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

AUTHORS: Nicholas Turner\textsuperscript{a,b}\#, Andrew Strand\textsuperscript{a,c}, Dilraj S. Grewal\textsuperscript{d}, Gary Cox\textsuperscript{a}, Sana Arif\textsuperscript{a}, Arthur W Baker\textsuperscript{a,b}, Eileen K Maziarz\textsuperscript{a}, Jennifer H Saullo\textsuperscript{a}, Cameron R Wolfe\textsuperscript{a}\#

AUTHOR AFFILIATIONS:
\textsuperscript{a}Duke University School of Medicine, Division of Infectious Diseases, Durham, NC
\textsuperscript{b}Duke Center for Antimicrobial Stewardship and Infection Prevention, Durham, NC
\textsuperscript{c}Tufts Medical Center, Division of Geographic Medicine and Infectious Diseases, Boston, MA
\textsuperscript{d}Department of Ophthalmology, Duke University Medical Center, Durham, NC

CORRESPONDING AUTHORS: Address correspondence to Cameron R Wolfe, cw74@duke.edu or Nicholas Turner, nick.turner@duke.edu

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ABSTRACT:

Treatment options for drug-resistant CMV are limited. Letermovir is a novel antiviral recently approved for CMV prophylaxis following hematopoietic cell transplantation, but efficacy in other settings is unknown. We recently used letermovir 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 letermovir while on therapy.
Ganciclovir-resistant 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 40-50% 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 CNS penetration (6-8). Letermovir is a novel agent which targets the viral terminase complex with a high specificity for CMV (9). Due to the unique mechanism of action, lettermovir 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 lettermovir 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 off-label use of lettermovir for 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 lettermovir for treatment of CMV disease between 11/2017 and 4/2018 (table 1). Four patients received lettermovir for treatment of ganciclovir-resistant CMV disease after failing therapy with ganciclovir/valganciclovir and developing nephrotoxicity from foscarnet. All patients had genotypically-proven resistance to ganciclovir with 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 1416 IU/mL. Induction letermovir doses were begun at 720 mg and in one case up-titrated to 960 mg daily due to 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 (2.4mg/0.1mL) or ganciclovir (4mg/0.1mL). Laboratory monitoring included serial hematologic, renal, and hepatic function testing. 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 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 (figure 1). No patients developed adverse effects attributable to letermovir. As predicted by letermovir’s inhibition of Cyp3A4, tacrolimus and warfarin required downward dose adjustment and close therapeutic monitoring.

The three patients (A, B, and C) with sustained or recurrent plasma CMV DNAemia raised concern for emergence of resistance on letermovir therapy. 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, re-emergence of virus with a wild-type UL-54 permitted resumption of valganciclovir with subsequent virologic suppression. Patient C had previously developed renal injury on foscarnet but was successfully re-challenged with this agent and achieved virologic suppression.

This case series highlights several promising features of letermovir that led us to use it as off-label salvage therapy for refractory CMV infection. First, as predicted by its unique mechanism of action, letermovir should retain \textit{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 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 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 two patients, while a third patient had clinical evidence of resistance. Serial viral passage under letermovir selective pressure has been associated with 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 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, use of letermovir to treat active CMV infection requires caution and 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: in one case due to reversion of a prior UL54 mutation, and in the second due to tolerance of foscarnet upon re-challenge.

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

In our patients, letermovir was well tolerated and was associated with 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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REFERENCES:


Table 1: Clinical features and outcomes for 5 patients with drug-resistant CMV treated with letermovir.

<table>
<thead>
<tr>
<th></th>
<th>A: 66 y/o male</th>
<th>B: 50 y/o male</th>
<th>C: 46 y/o male</th>
<th>D: 66 y/o male</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>CMV risk factor</strong></td>
<td>Bilateral orthotopic lung transplant (CMV donor+/recipient)</td>
<td>Bilateral orthotopic lung transplant (CMV donor+/recipient)</td>
<td>Orthotopic heart transplant (CMV donor+/recipient)</td>
<td>Orthotopic heart transplant (CMV donor+/recipient)</td>
</tr>
<tr>
<td><strong>Co-morbidities</strong></td>
<td>Sarcoidosis, chronic kidney disease</td>
<td>Interstitial lung disease, chronic kidney disease</td>
<td>CMV syndrome Retinitis</td>
<td>Retinitis</td>
</tr>
<tr>
<td><strong>Disease burden</strong></td>
<td>CMV syndrome Retinitis</td>
<td>CMV syndrome Retinitis</td>
<td>CMV syndrome Retinitis</td>
<td>CMV syndrome Retinitis</td>
</tr>
<tr>
<td><strong>Plasma CMV DNA at start of letermovir</strong></td>
<td>342 IU/mL</td>
<td>1416 IU/mL</td>
<td>745 IU/mL</td>
<td>&lt;137 IU/mL</td>
</tr>
<tr>
<td><strong>Prior CMV prophylaxis</strong></td>
<td>Valganciclovir</td>
<td>Valganciclovir</td>
<td>Valganciclovir</td>
<td>Valganciclovir</td>
</tr>
<tr>
<td><strong>Prior antiviral treatment</strong></td>
<td>CMV IgG</td>
<td>Ganciclovir</td>
<td>Valganciclovir</td>
<td>Maribavir Foscarnet</td>
</tr>
<tr>
<td></td>
<td>Ganciclovir</td>
<td>Valganciclovir</td>
<td>Valganciclovir</td>
<td>Foscarnet</td>
</tr>
<tr>
<td></td>
<td>Maribavir Foscarnet</td>
<td>Ganciclovir</td>
<td>Valganciclovir</td>
<td>Foscarnet</td>
</tr>
<tr>
<td></td>
<td>H520Q (UL97), C603W (UL97), T503I (UL54)</td>
<td>M460I (UL97), likely mixed population at N408K (UL54)</td>
<td>M460V (UL97)</td>
<td>Q578H (UL54)</td>
</tr>
<tr>
<td><strong>Letermovir dose</strong></td>
<td>720 mg daily</td>
<td>960 mg daily</td>
<td>720 mg daily</td>
<td>720 mg daily</td>
</tr>
<tr>
<td><strong>Duration of follow-up</strong></td>
<td>38 weeks</td>
<td>39 weeks</td>
<td>32 weeks</td>
<td>34 weeks</td>
</tr>
<tr>
<td><strong>Virologic suppression on letermovir</strong></td>
<td>Unsuppressed</td>
<td>Unsuppressed</td>
<td>Unsuppressed</td>
<td>Suppressed</td>
</tr>
<tr>
<td><strong>Mutations conferring letermovir resistance</strong></td>
<td>Negative for UL56 mutations</td>
<td>C325F mutation detected in UL56</td>
<td>C325Y mutation detected in UL56</td>
<td>Letermovir resistance testing not performed</td>
</tr>
<tr>
<td><strong>Management of rebound viremia and/or letermovir resistance</strong></td>
<td>-Letermovir stopped on day 138, transitioned to valganciclovir and CMV IgG -Subsequently achieved virologic suppression</td>
<td>-Letermovir stopped on day 110, transitioned to valganciclovir (given reversion of prior UL54 mutation) -Subsequently achieved virologic suppression</td>
<td>-Letermovir stopped on day 102, transitioned to foscarnet -Subsequently achieved virologic suppression</td>
<td>n/a</td>
</tr>
<tr>
<td>Clinical outcome</td>
<td>Improved on retinal exam</td>
<td>Improved on retinal exam</td>
<td>Improved on retinal exam</td>
<td>Improved on retinal exam</td>
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*V* indicates vitreal administration; all others systemic unless noted.

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

**Figure 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 intra-vitreal 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.