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PERSPECTIVE

New Perspectives on Antimicrobial Agents: Maribavir

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ABSTRACT Maribavir was approved by the U.S. Food and Drug Administration in November 2021 for the treatment of adult and pediatric patients with post-transplant cytomegalovirus (CMV) infection/disease that is refractory to treatment (with or without genotypic resistance) with ganciclovir, valganciclovir, cidofovir, or foscarnet. Maribavir is an oral benzimidazole riboside with potent and selective multimodal anti-CMV activity. It utilizes a novel mechanism of action which confers activity against CMV strains that are resistant to traditional anti-CMV agents, and also offers a more favorable safety profile relative to the dose-limiting side effects of previously available therapies. Maribavir was initially studied as an agent for CMV prophylaxis in solid organ and hematopoietic stem cell recipients, but initial phase III trials failed to meet clinical efficacy endpoints. It has been more recently studied as a therapeutic agent at higher doses for refractory-resistant (R-R) CMV infections with favorable outcomes. After an overview of maribavir's chemistry and clinical pharmacology, this review will summarize clinical efficacy, safety, tolerability, and resistance data associated with maribavir therapy.

KEYWORDS CMV, hematopoietic stem cell transplant, maribavir, solid organ transplant

Cytomegalovirus (CMV) is a common and serious complication in recipients of solid organ and hematopoietic stem cell transplantation (1, 2), causing increased morbidity and mortality (3–5) with serious complications, including loss of the transplanted organ, graft failure, and death (6, 7). Traditional anti-CMV therapies, including ganciclovir, valganciclovir, foscarnet, and cidofovir are limited by suboptimal efficacy (8, 9), and dose-limiting toxicities such as bone marrow suppression (leukopenia, thrombocytopenia), nephrotoxicity, and electrolyte disturbances, respectively (9–13). Additionally, the development of drug-resistant CMV, which has been described in up to 14% of transplant recipients (14–17), is associated with adverse outcomes (8, 18–21), thus conferring the need for development of alternate therapies.

Maribavir (formerly 1263W94) received U.S. FDA approval in November 2021 for the treatment of adult and pediatric patients (12 years of age or older, weighing at least 35 kg) with post-transplant CMV infection/disease that is refractory to treatment (with or without genotypic resistance) with ganciclovir, valganciclovir, cidofovir, or foscarnet (22). Maribavir is an orally bioavailable benzimidazole riboside with potent and selective multimodal anti-CMV activity (23–27). Unlike traditional anti-CMV agents which inhibit CMV DNA polymerase, maribavir inhibits protein kinase UL97 and its natural substrates, thus inhibiting CMV DNA replication, encapsidation, and nuclear egress (23, 24, 26, 27). This alternative mechanism confers *in vivo* and *in vitro* activity against CMV strains which are resistant to the aforementioned anti-CMV agents, including ganciclovir, valganciclovir, cidofovir, and foscarnet (23, 24, 28). Maribavir also offers a comparatively favorable side effect profile relative to the dose-limiting side effects of previously available anti-CMV therapies (myelosuppression with ganciclovir, and nephrotoxicity with cidofovir and foscarnet) (29).

After an overview of maribavir chemistry and pharmacology, pharmacokinetics, pharmacodynamics, drug-drug interactions, and mechanisms of resistance, this review will summarize clinical efficacy, safety, and resistance data associated with maribavir therapy. It will conclude with a discussion of future directions in the role of maribavir

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in the clinical management of refractory-resistance (R-R) CMV infections in transplant recipients.

CHEMISTRY AND PHARMACOLOGY

Chemistry and mechanism of action. Maribavir [formerly 1263W94, 5,6-dichloro-2-(isopropylamino)-1,β-L-ribofuranosyl-1-H-benzimidazole] competitively inhibits viral protein kinase UL97 (23). This inhibits phosphorylation of several downstream viral proteins, including UL44, thus inhibiting CMV DNA replication (25, 27, 30, 31), and phosphorylation of the nuclear lamina component lamin A/C, thus inhibiting viral nuclear egress, a process usually mediated by host Cdc2/Cyclin-dependent kinase 1 (CDK1) during mitosis in uninfected host cells (26).

***In vitro* antiviral and combination antiviral activity.** *In vitro* studies have demonstrated maribavir's potent and selective anti-CMV activity. *In vitro*, maribavir is inhibitory for CMV and Epstein-Barr virus, but has no activity against herpex simplex virus 1 (HSV-1), HSV-2, varicella-zoster virus, human herpesvirus 6 (HHV-6), or HHV-8 (24, 32). The mean effective concentration required for 50% inhibition of CMV viral replication in cell cultures (EC_{50}) is reported as 1 to 5 μM, compared to 6 μM for ganciclovir, 32 to 58 μM for foscarnet, and 0.22 to 0.51 μM for cidofovir, including for CMV strains that are resistant to ganciclovir, cidofovir and foscarnet (23, 24, 28).

The *in vitro* activity of maribavir has been studied in combination with other currently approved anti-CMV therapies. *In vitro*, maribavir antagonizes ganciclovir's anti-CMV effect, increasing the ganciclovir 50% inhibitory concentration (IC_{50}) of a sensitive strain by up to 13-fold (33), which is logically explained by ganciclovir's dependence on UL97-mediated phosphorylation to its active metabolite. Maribavir has no effect on the antiviral activity of cidofovir or foscarnet (33) since these do not require intracellular activation.

Other studies, however, have suggested an additive or indeterminate anti-CMV effect of maribavir in combination with ganciclovir, and a synergistic anti-CMV effect of maribavir in combination with cidofovir and foscarnet (34–36). One study also suggests strong synergy with mTOR inhibitor rapamycin, presenting a potentially useful therapeutic option in transplant recipients (36).

Pharmacodynamics. Maribavir does not require intracellular activation or processing, and the parent compound is pharmacologically active (23, 24). Its primary metabolite is VP4469, obtained through *N*-dealkylation of maribavir by CYP3A4, and is inactive against CMV (37). In dose-ranging trials of solid organ and hematopoietic stem cell transplant recipients, there has been no increased exposure-response relationship observed for the probability of an undetectable CMV DNA level when comparing maribavir doses of 400 mg twice daily with higher doses of 800 or 1,200 mg twice daily (38, 39).

Pharmacokinetics and metabolism. Maribavir's pharmacokinetics have been studied in animal models, single-dose phase I trials with healthy and HIV-infected human subjects, and later in phase II and III trials in recipients of solid organ and hematopoietic stem cell transplants. Single-dose phase I trials have studied maribavir doses from 50 to 1,600 mg in healthy and HIV-infected subjects (37, 40).

Oral maribavir is rapidly absorbed, with peak plasma concentration (C_{max}) occurring 1 to 3 h after dosing, and rapidly eliminated, with a mean half-life of 3 to 5 h (37). It has linear pharmacokinetics, with dose-proportional increases in the peak plasma concentrations (C_{max}) and the area under the concentration-time curve ($AUC_{0-\infty}$), predictable steady-state plasma profiles based on single-dose data, and minimal accumulation at steady-state (37, 40, 41). Crushing maribavir tablets or co-administrating them with food or antacids does not have a significant impact on maribavir exposure (42, 43).

Maribavir is 40% bioavailable, and is highly protein-bound (~98%), with free maribavir plasma concentrations being about 100-fold lower than total plasma drug concentrations (37, 44). Pharmacokinetic modeling has predicted that maribavir doses of 400 mg twice daily would maintain unbound maribavir concentrations above the CMV 50% inhibitory concentration (37, 44). Animal studies have suggested that it can penetrate the blood-retinal barrier, but does not cross the blood-brain barrier (43, 45).

Maribavir primarily undergoes biliary excretion, based on animal studies (37, 45). Maribavir is heavily metabolized after oral absorption, primarily by CYP3A4, and to a lesser extent by CYP1A2 (37). Maribavir administered at doses of 400 mg twice daily for 10 days did not change CYP1A2, CYP2C9, CYP2A, *N*-acetyl-transferase-2, or xanthine oxidase activity, but it may inhibit CYP2C19 and CYP 2D6 activity (41). Maribavir is a substrate and weak inhibitor of CYP3A4, and a weak inhibitor of P-plycoprotein, resulting in several significant pharmacokinetic interactions. Maribavir increases tacrolimus exposure by 51% (43, 46), as well as exposure of other immunosuppressants commonly used in transplant recipients. Maribavir exposure is decreased by 61% with rifampin (a potent CYP3A4 inducer) (43). Maribavir exposure is increased by 46% with ketoconazole (a potent CYP3A4 inhibitor) (43). Based on voriconazole's inhibition of CYP3A4, one would expect maribavir exposure to also be increased by voriconazole, though not necessarily to a clinically significant amount that would require maribavir dose adjustment (see section on drug-drug interactions). Conversely, one study showed that co-administration of maribavir and voriconazole (a substrate of CYP2C19 and inhibitor of CYP3A4) had no effect on the pharmacokinetics of voriconazole or voriconazole-*N*-oxide (43, 47).

About 30% to 40% of the oral dose of maribavir is cleared in the urine as its inactive *N*-dealkylated metabolite, and less than 2% of the oral dose eliminated unchanged in the urine (37).

Maribavir's pharmacokinetics are not significantly affected by mild (CrCl 50 to 80 mL/min) to severe ($<$30 mL/min) renal impairment, as demonstrated in one pharmacokinetic study of 12 subjects with normal renal function and 19 subjects with mild to severe renal impairment (48). Although renal impairment is associated with an increase in AUC values for an inactive metabolite of maribavir, there is no change in the total or unbound plasma concentrations of the parent drug (48). Maribavir has not been studied in patients with end-stage renal disease or severe hepatic impairment. Maribavir does not affect the QT interval (43, 49).

Dosage, drug administration, and drug-drug interactions. Maribavir is available as a 200-mg tablet and is administered orally at a dose of 400 mg twice daily. No dosage adjustment is required for mild, moderate, or severe renal impairment (50). No dosage adjustment is required for mild or moderate hepatic impairment (50). There is no adequate human data to assess the risk of maribavir administration in pregnancy (50). No serious reproductive risks were identified with maribavir in reproductive toxicity studies in animal models, although embryo-fetal survival *in utero* in rats (but not in rabbits) was marginally reduced (50, 51). The pharmacokinetics of maribavir in pediatric patients less than 18 years of age have not been studied. The recommended dosing regimen in patients above 12 years of age and above 35 kg was extrapolated using modeling assuming similar steady-state plasma exposures of maribavir in adults (50).

Maribavir co-administration with strong CYP3A4 inducers such as rifabutin and rifampin is not recommended due to the potential for decreased efficacy of maribavir (50) Dose adjustments of maribavir are required when co-administering with moderate CYP3A4 inducers to account for decreased plasma concentrations of maribavir. The dose of maribavir should be increased to 1,200 mg twice daily when it is co-administered with phenobarbital, primidone, or phenytoin/fosphenytoin. The dose of maribavir should be increased to 800 mg twice daily when co-administered with carbamazepine (50). Maribavir may be co-administered with strong CYP3A4 inhibitors (including azole antifungals such as ketoconazole and clarithromycin, which would increase plasma maribavir levels) without dose adjustment based on the lack of dose-limiting toxicity, wide therapeutic window, and less than 3-fold increase in anticipated plasma levels of maribavir (50, 52). Plasma levels of certain immunosuppressants (including sirolimus, tacrolimus, cyclosporine, and everolimus) should be closely monitored while on maribavir due to risk for increased plasma levels of immunosuppressant (50). Maribavir co-administration with valganciclovir/ganciclovir is not recommended due to the potentially antagonistic effect of maribavir on ganciclovir's antiviral activity (50). Table 1 provides a summary of maribavir's key drug-drug interactions (50).

TABLE 1 Significant drug-drug interactions with maribavir[a]

Drug class/drug name	Interaction effect	Recommendation for administration with maribavir
Antiarrhythmics		
Digoxin	Increased digoxin concn[c]	Co-administer with maribavir with caution. Monitor digoxin levels while on maribavir treatment
Antiepileptics		
Carbemazepine	Decreased maribavir concn	Increase maribavir dose to 800 mg twice daily
Phenytoin	Decreased maribavir concn	Increase maribavir dose to 1,200 mg twice daily
Phenobarbital	Decreased maribavir concn	Increase maribavir dose to 1,200 mg twice daily
Antimycobacterials		
Rifabutin	Decreased maribavir concn	Avoid co-administration with maribavir
Rifampin	Decreased maribavir concn	Avoid co-administration with maribavir
Antivirals		
Valganciclovir/ganciclovir	Antiviral antagonism	Avoid co-administration with maribavir
HMG-CoA reductase[b] inhibitors		
Rosuvastatin	Increased rosuvastatin concn	Monitor for adverse effects of rosuvastatin (ie. myopathy, rhabdomyolysis)
Immunosuppressants		
Cyclosporine	Increased cyclosporine concn	Monitor immunosuppressant levels throughout maribavir treatment, especially following maribavir initiation and discontinuation
Everolimus	Increased everolimus concn	
Sirolimus	Increased sirolimus concn	
Tacrolimus	Increased tacrolimus concn	

[a]Adapted from Takeda Liventicity prescribing information (50).
[b]β-Hydroxy β-methylglutaryl-CoA reductase.
[c]concn, concentration.

Mechanisms of maribavir resistance. *In vitro* studies with serial passage of laboratory CMV strains in the presence of maribavir have led to the identification of several mutations in viral genes UL97 and UL27 conferring maribavir resistance. (Table 2) Mutations in the viral gene UL97 (V353A, L397R, L337M, T409M, H411L, H411N, H441Y, F342, C480F) generally confer moderate to high-level maribavir resistance (ranging from a 3.5- to >200-fold increased maribavir EC_{50}) (31, 53–57), and mutations in the viral gene UL27 (R233S, W362R, W153R, L193F, A269T, V353E, L426F, E22stop, W362stop, 218delC, and 301–311del), generally confer low-level maribavir resistance (2- to 3-fold increase in maribavir EC_{50}) (58, 59). It is thought that UL27 mutants compensate for

TABLE 2 Cytomegalovirus mutations associated with maribavir and ganciclovir resistance[a]

	Fold increase in EC_{50} or IC_{50}		
UL97 genotype	Maribavir	Ganciclovir	Source or reference
V353A	12−27		53, 59
L397R	>200		53
T409M	78−90		31, 53, 56, 57
H411L	69		53
H411N	9		53
H411Y	12−20		53, 56, 57
L337M	3.4−7.2		55
C480F	224	2.3	56
F342Y	4.5	6.0	57
F342Y, H411Y	56	5.9	57
W153R	1.7		59
L193F	2.6		59
A269T	2		59
V353E	2.1		59
L426E	2.2		59
E22stop	2		59
W362stop	2.2		59
218delC	2.5		59
301−311del	3.1		59

[a]EC_{50}, 50% effective concentration; IC_{50}, 50% inhibitory concentration.

maribavir's inhibition of UL97 by destabilizing the histone acetyltransferase Tip60, thus increasing p21 expression, which inhibits cellular cyclin-dependent kinases (60, 61). The known UL97 mutations are located close to the kinase ATP-binding and catalytic domains, upstream of the ganciclovir-resistance mutations (53). In *in vitro* cell culture data, CMV strains which were resistant to ganciclovir, cidofovir, foscarnet, or combinations of these treatments remained sensitive to maribavir; *in vitro* maribavir-resistant strains remained conversely susceptible to ganciclovir, cidofovir, and foscarnet (28). For instance, T409 and H411L/N/Y mutations confer resistance to maribavir but not ganciclovir (31, 54). However, as detailed later, more recent genotype analyses of clinical data have shown treatment-emergent development of mutations (C480F, F342Y) which do confer cross-resistance to both maribavir and ganciclovir after maribavir exposure.

CLINICAL EFFICACY DATA

Early efficacy data: phase I trial. Early clinical trials studied the efficacy of oral maribavir in HIV-infected subjects. A multiple-dose, randomized, parallel-dose escalation study of oral maribavir at escalating doses (100, 200, or 400 mg three times daily, or 600 mg twice daily) for 28 days in 78 HIV-infected men with asymptomatic CMV shedding demonstrated safety, tolerability, and *in vivo* anti-CMV activity, with decreased CMV levels in semen (40). The antiviral activity exhibited by maribavir in this trial was taken as proof-of-activity.

Maribavir for CMV prophylaxis: phase II and III trials. A phase II trial of allogeneic stem cell transplant recipients demonstrated that post-transplant maribavir prophylaxis effectively prevented CMV infection compared with placebo. This randomized, double-blind, placebo-controlled, dose-ranging clinical trial demonstrated the efficacy and safety of oral maribavir for CMV prophylaxis in CMV-seropositive allogeneic stem cell transplant recipients (62). A total of 111 patients were randomized to receive CMV prophylaxis with either oral maribavir (100 mg twice daily, 400 mg once daily, or 400 mg twice daily) or placebo (62). In the first 100 days post-transplantation, maribavir was effective at reducing the incidence of CMV infection by approximately 70% compared with placebo, with a lower incidence of pp65 antigenemia (15%, $P = 0.046$; 19%, $P = 0.116$; 15%, $P = 0.053$; versus placebo 39%) and a lower incidence of plasma CMV DNA levels (7%, $P = 0.001$; 11%, $P = 0.007$; 19%, $P = 0.038$; versus placebo 46%) across each of the respective maribavir groups compared with placebo (62). Although CMV antigenemia and DNAemia did occur in up to 20% of maribavir recipients, anti-CMV therapy was used less often in all maribavir groups compared with the placebo group, and there were no cases of CMV disease in maribavir-treated patients, compared with 3 cases in the placebo group (62). According to this study, the lowest dose of maribavir (100 mg twice daily) was as effective as the higher doses for CMV prevention, provided similar trough plasma concentrations (albeit lower maximal concentration and area under the curve values), was better tolerated, and could avoid the myelosuppression seen with ganciclovir (62).

After these initially favorable phase II trial results, phase III trials failed to meet the endpoint for effectiveness of maribavir at a dose of 100 mg twice daily for CMV prophylaxis in high-risk CMV mismatch allogeneic stem-cell transplant recipients, and demonstrated the inferiority of maribavir compared to ganciclovir for CMV prophylaxis in high-risk CMV mismatch liver transplant patients. A phase III placebo-controlled, double-blind, multicenter study randomized 681 CMV recipient-seropositive or donor-seropositive allogeneic stem-cell transplant patients to receive either oral maribavir 100 mg twice daily or placebo for up to 12 weeks (63). There was no difference between the incidence of CMV disease within 6 months between the two groups, with 4% (20/454) in the maribavir group and 5% in the placebo group (odds ratio [OR]: 0.90; 95% confidence interval [CI]: 0.42 to 1.92) (63). Within 100 days after transplantation, there was no difference in CMV infection rates between the groups as measured by plasma CMV DNA levels (27.8% maribavir versus 30.4% placebo; OR: 0·88; 95% CI: 0.62

to 1.25), or by initiation of anti-CMV treatment (30.6% versus 37.4%; OR: 0.73, 95% CI: 0.52 to 1.03) (63).

A phase III double-blind, multicenter trial randomized 303 CMV recipient-seronegative and donor-seropositive liver transplant patients to receive either oral maribavir 100 mg twice daily or oral ganciclovir 1,000 mg three times daily for up to 14 weeks (64). There was no difference in the incidence of CMV disease within 6 months between the two groups, with 12% in the maribavir group and 8% in the ganciclovir group (event rate difference: 0.041; 95% CI: −0.038, 0.119) (64). Significantly fewer patients in the ganciclovir group compared to the maribavir group had CMV disease or CMV infection as determined by by pp65 antigenemia or CMV DNA PCR at 100 days (20% versus 60%; $P < 0.0001$) and at 6 months (53% versus 72%; $P = 0.0053$) (64).

Though controversial, the lack of efficacy in these trials for maribavir prophylaxis was possibly attributed to inadequate doses of maribavir (owing to the unreliable results of earlier, inadequately powered studies to detect a difference in efficacy between different maribavir doses), exclusion of high-risk patients, low CMV disease rates in control groups, or delayed timing of drug initiation (44, 65).

Maribavir for CMV treatment: phase II and phase III trials. After case series suggested that maribavir at doses of 400 to 800 mg twice daily could be used for treatment of active R-R CMV disease (65, 66), attention was turned to maribavir as a treatment option for R-R CMV. Phase II trials demonstrated the efficacy of maribavir at doses of at least 400 mg twice daily for treatment of R-R CMV infections in both solid and organ transplant recipients.

A phase II dose-ranging, double-blind study randomized 120 hematopoietic stem cell or solid organ transplant recipients with R-R CMV infection with CMV DNA levels of > 1,000 copies/mL to receive maribavir at doses of 400, 800, or 1,200 mg twice daily for up to 24 weeks (38). A total of 67% of patients achieved the primary efficacy endpoint of undetectable plasma CMV DNA level within 6 weeks of treatment (with rates of 70%, 63%, and 68%, respectively, in the different dosing groups) (38). Four patients died due to CMV disease. Recurrent CMV infections while on treatment occurred in 25 patients, 13 of whom developed mutations associated with maribavir resistance (38).

Another phase II trial compared the efficacy of maribavir with that of valganciclovir. In this open-label, dose-blinded trial, 161 hematopoietic stem cell and solid organ transplant recipients with CMV reactivation (defined as 1,000 to 100,000 CMV DNA copies/mL) were randomized to receive maribavir at a dose of 400, 800, or 1,200 mg twice daily, or the standard dose of valganciclovir, for up to 12 weeks (39). After 3 weeks of treatment, 62% of the maribavir-recipients and 56% of the valganciclovir recipients met the primary endpoint of treatment response (defined as undetectable CMV DNA level in plasma) (39). After 6 weeks of treatment, 79% and 67% of maribavir and valganciclovir recipients, respectively, had treatment response (relative risk (RR): 1.20, 95% CI: 0.95 to 1.51) (39). Similar percentages of patients responded to treatment across all maribavir dosing groups. The median time to undetectable CMV DNA level was not significantly different between the overall maribavir versus valganciclovir groups (21 and 17 days, respectively, hazard ratio (HR): 1.17). Recurrence of CMV infection recurred in 22% of the overall maribavir group and 18% of the valganciclovir group. Among treatment responders, 2 patients who had received maribavir doses of 800 mg twice daily developed CMV recurrence within 6 weeks (39). Mutations conferring maribavir resistance (T409M mutations in UL97 protein kinase) developed after baseline in both patients (39).

A pivotal phase III trial has recently demonstrated the efficacy of maribavir in the treatment of R-R CMV infection. This open-label, multicenter, active-controlled trial randomized 352 hematopoietic stem cell or solid organ transplant recipients with refractory CMV infection, with or without resistance, to receive either maribavir 400 mg twice daily ($n = 235$) or investigator-assigned therapy (IAT: one or a combination of valganciclovir/ganciclovir, foscarnet, or cidofovir, $n = 117$) for a treatment phase of 8 weeks, followed by a follow-up phase of 12 weeks during which patients were off study-assigned therapy (29). Patients originally assigned IAT could enter a maribavir

rescue arm after 3 weeks of treatment if they met certain prespecified criteria ($n = 22$) (29). A significantly higher proportion of patients in the maribavir group met the primary endpoint of CMV viremia clearance by the end of week 8 than in the IAT group (55.7% and 23.9%, respectively, adjusted difference 32.8% [22.8 to 42.74], $P < 0.001$), with consistent results across prespecified subgroups and transplant types (29). Similarly, a significantly higher proportion of patients in the maribavir group met the secondary endpoint of CMV viremia clearance and symptom control at the end of week 8, maintained through week 16, than in the IAT group (18.7% and 10.3%, respectively, adjusted difference 9.5% [2.02 to 16.88], $P = 0.01$) (29). All-cause mortality was similar in both groups (29). Clinically relevant recurrence occurred less frequently in the maribavir group than in the IAT group (26% versus 35.7%) (29). Of the 22 subjects who initially received IAT and then entered the maribavir rescue arm due to lack of response, 50% achieved confirmed CMV viremia clearance with maribavir (29).

CLINICAL SAFETY AND TOLERABILITY DATA

In clinical trials, maribavir has been shown to be safe and well-tolerated, with a favorable side effect profile compared with traditional anti-CMV therapies. Maribavir has been studied at a wide range of doses (from single doses of 50 to 1,600 mg, to twice- or three-times-daily doses ranging from 100 to 400 mg) and has shown a similar safety profile compared with placebo, with no significant difference in lab values and no evidence of bone marrow suppression or renal toxicity (37, 40, 62, 63).

The most common adverse effect associated with maribavir has been taste disturbance (described as bitter, metallic, chemical, or altered taste), at rates ranging from 15% to 82% across different trials (29, 38, 40, 62, 63). This side effect has been observed to be dose-proportional and reversible upon discontinuation of therapy, and has not led to high rates of maribavir discontinuation in clinical studies (29, 38, 40). In a phase III trial, although higher levels of taste disturbance were reported in subjects who received maribavir compared with placebo, there was no difference in other GI side effects, including nausea, vomiting, and diarrhea (63). Importantly, across clinical trials, maribavir has not been significantly associated with neutropenia or renal impairment (these being major dose-limiting effects of traditional anti-CMV agents (valganciclovir/ganciclovir and foscarnet/cidofovir, respectively).

A recent phase III clinical trial highlights maribavir's safety and tolerability profile at doses of 400 mg twice daily in comparison with traditional anti-CMV therapies (29). In this trial, fewer subjects discontinued study medication due to an adverse event in the maribavir group compared with the IAT (IAT: one or a combination of valganciclovir/ganciclovir, foscarnet, or cidofovir; 13.2% and 31.9%, respectively) (29). Maribavir was associated with less kidney injury compared with foscarnet (8.5% versus 21.3%), and with less neutropenia compared with valganciclovir/ganciclovir (9.4% versus 33.9%) (29). There were no cases of treatment-related neutropenia or acute kidney injury (AKI) leading to treatment-discontinuation of maribavir, whereas 19.6% of subjects discontinued valganciclovir/ganciclovir due to neutropenia and 12.8% of subjects discontinued foscarnet due to AKI (29).

CLINICAL RESISTANCE AND CROSS-RESISTANCE

The development of treatment-emergent maribavir resistance and cross-resistance mutations has been described. One study tested baseline and post-treatment genotype samples from 2 separate phase II trials for mutations in UL97, UL54, or UL24 (56). Data were obtained from the previously discussed phase II trial in which 120 hematopoietic or solid organ transplant recipients received escalating doses of maribavir for R-R CMV infection (38), and from the phase II trial in which 119 hematopoietic or solid organ transplant recipients received escalating doses of maribavir or valganciclovir for CMV reactivation (39). Of the combined 29 subjects who developed recurrent CMV viremia while on maribavir after an initial treatment response, 23 had available baseline UL97 genotypes (56). Seventeen developed known mutations associated with maribavir

resistance T409M or H411Y (which conferred 78-fold and 15-fold increases in maribavir EC_{50}, respectively), and five had a newly described C480F mutation which conferred high-level maribavir resistance (224-fold increase in maribavir EC_{50}) and low-level ganciclovir resistance (2.3-fold increase in ganciclovir EC_{50}) (56). Of the combined 25 subjects who did not respond to >14 days of maribavir therapy, 9 were found to have T409M or H411Y mutations and 4 were found to have the C480F mutation alone (56). C480F was the first clinically described mutation associated with maribavir and ganciclovir cross-resistance (56). Additional UL27 genotyping was performed in a total of 82 patients from both studies, and it identified a previously uncharacterized UL27 variant, G344D, which did not confer maribavir resistance (56).

Genotyping from maribavir-treated subjects from a phase III study (29) revealed that while only 4/214 (1.3%) of subjects had baseline mutations associated with maribavir resistance (notably, 3/4 carried F342Y, a cross-resistance mutation to maribavir and valganciclovir/ganciclovir), 58/214 (27.1%) developed post-baseline treatment-emergent mutations in UL97 (T409M, H411N, H411L, H411Y, F342Y, and C480F) after maribavir exposure (52). Development of additional mutations has been associated with increased levels of maribavir resistance. Alone, the F342Y mutation was associated with a 4.5-fold increase in maribavir EC_{50} and a 6-fold increase in ganciclovir EC_{50}, and the H411Y mutation was associated with a 12- to 20-fold increase in maribavir EC_{50} (57). Combined, the F342Y and H411Y mutations were associated with a 56-fold increase in maribavir EC_{50}, with a stable 5.6-fold increase in ganciclovir EC_{50} (57).

FUTURE DIRECTIONS

Maribavir is currently FDA-approved for treatment of R-R CMV infection. It is important to note that in the phase III clinical trial leading to maribavir's FDA approval, its use was restricted to 8 weeks. In clinical practice, however, CMV treatment does not follow a fixed duration and is usually continued until resolution of DNAemia on 1 or 2 consecutive weekly CMV PCRs (6). Although this is not how maribavir was studied, we expect that in clinical practice, the duration of maribavir therapy for R-R CMV infection will adhere to standard guidelines of therapy continuation until resolution of DNAemia. As maribavir becomes incorporated into clinical practice, it will be crucial to identify which patients will benefit most from maribavir therapy, such as those with dose-limiting side effects or contraindications to first-line therapies. Certain clinical questions will arise, such as whether there will be a viral load cutoff at which maribavir treatment is preferred, and whether there is a role for maribavir synergy in combination with certain currently available anti-CMV therapies (such as foscarnet or cidofovir), or even synergy with certain immunosuppressant regimens (given *in vitro* data supporting synergy with rapamycin) (36). Further investigation is also needed regarding key features of and risk factors for developing treatment-emergent resistance, and our resistance testing will need to be altered to reflect these emerging mutations.

Although the clinical role for maribavir is currently that of a second-line agent for R-R CMV infection, there is also an ongoing phase III clinical trial studying maribavir at a dose of 400 mg twice daily for up to 8 weeks as a first-line treatment of CMV infection in hematopoietic stem cell transplant recipients (unpublished data, ClinicalTrials.gov identifier: NCT05137717, https://clinicaltrials.gov/ct2/show/study/NCT05137717?cond=maribavir&draw=2).

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E.A.B. reports potential conflicts of interest with Takeda/Shire (site principal investigator for maribavir clinical trials with funds to the institution and unpaid scientific advisor), Merck (site principal investigator for letermovir clinical trials and unpaid clinical advisor), Hologic (site principal investigator for clinical trials of a testing platform for CMV), and Amplyx (served on the Data Safety Monitoring Board for monoclonal antibodies for BK). Other authors have no conflicts of interest to report.

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