



Use of Letemovir as Salvage Therapy for Drug-Resistant Cytomegalovirus Retinitis

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ABSTRACT Treatment options for drug-resistant cytomegalovirus (CMV) are limited. Letemovir is a novel antiviral recently approved for CMV prophylaxis following hematopoietic cell transplantation, but its efficacy in other settings is unknown. We recently used letemovir for salvage treatment in four solid organ transplant recipients with ganciclovir-resistant CMV retinitis. All patients improved clinically without known adverse drug events. However, three patients failed to maintain virologic suppression, including two patients who developed genotypically confirmed resistance to letemovir while on therapy.

KEYWORDS cytomegalovirus, ganciclovir-resistant, letemovir

Ganciclovir-resistant cytomegalovirus (CMV) disease poses a substantial clinical problem within the transplant population. Mutations in either the viral kinase (UL97) or polymerase (UL54) can mediate resistance to ganciclovir and valganciclovir, which are first-line treatment agents. The incidence of ganciclovir resistance increases with cumulative drug exposure, ranging as high as 40% to 50% in patients receiving prolonged prophylaxis or repeated courses of treatment (1–3). Ganciclovir resistance is associated with worse clinical outcomes across a range of transplant types, including higher risk of recurrent CMV disease and increased mortality (4, 5). The FDA-approved alternative agents available to treat ganciclovir-resistant CMV are often poorly tolerated due to high rates of renal insufficiency (e.g., foscarnet and cidofovir) or neutropenia (e.g., high-dose ganciclovir and cidofovir). Brincidofovir and maribavir may also retain activity against ganciclovir-resistant CMV, but both drugs have failed phase 3 prophylaxis trials, and maribavir is limited by poor ocular and central nervous system (CNS) penetration (6–8). Letemovir is a novel agent which targets the viral terminase complex with a high specificity for CMV (9). Due to the unique mechanism of action, letemovir remains active against CMV carrying mutations in UL97 or UL54 (10). While it is currently approved for CMV prophylaxis in hematopoietic cell transplant recipients, experience with letemovir for treatment or secondary prophylaxis of CMV disease for other types of patients or scenarios is limited to case reports (11–14). This case series highlights our single-center experience with an off-label use of letemovir for the treatment of ganciclovir-resistant CMV disease in patients who either failed or were unable to tolerate traditional therapies for resistant CMV.

We analyzed clinical data from all adult patients at a tertiary care hospital in North Carolina who initiated letemovir for treatment of CMV disease between November 2017 and April 2018 (Table 1). Four patients received letemovir for treatment of ganciclovir-resistant CMV disease after failing therapy with ganciclovir-valganciclovir and developing nephrotoxicity from foscarnet. All patients had genotypically proven

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TABLE 1 Clinical features and outcomes for 4 patients with drug-resistant CMV treated with letermovir

Feature	Information for patient:			
	A (66-y-old male)	B (50-y-old male)	C (46-y-old male)	D (66-y-old male)
CMV risk factor	Bilateral orthotopic lung transplant (CMV donor+/recipient-)	Bilateral orthotopic lung transplant (CMV donor+/recipient-)	Orthotopic heart transplant (CMV donor+/recipient-)	Orthotopic heart transplant (CMV donor+/recipient-)
Comorbidities	Sarcoidosis, chronic kidney disease	Interstitial lung disease, chronic kidney disease	CMV syndrome retinitis colitis	Retinitis
Disease burden	CMV syndrome retinitis	CMV syndrome retinitis	745 IU/ml	<137 IU/ml
Plasma CMV DNA at start of letermovir	342 IU/ml	1,416 IU/ml		
Prior CMV prophylaxis	Valganciclovir	Valganciclovir	Valganciclovir	Valganciclovir
Prior antiviral treatment	CMV IgG, ganciclovir, valganciclovir, maribavir, foscarnet	Ganciclovir, valganciclovir, maribavir, foscarnet	Ganciclovir, valganciclovir, foscarnet	CMV IgG, ganciclovir, valganciclovir, foscarnet
Known CMV mutations prior to letermovir initiation	M460V (UL97)	Q578H (UL54)	M460I (UL97), likely mixed population at N408K (UL54)	H520Q (UL97), C603W (UL97), T503I (UL54)
Letermovir dose (mg daily)	720	960 ^a	720	720
Concomitant therapies	CMV IgG, foscarnet (V) ^b	CMV IgG, foscarnet (V), ganciclovir (V)	n/a	CMV IgG, foscarnet (V)
Duration of follow-up (weeks)	38	39	32	34
Virologic suppression on letermovir	Unsuppressed	Unsuppressed	Unsuppressed	Suppressed
Mutations conferring letermovir resistance	Negative for UL56 mutations	C325F mutation detected in UL56	C325Y mutation detected in UL56	Letermovir resistance testing not performed
Management of rebound viremia and/or letermovir resistance	Letermovir stopped on day 138, transitioned to valganciclovir and CMV IgG; subsequently achieved virologic suppression	Letermovir stopped on day 110, transitioned to valganciclovir (given reversion of prior UL54 mutation); subsequently achieved virologic suppression	Letermovir stopped on day 102, transitioned to foscarnet; subsequently achieved virologic suppression	n/a ^c
Clinical outcome	Improved on retinal exam	Improved on retinal exam	Improved on retinal exam	Improved on retinal exam

^aPatient B began at 720-mg dose letermovir, but the dose was up-titrated to 960 mg due to lack of response.

^b(V) indicates vitreal administration; all others systemic unless noted.

^cn/a, not applicable: patient D did not suffer any rebound viremia.

resistance to ganciclovir with a history of clinical failure on multiple traditional antiviral agents. Two of four patients in our cohort had CMV retinitis proven by CMV PCR from the aqueous obtained by an anterior chamber paracentesis (testing performed at University of Colorado Hospital, Denver, CO); two patients (A and C) were presumptively diagnosed with CMV retinitis based on CMV viremia with a fundoscopic examination showing retinitis. Plasma CMV viral loads at the time of letermovir initiation for the four-patient cohort ranged from 137 to 1,416 IU/ml. Induction letermovir doses were begun at 720 mg and in one case up-titrated to 960 mg daily due to a lack of effect. While efficacy at these higher doses has not been formally clinically assessed, these dose ranges were chosen in consultation with Merck pharmacists on the basis of tolerance and safety data from phase I studies (available in drug product insert). Three patients received concomitant CMV immune globulin, as well as intravitreal therapy with either foscarnet (2.4 mg/0.1 ml) or ganciclovir (4 mg/0.1 ml). Laboratory monitoring included serial hematologic, renal, and hepatic function testing. A genotypic assessment for resistance to letermovir at gene UL56 was performed for three patients (Viracor Eurofins, Lee's Summit, MO).

All four patients showed clinical and fundoscopic improvement with resolution of the retinitis. However, three patients failed to achieve sustained virologic suppression. Patient A exhibited prolonged, intermittent, low-level DNAemia, while patients B and C developed high-grade CMV DNAemia after more than a month of therapy with letermovir (Fig. 1). No patients developed adverse effects attributable to letermovir. As predicted by the inhibition of Cyp3A4 by letermovir, tacrolimus and warfarin required a downward dose adjustment and close therapeutic monitoring.

The finding of three patients (A, B, and C) with sustained or recurrent plasma CMV DNAemia raised a concern for the emergence of resistance on letermovir therapy. A genotypic assessment demonstrated UL56 mutations within the same codon for patients B (C325F) and C (C325Y). Resistance testing did not reveal *in vitro* resistance for patient A; however, a mutation conferring resistance could have occurred at a UL56 site that was not sequenced or a different terminase complex component (e.g., UL51 or UL89) (15). Patient A was transitioned back to valganciclovir plus CMV IgG and demonstrated virologic suppression. For patient B, a reemergence of virus with a wild-type UL-54 permitted the resumption of valganciclovir with subsequent virologic suppression. Patient C had previously developed renal injury on foscarnet but was successfully rechallenged with this agent and achieved virologic suppression.

This case series highlights several promising features of letermovir that led us to use it as an off-label salvage therapy for refractory CMV infection. First, as predicted by its unique mechanism of action, letermovir should retain *in vitro* activity in patients with phenotypic and/or genotypic resistance to ganciclovir. Second, it was well-tolerated, both in our experience at doses up to 960 mg daily and in the previously published trials within the hematopoietic cell transplantation (HCT) population. Finally, it appeared at least initially effective as a component of variable, real-world treatment for CMV retinitis. All four of our patients had CMV retinal disease, and while three of four patients also received intravitreal injections of foscarnet during initial treatment with letermovir, none experienced any recurrent retinitis or vision loss while on letermovir for ongoing suppression.

These cases also emphasize the important concern for emergence of resistance while receiving letermovir. Three patients failed to achieve sustained virologic suppression despite demonstrable clinical improvement in retinitis. Genotyping confirmed treatment-emergent UL56 mutations in two patients, while a third patient had clinical evidence of resistance. Serial viral passage under letermovir selective pressure has been associated with a relatively rapid selection of UL56 mutations, particularly within codons 231 to 369 (16, 17). The possibility exists that the observed cases of letermovir resistance resulted from a selection of resistant subpopulations of CMV rather than as a consequence of a low barrier to resistance. However, regardless of the mechanism, the high rate of clinically significant resistance in our cohort has important implications. In particular, the use of letermovir to treat active CMV infection requires caution and

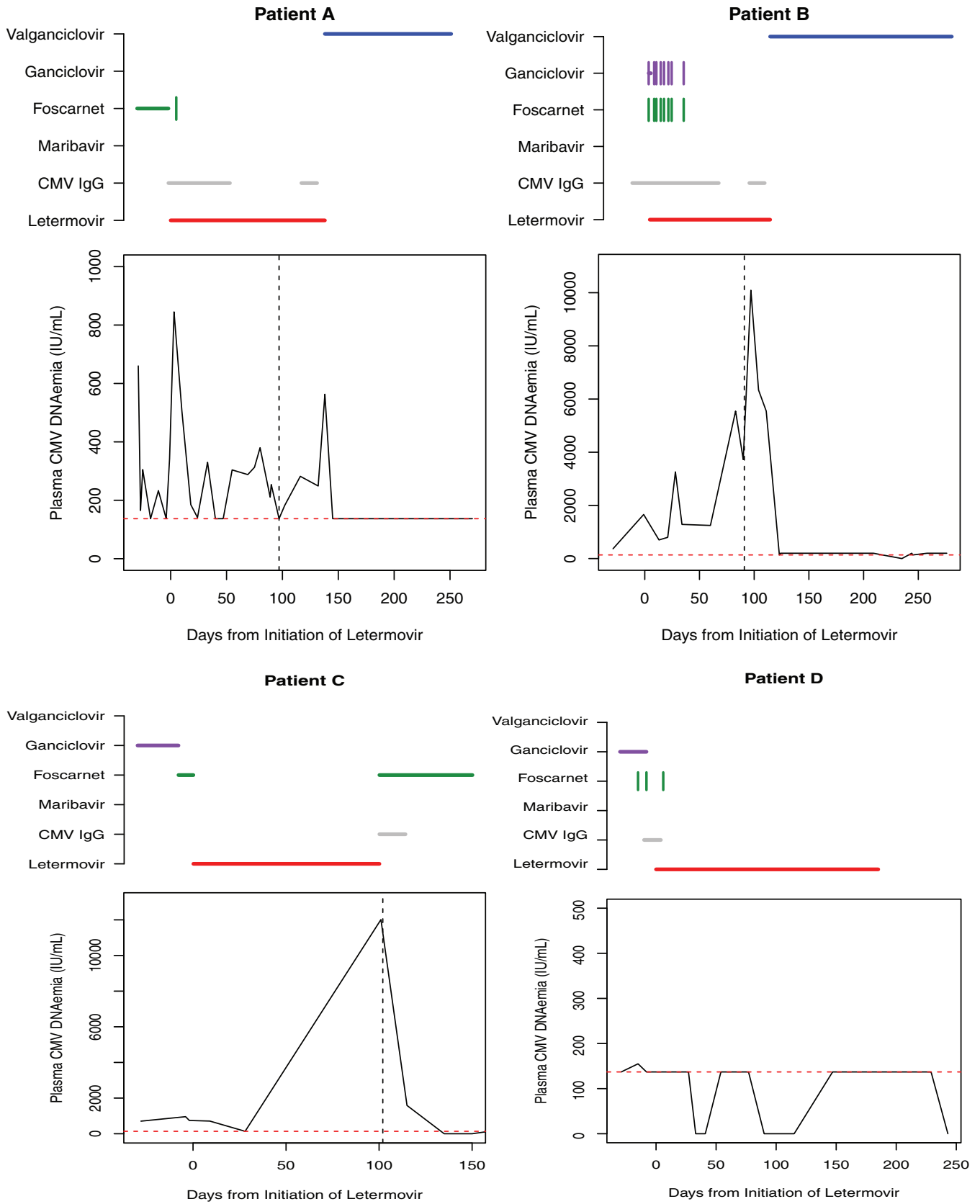


FIG 1 CMV Plasma DNAemia response kinetics on letermovir treatment. Horizontal lines above each graph represent the time period on systemic therapy with each agent. Vertical tick marks indicate intravitreal doses. The horizontal dashed line indicates the threshold for quantitative detection of CMV plasma DNA by the assays used in this series (137 IU/ml). The vertical dashed line indicates timing of letermovir drug resistance testing.

close clinical monitoring, particularly in the setting of persistent viremia. Fortunately, in each instance of confirmed resistance in this cohort, it was possible to transition to an alternative agent, namely, in one case due to the reversion of a prior UL54 mutation and in the second due to tolerance of foscarnet upon rechallenge.

In addition to potential resistance development, letermovir inhibits Cyp3A4, leading to many potentially significant drug interactions. We made preemptive dose adjustments for statins, warfarin, and tacrolimus without noting adverse clinical effects. Serial tacrolimus drug levels and close international normalized ratio (INR) monitoring (for patients receiving warfarin) were required.

In our patients, letermovir was well tolerated and was associated with the resolution of CMV retinitis. There was no recurrence of retinitis during the follow-up period after cessation of intravitreal therapy. However, three patients developed recurrent or persistent DNAemia while receiving letermovir, including two patients with confirmed treatment-emergent UL56 resistance. Although letermovir may prove to be a useful treatment for some patients with CMV infection who have either failed prior therapies or are unable to tolerate traditional antiviral agents, providers will need to remain vigilant for treatment failure and emergence of resistance.

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