Abstract # 1897

Use of Letermovir as Salvage Therapy for Drug-resistant CMV: A Case Series

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Abstract

Background: Limited treatment options exist for ganciclovir-resistant CMV disease. Foscarnet can cause renal insufficiency, and maribavir has poor ocular penetration. Letermovir is approved for primary CMV prophylaxis in hematopoietic stem cell transplantation, but efficacy in treatment of CMV disease or secondary prophylaxis is not known.

Methods: We analyzed data from all adult patients at a single center who initiated letermovir for treatment of CMV disease or secondary prophylaxis of CMV retinitis from 11/2017 through 4/2018. We described patient characteristics, extent of CMV disease, prior antiviral therapies, kinetics of CMV DNAemia, and clinical outcomes.

Results: Four patients received letermovir for treatment, and one for secondary suppression, of CMV DNAemia and CMV retinitis (Table). All patients had proven genotypic resistance with complications and/or clinical failure on prior antivirals. Letermovir doses ranged from 480mg to 720mg daily. 3 patients received concomitant CMV immune globulin and intravitreal therapy with foscarnet and/or ganciclovir. No patients developed side effects attributable to letermovir, and expected increases in tacrolimus levels occurred. All 5 patients demonstrated clinical and retinoscopic improvement (Figure 1), but two patients did not achieve complete resolution of DNAemia (Figure 2).

Conclusion: Use of letermovir, often in combination with intravitreal therapy, was associated with sustained clinical improvement in 5 patients with CMV retinitis. Treatment doses of up to 720mg were well tolerated. Despite marked improvement of ocular disease, two patients did not achieve sustained suppression of DNAemia.

Background

- Ganciclovir resistant CMV is a significant problem within the transplant population. The incidence of resistance may be as high as 45% among those previously exposed to valganciclovir prophylaxis.[1] There are few alternative treatment options, and nearly all are limited by adverse effects.
- Letermovir, an oral antiviral agent highly specific for CMV, was recently approved for CMV prophylaxis in hematopoietic cell transplant (HCT) patients.[2,3]
- Highly tolerable and orally bioavailable, letermovir also shows many favorable characteristics as an alternative agent for treating ganciclovir-resistant CMV disease.[4]

Methods

- We analyzed clinical data from 5 adult patients at Duke University Hospital who received letermovir for either treatment of secondary suppression of CMV disease between 11/2017 and 4/2018.
- 4 of 5 patients were solid organ transplant recipients; the fifth patient (E) was on immunosuppression for Susac syndrome.

Results

- **Table 1** Summary of clinical features and outcomes for the five patients with CMV disease receiving letermovir.

	A: 66 y/o male	B: 50 y/o male	C: 46 y/o male	D: 66 y/o male	E: 43 y/o female
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	Susac syndrome
Co-morbidities	Sarcoidosis, chronic kidney disease	Interstitial lung disease, chronic kidney disease			
Disease burden	CMV syndrome Retinitis	CMV syndrome Retinitis	CMV syndrome Retinitis Colitis	Retinitis	Retinitis Colitis
Plasma CMV DNA at start of letermovir	342 IU/mL	1416 IU/mL	745 IU/mL	<137 IU/mL	0 IU/mL
Prior CMV prophylaxis	Valganciclovir	Valganciclovir	Valganciclovir	Valganciclovir	Not applicable
Prior antiviral treatment	CMV IgG Ganciclovir Valganciclovir Maribavir Foscarnet	Ganciclovir Valganciclovir Maribavir Foscarnet	Ganciclovir Valganciclovir Foscarnet	CMV IgG Ganciclovir Valganciclovir Foscarnet	CMV IgG Ganciclovir Valganciclovir Foscarnet Foscarnet (V)
Known CMV mutations prior to letermovir initiation	M460V (UL97)	Q578H (UL54)	M460I (UL97), likely mixed population at N408K (UL97)	H520Q (UL97), C603W (UL97), T503I (UL54)	A594V (UL97)
Letermovir use	Treatment	Treatment	Treatment	Treatment	Secondary suppression
Letermovir dose	720 mg daily	960 mg daily	720 mg daily	720 mg daily	480 mg daily
Concomitant therapies	CMV IgG Foscarnet (V)	CMV IgG Foscarnet (V) Ganciclovir (V)	n/a	CMV IgG Foscarnet (V)	n/a
Duration of follow-up	28 weeks	30 weeks	22 weeks	25 weeks	40 weeks
Virologic suppression on letermovir	Unsuppressed	Unsuppressed	Unsuppressed	Suppressed	Suppressed
Mutations conferring letermovir resistance	Negative for UL56 mutations	C325F mutation detected in UL56	C325Y mutation detected in UL56	Letermovir resistance testing not performed	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	n/a
Clinical outcome	Improved on retinal exam	Improved on retinal exam	Improved on retinal exam	Improved on retinal exam	Improved on retinal exam

Results (continued)

- Letermovir was well-tolerated, with no adverse drug effects observed for any of the five patients. Dose adjustments were made for concomitant medications metabolized via the Cyp3A4 pathway (e.g., tacrolimus, warfarin).
- All patients had retinoscopic improvement of their CMV retinitis, however 3 of 5 failed to achieve viral suppression raising concern for resistance emergent on treatment. Among the 3 with failed virologic suppression, 2 had genotyping confirmed mutations in the viral terminase (UL56) known to mediate resistance to letermovir.
- Among patients with letermovir resistance, all three were converted to a different anti-CMV agent. Two of the three demonstrated reversion of their prior ganciclovir resistance. All three eventually achieved virologic suppression on alternative therapies.

Figure 1: Retinoscopic improvement for patient E on letermovir secondary suppression.

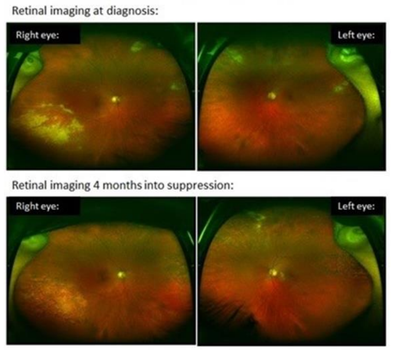
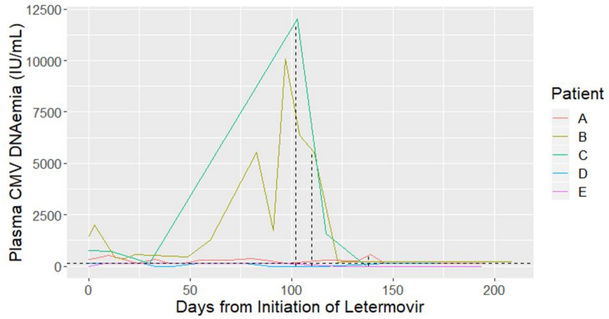


Figure 2: CMV Plasma DNAemia Kinetics on Letermovir Treatment. Vertical dashed lines indicate letermovir discontinuation. Horizontal dashed line indicates detection limit for CMV DNAemia from plasma.



Conclusions

- Letermovir was an effective salvage agent for treatment and suppression of retinitis from resistant CMV
- Despite clinical improvement, 3 of 5 patients had rebound DNAemia and required alternative therapies
- The barrier to resistance appears low, both in our patient cohort and in *in vitro* studies[4]
- Letermovir should be used with caution in patients with persistent CMV viremia.

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