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CORRESPONDENCE

Maribavir for Cytomegalovirus Treatment in the Real World—Not a Silver Bullet

To the Editor—Cytomegalovirus (CMV) infection remains a frequent cause of morbidity and mortality among stem-cell and solid organ transplant recipients, with devastating complications including graft failure and death [1, 2]. Limitations of existing anti-CMV agents such as valganciclovir, ganciclovir, foscarnet, and cidofovir include toxicity (bone marrow suppression, renal failure, electrolyte disturbances), route of administration, and potential for resistance [1, 2].

Maribavir is an oral benzimidazole nucleoside inhibiting viral kinase UL97 that was Food and Drug Administration–approved in November 2021 for refractory/resistant posttransplant CMV infection [3]. In the SOLSTICE phase 3 trial of maribavir compared to investigator-assigned therapy, maribavir demonstrated superior viral clearance at week 8 (55.7% vs 23.9%, $P < .0001$) and fewer side effects such as neutropenia (9.4% vs 22.4%) and kidney injury (8.5% vs 9.5%) [4]. However, recurrence after treatment discontinuation occurred in 50% of initial responders [3, 4]. Additionally, treatment-emergent UL97 mutations conferring reduced maribavir susceptibility, including some conferring cross-resistance to ganciclovir/valganciclovir, occurred frequently (up to 25% of enrolled subjects) in both SOLSTICE and prior phase 2 studies [3–7]. Outside of clinical trial settings, little is known about outcomes of maribavir therapy. Here, we present 2 transplant recipients receiving maribavir who developed breakthrough CMV infection, including 1 with resistance.

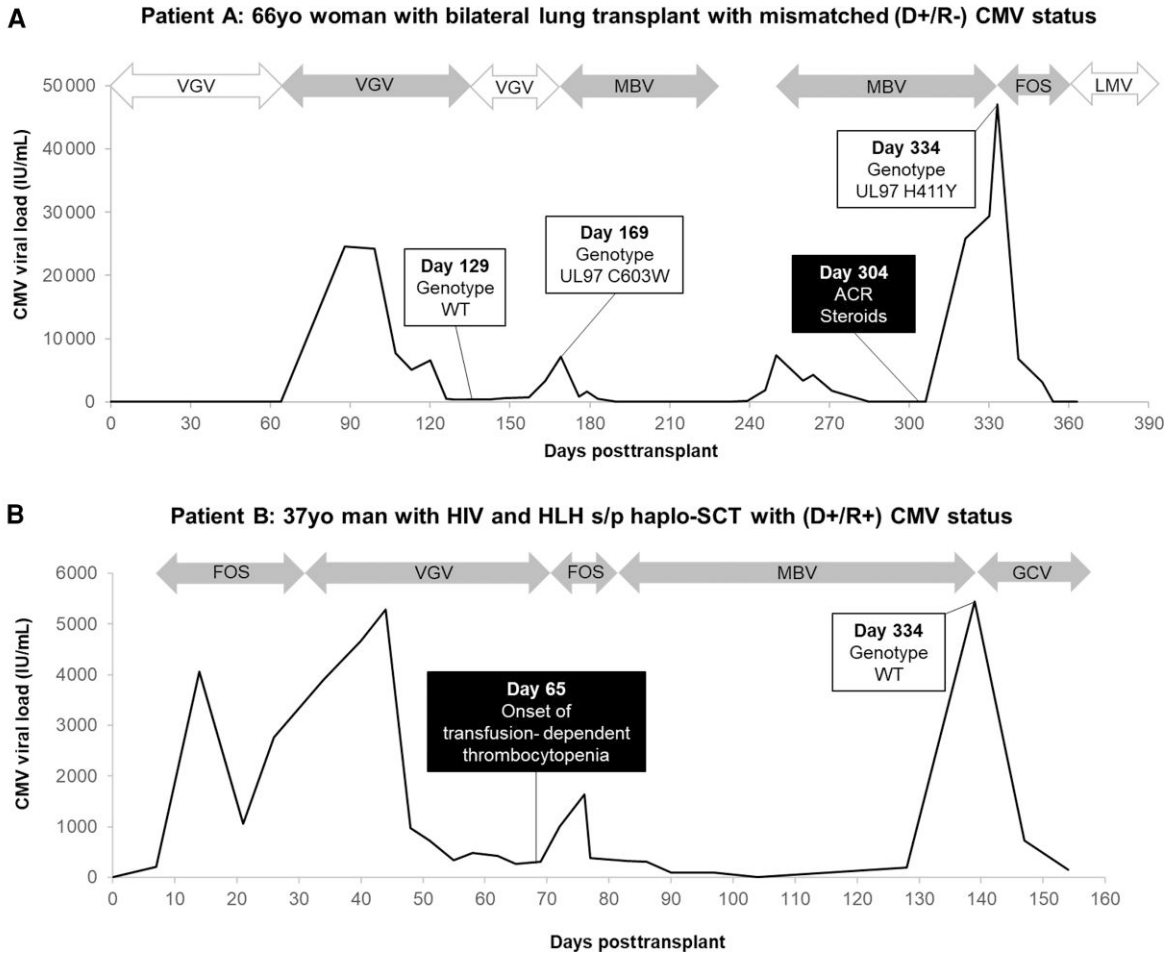

Figure 1. Timeline of events for patient A (*A*) and patient B (*B*). White arrows indicate prophylaxis agent. Gray arrows indicate treatment agent. Abbreviations: ACR, acute cellular rejection; CMV, cytomegalovirus; D+/R-, donor-positive, recipient-negative; D+/R+, donor-positive, recipient-positive; FOS, foscarnet; GCV, ganciclovir; haplo-SCT, haploidentical stem cell transplant; HIV, human immunodeficiency virus; HLH, hemophagocytic lymphohistiocytosis; LMV, letermovir; MBV, maribavir; s/p, status post; VGV, valganciclovir; WT, wild-type.

Patient A is a 66-year-old lung transplant recipient with mismatched donor-positive, recipient-negative CMV status who developed ganciclovir-resistant then maribavir-resistant CMV (Figure 1*A*). After the patient developed breakthrough CMV infection on valganciclovir prophylaxis with high-grade ganciclovir-resistant (UL97 C603 mutation) virus on day 169 posttransplant, she transitioned to oral maribavir. Viral load (VL) became undetectable (day 196) on 8 weeks of maribavir (through day 224), but recurred 2 weeks posttherapy (day 250) to 7399 IU/mL. Maribavir was reinitiated with appropriate VL decline (detected below threshold). On day 304, patient was diagnosed with acute cellular rejection and treated with high-dose steroids then tapered. While still on maribavir, VL rebounded to 47 000 IU/mL and the patient was admitted (day 333) for intravenous foscarnet; genotyping demonstrated UL97 H411Y mutation conferring maribavir resistance. With foscarnet, CMV immunoglobulin, and decreased immunosuppression, the patient's CMV viremia responded, but she experienced infusion-related complications and nephrotoxicity. After 4 weeks of foscarnet (day 366), the patient was transitioned to letermovir prophylaxis planned until immunosuppression is further tapered.

Patient B is a 37-year-old man with human immunodeficiency virus (pretransplant CD4 count 147 cells/μL, VL undetectable) on dolutegravir/rilpivirine who underwent haploidentical stem-cell transplant (CMV donor-positive/recipient-positive) for primary hemophagocytic lymphohistiocytosis complicated by relapsed Kaposi sarcoma and CMV viremia (Figure 1*B*). Day 14 posttransplant, CMV viremia of 4065 IU/mL was detected and intravenous foscarnet was started with persistent VL elevation, prompting transition to valganciclovir with subsequent improvement. Due to transfusion-dependent cytopenias, the patient was transitioned back to foscarnet (days 76–83) then to maribavir (day 84). During week 8 of maribavir therapy after receiving a cycle of doxorubicin for Kaposi sarcoma, CMV VL rebounded to 5436 IU/mL; genotype demonstrated wild-type virus with no maribavir resistance mutations. Intravenous ganciclovir resulted in appropriate VL decline.

While maribavir is an important therapeutic development in CMV management, outcomes such as relapse, breakthrough infection, and development of resistance are not well understood outside of clinical trials. Additional studies characterizing maribavir outcomes in the real world are needed to guide optimal maribavir use (duration, VL threshold, as combination therapy) for difficult CMV infections.

Notes

Patient consent. Verbal consent was obtained from the 2 patients included in this report. This work aligns with the University of California, San Francisco institutional review board ethics standards.

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