections was about three times higher during neutropenia grade 3 and 4 [12]. In a retrospective study, neutropenic patients experienced more bacterial infections compared with those who did not (43% versus 32%, $p = 0.04$) [9]. Grade of neutropenia correlated with the global risk of infection [9].

Stopping VGCV can increase the risk of CMV infection, especially in D+/R− patients, and requires starting strict weekly CMV DNAemia monitoring to prevent CMV disease [13]. Reducing the dose of VGCV means giving a dose below the recommended dose adapted to kidney function, which can increase the risk of antiviral drug resistance [1, 14]. Therefore, VGCV dose reduction should be avoided. With respect to mycophenolic acid discontinuation and dose reduction, several studies have previously shown an increased risk of acute rejection and even graft loss when transplant patients are not given a complete dose [9, 10, 15–17]. In a study by Brar et al. [10], neutropenia in kidney transplant patients was associated with increased risks of VGCV or mycophenolic acid dose reductions or discontinuations, of acute rejection, and of hospitalization.

Hence, there is a need for an antiviral drug that is as effective as VGCV for preventing CMV and does not have its main side effect, namely myelotoxicity. Letermovir, a selective terminase inhibitor, is a new anti-CMV drug that inhibits formation and release of viral particles. It was previously approved for prophylaxis in hemopoietic-stem cell-transplant (HSCT) patients. Significantly less clinically significant CMV events were observed in HSCT patients given letermovir compared with those who received placebo [18]. No letermovir-related myelotoxicity was observed in letermovir-treated patients. A phase III trial was conducted in 600 D+/R− kidney-transplant-patients to compare letermovir with VGCV prophylaxis to prevent CMV for 28 weeks after transplantation [19]. The results were recently reported. The proportion of patients with CMV disease through the first year after transplantation was similar with both drugs, i.e., 10.4% with letermovir and 11.8% with VGCV. Conversely, drug-related adverse events during the 28 weeks after transplantation were reported more often with VGCV (35%) compared with letermovir (19.9%). The incidence of neutropenia, defined as an absolute neutrophil count $< 1000/\mu L$, during the treatment phase was lower with letermovir than with VGCV (4.1% versus 19.5%; difference, −15.4%; 95% CI, −20.7, −10.5). This study shows that letermovir was not inferior to VGCV for preventing CVM disease during the first year after transplantation and had a lower rate of myelotoxicity [19].

Development of Resistant/Refractory CMV Infection

Resistant CMV infection is defined as detection of a known viral genetic mutation(s) that decreases the susceptibility to one or more anti-CMV medications, while refractory CMV infection is characterized by persistent signs and symptoms of CMV disease and/or persistent CMV DNAemia that fails to improve, defined as a < 1 $\log^{10}$ ($< 10\times$) decrease in CMV viral load or increases after at least 2 weeks of appropriately dosed antiviral therapy [14].

Clinical disease from resistant/refractory (R/R) CMV ranges from asymptomatic infection to severe or even fatal tissue invasive disease. Across multiples studies, it is associated with poor outcomes, including higher rates of hospitalization, increased length of hospital stay, higher costs, increased adverse events from alternative CMV therapies, increased rates of rejection and allograft loss, and increased mortality [7, 20–22]. The most significant risk factor for resistant CMV across numerous trials is the lack of prior CMV immunity, seen in CMV mismatched D+/R− recipients; other risk factors for development of resistant CMV include inadequate antiviral drug dose or delivery, prolonged antiviral drug exposure (usually > 5 months), ongoing active viral replication while on antiviral therapy, intense immunosuppressive therapy, and exposure to therapeutic antiviral drugs with a lower barrier to resistance. When used for treatment, letermovir seems to have the lowest barrier, followed

by maribavir and GCV/VGCV [20, 23–27]. Robust data on rates of letermovir resistance are not available, as the drug has not been used for treatment; low rates were seen after prophylaxis, similar to prophylaxis trials with other agents [28].

The frequency of CMV resistance in the SOT population is quite variable across different organs and programs. The incidence of resistance after GCV therapy in SOT patients is generally low (< 5%), although it seems to be higher in some published reports, ranging from 5% to 12% [25, 29, 30], and as high as 18% in lung recipients [31, 32] and 31% in intestinal and multivisceral organ transplant recipients [33, 34]. Rates of genetic resistance have been measured routinely in only a few large trials. In the IMPACT trial comparing 100 days versus 200 days of VGCV prophylaxis in D+/R− kidney recipients, the incidence of resistance was similar at ~ 2% after 100–200 days of either GCV or VGCV prophylaxis [35]. In the VICTOR trial comparing treatment with intravenous GCV with oral VGCV, 3% of both groups (almost half of whom had prior prophylaxis with GCV or VGCV) had documented resistance testing at the time of treatment initiation [36].

After GCV/VGCV exposure, the most common mutations occur in the UL97 gene, followed by the UL54 DNA polymerase gene. Seven canonical mutations (M460V/I, H520Q, A594V, L595S, C603W, and C592G) account for the majority of the UL97 mutations, most of which convey high-level GCV resistance [7]. Mutations in the UL56 gene are seen after exposure to letermovir (more rarely in the UL89 and UL51 genes) [37].

In a phase 3 study comparing maribavir versus investigator assigned therapy for R/R CMV, DNA sequence analysis of the entire coding regions of pUL97 and pUL27 was done on 134 paired sequences from maribavir-treated patients, and genetic resistance was found in 58/235 (~ 25%) subjects, including 47 subjects considered on-treatment failures and 11 subjects with relapse infection [38]. Among the treatment-emergent pUL97 mutations were F342Y (4.5-fold reduced susceptibility to maribavir), C480F (224-fold), T409M (78-fold), and H411L/N/Y (69-, 9-, and 12-fold, respectively). The first two, F342Y and C480F, confer > 1.5-fold reduced susceptibility to VGCV/GCV; development of cross-resistance, seen with all antiviral agents, is concerning.

Diagnosis of Resistant/Refractory CMV Infection

Antiviral drug resistance should be suspected when there is persistent or recurrent CMV DNAemia or disease during prolonged antiviral therapy; it very rarely occurs after brief exposure to treatment. For GCV, prolonged therapy is usually 6 or more weeks of cumulative drug exposure, including at least 2 weeks of ongoing full-dose therapy [20, 29]. Although a higher level of CMV DNAemia may commonly be noted a week into therapy, guidelines suggest that this is not yet concerning for R/R disease, and do not recommend sending testing or switching therapy, unless there is severe disease; by definition, R/R disease is after at least 2 weeks of full-dose antiviral therapy [7, 14]. Clinicians should be aware that the kinetics of CMV DNAemia response and the risk for early emergence of resistance may be different with newer antiviral drugs, especially those that have a lower barrier to resistance.

Sequencing of each genetic locus (UL97, UL54, UL56) is necessary to detect resistance mutations, and should be determined on the basis of prior drug exposure, as this predicts the likelihood of a mutation. A sample (most often from blood, although also possible from viral culture; sequencing from tissue biopsies is rarely possible) should be sent for mutation sequencing analysis, most commonly in UL97 after VGCV exposure, but also in UL54 with more complex or prolonged exposures, and in UL56 after letermovir exposure. Sequencing of each gene adds cost. Results are more feasible and reliable if the CMV DNAemia in the specimen is at least 1000 IU/mL [39].

False-negative resistance sequencing can occur, due to insensitivity in detecting mutant subpopulations representing less than 20–30% of the total, which may still be clinical significant [39, 40]. Emerging, next-generation deep sequencing technologies offer the possibility of

detecting small mutant subpopulations [41]. There have been reports of discordant findings of resistance mutations in varied body sites (e.g., eye, spinal fluid) [42–44]. Progressive disease at tissue sites despite negative testing in blood may warrant the genotypic testing of tissue-specific specimens, when virus is detectable at adequate levels.

Treatment and Prophylaxis of Resistant/Refractory CMV Infection

While no controlled trial data define a best practice for treatment of R/R CMV infection, clinically useful published algorithms are based on expert opinion and experience [7, 45, 46]. In general, the first step is to consider reducing the transplant-related immunosuppressive therapy to the lowest feasible amount, often after careful discussions with the transplant team.

Therapeutic choices, often decided prior to return of sequencing data, often depend on the extent of disease. For asymptomatic or mildly symptomatic disease, or with low-level DNAemia, guidelines recommend the use of high-dose GCV (from 7.5 to 10 mg/kg every 12 h in normal renal function) [7]. Data supporting this in SOT patients are limited; one series showed successful outcomes in six patients with low-level DNAemia [47]. In general, given that most of the common mutations convey high-level resistance to VGCV, this therapeutic approach has a narrow applicability but may be useful in the setting of refractory infection (i.e., perhaps with malabsorption or other issues with drug delivery), and cases of low-level resistance mutations (i.e., UL97 gene C592G).

For severe, life-threatening, or sight-threatening disease, international guidelines recommend the use of foscarnet [7]. An updated clinical decision support tool, developed by several of the guidelines authors, also recommends maribavir, although not with retinitis or encephalitis due to poor drug penetration, where foscarnet would be preferred [45]. Unfortunately, a review of foscarnet for R/R CMV showed a mortality of 31%, with significant renal toxicities, highlighting the need for new therapies [22]. Maribavir has recently been approved in the USA and Europe for treatment of R/R CMV. This oral drug is a safe and effective therapeutic agent, based on a recent phase 3 trial [48]. The main side effect was dysgeusia, seen in 37%. Although those subjects were treated for 8 weeks, it is possible that shorter treatments may be effective, similar to those standardly used with GCV/VGCV [7]; such research has not yet been done. Furthermore, only 6% of the phase 3 trial subjects had high viral loads, with limited severe end-organ disease, such that some experts suggest using foscarnet induction therapy followed by maribavir treatment. Twenty-five percent of subjects underwent sequencing and developed mutations conveying resistance to maribavir [38]. Clinicians should be aware that maribavir treats only CMV, and may wish to provided acyclovir or another similar agent to protect against reactivation varicella and herpes. Brincidofovir was previously evaluated for CMV treatment, but is not currently available for that indication at the time of this review. Letermovir, approved for prophylaxis after stem cell transplant, is not being developed as a treatment agent. Small, uncontrolled studies have shown that it may be helpful in R/R CMV, although it has a very low barrier to resistance and is probably better used as prophylaxis [49].

Additional adjunctive therapies, such as the use of CMV immunoglobulin, may be useful. Other agents such as mTor inhibitors (e.g., sirolimus and everolimus), leflunomide, and artesunate, have anti-CMV effects in vitro that may sometimes act synergistically with conventional antivirals [50, 51], although none of these is strongly evidence based [7]. Given the mechanisms of action, the combination of maribavir and GCV/VGCV may be antagonistic and should be avoided [52]. Early data suggest that infusions of CMV-specific T cells may improve antiviral host defenses [53, 54].

Prophylaxis after treatment of R/R CMV infection can be challenging, especially if there is multidrug resistance. Maribavir is rarely available and not approved for prophylaxis, VGCV is usually ineffective, and foscarnet is often considered impractical and too toxic. In general, we recommend preserving letermovir for prophylaxis after treatment of R/R CMV,

rather than using it for treatment, given the lower barrier to developing resistance with letermovir treatment. Other options that may be effective, depending on prior exposures and resistance mutations, include CMV immunoglobulin and cidofovir every 2 weeks.

Very Low DNAemia and Diagnosis of Resistant/Refractory Disease

The advent of ultrasensitive CMV DNAemia testing has proven to be somewhat enigmatic for transplant clinicians. The use of real-time PCR seems to have created more artifact, or at least results of unclear clinical significance, in the lower ranges (generally below 500 IU/mL in whole blood or plasma). In the absence of signs and symptoms of disease, this may not represent R/R CMV but rather diagnostic artifact of DNAemia of unclear significance, and in the right clinical setting, clinicians may wish to monitor this with weekly CMV DNAemia testing and consider possible slight reduction of immunosuppression, which, in our experience, can often resolve this low-level DNAemia. In one series, almost half of patients with a CMV DNAemia of < 1000 IU/mL resolved without treatment [55]. A recent study on the use of letermovir in 37 subjects with very low viral loads (< 1000 IU/mL) showed good virologic outcomes, although may also have resolved DNAemia without treatment [49].

While earlier guidelines recommended treating until the CMV DNAemia was negative or undetectable [56], when using ultrasensitive CMV DNAemia testing, newer guidelines recommend treating until there are one or two negative or very low CMV DNAemia tests a week apart [7]. Clinicians should be aware of the impact of ultrasensitive CMV DNAemia testing, and not to overdiagnose R/R CMV at these lower levels of DNAemia.

CONCLUSIONS

Novel therapies for preventing and treatment of CMV have emerged as beneficial within the last few years. While VGCV has been very effective for more than two decades, letermovir may be as efficient as VGCV for preventing CMV disease with fewer hematological side effects. Maribavir is now approved for treating refractory/resistant CMV infection. Further studies are still required to improve the rate of sustained virological clearance and outcome in this setting.

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