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REVIEW

Current Perspectives on Letermovir and Maribavir for the Management of Cytomegalovirus Infection in Solid Organ Transplant Recipients

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Abstract: Cytomegalovirus (CMV) infection is arguably the most important infectious complication that negatively affects the outcome of solid organ transplantation. For decades, CMV management after transplantation has relied on antiviral drugs that inhibit viral DNA polymerase (ganciclovir, foscarnet, and cidofovir). However, their use has been complicated by myelosuppression, nephrotoxicity, and selection of drug-resistant viruses. During the past few years, the therapeutic armamentarium for the management of CMV in solid organ transplant recipients has expanded with the approval of letermovir for CMV prophylaxis in high-risk CMV D +/R- kidney recipients, and maribavir for the treatment of refractory and resistant CMV infection. Both drugs offer significant improvement when compared to standard anti-CMV therapies; letermovir was as efficacious for CMV prevention, whereas maribavir was more effective in treating refractory and resistant CMV infections. Both letermovir and maribavir have favorable safety profiles compared to CMV DNA polymerase inhibitors, without the risk of neutropenia and leukopenia associated with ganciclovir and renal toxicities associated with foscarnet and cidofovir. Moreover, letermovir and maribavir are orally bioavailable, which allows convenient outpatient treatment. However, letermovir and maribavir have a significant drug interaction potential in solid organ transplant recipients, resulting in higher levels of calcineurin inhibitors (cyclosporine and tacrolimus) and mTOR inhibitors (sirolimus and everolimus). Both letermovir and maribavir are CMV-specific and do not have clinical efficacy against other herpes viruses. Thus, there is a need for additional antiviral drugs to prevent herpes simplex and other herpes viruses when clinically indicated. This article provides a comprehensive review of the clinical data supporting the use of letermovir and maribavir in clinical practice. The author provides perspectives on the role of these newly approved drugs in the current management landscape of CMV infection in solid organ transplantation.

Keywords: cytomegalovirus, maribavir, letermovir, ganciclovir, drug resistance, prophylaxis, treatment

Introduction

Cytomegalovirus (CMV) is a ubiquitous virus that infects more than half of the global population.[1] After mild self-limiting primary infection in immunocompetent individuals, CMV establishes a state of lifelong latency. During periods of intense immunosuppression, such as after solid organ transplantation (SOT), primary CMV infection or reactivation of latent infection can lead to a spectrum of illnesses ranging from asymptomatic to severe and potentially fatal diseases.[2] Severe CMV disease is particularly observed among highly immunosuppressed SOT recipients, such as those with severe lymphopenia and lack of CMV-specific cellular and humoral immunity.[3] In these individuals, CMV may be manifested as febrile illness and organ-invasive diseases involving the gastrointestinal tract, lungs, brain, the transplanted allograft, among other organs in the body.[2] Among end-organ CMV diseases, involvement of the gastrointestinal tract is the most common, while central nervous system and retinal involvement is rare. In addition, CMV is associated with a reduced overall allograft and patient survival.[4]

Because of the negative effects of CMV on SOT outcomes, its prevention is an essential component of posttransplant management.[2] CMV prevention after SOT can be accomplished using universal antiviral prophylaxis or preemptive

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treatment for asymptomatic CMV replication.[2] For more than three decades, the main antiviral drug used against CMV has been ganciclovir (Table 1). The guanosine analog ganciclovir is phosphorylated by viral UL97 and cellular kinases into active ganciclovir-triphosphate, which serves as a competitive substrate for UL54-encoded CMV DNA polymerase, effectively terminating CMV DNA synthesis.[5] Ganciclovir is available as an intravenous drug while valganciclovir is its oral formulation.[5] Initially approved for the treatment of CMV retinitis in patients with acquired immunodeficiency syndrome, multiple studies have demonstrated that ganciclovir is highly effective for the prevention and treatment of CMV in SOT recipients.[2,5] However, ganciclovir and valganciclovir are commonly complicated by hematologic toxicity, most notably, leukopenia and neutropenia. In addition, the optimal dosing of ganciclovir and valganciclovir has been challenging among transplant recipients with evolving and dynamic renal function. Failure to adjust ganciclovir or valganciclovir dose may result in a suboptimal systemic level that has been implicated in the selection of drug-resistant viral strains. Indeed, ganciclovir-resistant CMV has emerged as an important concern among transplant recipients, most commonly due to mutations in UL97 that impair the phosphorylation and activation of ganciclovir.[6] In these situations, alternative drug treatment options include foscarnet and cidofovir, both of which have undesirable renal toxicities (Table 1). Similar to ganciclovir, foscarnet and cidofovir act by halting CMV DNA synthesis through inhibition of UL54-encoded DNA polymerase. However, CMV has also developed UL54 mutations that may confer single-, double-, and pan-resistance to CMV DNA polymerase inhibitors (ganciclovir, cidofovir, and foscarnet), resulting in limited therapeutic options.[6] Therefore, novel antiviral therapies that are safer and more effective are required.

In this article, I review the scientific and clinical evidence regarding letermovir and maribavir, two recently approved antiviral drugs for the management of CMV in SOT recipients. I provide my perspectives on their roles and how they fit the current CMV-management landscape.

Table 1 Antiviral Drugs for the Prevention and Treatment of Cytomegalovirus Infection and Disease in Solid Organ Transplant Recipients

	Cidofovir	Foscarnet	Ganciclovir Valganciclovir	Letermovir	Maribavir
Drug type / class	Cytidine monophosphate analogue inhibitor of CMV DNA polymerase	Pyrophosphate analogue inhibitor of CMV DNA polymerase	Guanosine analogue inhibitor of CMV DNA polymerase	UL56/UL89/UL51 viral terminase complex inhibitor	UL97 kinase inhibitor
Antiviral effect	Inhibits viral DNA synthesis	Inhibits viral DNA synthesis	Inhibits viral DNA synthesis	Inhibits cleavage of concatameric DNA into unit-length monomers that is packaged into a viral capsid	Multimodal effect; it inhibits phosphorylation of proteins needed for viral replication, encapsidation and egress
Viral activity	Broad-spectrum against many DNA viruses, including CMV and other herpesviruses	All herpes viruses, including CMV	All herpes viruses, including CMV	CMV only (no activity against other herpes viruses)	CMV only EBV in vitro (no activity against other herpes viruses)
FDA-approved clinical uses	Treatment of CMV retinitis in patients with AIDS	Treatment of CMV retinitis in patients with AIDS; treatment of acyclovir-resistant herpes simplex virus infection	Treatment of CMV retinitis in patients with AIDS; prevention of CMV disease in transplant recipients	Prophylaxis against CMV disease in CMV D+/R- kidney recipients and in CMV R+ allogeneic HSCT recipients	Treatment of refractory or resistant CMV
Dosage	5 mg/kg IV once weekly x 2 doses then every 2 weeks	90 mg/kg IV every 12 hours (or 60 mg/kg every 8 hours)	Ganciclovir Prophylaxis: 5 mg/kg every 24 hours Treatment: 5 mg/kg IV every 12 hours Valganciclovir: Prophylaxis: 900 mg PO once daily Treatment: 900 mg PO twice daily	480 mg PO once daily (reduce to 240 mg PO once daily in presence of cyclosporine)	400 mg PO twice daily (increase dose to 800 mg or 1200 mg PO twice daily when co-administered with certain anticonvulsants)

(*Continued*)

Table 1 (Continued).

	Cidofovir	Foscarnet	Ganciclovir Valganciclovir	Letermovir	Maribavir
Pharmacokinetic activation	Needs phosphorylation by cellular enzymes	No significant metabolism; excreted in urine	Needs triphosphorylation by UL97 kinase and cellular enzymes	Active parent drug; no need for phosphorylation	Active parent drug; no need for phosphorylation
Half-life	Plasma half-life: 2.6 hours; but the drug persists in cells for prolonged period	Plasma half-life: 5.5 hours; the drug has triphasic elimination process	Ganciclovir IV: 2.5–3.6 hours; valganciclovir PO: 3.1–5.5 hours	12 hours	4.32 hours
Oral bioavailability	NA	NA	Valganciclovir: 60%	94% in healthy subjects; 35% in HSCT recipients; 85% in HSCT recipients on cyclosporine	30–40%
Metabolic pathways	Metabolized into diphosphate intracellularly; no metabolites in plasma; over 80% excreted in urine as unchanged drug	Not metabolized; renal excretion; bone deposition	Tri-phosphorylated by viral UL97 and cellular kinases; minimal degree of metabolism; 90% excreted as unchanged drug in urine	No significant metabolism; 93% excreted in feces (70% as unchanged drug); minimal metabolism by UGT1A1/1A3	CYP3A4 (major) CYP1A2 (minor)
Renal dose adjustment	Yes	Yes	Yes	No	No
Hepatic dose adjustment	No	No	No	No	No
Adverse reactions (selected)	Renal failure, ocular hypotonia, leukopenia	Renal failure, electrolyte disturbance (hypocalcemia, hypophosphatemia, hypomagnesemia)	Myelosuppression, especially leukopenia and neutropenia	Gastrointestinal (nausea, vomiting, diarrhea)	Taste disturbance; gastrointestinal (nausea, vomiting, diarrhea)
Drug resistance mechanisms	UL54 mutations (multiple)	UL54 mutations (multiple)	UL97 mutations are most common (multiple; clustered at codons 460, 520, and 590–607); UL54 mutations less common	UL56 mutations (maps at codon 231–369); C325Y/F/W/R is most common mutation	UL97 mutations (C480F, F342Y, H411Y, H411N, K359E, K359Q, T409M)

Note: AIDS, acquired immunodeficiency syndrome; CMV, cytomegalovirus; EBV, Epstein Barr virus; D+/R-, donor-positive/recipient-negative; IV, intravenous; PO, per orem.

Methods

Using PUBMED, a search of the scientific literature was made using the terms "maribavir" or "letermovir" and "transplantation". The search yielded a total of 403 publications. The abstracts of these articles were reviewed in detail to screen and select those relevant to CMV prevention and treatment in SOT recipients. Controlled clinical trials, retrospective reports, case series, and case reports were included. When needed (such as when data from the SOT population were non-existent), supporting data from studies conducted in allogeneic hematopoietic stem cell transplant (HSCT) recipients were retrieved and included in this review.

Drug Reviews

Letermovir

Description and Mechanism of Action

Letermovir is a first-in-class anti-CMV drug that targets viral terminase, a heterotrimeric complex formed by pUL56, pUL51 and pUL89.[7] Viral terminase cleaves concatameric viral DNA and packages unit-length genomes into viral capsids. Letermovir potently hinders the processing and packaging of CMV DNA progeny by inhibiting the function of the viral terminase complex, thereby effectively halting the formation of mature virions.[7,8]

Pharmacokinetics

Letermovir is available as both oral (PO) and intravenous (IV) formulations. The dose is 480-mg PO or IV once daily (this is reduced to 240-mg PO or IV once daily in patients receiving cyclosporine; see drug interactions below) (Table 1).

After oral administration (with or without food), letermovir is rapidly absorbed with a median time to peak plasma concentration of 45 minutes–2.25 hours.[9] Bioavailability is estimated to be 35% (in HSCT recipients not receiving cyclosporine, which increases to 85% in the presence of cyclosporine). The median half-life was 12 hours. Letermovir is highly protein-bound, with 99% of the drug bound to plasma proteins.[9] Most of the drug in the plasma (97%) was the unchanged parent compound, and no major metabolites were detected. Letermovir undergoes only a minor degree of metabolism by liver enzymes uridine diphosphate glucuronosyltransferase 1A1 (UGT1A1) and UGT1A3, resulting in glucuronide metabolites. It is eliminated via hepatic uptake by organic anion-transporting polypeptide 1B1/3 (OATP1B1/3) transporters.[9] Cyclosporine is an inhibitor of OATP1B1/3, thereby reducing hepatic uptake and elimination of letermovir (leading to increased letermovir concentrations. Hence, it is recommended to reduce the letermovir dose by 50% in patients receiving cyclosporine).

The majority of letermovir (93%) is excreted as an unchanged drug in feces;[9] less than 2% is excreted in urine. As this drug is not renally excreted, no dosage adjustment is required in patients with impaired renal function (ie, creatinine clearance >10 mL/min). However, no clinical data are available for dialysis patients. There is a risk of accumulation of hydroxypropyl betadex, the vehicle for IV formulation, in patients with renal dysfunction.

Clinical Uses of Letermovir in SOT Recipients

In 2017, letermovir was approved by the United States (US) Food and Drug Administration (FDA) for CMV prophylaxis in CMV-seropositive allogeneic HSCT recipients.[10] This approval was based on the results of a randomized controlled clinical trial of 565 CMV-seropositive allogeneic HSCT recipients, which showed that letermovir prophylaxis for up to 100 days significantly lowered the rate of clinically significant CMV infection or disease by week 24 (37.5% vs 60.6% for placebo).[10] Moreover, letermovir prophylaxis may reduce mortality by preventing or delaying clinically significant CMV infections in HSCT recipients.[11] Since its approval, letermovir has been used off-label for various clinical indications in SOT recipients (discussed below). In 2023, letermovir received FDA approval for the prevention of CMV disease in CMV D+/R − kidney transplant recipients.[12]

CMV Prophylaxis in CMV D+/R- Kidney Transplant Recipients

In a Phase 3 randomized clinical trial, letermovir was compared with valganciclovir for CMV prophylaxis over 200 days in a cohort of 601 CMV D+/R − kidney recipients.[12] The primary endpoint of CMV disease through week 52 after kidney transplantation was not significantly different between the two antiviral drugs (10.4% vs 11.8%).[12] Quantifiable CMV DNA by week 28 was reported in 2.1% of patients who received letermovir prophylaxis, compared to 8.8% of those who received valganciclovir prophylaxis.[12] Among patients with suspected CMV disease or DNAemia, resistance-associated amino acid substitutions were not detected in patients who received letermovir compared with 12.1% among those who received valganciclovir.[12] Patients who received letermovir prophylaxis had significantly less neutropenia or leukopenia than those who received valganciclovir prophylaxis (25% vs 64%, respectively). Fewer patients receiving letermovir prophylaxis discontinued the drug due to adverse events than those receiving valganciclovir (4.1% vs 13.5%).[12] This study supported the US FDA approval of letermovir as antiviral prophylaxis in CMV D+/R- kidney transplant recipients.

CMV Prophylaxis in Non-Kidney SOT Recipients

Letermovir has not been subjected to randomized clinical trials in non-kidney SOT recipients. Hence, data regarding the use of letermovir in non-kidney SOT recipients are limited to anecdotal and retrospective studies. In these reports, SOT recipients were switched to letermovir when they developed myelosuppression from the valganciclovir prophylaxis.

Letermovir was administered to 75 SOT recipients who developed leukopenia during valganciclovir prophylaxis, and one patient developed breakthrough CMV during letermovir prophylaxis.[13] Among eight heart or lung transplant patients receiving letermovir prophylaxis, three (37.5%) developed breakthrough CMV DNAemia.[14] Among the 26 heart or lung recipients who were switched from valganciclovir to letermovir prophylaxis because of myelosuppression, transient low-level CMV DNAemia was reported in 35.7% of the patients, but they did not require treatment.[15] Among 17 heart recipients who were switched to letermovir because of valganciclovir-induced leukopenia, two developed breakthrough

CMV that was deemed to be clinically insignificant.[16] A small-bowel transplant recipient who was switched to letermovir prophylaxis because of ganciclovir-induced neutropenia developed breakthrough asymptomatic and low-level CMV DNAemia during intensification of immunosuppression but did not require antiviral treatment.[17] These data suggest that CMV DNAemia during letermovir prophylaxis is not uncommon; however, it may not necessarily indicate true infection. One study (on HSCT recipients) suggested that breakthrough CMV DNAemia during letermovir prophylaxis might reflect a product of an incomplete replication cycle, suggesting abortive infections.[18] One study in SOT recipients did not find a significant difference in the rate of breakthrough CMV DNAemia between those who were switched to letermovir and those who remained on valganciclovir prophylaxis.[19]

Preemptive Treatment of Asymptomatic CMV Reactivation

During a clinical trial that investigated letermovir for CMV prophylaxis in allogeneic HSCT recipients,[20] 70 patients had pre-prophylaxis CMV DNAemia detected at baseline, including 48 patients who were subsequently randomized to receive letermovir. Compared with the 22 CMV DNAemic patients who received placebo, those who were randomized to receive letermovir had a significantly reduced rate of clinically significant CMV infection.[20] This suggests that letermovir may be effective in the treatment of CMV. However, letermovir as a preemptive treatment for CMV reactivation in heart recipients does not prevent progression to CMV esophagitis.[21]

Treatment of Resistant or Refractory CMV Infection

Because of its distinct mechanism of action, letermovir remains active in vitro against CMV that developed resistance to ganciclovir, foscarnet and cidofovir.[8,22–24] Accordingly, letermovir has been used off-label for the treatment of CMV infection due to UL97-mutant virus in SOT recipients,[25,26] including the lung,[27,28] heart,[29] kidney,[30] pancreas,[31] liver,[32] and small bowel recipients.[33]

Viral clearance was observed after 18 weeks of letermovir treatment in four lung recipients who developed refractory and resistant CMV or were intolerant of standard therapies.[28] However, treatment-emergent resistance has been observed during letermovir use, which is characterized by UL56 mutation.[32] In a cohort of eight kidney transplant recipients (all except one were CMV D+/R-) who developed breakthrough refractory CMV infection during valganciclovir prophylaxis, letermovir successfully eradicated CMV DNAemia after 24 weeks in four patients; however, two patients had persistent low-level CMV DNAemia and the other two developed treatment-emergent letermovir resistance.[34] Among 28 lung recipients with ganciclovir refractory and resistant CMV infection, letermovir treatment led to a rapid decline in viral load, with a >1 log decline in 17 days.[27] However, five patients (18%) were letermovir non-responders, including three who developed the UL56 C325Y mutation.[27] Among the four lung or heart transplant recipients with drug-resistant CMV retinitis, letermovir treatment led to clinical and funduscopic improvement; however, three patients failed to maintain virologic suppression, including two who had a virus with a C325Y/F mutation.[35]

Collectively, these reports highlight the emergence of resistant viruses following letermovir exposure. The clinical outcomes of letermovir treatment appear to be better when the viral load is <1000 IU/mL at the initiation of treatment, whereas outcomes are mixed at higher viral levels.[26] Because it is available in oral form, letermovir has also been used as step-down therapy once the viral load is controlled with initial treatment with foscarnet.[36,37] The practice of transitioning to oral treatment reduced the length of hospitalization.[36]

Letermovir as Secondary Prophylaxis

Letermovir has also been used off-label as secondary prophylaxis in SOT recipients who are deemed at a high risk of relapse after treatment of resistant or refractory CMV infection.[21,38] Letermovir was used as secondary prophylaxis in 16 heart or lung recipients who did not tolerate or develop resistance to ganciclovir.[15] Secondary letermovir prophylaxis was administered to prevent relapse after viral load was reduced by cidofovir[39] and when patients developed significant toxicities from cidofovir or foscarnet.[38]

However, secondary letermovir prophylaxis is complicated by the selection of CMV UL56 mutations.[40] When letermovir was used as secondary prophylaxis in a small cohort of abdominal organ transplant recipients, there was a high rate of breakthrough CMV DNAemia or disease (5 of 8 patients; 62.5%).[41] Failure of secondary letermovir

prophylaxis has also been reported in a lung and liver recipient who developed CMV recurrence or selected a resistant virus with the UL56 C325F mutation.[42]

Additional Clinical Considerations

CMV-Specificity

Letermovir is CMV-specific and does not show activity against herpes simplex and varicella zoster viruses. Accordingly, antiviral drugs such as (val)acyclovir should be administered (in addition to letermovir) to prevent herpes infections after transplantation.

Viral Load Monitoring

Viral load surveillance captured cases of breakthrough CMV DNAemia during primary letermovir prophylaxis; however, some data suggest that this may be reflective of an abortive infection.[18] Accordingly, the need for routine serial CMV surveillance is highly debated during primary letermovir prophylaxis. However, viral surveillance is recommended during secondary letermovir prophylaxis to capture the emergence of breakthrough infections caused by resistant viruses. During off-label use for the treatment of CMV infection, there is a theoretical lag in the decline of viral load after starting letermovir. The transient rise or lag in CMV DNA clearance for approximately 1–3 weeks after letermovir treatment was attributed to the inability of letermovir to directly inhibit CMV DNA synthesis (its mechanism of action is at the post-DNA replication stage).[27]

Drug Interactions

Letermovir is a substrate of organic anion-transporting polypeptide 1B1/3 (OATP1B1/3) transporters. Co-administration with inhibitors of OATP1B1/3 such as cyclosporine may result in increased letermovir concentrations. Accordingly, the letermovir dose was reduced from 480-mg to 240-mg per day in SOT recipients receiving cyclosporine.

Letermovir is a moderate inhibitor of CYP3A4/5 and is anticipated to have many clinically relevant drug–drug interactions.[43] Co-administration of pimozide and ergot alkaloids is contraindicated because of the risk of torsades de pointes and ergotism, respectively. In SOT recipients, one major anticipated effect of letermovir is an increase in blood levels of calcineurin inhibitors (tacrolimus) and mTOR inhibitors (sirolimus).[9] In a study of 14 SOT recipients, the median weight-based tacrolimus dose declined from 0.09 mg/kg/day to 0.05 mg/kg/day when letermovir was used, while the corrected trough concentrations increased from 1.54 to 2.16 ng/mL/mg.[44] These observations suggest that an approximate tacrolimus dose reduction of 30% may be warranted when letermovir therapy is initiated in SOT recipients.[44] Another study recommended to reduce the dose of tacrolimus by 40–50% at the initiation of letermovir.[19] In a cohort of eight patients who were administered letermovir, tacrolimus levels increased by 43% despite a preemptive dose reduction of 30%.[45] Indeed, despite preemptive adjustment of tacrolimus dose during letermovir use, one patient was hospitalized because of symptomatic tacrolimus toxicity.[16] Therefore, frequent monitoring of tacrolimus, sirolimus, and cyclosporine is recommended during and after letermovir treatment.

Other drugs that may have increased in concentration when used concomitantly with letermovir include amiodarone, glyburide, rosiglitazone, atorvastatin, and HMG-CoA reductase inhibitors. In contrast, letermovir may reduce the concentration of omeprazole, pantoprazole, warfarin, voriconazole, and phenytoin. The reduction of azole concentrations by letermovir is variable; letermovir administration reduced voriconazole but did not affect posaconazole and isavuconazole levels to a significant degree. Inducers of CYP3A such as rifampin, may result in reductions in letermovir concentrations (potentially impairing its antiviral efficacy and increasing the risk of resistance); however, the co-administration of rifampin and letermovir is not recommended. Close clinical monitoring is recommended to reduce the potential adverse reactions related to these drug-drug interactions.

Adverse Reactions

Letermovir is generally well tolerated.[12] The adverse effects of letermovir are primarily mild gastrointestinal symptoms such as nausea, diarrhea, and vomiting. Nausea is the most common reason for discontinuation of letermovir in clinical trials.[12] Headache, fatigue, and abdominal pain were reported less frequently. In a retrospective study, one patient

discontinued letermovir prophylaxis because of headache and myalgia.[16] Letermovir does not cause significant myelotoxicity or nephrotoxicity.[12]

Letermovir Resistance

Letermovir has been reported to have a low barrier to resistance development, based on in vitro and early clinical studies.[22,40,46] In vitro studies have mapped letermovir resistance mutations to a region between codons 229 and 369 of UL56, and rarely to UL51 and UL89 of the viral terminase complex. Experimental studies demonstrated the early selection of low-grade resistance mutations UL56 V236A, L328V, and A365S during letermovir exposure, which was later accompanied by high-level mutations in codon 325 conferring absolute letermovir resistance.[47] Comparatively, UL56 mutations during letermovir exposure occurred more easily and at an earlier time period than the development of UL54 or UL97 mutations during ganciclovir exposure.[47]

In the clinical setting, poor outcomes have been reported when letermovir was used for treatment, especially when the viral load was high[26] and when it was used for secondary prophylaxis. CMV UL56 C325Y developed in a lung recipient when letermovir was used to treat recurrent CMV DNAemia.[48] Breakthrough CMV DNAemia was observed in three of eight lung transplant recipients within 2 months of starting secondary letermovir prophylaxis.[14] Collectively, these reports suggest a low barrier to resistance when letermovir was used during active CMV replication.

Maribavir

Description and Mechanism of Action

Maribavir is an oral benzimidazole L-riboside with potent multimodal selective activity against CMV (Table 1). Maribavir inhibits UL97 kinase; it competitively inhibits adenosine triphosphate (ATP) binding to pUL97, a protein kinase responsible for phosphorylating several downstream viral proteins essential for CMV replication.[24] Through ATP inhibition, maribavir prevents the phosphorylation required for CMV DNA replication, encapsidation, and nuclear egress of viral capsids.[49,50]

Maribavir has in vitro activity against EBV but not against herpes simplex viruses, varicella zoster virus, and human herpes viruses 6 and 8.[51] In vitro, maribavir antagonizes the antiviral activity of ganciclovir, likely because of its dependence on UL97-mediated phosphorylation (which is inhibited by maribavir).[52] In contrast, there is potential synergistic anti-CMV effect of maribavir combined with foscarnet or cidofovir in vitro.[53]

Pharmacokinetics

Maribavir is an orally administered drug. The recommended dose was 400 mg PO, twice daily. The dose was increased to 800 mg twice daily if co-administered with carbamazepine or to 1200 mg twice daily if co-administered with phenytoin or phenobarbital (see drug interactions below).

After oral ingestion (with or without food), maribavir is rapidly absorbed with a bioavailability of 30–40%.[54] It exhibits linear pharmacokinetics and achieves Cmax 1–3 hours after administration. Maribavir is highly protein-bound (98%) and has a plasma half-life of 3–5 hours. Maribavir does not require intracellular activation for its antiviral activity. The parent compound is pharmacologically active and inhibits CMV replication at concentrations <1–15 μM.[55]

Maribavir is metabolized in the liver by CYP3A4 and is primarily eliminated by biliary excretion. Patients with moderate hepatic impairment have higher plasma maribavir concentrations, a longer half-life, and lower clearance.[56] However, this is predicted to have limited clinical relevance given the wide therapeutic index of maribavir. Accordingly, no dose adjustments are required in patients with mild-to-moderate hepatic dysfunction.[56]

The renal clearance of maribavir is minimal.[54] However, approximately 30–40% is excreted in the urine as an inactive metabolite, and <2% is excreted unchanged in the urine. Renal impairment is associated with increased levels of inactive metabolites, although there is no change in the total concentrations of the parent drug; thus, the dose is not adjusted in patients with mild, moderate, or severe renal dysfunction.[57,58]

Clinical Uses of Maribavir in SOT Recipients

Despite its potent in vitro activity against CMV, early phase clinical trials did not confirm the clinical efficacy of maribavir for CMV prophylaxis in allogeneic HSCT and liver transplant recipients at a dose of 100 mg twice daily.[59,60]

In these trials, maribavir was well-tolerated and safe. The clinical trial in liver recipients was terminated early based on the lack of efficacy of maribavir at a dose of 100 mg twice daily to prevent CMV infection in HSCT recipients.[60] Interim analysis of the liver trial showed inferior activity of maribavir compared with that of ganciclovir.[59] However, data from the compassionate use of maribavir (at higher doses) for refractory and resistant CMV were promising, which eventually led to its further clinical development.[61]

Treatment of Refractory and Resistant CMV Infection

At higher doses (400 mg PO twice daily), maribavir was successful in the treatment of drug-resistant CMV disease, including 5 SOT recipients who failed to respond to standard therapies or had ganciclovir-resistant CMV.[61,62] In this case series, 4 patients had no detectable CMV DNA in the blood within 6 weeks of maribavir treatment.[61] However, the patient with an initial viral load of 1.8 million copies per mL selected for CMV infection with multiple maribavir-resistance mutations.[61]

A Phase 2 clinical trial investigated maribavir at different doses (400, 800, and 1200 mg PO twice daily for up to 24 weeks) in 120 SOT (and HSCT) recipients with resistant and refractory CMV. The majority were SOT recipients (60%).[63] Most of the patients (64%) were asymptomatic. Across different treatment doses, the rates of undetectable CMV DNA were similar at 6 weeks (primary endpoint, 67%) and 24 weeks (end of treatment, 72%).[63] However, CMV recurrence occurred in 29% of patients after maribavir discontinuation, and 52% of patients had maribavir-resistant mutations.[63]

In a subsequent phase 3 open-label clinical trial, 352 SOT and HSCT transplant recipients with refractory or resistant CMV were randomized to receive maribavir 400 mg PO twice daily or an investigator-assigned therapy (ganciclovir/valganciclovir, foscarnet, and cidofovir) for a fixed duration of 8 weeks.[64] The study cohort included 211 patients with SOT. At 8 weeks, patients treated with maribavir achieved a higher rate of CMV clearance in the blood than those who received investigator-assigned therapy (55.7% vs 23.9%).[64] The results were consistent across the transplant types. The time to CMV DNAemia clearance was earlier in patients who received maribavir than in those who received investigator-assigned therapy (22 days vs 27 days). Among patients with documented genotypic resistance (to one of the investigator-assigned therapies), CMV DNAemia clearance was significantly higher among those treated with maribavir (62.8% vs 20.3%).[64] Among patients with refractory CMV (but without documented genetic resistance mutations), viral clearance was higher with maribavir than with investigator-assigned therapy (43.8% vs 32.4%), but this difference was not statistically significant. Treatment response was influenced by the baseline viral load at the initiation of maribavir treatment; it was less effective in patients with a viral load > 50,000 IU/mL.[64] In particular, the response rates declined from 62% among those with a viral load <9100 IU/mL to 47% among those with a viral load >9100 IU/mL, 33% among those with a viral load >50,000 IU/mL, and 29% among those with a viral load >91,000 IU/mL. Many patients relapsed after discontinuation of therapy; recurrent CMV DNAemia after initial virologic clearance occurred in 50% of the patients who initially responded to maribavir treatment. Despite this, there was still a significantly higher proportion of patients who maintained CMV DNAemia clearance through week 16 if they received maribavir compared to investigator-assigned therapy (18.7% vs 10.3%).[64] The results of this trial led to US FDA approval of maribavir for the treatment of persons over 12 years of age with post-transplant CMV infection or disease refractory to treatment with ganciclovir, valganciclovir, cidofovir, or foscarnet, with or without genotypic resistance.

A retrospective review of a subgroup of patients who participated in the trial and received maribavir was performed to assess their clinical status at 52 weeks.[65] Of the 109 patients reviewed, 68 were SOT recipients. Of the 68 SOT recipients, 8 had graft complications, such as acute or chronic rejection. However, none of the patients experienced graft failure or loss. At 52 weeks, survival was 96%; only three patients died (4.4%).[65]

Step-Down Treatment of Refractory or Resistant CMV Infection

Because maribavir is available as an oral drug, it has been used as a step-down therapy for the treatment of ganciclovir-resistant CMV once the viral load is controlled by initial treatment with foscarnet.[36] This practice results in a reduced length of hospitalization, which is often prolonged by intravenous foscarnet administration.[36]

Preemptive Treatment of Non-Resistant CMV

In a phase 2 open-label clinical trial, maribavir (doses ranging from 400 mg to 1200 mg PO twice daily) was compared with valganciclovir for the preemptive treatment of CMV reactivation (viral load, 1000 to 100,000 DNA copies/mL) in 159 HSCT and SOT recipients.[66] Undetectable CMV DNA was observed within 6 weeks in 79% of patients treated with maribavir compared to 67% among those treated with valganciclovir. Two patients developed recurrence of CMV DNAemia within 6 weeks of maribavir treatment because of a virus that possessed the UL97 T409M mutation.[66] A greater percentage of patients discontinued maribavir owing to an adverse event (23% vs 12%); the most common adverse event was gastrointestinal symptoms.[66] Recently, maribavir was evaluated as a preemptive therapy for CMV reactivation in 547 allogeneic HSCT recipients;[67] viral eradication at the end of eight weeks of treatment was significantly lower with maribavir than with valganciclovir (69.6% vs 77.4%, respectively).[67] However, a significant difference was not evident at week 12 follow-up. Fewer patients treated with maribavir developed neutropenia (16.1%) than those treated with valganciclovir (52.9%).[67]

Additional Clinical Considerations

CMV-Specificity

Maribavir is highly specific to CMV and shows no activity against other herpes viruses. Thus, additional antiviral drugs with activity against herpes simplex viruses are required. It may have activity against EBV in vitro; however, clinical data to support this are not available.

Antiviral Antagonism

Because maribavir inhibits UL97 kinase, which is required for the activation of (val)ganciclovir, the co-administration of maribavir and ganciclovir is antagonistic and should be avoided.[52,68]

Central Nervous System (CNS) Penetration

Animal studies have demonstrated that maribavir has poor CNS penetration.[69] Therefore, patients with CMV CNS disease or retinitis were not included in the clinical trials.[64] Maribavir was not detected in the cerebrospinal fluid (CSF) of a heart or kidney recipient receiving maribavir and foscarnet for CMV disease. Although the plasma maribavir concentration was satisfactory, the maribavir concentration in the CSF (at three different time periods of testing) was below the lower limit of quantification.[70] Studies have suggested that maribavir may penetrate the blood-retinal barrier,[69] and some clinical improvements have been reported when used for CMV retinitis (when combined with reduction in immunosuppression).[71]

Drug Interactions

Maribavir is a substrate and weak inhibitor of CYP3A4 and P-glycoprotein that can lead to clinically significant drug interactions. In SOT recipients, one anticipated effect of maribavir is a higher level of calcineurin inhibitors (cyclosporine and tacrolimus) and mTOR inhibitors (sirolimus and everolimus). Higher levels of immunosuppressants have been reported in maribavir-treated patients than in those treated with standard antiviral drugs (9.0% vs 0.9%).[61,64] In a study of kidney recipients, maribavir increased the Cmax of tacrolimus by 38%, trough concentration by 57%, and tacrolimus AUC by 51%.[72] However, a recent study showed that tacrolimus trough concentrations increased by only 14%.[73] Frequent routine monitoring of immunosuppressed drug levels is recommended during and after maribavir administration.

Maribavir concentrations increase when used concomitantly with ketoconazole (a potent CYP3A4 inhibitor), although they are not affected by voriconazole.[74,75] Conversely, co-administration of maribavir with strong CYP3A4 inducers, such as rifampin and rifabutin, may result in markedly reduced maribavir concentrations (theoretically impairing efficacy and increasing the risk of resistance). Maribavir concentration was reduced by 61% with rifampin.[74] When co-administration with CYP3A4 inducer is unavoidable (such as when anticonvulsants are essential), the dose of maribavir should be upadjusted accordingly (600 mg twice daily with carbamazepine; 1200 mg twice daily with phenytoin or phenobarbital).

Adverse Reactions

Maribavir has a favorable safety profile. The most common adverse effect of maribavir is taste disturbance (dysgeusia), which is described as bitter, metallic, or altered taste. It was reported in 37.2%-46% of patients who received

maribavir.[61,64] Dysgeusia is mild and resolves spontaneously during treatment or at a median of seven days of treatment.[61,64] Other common adverse effects include nausea, diarrhea, vomiting, headache, rashes, and fatigue. However, the rates of nausea (21.4% vs 21.6%), vomiting (14.1% vs 16.4%), and diarrhea (18.8% vs 20.7%) were similar between the patients treated with maribavir and those who received investigator-assigned therapy.[64] No significant hematologic, hepatic, or renal toxicity was observed. Neutropenia was reported in 9.4% of maribavir-treated patients compared to 22.4% of patients who received investigator-assigned treatment; when compared to valganciclovir, the rates of neutropenia was significantly lower with maribavir (1.7% vs 25.0%). Acute kidney injury occurred less frequently in maribavir-treated patients than in those who received foscarnet (1.7% vs 19.1%).[64]

Cost Considerations

An exploratory analysis evaluated hospital admissions in patients who participated in a trial comparing maribavir and investigator-assigned treatments.[76] Patients who received maribavir showed a 34.8% reduction in hospitalization rate and a 53.8% reduction in length of hospital stay during the treatment phase.[76] This is likely due to the need for intravenous access to investigator-assigned treatment and the management of its adverse effects (such as electrolyte disturbances). However, this difference in health resource utilization was no longer observed during the follow-up phase.[76] In another modeling study, the mean healthcare resource utilization was 29%-64% lower when using maribavir compared to standard antiviral therapy for the treatment of refractory and resistant CMV.[77]

Maribavir Resistance

Mutations that confer resistance to maribavir have been mapped to UL97, in the vicinity of the ATP-binding domain. Mutations in UL27 confer low-level resistance.[78,79] Treatment-emergent resistance is observed during maribavir treatment.[80] In one report, the maribavir-resistant mutations UL97 T409M and H411Y emerged during rebound CMV DNAemia after an initial response to maribavir treatment.[81]

In a phase 2 clinical trial that evaluated maribavir as a preemptive treatment for CMV reactivation,[66] 25 of the 120 patients (20.8%) developed recurrent CMV DNAemia during maribavir treatment. Mutations in UL97 were documented in 13 of these 25 patients, including T409M and H411Y mutations.[66] In another genotypic analysis of patients who participated in phase 2 maribavir clinical trials (dose of 400–1200 mg twice daily), selection of CMV UL97 T409M, H411Y, and C480F was reported, which conferred resistance to maribavir.[82]

In a phase 3 clinical trial, post-treatment maribavir resistance mutations were detected in 60 patients (26%) who received maribavir.[83] Six UL97 mutations accounted for maribavir resistance; however, the most common were UL97 T409M, H411Y, and C480F, and combinations of two or more resistance mutations were observed. The initial selection of low-grade resistance mutations may lead to additional mutations that further increase resistance. Mutations were detected at a median of 56 days (range, 26–130 days) after the start of maribavir treatment.[83] The median viral load at the time of resistance development was 10,277 IU/mL.[83] Subsequent real-world reports have described the occurrence of CMV DNAemia relapse during maribavir treatment due to the development of UL97 H411F, T409M, and C480F, which confer moderate-to-high-level resistance to maribavir.[84]

UL97 mutations may confer cross-resistance between ganciclovir and maribavir, although this is not common because the major resistance mutations for the two drugs map to different regions in the UL97 genes.[82] However, UL97 F342Y and C480F have been reported to confer cross-resistance to ganciclovir and maribavir.[82] Notably, while UL97 C480F confers high-level maribavir resistance, it only confers low-grade ganciclovir resistance; (val)ganciclovir has been used to treat maribavir-resistant infection due to C480F mutation.

Discussion

The therapeutic armamentarium for the management of CMV in SOT recipients has expanded with the US FDA approval of letermovir for CMV prophylaxis in high-risk CMV D+/R- kidney recipients[12] and maribavir for the treatment of refractory and resistant CMV infection.[64] Both drugs offer significant improvement when compared to the standard anti-CMV therapies; letermovir was as efficacious for CMV prevention, whereas maribavir was even more effective for the treatment of refractory and resistant CMV infections. Both drugs have remarkably better safety profiles than standard

anti-CMV therapeutics, without the risk of neutropenia and leukopenia associated with (val) ganciclovir and renal toxicities associated with foscarnet and cidofovir. Moreover, they are orally bioavailable, which allows convenient outpatient treatment. However, both drugs have significant drug interaction potential; therefore, their use should be considered in the context of other essential medications such as cyclosporine and tacrolimus. Finally, both drugs are highly CMV-specific; thus, there is a need for additional antiviral drugs to prevent herpes simplex virus and other herpes viruses when clinically indicated.

Approval of letermovir for CMV prophylaxis in CMV D+/R − kidney recipients is important for several reasons. First, letermovir is highly effective, with efficacy for CMV prevention similar to that of valganciclovir; the rate of post-prophylaxis delayed onset CMV infection is not significantly different between the two drugs.[12] Second, the safety profile of letermovir is favorable and much better than valganciclovir.[12] Although gastrointestinal adverse effects are commonly observed, they are mild and do not lead to drug discontinuation. In contrast, myelosuppression associated with (val) ganciclovir is common and often leads to discontinuation of the drug, cessation of other essential drugs (such as trimethoprim-sulfamethoxazole for *Pneumocystis jirovecii* prevention or mycophenolate mofetil), or administration of granulocyte colony-stimulating factor. Occasionally, opportunistic infections related to severe ganciclovir-associated neutropenia can occur. Third, the concern for letermovir resistance (owing to the reported low genetic burden) may not be a significant issue when it is used as primary prophylaxis, even though there are cases of breakthrough infections.[12] There is no compelling evidence that resistance commonly emerges during primary letermovir prophylaxis (when t is initiated during periods without CMV replication). Therefore, screening patients for CMV DNAemia before the initiation of letermovir prophylaxis is important. Fourth, the preferential use of letermovir as primary prophylaxis may preserve the clinical utility of (val) ganciclovir for the treatment of CMV disease. Avoiding prolonged ganciclovir exposure during prophylaxis may reduce the potential of selecting UL97 and UL54 resistance mutations, thus preserving the clinical utility of ganciclovir when needed for the treatment of CMV disease. However, these benefits should be considered in the context of drug costs. Currently, letermovir is a much more expensive drug when compared to valganciclovir, and this factor should be considered in the decision on what drug to use for CMV prophylaxis. The conduct of health economic studies is encouraged to systematically assess the overall health resource utilization between letermovir and valganciclovir prophylaxis, including the outcomes of treating drug-resistant CMV infections.

The clinical benefits of letermovir after SOT have only been demonstrated in high-risk CMV D+/R − kidney recipients.[12] No controlled clinical trials have demonstrated the efficacy and safety of letermovir prophylaxis in CMV D+/R- non-kidney SOT recipients or CMV-seropositive SOT recipients. Although controlled clinical trials are desirable to establish this clinical use in these populations, none are currently being conducted. Therefore, the only clinical data were from retrospective studies reporting the off-label use of letermovir for primary prophylaxis in SOT patients who were intolerant to valganciclovir prophylaxis. Reporting real-world experiences is suggested to provide further evidence of the potential utility of off-label letermovir for prophylaxis. In this context, it is also evident from multiple retrospective reports, case series, and case reports that letermovir should not be used as first-line treatment for refractory and resistant CMV infections. The genetic barrier to the development of resistance is low, particularly when letermovir is administered during high-level viral replication. In these situations, maribavir should be considered as a potential first-line treatment if clinically appropriate.

Indeed, recent approval of maribavir for the treatment of refractory and resistant CMV infections is important for several reasons. First, the efficacy of maribavir is superior to that of standard antiviral therapies, such as ganciclovir, foscarnet, and cidofovir, for the treatment of refractory and resistant CMV infections.[64] Second, it has a favorable and better safety profile, with a lower risk of neutropenia than ganciclovir and a lower risk of renal toxicity than foscarnet.[64] Third, it is given orally which allows for the convenience of outpatient management; in contrast, parenteral ganciclovir and foscarnet require frequent intravenous infusions daily which may require hospitalizations for some patients. Accordingly, oral maribavir treatment has significantly reduced the utilization of healthcare resources.

However, maribavir may not be the preferred drug for every SOT patient with refractory or resistant CMV.[85] First, maribavir is much less effective when the viral load is high (>9,100 IU/mL).[12] In this situation, foscarnet (if susceptible) should still be the first-line treatment for ganciclovir-resistant CMV infection.[85] Second, maribavir has limited penetration into the CNS, which prevents its use for the treatment of refractory or resistant CMV infections with retinal and CNS

involvement. Third, treatment-emergent resistance mutations commonly occur in the clinical setting.[83] Notably, the clinical scenario in which maribavir is indicated involves a highly selected patient population that is generally at a high risk of developing resistance, probably as a result of over-immunosuppression. Therefore, it is important to complement antiviral therapeutics with intentional efforts to minimize pharmacological immunosuppression. In this regard, providers should acknowledge that maribavir may further augment pharmacological immunosuppression because it inherently increases the levels of calcineurin and mTOR inhibitors. Therefore, it is critical that the doses of calcineurin inhibitors and mTOR inhibitors be proactively down-adjusted when maribavir is used, with routine monitoring to titrate immunosuppression to the lowest possible serum concentrations.

Drug–drug interactions are anticipated when maribavir and letermovir are used in the SOT population. Almost all patients with SOT are treated with calcineurin inhibitors or mTOR inhibitors, and many others are also receiving medications to treat mycoses (azoles), mycobacterial diseases (rifamycins), hypercholesterolemia (HMG-CoA reductase inhibitors), and seizures (phenytoin). Meticulous evaluation of all prescribed and over-the-counter medications is needed, and partnerships with transplant pharmacists are highly recommended for medication reconciliation and adjustments to allow the safe use of these drugs in our SOT populations.

Finally, the distinct mechanisms of action of letermovir and maribavir, which are different from those of ganciclovir, foscarnet, and cidofovir, have raised the potential for the combination treatment of severe and resistant CMV infections. However, resistance to maribavir and letermovir is predicted to occur as their clinical use becomes more widespread, whether they are used as a single therapy or as part of a combination therapy. Early clinical experience with these drugs has already demonstrated the common occurrence of letermovir resistance when used during active CMV replication and the common occurrence of maribavir resistance in SOT patients with refractory and resistant CMV infection. The major risk factor for the development of antiviral drug resistance is markedly impaired or a lack of CMV-specific immunity, and this is also predicted to be the factor predisposing for the development of resistance to letermovir and maribavir.[6] Accordingly, a reduction in pharmacological immunosuppression should be promoted as a critical component of the management of these patients.[2]

In conclusion, the approval of letermovir and maribavir for clinical use in SOT recipients has expanded the therapeutic arsenal for CMV management in this vulnerable population. Their availability has afforded different options for the safe management of CMV, based on the patient's clinical situation. The therapeutic lifespan of letermovir and maribavir in the clinical setting will be better preserved when combined with optimization of immunosuppression to allow for CMV-specific immunity, which is needed for durable control of CMV after SOT.[85] Indeed, there is no better anti-CMV therapy than a functioning cell-mediated immunity.

Disclosure

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