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Review

Maribavir for Management of Cytomegalovirus in Lung Transplant Recipients: A Case Series and Literature Review

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Abstract

Lung transplant recipients represent a high-risk group for cytomegalovirus (CMV) infection and disease, even among solid organ transplant (SOT) recipients, due to multiple factors. Additionally, CMV has significant consequences in this group including pneumonitis, acute rejection, and chronic lung allograft dysfunction. For the past two plus decades, treatment of CMV in SOT recipients has been limited to off-label use of 4 antiviral medications associated with significant toxicities including myelosuppression and nephrotoxicity. In November 2021, maribavir became the first antiviral agent approved by the United States Food and Drug Administration for the treatment of resistant or refractory CMV in transplant recipients. Herein, we present two reports of the successful use of maribavir at our center along with a review the evidence for maribavir for CMV management in lung transplant recipients.

Keywords
Lung transplantation; maribavir; cytomegalovirus; solid organ transplantation; drug resistance

1. Introduction

Cytomegalovirus (CMV) infection remains one of the most significant viral complications in solid organ transplant. Among this group, lung transplant recipients (LTR) have an increased risk of CMV infection and disease due to increased transmission of CMV-infected cells in the allograft, long term requirement of a higher degree of immunosuppression, and a pro-inflammatory environment created by rejection episodes [1]. CMV has multiple direct and indirect consequences in LTR. Namely, pneumonitis, acute rejection, and chronic lung allograft dysfunction which is a leading cause of morbidity and mortality.

Prophylactic antiviral therapy for CMV is continued for longer durations in LTR compared with other organ groups, typically extending to one-year post-transplant. Despite this approach, early post-transplant reactivation, late-onset infections, and the development of drug-resistant strains continue to pose significant challenges.

Conventional antiviral therapies including ganciclovir, valganciclovir, and foscarnet have been the cornerstone of CMV management. However, these agents are limited by toxicity including myelosuppression and nephrotoxicity as well as drug-resistance.

Maribavir, a novel benzimidazole riboside antiviral approved by the United States (US) FDA in 2021, is a promising agent for management of CMV in this population. It works differently from other available antivirals that inhibit DNA polymerase (ganciclovir, valganciclovir, foscarnet) or the newer CMV DNA terminase complex inhibitor (letermovir) [2]. Maribavir targets UL97 protein kinase which preserves its activity in cases of resistance related to DNA polymerase mutations. Additionally, maribavir does not carry risk of toxicities associated with other available agents including myelosuppression (ganciclovir, valganciclovir) or nephrotoxicity (foscarnet) [3], adverse effects that LTR are already vulnerable to with standard immunosuppressive regimens.

We present two clinical cases from our center demonstrating successful treatment with maribavir and review the current literature on its use in LTR. The purpose is to assess the utility of maribavir for prevention and treatment of CMV in LTR. We will review available clinical trial data, case series, and case reports. Additionally, we will describe the current role of maribavir in LTR and future directions.

1.1 Ethics Statement

The UC San Diego Institutional Review Board deemed that case reports do not fall under human subjects research and therefore do not require review and approval.

2. Case Series

We describe two LTR at our center who have been treated with maribavir. The CMV viral load and antiviral therapy for both cases are presented in Figure 1.

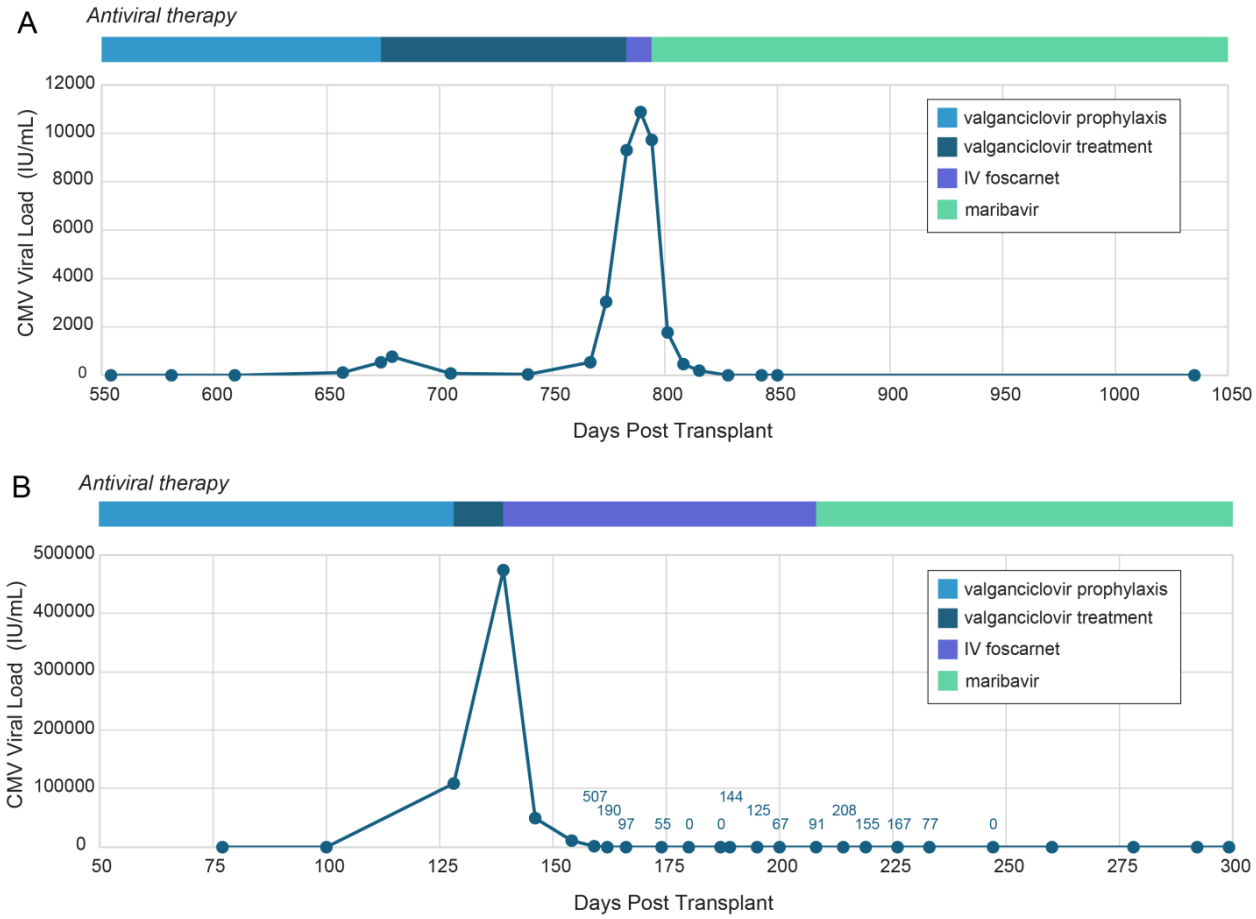

Figure 1 These charts illustrate the virologic progression and antiviral therapy for the two clinical cases from our center. For Case B, data labels are displayed for viral load measurements beyond post-operative day 160, except for undetectable values recorded after post-transplant day 250. IU = international units; IV = intravenous.

Case A: A 69-year-old male underwent bilateral lung transplantation due to idiopathic pulmonary fibrosis (IPF). CMV serology status D+/R-. Post-operatively, the patient was initiated on valganciclovir 900 mg once daily for CMV prophylaxis. Due to impaired renal function, the valganciclovir dose was reduced to 450 mg orally once daily, in accordance with the recommended dosing for prophylaxis per package insert [4].

A CMV T-cell immunity assay (CMV insight™ Eurofins Viracor Labs) was conducted at 17 months post-transplant, revealing an absence of immunity to CMV; (CD4+ CMV interferon-gamma cells of 0.01% and CD8+ CMV interferon-gamma cells of <0.01%, which falls in the high-risk category) therefore, the patient continued renally adjusted valganciclovir for CMV prophylaxis. Five months later, the patient developed CMV viremia, as evidenced by follow-up laboratory tests. Consequently, the valganciclovir was increased to a treatment dose of 900 mg orally twice daily, and maintenance immunosuppression was lowered. Despite the increased valganciclovir dosage and lower degree of immunosuppression, the CMV viral load continued to rise, accompanied by a decline in the white blood cell (WBC) count.

Due to worsening CMV viremia and 3-week symptoms of blurred vision and loose stools, the patient was admitted to the hospital. At the time of admission, the CMV PCR revealed a viral load of 9,320 IU/mL. During the hospitalization, valganciclovir was replaced by intravenous (IV) foscarnet,

and a CMV drug resistance panel was ordered which identified two UL97 mutations (C592G and A594V), indicative of ganciclovir resistance. Due to intolerance to IV foscarnet, the patient was discharged on maribavir 400 mg orally twice daily. The patient has been maintained on maribavir for secondary prophylaxis without dose adjustment. The patient has had undetectable CMV PCR beginning one month following the initiation of maribavir therapy and is currently in stable condition without any CMV reactivation or further complications reported.

Case B: A 56-year-old male underwent a bilateral sequential lung transplant for IPF. CMV serology status D+/R-. Post-operatively, the patient was initiated on valganciclovir at a prophylaxis dose of 900 mg by mouth once daily.

At 4 months post-transplant, the CMV viral load increased to 108,000 IU/mL. At that time, the patient was asymptomatic. The valganciclovir dose was increased to 900 mg by mouth twice daily, and the maintenance immunosuppression was lowered. Ten days later, the patient developed fevers, chills, and weakness and was admitted to the hospital. The patient was neutropenic on admission to the hospital and chest CT was negative for pneumonitis. The CMV viral load had increased to 474,000 IU/mL. The patient was started on IV foscarnet which was continued on hospital discharge. The CMV resistance panel identified a UL97 mutation del599 indicating ganciclovir resistance.

After 8 weeks on IV foscarnet, the patient was transitioned to maribavir 400 mg by mouth twice daily due to foscarnet intolerance and persistent low-level CMV viremia. The viral load at the time of starting maribavir was 208 IU/mL. He continued maribavir at the same dosage for three months prior to transferring care to another transplant center. Notably, the patient had an undetectable CMV PCR one month following the initiation of maribavir therapy.

3. Literature Review Methods

We conducted a search of multiple electronic databases including PubMed, Embase, Cochrane, Web of Science, and Google Scholar using the search terms maribavir, cytomegalovirus, solid organ transplantation, and lung transplantation. We included papers published between January 2020 and October 2024. Prospective, randomized studies, retrospective studies, case series, and case reports were considered for inclusion. Reports available only in abstract form and reviews were excluded. References of included publications were also searched.

Criteria for reference selection included study population (lung transplant recipients), treatment regimens (maribavir alone, in combination with other antivirals, or compared with ganciclovir, valganciclovir, foscarnet), and outcome measures (virologic response, clinical success, resistance patterns, safety, cost).

4. Maribavir

Maribavir is a competitive inhibitor of UL97, a protein kinase encoded by human CMV that is vital for phosphorylation of downstream proteins necessary for CMV to replicate. It does not require intracellular activation for its antiviral activity. Maribavir has been shown in vitro to have activity against Epstein-Barr Virus but has no activity against Herpes Simplex Virus [2].

Maribavir is supplied as a 200 mg oral tablet with recommended dosing of 400 mg by mouth twice daily; higher dosing is recommended with certain CYP enzyme inducers as it is metabolized in the liver by CYP3A4 [3].

It is an inhibitor of p-glycoprotein and breast cancer resistance protein and a weak inhibitor of CYP3A4. Therefore, concentrations of immunosuppressants including tacrolimus, cyclosporine, sirolimus, and everolimus among other medications may be increased [3]. The clinical impact of this interaction has not been proven; however, one small study showed a median increase of 14% in tacrolimus concentrations with initiation of maribavir [5]. Interactions with CYP3A4 inhibitors including azole antifungals are not considered clinically significant [3].

Maribavir has been shown to penetrate the central nervous system (CNS) poorly. Therefore, it is not recommended for treatment of CMV meningitis or retinitis [6, 7].

As UL97 kinase (inhibited by maribavir) is required for activation of ganciclovir and its prodrug valganciclovir, these agents should not be used in combination with maribavir due to diminished antiviral activity of ganciclovir/valganciclovir [2, 3].

5. Maribavir for CMV Prophylaxis

Only one study evaluated the efficacy of low dose maribavir 100 mg by mouth twice daily for prophylaxis of CMV in SOT, specifically CMV serological high risk (D+/R-) liver transplant recipients. Three-hundred and three patients were randomized to receive oral ganciclovir or maribavir and received at least one dose of study drug. Maribavir did not demonstrate non-inferiority to ganciclovir. At 6 month follow-up, there was no difference in CMV disease between groups. However, CMV disease was significantly lower in the ganciclovir group within 100 days of transplant (4% vs. 33%, $p < 0.0001$) [8].

Although the established effective dose of maribavir for treatment of CMV was later determined to be 400 mg twice daily, no additional studies have been completed to date with higher dosing for prophylaxis. Therefore, the agent is not currently recommended for primary prophylaxis of CMV in SOT recipients.

6. Maribavir for Treatment of CMV Infection and Disease in Lung Transplant

A phase 2, randomized, double-blind study of maribavir for treatment of refractory or resistant CMV in hematopoietic stem cell transplant (HSCT) and SOT recipients randomized patients to 3 dosing arms of maribavir: 400 mg, 800 mg, or 1200 mg twice daily for up to 24 weeks of therapy. Twenty patients (16.7%) were lung transplant recipients. Sixty-seven percent of the entire intention-to-treat cohort (n = 120) achieved the primary endpoint of CMV DNA < 200 copies/mL by week 6, and this rate of viral clearance was similar across doses. Notably, 30/86 (35%) patients who achieved undetectable CMV DNA on therapy subsequently had recurrent CMV viremia (25/30 while still on maribavir). Fifty-two percent (13/25) of patients with recurrent viremia while on maribavir developed UL97 mutations conferring resistance to the drug with cases in all 3 dosing arms. The most common adverse effects to maribavir were dysgeusia (65%), nausea (34%), and vomiting (29%) [9].

Given similar efficacy outcomes among the 3 dosing arms in the phase 2 trial, the phase 3, randomized, active-control SOLSTICE trial was conducted using a standard maribavir treatment dose of 400 mg twice daily at a fixed duration of 8 weeks compared with investigator-assigned therapy (IAT). Again, the population was comprised of HSCT and SOT recipients with refractory or resistant CMV. The study population included lung transplant recipients in both groups: maribavir 28% (40/142) and IAT 32% (22/69). IAT included ganciclovir/valganciclovir (48%), foscarnet (41%),

cidofovir (5%), or combination therapy (6%). Considering the whole cohort, more patients in the maribavir group achieved CMV DNA < 137 IU/mL (55.7% vs 23.9%, p < 0.001) at week 8. In this phase 3 trial, CMV recurrence after having a viral load under the lower-limit of quantification (<137 IU/mL) occurred 18% (33/184) in the maribavir group and 12% (8/65) in the IAT group. Viral response rate was lower in patients with higher baseline CMV DNA: baseline <9,100 IU/mL (62.1% maribavir vs 24.7% IAT), ≥9,100 IU/mL (43.9% maribavir vs 21.9% IAT). Again, dysgeusia was the most common adverse effect to maribavir (37.2% vs 3.4%), but nausea, vomiting, and diarrhea were similar. On the other hand, neutropenia was the most common adverse effect among IAT patients (9.4% vs 22.4%) [10].

A retrospective review of the maribavir arm of the SOLSTICE trial was conducted with up to 1 year of follow-up. Sixty-eight of the 109 total maribavir subjects were SOT recipients including 7 (10.3%) lung transplant recipients. The 12-month survival was 96% in the SOT group. There were no graft failures or retransplants. Eight patients reportedly had graft complications including acute rejection, chronic rejection, or other complications and of these, 25% (2/8) occurred in LTR [11]. A subgroup analysis of the phase 3 SOLSTICE trial was also published looking at just the SOT subgroup which demonstrated consistent efficacy in LTR as with other SOT recipients. CMV viremia clearance at week 8 was higher for maribavir (compared with IAT) in each organ group: kidney (59.5%, 34.4%), lung (47.5%, 13.6%), and heart (42.9%, 11.1%; p = 0.063), and this was statistically significant for kidney (p = 0.006) and lung (p < 0.001) [12].

A number of case reports have been published to date showcasing the use of maribavir in practice. Importantly, several of these reports describe maribavir failures with or without evidence of maribavir-resistance mutations. Details on the available case reports in LTR can be found in Table 1.

Table 1 Case Reports of Maribavir in Lung Transplant Recipients.

Study	Patient description	Summary of findings	CMV response	Notes
Fung 2022 [13]	66 yo LTR (D+/R-) with CMV viremia while on VGCV prophylaxis (UL97 C603 mutation; GCV resistance)	Treated with MBV ×8 weeks with undetectable viral load Recurrence of CMV 2 weeks later; MBV restarted and achieved detectable but non-quantifiable viral load. Then had rebound CMV viremia when treated for ACR with pulse steroids. Found to have UL97 H411Y mutation (MBV resistance)	Initial response, recurrence, failure in the setting of augmented IMS; treated with FOS	
Sabatino 2022 [5], Sabatino 2023 [14]	13 SOT recipients, 4/13 LTR 4/13 cases of breakthrough CMV viremia on MBV; 2/4 patients with breakthrough were LTR			2/4 LTR in the original case series had successful CMV clearance with MBV and did not have viral breakthrough or recurrence The other 2/4 breakthrough cases were kidney transplant recipients
	(1) 59 yo F (D+/R-) bilateral LTR with CMV viremia 2 weeks after completing 12 months of VGCV prophylaxis	(1) Initial response to VGCV with viral rebound and pneumonitis, found to have GCV resistance (UL97 mutation H520Q) subsequently treated with FOS until resolution of symptoms and detectable but non-quantifiable viral load then transitioned to MBV secondary prophylaxis	(1) Viral load rebounded day 57 of MBV, found to have MBV resistance (UL97 mutation T409M) but absence of original UL97 mutation so treated with IV GCV	
	(2) 65 yo M (D+/R-) single LTR with breakthrough viremia on treatment dose VGCV	(2) Found to have resistance to GCV and cidofovir (UL54 mutation DEL524) so changed to MBV	(2) Initial viral clearance day 23, rebounded day 37 with associated diarrhea and fatigue. Found to have new resistance mutations (UL97 C603W and	

			H411Y) conferring resistance to GCV, cidofovir, and MBV so treated with FOS	
Horsten 2024 [15]	3 cases of SOT recipients from the same donor; 1 received lungs, another was recipient of a kidney but with history of prior lung transplant			3rd recipient from same donor (CMV with GCV resistance mutation), no history of lung transplant; ultimately explanted due to refractory rejection with discontinuation of IMS
	(1) 55 yo F bilateral LTR (D+/R-), completed VGCV prophylaxis day 180, CMV viremia day 232. Treated twice with GCV/VGCV	(1) Found to have PK-L595S substitution (GCV resistance), treated with MBV ×8 weeks day 324. Day 394, found to have MBV resistance (PK-T409M substitution)	(1) Initial response to treatment not reported, ultimately treated with FOS and CMV immunoglobulin after discovery of MBV resistance	
	(2) 57 yo kidney transplant recipient (D+/R-) with a history of lung transplantation (D-/R-)	(2) Day 297, acute CMV infection/disease with hepatitis and pneumonitis. Initially treated with GCV then transitioned to MBV	(2) No CMV response reported, patient ultimately died from infectious lung disease	
Kroll 2024 [16]	59 yo M bilateral LTR (D+/R-); CMV colitis and pneumonitis refractory to GCV, treatment-prohibitive nephrotoxicity with FOS, no resistance mutations, on ECMO	Changed to MBV ×2 weeks	Subsequent rise in CMV viral load after switching to MBV so changed back to FOS, then GCV	Suspect ECMO circuit sequestration leading to MBV treatment failure. No levels, based on pharmacokinetic characteristics of high lipophilicity (logP 2.2) and protein binding (98%) which are known to increase risk of circuit sequestration. For comparison (logP, protein binding): GCV (-2.5, 1-2%) VGCV (-1.5, 1-2%) FOS (-2, 14-17%)

Tsui 2024 [17]	72 yo M LTR (D+/R+) with persistent CMV viremia on VGC (UL97 C603W mutation) found to have bilateral CMV retinitis	Received intravitreal FOS ×2 to the right eye, no intravitreal therapy to the left eye, initiated MBV therapy 8 days after initial ophthalmology consultation	CMV viral load undetectable beginning 4 weeks after MBV initiation, improvement in retinitis lesions in both eyes Qualitative CMV PCR testing from right aqueous humor still positive at 71 day follow up, no quantitative testing available, retinitis clinically regressed	The authors concluded that the patient had successful response to systemic MBV therapy for bilateral retinitis as the left eye (without intravitreal injections) also improved. Importantly, MBV has been shown to have poor CNS penetration in animal studies [6] and in a single human case report [18]. Therefore, we caution against using MBV monotherapy in cases of CNS disease.
Ni 2024 [19]	15 SOT recipients treated with MBV for refractory/resistant CMV; 4/15 were LTR (All patients D+/R-) 2 cases of viremia, 2 cases with disease (probable pneumonitis). All LTR had resistance mutations: UL97 (A594V, C603W, L595F) and UL54 (C539R, S290R)	3/4 patients initially treated with alternatives including GCV, VGCV, FOS, CMV-Ig 1 patient received MBV as first therapy	2 patients had successful clearance of CMV viremia after 56-104 days of treatment 1 patient had relapse of CMV 13 days after a 77-day course of MBV followed by successful re-treatment with 105 days of MBV 1 patient had partial response with viral load 391 IU/mL after 59 days of MBV which was stopped early due to MBV availability; subsequently treated with high-dose LET and FOS	In the overall cohort (n = 15), those with treatment failure or early recurrence had higher median CMV viral load at start of MBV therapy (n = 7) (41,001 [IQR 31,750–48,144] IU/mL) compared to patients that achieved and maintained CMV clearance (n = 6) (1,434 [IQR 1,145–3,598] IU/mL).

CMV = cytomegalovirus; CMV-Ig = CMV-specific immunoglobulin; CNS = central nervous system; FOS = foscarnet; GCV = ganciclovir; IMS = immunosuppression; LET = letermovir; LTR = lung transplant recipients; MBV = maribavir; SOT = solid organ transplant; VGCV = valganciclovir.

7. Maribavir in Resistant Strains of CMV

Maribavir has a unique mechanism of action compared to other available CMV antivirals which contributes to its efficacy specifically against resistant CMV strains. Ganciclovir, valganciclovir, and foscarnet exert their effects by inhibiting CMV viral polymerase; whereas maribavir selectively inhibits the UL97 protein kinase. Through inhibition of UL97, maribavir disrupts several key viral processes including preventing phosphorylation of pUL44, an essential cofactor for UL54 CMV DNA polymerase (hindering viral DNA synthesis), inhibiting viral capsid nuclear egress (preventing viral replication and spread), and affecting phosphorylation of host proteins (further impairing viral replication) [20].

In clinical testing, mutations in genes encoding for UL97, UL54, UL27, and UL56 have been associated with varying antiviral resistance owing to differences in drug activation in vivo and mechanism of action. Maribavir targets UL97 but uses a different binding site than ganciclovir. Ganciclovir requires UL97 activity for initial phosphorylation, followed by additional phosphorylation by cellular kinases to exert its anti-CMV activity. Therefore, mutations in UL97 confer resistance to ganciclovir and/or maribavir. Importantly, maribavir retains its efficacy in several UL97 ganciclovir-resistance mutations owing to its alternative binding site [20]. Maribavir efficacy is not impacted by mutations in the targets of other CMV antivirals: UL54 (ganciclovir, foscarnet, cidofovir resistance) or UL56 (letermovir resistance, used only for prophylaxis; additionally impacted by UL51 and UL89) [21]. UL27 uniquely confers maribavir resistance as it can allow CMV to replicate in the absence of UL97 activity [22].

8. Maribavir Resistance

Management of ganciclovir-resistant CMV poses a challenge for the transplant community. There have been a number of identified risk factors for development of ganciclovir-resistant CMV including high risk serostatus (D+/R-), longer duration of ganciclovir exposure, high-level immunosuppression, receipt of T-cell depleting induction agents, and receipt of lung allograft in comparison to other transplant types [23-25]. In addition, peak CMV viral load and duration of CMV viremia have been shown to contribute to resistance risk [26]. Current guidelines recommend testing for genotypic resistance in the following scenarios: CMV viral load is unchanged or increased or CMV disease is not improved after two weeks of appropriately dosed antiviral therapy, and after at least 6 weeks of ganciclovir exposure [27].

Although maribavir is an attractive option for cases of ganciclovir-resistant CMV due to its previously discussed advantages over other agents, maribavir-resistance is also seen. Resistance to maribavir is primarily induced by mutations in pUL97 and less commonly UL27 [28, 29].

An analysis of the Phase 3 SOLSTICE trial described drug resistance mutations (DRM) from samples collected in the study population. Genotypic testing was completed at baseline and with any evidence of sub-optimal response or discontinuation of study-drug. At baseline testing, UL97 and UL54 DRMs associated with ganciclovir-resistance were present in 56% patients in the maribavir group and 68% in the IAT group. This is in comparison with baseline maribavir-resistance mutations which were minimal: 1 UL27 mutation in the maribavir group and 3 maribavir-resistance UL97 mutations in the IAT group. After treatment, 26% (60/234) of patients in the maribavir group had maribavir drug-resistance mutations first detected at a median of 56 days (26-130), and 10%

(24/234) had detected UL97 F342Y and C480F mutations conferring resistance to both maribavir and IAT. In comparison, 12% (11/94) IAT patients had detectable IAT-DRM after treatment and no maribavir-resistance mutations. There were another 22 patients in the cross-over group who received maribavir-rescue after IAT-failure. Of these, 14% (3/22) developed IAT-DRM before maribavir treatment, 9% (2/22) developed IAT-DRM after maribavir, and 23% (5/22) developed maribavir-DRM only after receiving maribavir treatment. Six UL97 mutations contributed to cases of treatment-emergent maribavir resistance: T409M, H411Y, and C480F amino acid substitutions were most common (moderate-high grade resistance) followed by combinations of DRMs (H411Y and T409M; H411Y and C480F) [29].

Genotyping for drug-resistance mutations is imperative in the setting of non-response or viral rebound. Since there is overlap in drug-resistance with certain mutations, access to up-to-date information to guide clinical decision making is key. In an effort to expand community access to a comprehensive collection of known gene mutations related to antiviral resistance, an international group compiled the open access Comprehensive Herpesviruses Antiviral Resistance Mutation Database (CHARMD), a useful tool in managing resistant CMV [21, 30].

9. Cost Assessment

Treatment of resistant CMV has been shown to have a large economic burden with increased costs due to prolonged hospitalization, high-cost anti-viral therapy, and increased rates of complications in terms of patient and graft survival.

Maribavir has been shown to reduce the hospital length of stay (LOS) and the duration of IV foscarnet by providing oral step-down therapy. A case series of lung and kidney transplant recipients demonstrated that patients converted from IV foscarnet to oral step-down therapy with letermovir or maribavir reduced hospital LOS (16 ± 3 vs 33 ± 21 days; $p < 0.001$) and the duration of IV foscarnet (7 ± 4 vs 37 ± 25 days, $p = 0.017$) [31]. The reduction in hospital LOS was estimated to have saved $46,053 per patient in this study. The authors note that letermovir, although active for CMV with the UL97 mutation, has the best efficacy with viral loads <1000 IU/mL, compared to maribavir which can be used with higher viral loads.

In the US, the wholesale acquisition cost of maribavir is $222 per 200 mg tablet, resulting in a daily treatment cost of $888 for a 400 mg dose administered orally twice daily. Although this therapy is costly, the estimated daily cost is lower than that of intravenous foscarnet, which is approximately $1,204 per day [31].

Post-hoc analysis of the data from the SOLTICE trial have been published investigating the healthcare related costs and cost-effectiveness of maribavir. One such study developed an economic model to estimate health care resource utilization (HCRU) based on SOLSTICE trial data. This analysis showed mean per-patient-per-year HCRU was 29-64% lower for those patients that received maribavir versus standard of care treatment [32]. Another study performed a cost-effectiveness analysis of maribavir versus IAT from a US payer perspective. Results from this analysis showed maribavir treatment to be lower in total costs ($139,751 vs $147,949) and more effective as measured by greater total quality-adjusted life years (QALYs) per patient (6.04 vs 5.83 years). The greater QALYs with maribavir compared to IAT was due to more time spent without CMV [33].

10. Discussion

Maribavir is the first oral antiviral agent for treatment of CMV approved by the US FDA since valganciclovir in 2001. Given its novel mechanism of action, it retains efficacy in cases of CMV that are resistant to other antivirals or refractory to prior treatment. It is orally administered, can be crushed, has minimal clinically significant drug interactions, and lacks serious toxicities. Maribavir is not plagued by the significant neutropenia and thrombocytopenia associated with ganciclovir and valganciclovir, the nephrotoxicity of foscarnet and cidofovir, or the need for intravenous administration (ganciclovir, foscarnet).

Still, maribavir has not replaced the first line agents ganciclovir and valganciclovir due to several barriers limiting its widespread use. Namely, higher medication cost, limited indication, clinician comfort, and lack of long-term data in lung transplant recipients. Maribavir cost per day is about 4 times higher than generic valganciclovir tablets [34]. Although this cost may be offset by differences in efficacy and safety, it may preclude use due to insurance coverage restrictions or budget constraints. It is currently labeled for use in resistant or refractory CMV which limits access in cases of drug-toxicity or intolerance with other agents, non-resistant CMV, or for secondary prophylaxis. Potential strategies to overcome these barriers include ongoing research in lung transplant recipients, provider education, and broader incorporation into treatment guidelines. Until acquisition cost declines, providers should assist patients in exploring available drug-assistance programs.

11. Conclusion

Maribavir has been shown to be both effective and safe in lung transplant recipients, a high-risk group for CMV infection and disease, difficult to treat CMV, and drug toxicities/intolerabilities. In addition to reviewing the current body of evidence for the use of maribavir in LTR we have added our center's current clinical experience with the medication presented as a case series. In current practice, maribavir is reserved for cases of resistant or refractory CMV. Increased utilization for treatment and viability for prophylaxis of CMV in lung transplant recipients remain to be explored.

Abbreviations

CMV	cytomegalovirus
CMV-Ig	CMV-specific immunoglobulin
CNS	central nervous system
DRM	drug resistance mutation
FOS	foscarnet
GCV	ganciclovir
HCRU	health care resource utilization
HSCT	hematopoietic stem cell transplant
IAT	investigator assigned therapy
IMS	immunosuppression
IPF	idiopathic pulmonary fibrosis
IV	intravenous
LET	letermovir

LOS	length of stay
LTR	lung transplant recipients
MBV	maribavir
QALYs	quality-adjusted life years
SOT	solid organ transplant
US	United States
VGCV	valganciclovir
WBC	white blood cell

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Author Contributions

JMK (Conceptualization, Data curation, Methodology, Project administration, Writing – original draft, Writing – review & editing), KA (Conceptualization, Writing – review & editing), AF (Conceptualization, Data curation, Methodology, Writing – original draft, Writing – review & editing).

Competing Interests

The authors have declared that no competing interests exist.

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