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 prophylaxis, of CMV DNAemia and CMV retinitis (Table). All patients had proven genotypic resistance with complications and/or clinical failure on prior antiviral. Letermovir doses ranged from 480mg to 720mg daily. Three 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 virologic suppression on letermovir.

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.

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.

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.
- Letermovir should be used with caution in patients with persistent CMV viremia.