Post-Transplant CMV Infection: Latest Advances in the Management of Refractory Disease

Toolkit for Healthcare Professionals

This toolkit was developed by **My-Ime.com** in collaboration with **Dr. Genovefa Papanicolaou** (Memorial Sloan Kettering Cancer Center, New York), **Dr. Marcus Pereira** (Columbia University Irving Medical Center, New York) and **Dr. Catherine Lee** (Fred Hutchinson Cancer Center, Seattle). This activity was supported by an independent medical grant by **Takeda**.

You can watch our **roundtable** in full on **www.IME.healthcare**, where you can also find the two **patient vignettes** presented.

Approximately 86% of blood or organ donors are seropositive for CMV.[1,2] CMV has incidence rates of 5–30% in HCT and 8–75% in SOT.[3,4] CMV infection typically occurs within the first 3–6 months after transplant, while patients are highly immunosuppressed.[5]

Risk factors for refractory CMV infection and/or resistance in HCT/SOT recipients [6,7]

Host factors	Viral factors
HCT: CMV D–/R+ **SOT: CMV D+/R– (high risk), R+ (intermediate)** HCT: Haploidentical, allogeneic, or cord blood HCT SOT: Type of organ transplanted (high risk: lung, heart-lung, composite transplants, intestine, pancreas; moderate risk: kidney, liver; low risk: cornea) Previous or prolonged antiviral CMV drug exposure (>3 months) Inadequate antiviral CMV drug absorption and bioavailability Inadequate antiviral CMV oral prodrug conversion Variation in antiviral CMV drug clearance Subtherapeutic antiviral CMV drug level Poor patient compliance with antiviral drug regimen T cell depletion Delayed immune reconstitution Treatment with antithymocyte antibodies Active GvHD (HCT) / Graft rejection (SOT) Presence of comorbidities	CMV viral load after >2 weeks of adequate treatment Failure of CMV viral load to fall despite appropriate treatment Rise in CMV viral load after initial decline while receiving appropriate treatment Intermittent low-level CMV viremia High CMV viral loads

Most of the risk factors for CMV resistance pertain to SOT as well, in addition to graft rejection (instead of GvHD) and CMV serostatus.

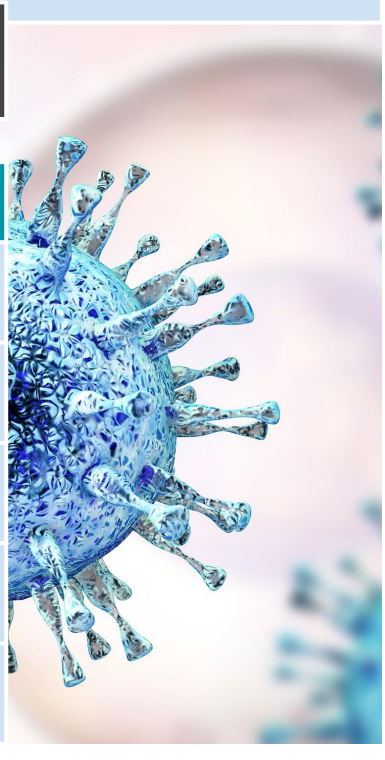
Routine surveillance is warranted for at least 4–6 weeks after discontinuation of prophylaxis.[8] Serial CMV viral load testing is recommended at least weekly to monitor response to antiviral treatment.[9,10]

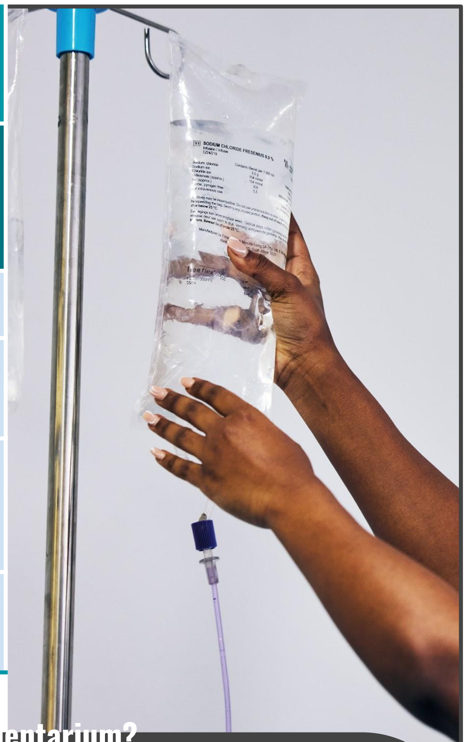
Refractory CMV infection may occur with or without a **genetic variant** conferring resistance.[11]

Resistance to (val)ganciclovir has been reported in 5–22% of SOT recipients, and 1–5% of HCT. [9]

Defining resistant/refractory CMV infection/disease in transplant recipients [6]

Refractory CMV infection	CMV viremia that increases after ≥2 weeks of appropriate antiviral therapy.
Probable refractory CMV infection	Persistent viral load after ≥2 weeks of appropriately dosed antiviral therapy.
Refractory CMV end-organ disease	Worsening in signs/symptoms and/or progression into EOD after ≥2 weeks of appropriately dosed antiviral therapy.
Probable refractory CMV end-organ disease	Lack of improvement in signs and symptoms after ≥2 weeks of appropriately dosed antiviral therapy.
Antiviral drug resistance	Viral genetic alterations of *UL97*, *UL54*, *UL27*, *UL51*, *UL56*, and *UL89* decreasing susceptibility to ≥1 anti-CMV drug.





Conventional therapy for the treatment of CMV infection/disease in HCT and SOT recipients [12-14]

Agent	Treatment (adults) [a]		Major toxicities
	Induction	Maintenance	
Ganciclovir (IV)	5 mg/kg BID [b]	5 mg/kg QD	Cytopenia
Valganciclovir (PO)	900 mg BID [c]	900 mg QD	Cytopenia
Foscarnet (IV)	90 mg/kg q 12 h or 60 mg/kg q 8 h	90 mg/kg QD	Renal, electrolyte wasting, GI
Cidofovir (IV, PO)	5 mg/kg/week for 2 weeks	5 mg/kg q2wk	Renal, headache, neutropenia, uveitis, iritis, GI, ocular hypotony

a) All agents require dose adjustment in the setting of renal dysfunction. **b)** If CMV remains detectable, further ID evaluati[illegible]

ne[illegible]

What does maribavir bring to the therapeutic armamentarium?

Maribavir acts on the pUL97 viral kinase, affecting different replication steps compared with pUL54-targeted antivirals.[10,15] It has been approved in the United States for the **treatment of adult and pediatric patients (age >12 years, weighing ≥35 kg) with post-transplant CMV infection/disease that is refractory to treatment (with or without genotypic resistance) with ganciclovir, valganciclovir, cidofovir, or foscarnet.**[16]

Investigator assigned therapy (IAT)
(Val)ganciclovir
Foscarnet
Cidofovir

What does the data say?

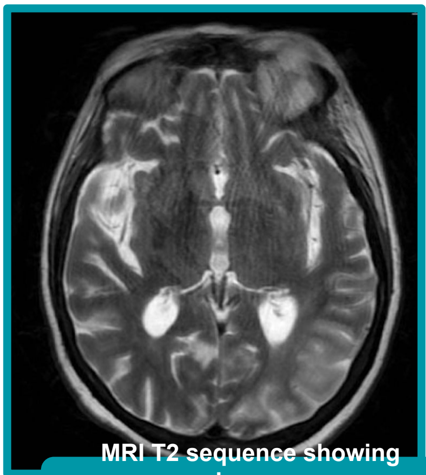
Phase 3, multicenter, randomized study (*N*=352; 211 SOT, 141 HCT) of maribavir (*n*=235) vs. IAT (*n*=117)

Maribavir was superior to IAT (*n*=117) for CMV viremia clearance and symptom control maintenance post-therapy in transplant recipients with **refractory CMV infection (with or without resistance)**.[17]

Reduced treatment-related neutropenia (9.4% vs. 33.9% with [val]ganciclovir).[17]

Reduced acute kidney injury (8.5% vs. 21.3% with foscarnet).[17]

Most common **treatment-emergent adverse events**: dysgeusia, nausea, diarrhea, vomiting, and fatigue, rarely leading to discontinuation.[16]



MRI T2 sequence showing changes consistent with CMV [illegible].[18]

REMEMBER!

- Maribavir has no activity against HSV/VZV, so co-administration of effective prophylaxis for these viruses, such as (val)aciclovir, is required.
- Co-administration with (val)ganciclovir is not recommended due to the potential antiviral activity antagonism.[16]
- Maribavir has poor CNS penetration and should not be used to treat CMV disease involving the CNS, including retinitis.[19] Alternative antivirals should be used if CNS disease or retinitis is suspected.[19]
  - *CNS involvement by CMV should be excluded in patients who develop neurologic symptoms while on maribavir.*

Abbreviations: BID, twice daily; CMV, cytomegalovirus; CNS, central nervous system; D+/D–, seropositive/negative donor; EOD, end-organ disease; GI, gastrointestinal; GvHD, graft-versus-host disease; HCT, hematopoietic cell transplant; HSV, herpes simplex virus; IAT, investigator-assigned therapy; ID, infectious diseases; IV, intravenous; MRI, magnetic resonance imaging; PO, orally; q, every; q2wk, every 2 weeks; QD, once daily; QOD, every other day; R+/R–, seropositive/negative recipient; SOT, solid organ transplant; VZV, varicella zoster virus.

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