CMV: nuovi approcci in profilassi e terapia

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Introduction: CMV the troll of transplantation

"Cytomegalovirus (CMV) is the most common recognized pathogen in the first six months after renal transplantation.
Although once considered a commensal organism, evidence is now overwhelming that CMV is a major cause of posttransplant fever and leukopenia in renal allograft recipients, and is often responsible for pneumonitis, hepatitis, retinitis, encephalitis, and even death.
Cytomegalovirus infections complicate bone marrow and cardiac transplantation as well.
Specific treatment of posttransplant CMV infection is still not possible.
Vidarabine (adenine arabinoside), which appears therapeutic for certain herpes group infections, has been ineffective for treatment of CMV in renal allograft recipients. In addition, the drug may have CNS toxicity in patients with impaired renal function.
The best we can do at present is to document CMV infection and then decrease immunosuppression to permit the host to combat the virus himself.
In so doing, we risk loss of the allograft."

Balfour *Arch Intern Med*. 1979

Introduction: how to deal with CMV?

Foscarnet (1991) → Ganciclovir (1994) → Cidofovir (1996) → Valganciclovir (2001) → Letermovir (2017) → Maribavir (2021)

Only approved for prophylaxis in allogenic HSCT

Only approved for resistant/refractory CMV infection

Antiviral drugs

CMV-specific T-cell therapy

Immunoglobulins

Reduce immunosuppression or switch in molecules

Vaccination

CMV definitions: infection and reactivation

CMV infection/CMV replication	Virus isolation/viral antigens/nucleic acid in any body fluid or tissue specimen
Primary CMV infection	First identification of CMV infection in an individual who has no evidence of CMV exposure before transplantation
Recurrent CMV infection	New CMV infection in a patient with previous evidence of CMV infection who has not had virus detected for an interval of at least 4 weeks [Recurrent infection may result from reactivation of latent virus (**endogenous**) or reinfection (**exogenous**)]
CMV reinfection	In recurrent CMV infection, the detection of a CMV strain that is distinct from the strain that caused the initial infection
CMV reactivation	In recurrent CMV infection, the detection of 2 viral strains indistinguishable

Ljungman et al. *CID* 2017
Ljungman et al. *CID* 2024

CMV definitions: DNAemia and “blip”

CMV DNAemia	**CMV DNA detection** by quantitative polymerase chain reaction (qPCR) on peripheral blood samples
CMV “blip”	**A single detections of CMV DNA**, usually with a low viral load (either incomplete viral replication or immune system clearance of CMV)
Clinically Significant CMV Infection	The **occurrence of CMV disease or the initiation of anti-CMV preemptive therapy** based on prespecified CMV DNAemia thresholds (Not applicable to SOT)

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Ljungman et al. *CID* 2024

CMV disease: pneumonia

Proven CMV pneumonia	**Clinical symptoms and/or signs of pneumonia** such as new infiltrates on imaging, hypoxia, tachypnea, and/or dyspnea	**CMV documented in tissue** by virus isolation, rapid culture, histopathology, immune-histochemistry, or DNA hybridization techniques
Probable CMV pneumonia after HSCT	**Clinical symptoms and/or signs of pneumonia** such as new infiltrates on imaging, hypoxia, tachypnea, and/or dyspnea	Detection of CMV by viral isolation, rapid culture of BAL fluid, or the **quantitation of CMV DNA in BAL fluid**
Probable CMV pneumonia after SOT	**Clinical symptoms and/or signs of pneumonia** such as new infiltrates on imaging, hypoxia, tachypnea, and/or dyspnea	**Detection of "high" CMV** by viral isolation, rapid culture of BAL fluid, or the quantitation of CMV DNA in BAL fluid*
Possible CMV pneumonia	**Clinical symptoms and/or signs of pneumonia** such as new infiltrates on imaging, hypoxia, tachypnea, and/or dyspnea	A **"high" CMV viral load in BAL fluid** together with **another opportunistic pathogen**

*The recommendation is to exclude probable CMV pneumonia in lung transplant recipients as an end point in clinical trials.

Table 2. DNA Levels in Bronchoalveolar Lavage Fluid (IU/mL) for Diagnosis of Probable or Unlikely Cytomegalovirus Pneumonia

Patient Category	Probable	Unlikely
Allogeneic HCT patients[a]	$> 10^{3}$ [a]	$< 5 \times 10^{2}$
Autologous HCT patients CAR T cell-treated patients	Cannot be defined	$< 5 \times 10^{2}$
Solid organ transplant patients except lung transplant patients isolated or combined	Cannot be defined	$< 5 \times 10^{2}$
Lung transplant patients	Cannot be defined	Cannot be defined

Abbreviation: CAR, Chimeric Antigen Receptor; HCT, hematopoietic cell transplant.

[a]Possible cytomegalovirus pneumonia is defined as the same viral load + presence of co-pathogens.

- The likelihood for CMV pneumonia increases with increasing DNA viral load.
- A negative CMV DNA test in the BAL fluid has a negative predictive value close to 100% and therefore excludes the possibility of CMV pneumonia.

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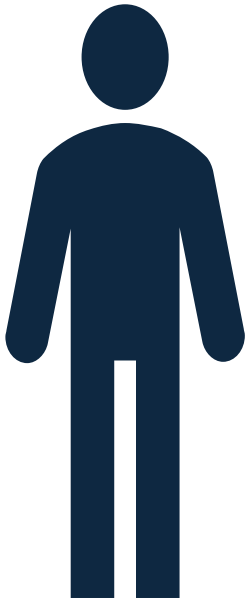
CMV disease: GI and retinitis

Proven CMV Gastrointestinal Disease	**Upper and/or lower GI symptoms** plus **macroscopic mucosal lesions**	**CMV documented in tissue** by histopathology, virus isolation, rapid culture, immunohistochemistry, or DNA hybridization techniques
Probable CMV Gastrointestinal Disease	**Upper and/or lower GI symptoms**	**CMV documented in tissue** by histopathology, virus isolation, rapid culture, immunohistochemistry, or DNA hybridization techniques[§]
Possible CMV GI disease after SOT	**Upper and/or lower GI symptoms** (in absence of other possible causes) with CTCAE severity >=2	High or increasing CMV blood viral load
Possible CMV GI disease after HSCT	**Upper and/or lower GI symptoms**	Identification of CMV in tissue by PCR* without macroscopic mucosal lesions
Proven retinitis	**Typical ophthalmologic exam findings for CMV retinitis**	The **presence of CMV DNA** in vitreous fluid or another part of the eye.
Probable retinitis	**Typical ophthalmologic exam findings**	

*Quantitative PCR is not accepted as a diagnostic criterion for proven or probable CMV GI disease.

Ljungman et al. *CID* 2017
Ljungman et al. *CID* 2024

Probable CMV syndrome*



Clinical and laboratory criteria (**at least 2 criteria are required**) and **detection of CMV DNA** or antigen in whole blood or plasma within 1 week of symptoms:

- **Fever ≥38°**C for at least 2 days of which at least 1 measurement is documented in a healthcare setting and without another identified cause of the fever
- New or increased **malaise** (toxicity grade 2) or new or increased **fatigue** (toxicity grade 3)
- A **WBC count of <3500/µL** if the WBC count prior to the development of clinical symptoms was ≥ 4000/µL or **a WBC decrease of >20%** if the WBC count prior to the development of clinical symptoms was <4000/µL; the corresponding **neutrophil counts are <1500/µL or a decrease of more than 20%** if the neutrophil count before the onset of symptoms was below 1500/µL
- Greater than or equal to **5% atypical lymphocytes**
- **Thrombocytopenia** defined as a platelet count of<100000 cells/µL if the platelet count prior to the development of clinical symptoms was ≥115000 cells/µL or a decrease of >20% if the platelet count prior to the development of clinical symptoms was <115 000 cells/µL.
- **Elevation of hepatic aminotransferases** (ALT or AST) to 2 times the upper limit of normal (applicable to non–liver transplant recipients), baseline defined as last value before cytomegalovirus viremia was documented (applicable to non-liver transplant recipients)

*only applicable to SOT

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CMV definitions: resistant/refractory

Refractory CMV infection	**CMV viremia (DNAemia or antigenemia) that increases** (ie, >1 log10 increase in CMV DNA levels in the same blood compartment from the peak viral load as measured in the same laboratory and/or withthe same commercial assay) **OR persists** (≤1 log10 increase or decrease in CMV DNA levels) **after at least 2 weeks of appropriate antiviral therapy.**
Refractory CMV end-organ disease	**Worsening in signs and symptoms or progression to end-organ disease** (for a patient not previously diagnosed with CMV end-organ disease) **OR lack of improvement in signs and symptoms after at least 2 weeks of appropriately dosed antiviral therapy.***
Resistant CMV	**Refractory CMV infection in addition to viral genetic alteration that decreases susceptibility to 1 or more antiviral drugs**. Drug resistance is defined by the occurrence of viral genetic alteration that affects in vitro susceptibility and/or clinical response.

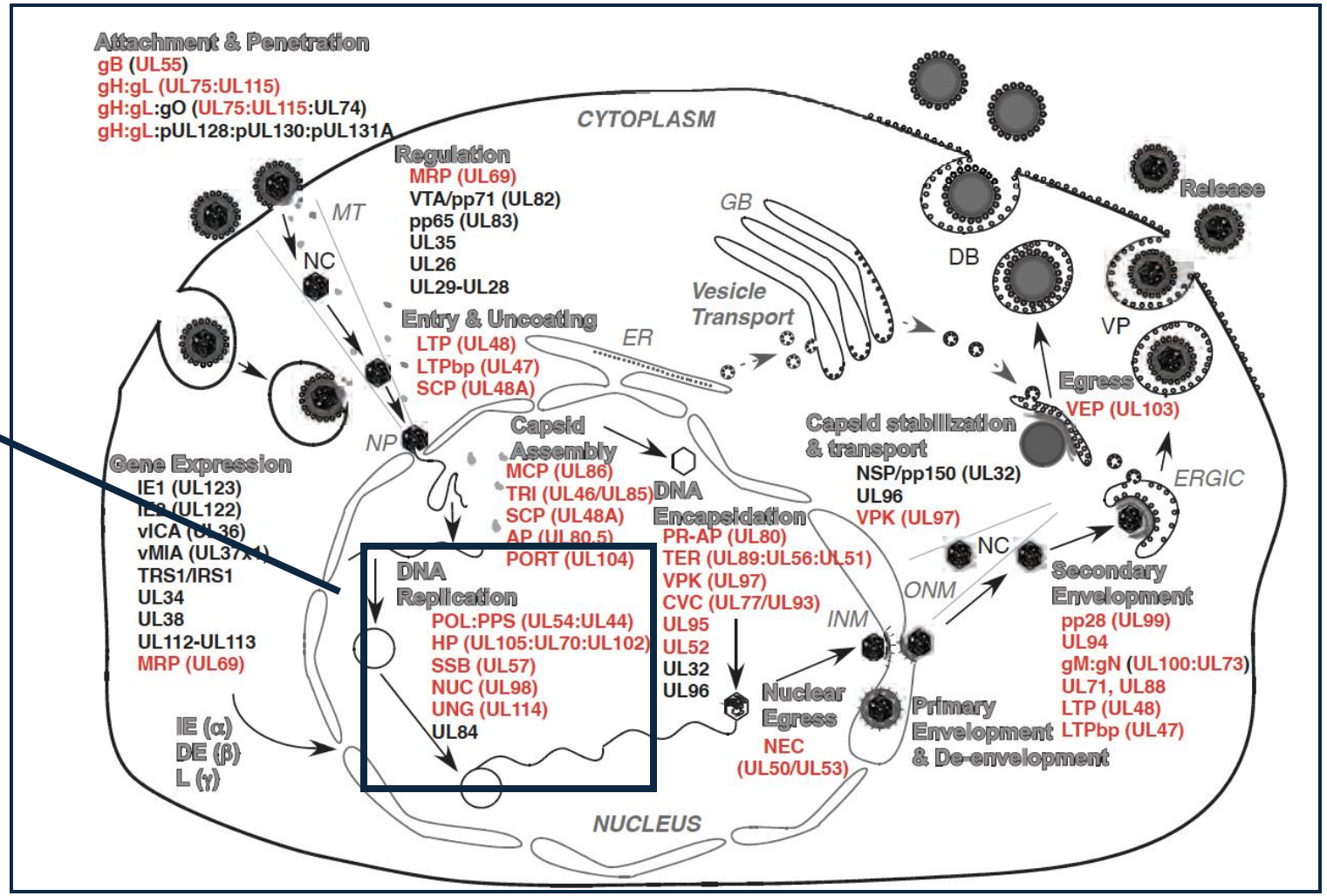
*Certain CMV end-organ disease are not always associated with measurable viral loads in serum or whole blood. In these cases, CMV may be replicating locally at tissue sites and may not be recovered for resistance testing.

Razonable and Humar. *Clin Transp* 2019

Ljungman et al. *CID* 2024

The “classic weapons”: targets

Cidofovir
(Val)ganciclovir
Foscarnet

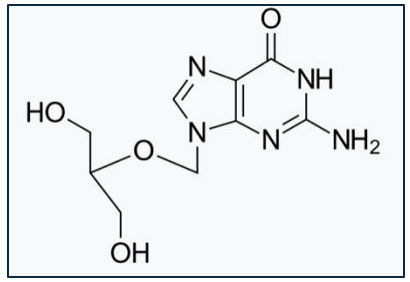


The “classic weapons”: agents

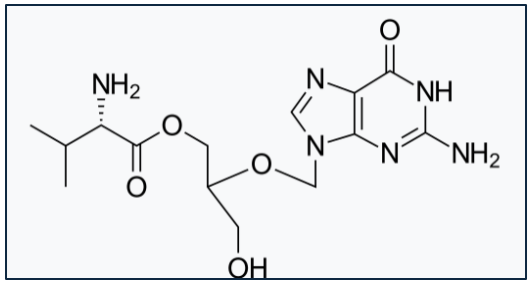
Table 1
Antiviral drugs for prophylaxis and treatment of cytomegalovirus infection and disease

Drug	Target	Route	Indications/clinical uses	Major toxicities	Activity against other herpes viruses	Comments
Cidofovir	UL54 DNA polymerase	IV	Treatment	Nephrotoxicity, myelosuppression, ocular, and alopecia	Yes: HSV, VZV, and HHV6	Alternative for treatment due to high risk of toxicity
Foscarnet	UL54 DNA polymerase	IV	Treatment	Nephrotoxicity, electrolyte loss, and myelosuppression	Yes: HSV, VZV, and HHV6	Alternative for treatment due to high risk of toxicity
Ganciclovir	UL54 DNA polymerase	IV	Treatment and prophylaxis	Myelosuppression, especially leukopenia and neutropenia	Yes: HSV, VZV, and HHV6	First-line treatment of CMV disease, especially if severe and life-threatening
Valganciclovir	UL54 DNA polymerase	Orally or by mouth	Treatment and prophylaxis	Myelosuppression, especially leukopenia and neutropenia	Yes: HSV, VZV, and HHV6	First-line treatment of asymptomatic and mild-to-moderate CMV disease

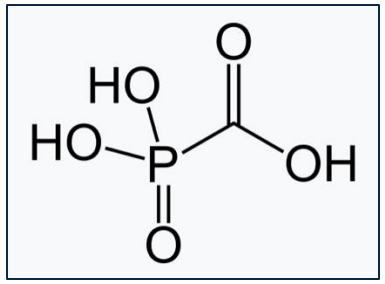
The dosages of the antiviral medications should be adjusted on the basis of renal function. Please refer to package insert of each drug for appropriate dosing on the basis of renal function and other considerations.
CMV, cytomegalovirus; CNS, central nervous system; EBV, Epstein Barr virus; HHV-6, human herpesvirus-6; HSV, herpes simplex virus; IV, intravenous; VZV, varicella zoster virus.



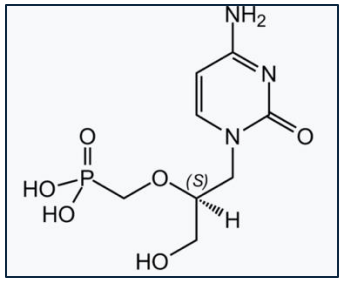
Ganciclovir



Valganciclovir



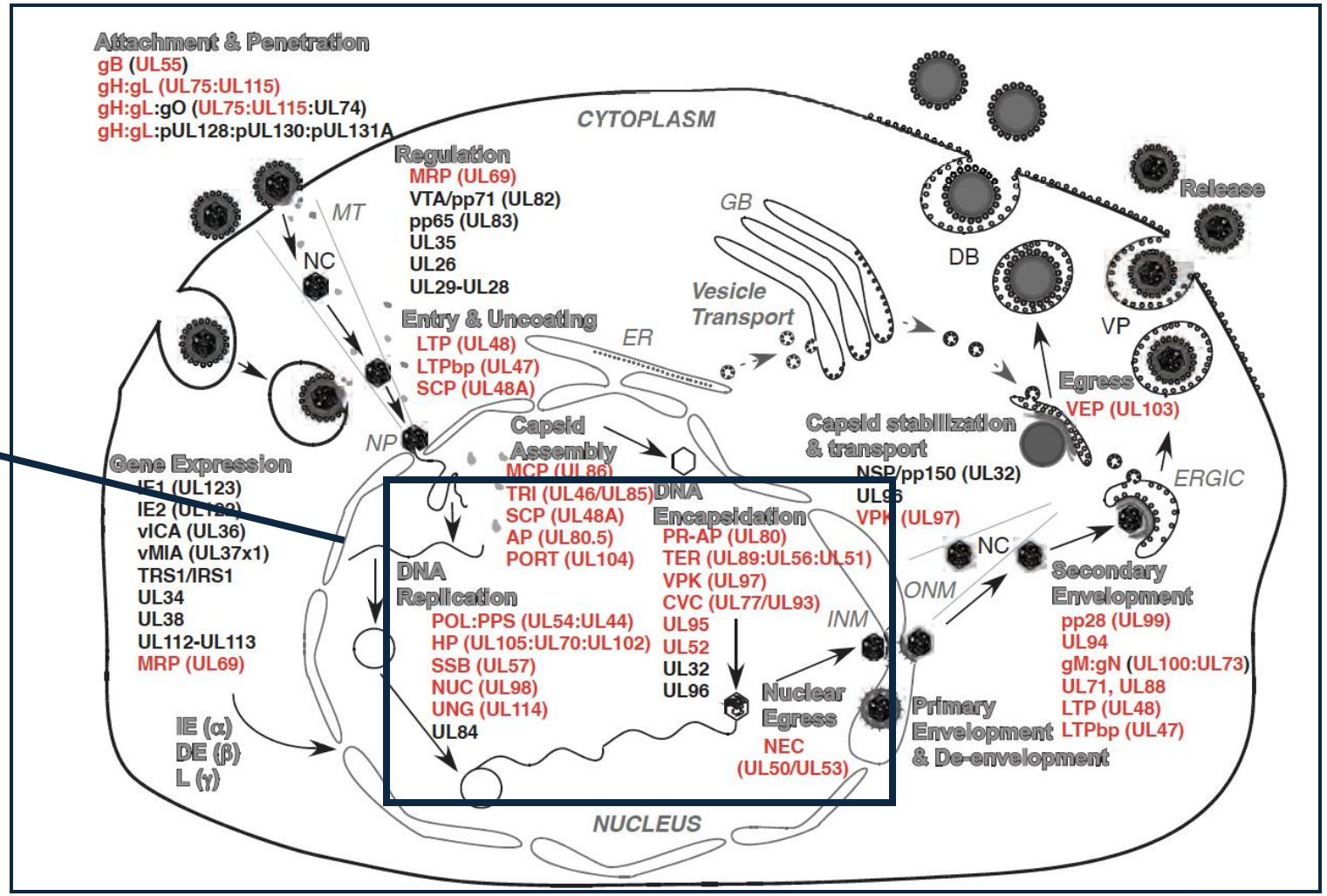
Foscarnet



Cidofovir

The “new weapons”: targets

Maribavir
Letermovir



The “new weapons”: maribavir

200 mg tablet
2 tablets q12h
with/without food

- **Inhibitor of protein kinase UL97** and its natural substrates, thus inhibiting CMV DNA replication, encapsidation, and nuclear egress
- *In vivo* and *in vitro* activity against CMV strains which are resistant to ganciclovir, valganciclovir, cidofovir, and foscarnet

- No dose adjustment required for patients with mild, moderate or severe renal impairment
- No dose adjustments is expected to be required for patients on dialysis due to the high plasma protein binding

- No dose adjustment required for patients with mild (Child-Pugh Class A) or moderate hepatic impairment (Child-Pugh Class B)
- Administration in patients with severe hepatic impairment (Child-Pugh Class C) has not been studied

- No data in pts < 18 years of age
- No data in pregnancy/lactation

- Adverse events: taste disturbance (46%), nausea (21%), diarrhoea (19%), vomiting (14%), fatigue (12%)

Approved by FDA/EMA for treatment of CMV disease due to resistant/refractory CMV in HSCT/SOT recipients

Maribavir drug-drug interactions

TABLE 1 Significant drug-drug interactions with maribavir[a]

Drug class/drug name	Interaction effect	Recommendation for administration with maribavir
Antiarrhythmics		
Digoxin	Increased digoxin concn[c]	Co-administer with maribavir with caution. Monitor digoxin levels while on maribavir treatment
Antiepileptics		
Carbemazepine	Decreased maribavir concn	Increase maribavir dose to 800 mg twice daily
Phenytoin	Decreased maribavir concn	Increase maribavir dose to 1,200 mg twice daily
Phenobarbital	Decreased maribavir concn	Increase maribavir dose to 1,200 mg twice daily
Antimycobacterials		
Rifabutin	Decreased maribavir concn	Avoid co-administration with maribavir
Rifampin	Decreased maribavir concn	Avoid co-administration with maribavir
Antivirals		
Valganciclovir/ganciclovir	Antiviral antagonism	Avoid co-administration with maribavir
HMG-CoA reductase[b] inhibitors		
Rosuvastatin	Increased rosuvastatin concn	Monitor for adverse effects of rosuvastatin (ie. myopathy, rhabdomyolysis)
Immunosuppressants		
Cyclosporine	Increased cyclosporine concn	Monitor immunosuppressant levels throughout maribavir treatment, especially following maribavir initiation and discontinuation
Everolimus	Increased everolimus concn	
Sirolimus	Increased sirolimus concn	
Tacrolimus	Increased tacrolimus concn	

[a]Adapted from Takeda Liventicity prescribing information (50).
[b]β-Hydroxy β-methylglutaryl-CoA reductase.
[c]concn, concentration.

TDM !

Dosage adjustment:

- 1200 mg q12h when it is co-administered with **phenobarbital**, **primidone**, or **phenytoin**
- 800 mg q12h when it is co-administered with **carbamazepine**
- No adjustment required while co-administered with **voriconazole**

Halpern-Cohen and Blumberg, *AAC* 2022

Maribavir: registration study

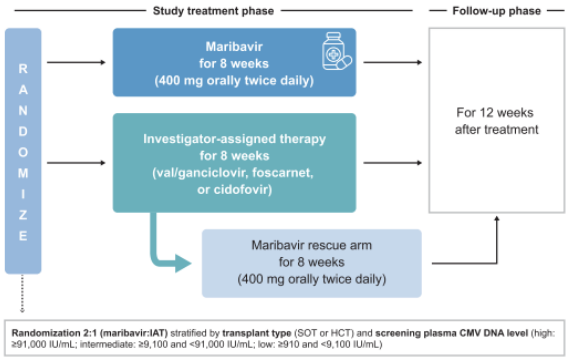
Maribavir for Refractory Cytomegalovirus Infections With or Without Resistance Post-Transplant: Results from a Phase 3 Randomized Clinical Trial

Robin K. Avery, Sophie Alain, Barbara D. Alexander, Emily A. Blumberg, Roy F. Chemaly, Catherine Cordonnier, Rafael F. Duarte, Diana F. Florescu, Nassim Kamar, Deepali Kumar, Johan Maertens, Francisco M. Marty, Genovefa A. Papanicolaou, Fernanda P. Silveira, Oliver Witzke, Jingyang Wu, Aimee K. Sundberg, and Martha Fournier, for the SOLSTICE Trial Investigators

INTRODUCTION

This was a phase 3, multicenter, randomized, open-label, active-controlled study to assess the efficacy and safety of maribavir compared with IAT in HCT and SOT recipients with CMV infections refractory to most recent treatment, with or without resistance to ganciclovir/valganciclovir, foscarnet, and/or cidofovir.

STUDY DESIGN



STUDY ENDPOINTS

The primary endpoint was confirmed CMV viremia clearance at the end of Week 8 (regardless of premature treatment discontinuation).

The key secondary endpoint was a composite of confirmed CMV viremia clearance and symptom control at the end of Week 8, maintained through Week 16 after receiving exclusively study-assigned treatment.

RESULTS

352 patients were randomized (maribavir, n=235; IAT, n=117)

PRIMARY ENDPOINT (WEEK 8)

Adjusted difference (95% CI): 32.8 (22.80–42.74)

A significantly higher proportion of patients treated with maribavir achieved the primary endpoint of confirmed CMV viremia clearance at Week 8 compared with IAT.

KEY SECONDARY ENDPOINT (WEEK 16)

Adjusted difference (95% CI): 9.5 (2.02–16.88)

A greater proportion of patients treated with maribavir achieved the composite key secondary endpoint of CMV viremia clearance and symptom control at Week 8, with maintenance through Week 16 compared with IAT.

SAFETY

Median (range) duration of exposure was 57 (2–64) days with maribavir and 34 (4–64) days with IAT.

Fewer patients discontinued maribavir than IAT due to TEAEs (13.2% vs 31.9%).

Dysgeusia was the most frequently reported TEAE in the maribavir group (maribavir: 37.2%; IAT: 3.4%).

Maribavir was associated with less acute kidney injury versus foscarnet (8.5% vs 21.3%) and neutropenia versus valganciclovir/ganciclovir (9.4% vs 33.9%).

One patient per treatment group had fatal treatment-related TEAEs.

CONCLUSIONS

Maribavir was superior to IAT for cytomegalovirus viremia clearance, and viremia clearance plus symptom control, with maintenance of these effects post-therapy in transplant recipients with refractory cytomegalovirus infections with or without resistance.

Maribavir demonstrated an improved safety profile versus valganciclovir/ganciclovir for myelotoxicity and versus foscarnet for nephrotoxicity, with fewer patients discontinuing maribavir than IAT.

The availability of an orally bioavailable therapy without the tolerability issues associated with current therapies may confer patient management benefits.

CMV, cytomegalovirus; HCT, hematopoietic-cell transplant; IAT, investigator-assigned therapy; SOT, solid-organ transplant; TEAE, treatment-emergent adverse event.

ClinicalTrials.gov: NCT02931539
This study was funded by Takeda Development Center Americas, Inc., Lexington, MA

Maribavir: resistances emerges under treatment

- **26% of transplant recipients** receiving up to 8 weeks of maribavir therapy for CMV infection after failing conventional therapy developed genotypic evidence of maribavir resistance.
- Treatment non-responders, particularly those who experienced **a viral load rebound while on therapy**, were at higher risk and merit closer monitoring for resistance.
- The most common genotypic resistance markers for maribavir resistance are confirmed to **be UL97 T409M, H411Y, and C480F**.
- Baseline resistance to standard therapy (IAT) did not preclude a treatment response to maribavir
- A majority of those who developed maribavir resistance eventually achieved viremia clearance with alternative therapy.

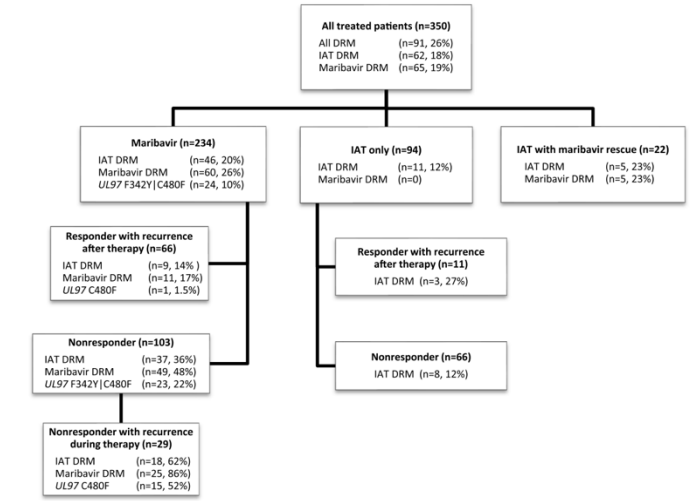


Figure 2. Treatment-emergent drug resistance mutations by patient category. Each treatment and outcome category is listed in bold with the number of patients (n). The number and percent of each group that developed maribavir-DRMs or IAT-DRMs is listed. *UL97* F342Y and C480F are counted under both maribavir-DRMs and IAT-DRMs, and also listed separately if present. Abbreviations: DRM, drug resistance mutation; IAT, investigator-assigned therapy.

Table 1. Distribution of Treatment-Emergent Maribavir DRM

rMed	Gene	Amino Acid Substitution	n	Fold Increase Maribavir EC_{50}	Reference for EC_{50}
IAT[a]	*UL97*	T409M	4	78–90	[10, 15]
IAT[a]	*UL97*	H411L	1	69	[18]
IAT[a]	*UL97*	H411Y	2	12–18	[15, 18]
Maribavir	*UL97*	F342Y[b]	3	4.5	[15]
Maribavir	*UL97*	T409M	30	78–90	[10, 15]
Maribavir	*UL97*	H411L	1	69	[18]
Maribavir	*UL97*	H411N	3	9	[18]
Maribavir	*UL97*	H411Y	24	12–18	[15, 18]
Maribavir	*UL97*	C480F[c]	21	224	[10]

Abbreviations: EC_{50}, drug concentration that reduces viral growth by 50%; DRM, drug resistance mutation; IAT, investigator-assigned therapy; rMed, randomized medication assignment.

[a]Genotyped after receiving maribavir rescue.

[b]Also has 6-fold increased ganciclovir EC_{50}.

[c]Also has 2.3-fold increased ganciclovir EC_{50}.

Chou et al. *JID* 2024

Maribavir: AURORA study (i)

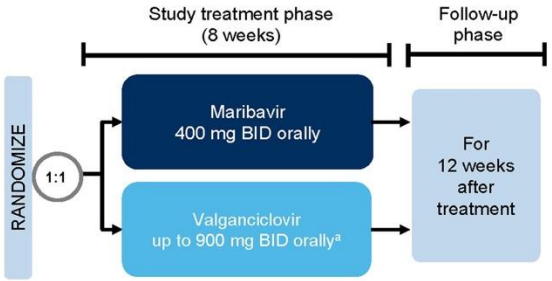
Treatment for First Cytomegalovirus Infection Post-Hematopoietic Cell Transplant in the AURORA Trial: A Multicenter, Double-Blind, Randomized, Phase 3 Trial Comparing Maribavir with Valganciclovir

Genovefa A. Papanicolaou, Robin K. Avery, Catherine Cordonnier, Rafael F. Duarte, Shariq Haider, Johan Maertens, Karl S. Peggs, Carlos Solano, Jo-Anne H. Young, Martha Fournier, Rose Ann Murray, Jingyang Wu, and Drew J. Winston, for the AURORA Trial Investigators

OBJECTIVE

This was a phase 3, randomized, multicenter, double-blind, double-dummy, active-controlled study to compare the efficacy and safety of maribavir with valganciclovir for pre-emptive treatment of first documented asymptomatic CMV infection following HCT.

STUDY DESIGN



Randomization stratified by **screening plasma** (or equivalent whole blood) **CMV DNA concentration** (high, ≥9100 IU/mL to ≤91 000 IU/mL; low, ≥910 IU/mL to <9100 IU/mL; very low, ≥455 IU/mL to <910 IU/mL) and **presence or absence of acute GVHD**.

STUDY ENDPOINTS

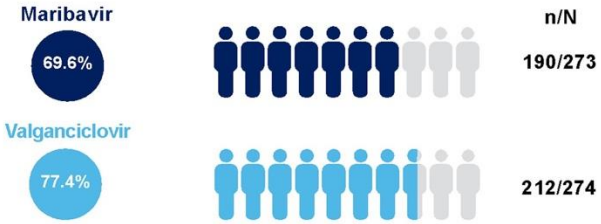
Primary endpoint: Confirmed CMV viremia clearance at week 8 (prespecified non-inferiority margin of 7.0%).

Key secondary endpoint: Achievement of CMV viremia clearance with no clinical findings of CMV tissue-invasive disease at week 8, maintained through week 16.

RESULTS

553 patients randomized; analyses were performed in patients who received treatment (maribavir, n=273; valganciclovir, n=274)

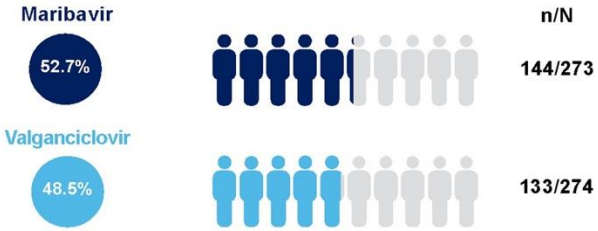
Primary endpoint (week 8)



Adjusted difference (95% CI): −7.7% (−14.98, −0.36)

Non-inferiority of maribavir to valganciclovir for the primary endpoint was not met based on the prespecified margin of 7.0%.

Key secondary endpoint (week 16)



Adjusted difference (95% CI): 4.4% (−3.91, 12.76)

In both arms, a similar proportion of patients achieved CMV viremia clearance with no clinical findings of CMV tissue-invasive disease at week 8, maintained through week 16.

SAFETY

In both arms, 98.2% of patients had ≥1 TEAE.
- Treatment-related TEAEs were more common with valganciclovir than maribavir (61.3% vs 54.2%).

Neutropenia was less common with maribavir than valganciclovir (16.1% vs 52.9%).

Fewer patients discontinued maribavir than valganciclovir due to a TEAE (27.8% vs 41.2%).

Neutropenia was the most common reason for discontinuation with maribavir (4.0%) and valganciclovir (17.5%).

CONCLUSIONS

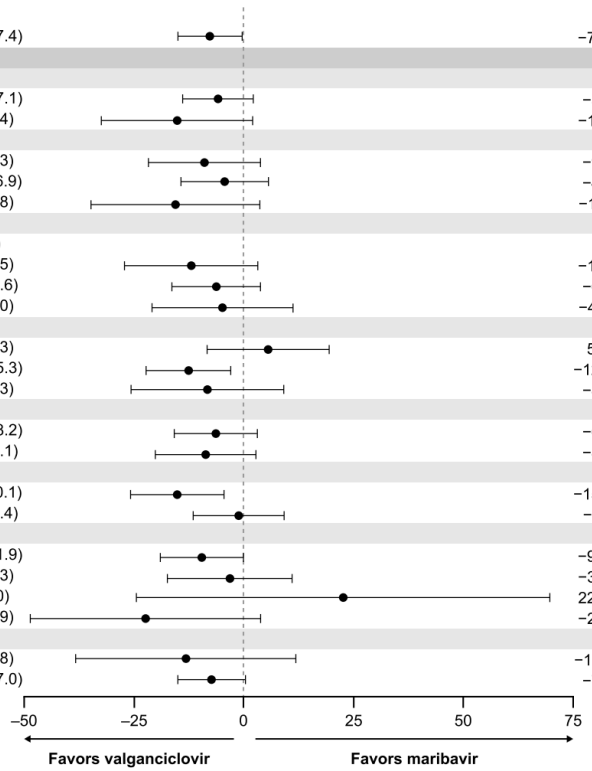
- At week 8, maribavir did not demonstrate non-inferiority to valganciclovir for achievement of CMV viremia clearance based on a prespecified margin of 7.0%.
- Maribavir demonstrated a comparable treatment effect to valganciclovir post-therapy.
- Maribavir was associated with a lower rate of treatment discontinuation due to neutropenia than valganciclovir.

[a]Dose adjustments were allowed for moderate renal impairment.

Abbreviations: BID, twice daily; CI, confidence interval; CMV, cytomegalovirus; GVHD, graft versus host disease; HCT, hematopoietic cell transplant; TEAE, treatment-emergent adverse event. **Funding**: Takeda Development Center Americas, Inc., Lexington, MA.

Maribavir: AURORA study (ii)

	Maribavir (N = 273)	Valganciclovir (N = 274)	Adjusted difference in proportion of responders (95% CI), *P*-value
Primary endpoint: Confirmed CMV viremia clearance at week 8	190/273 (69.6)	212/274 (77.4)	−7.7 (−14.98. −0.36), .040
Subgroup analyses	n/N (%) of responders		
Acute GVHD			
Absent	157/221 (71.0)	172/223 (77.1)	−5.9 (−13.96, 2.13), .150
Present	33/52 (63.5)	40/51 (78.4)	−15.2 (−32.45, 1.96), .083
CMV DNA viral load			
Very low	58/78 (74.4)	65/78 (83.3)	−9.0 (−21.74, 3.75), .167
Low	105/145 (72.4)	113/147 (76.9)	−4.4 (−14.35, 5.58), .388
High	26/49 (53.1)	33/48 (68.8)	−15.6 (−34.80, 3.62), .112
Age group			
<18 years	0/1 (NA)	2/3 (NA)	NA
18–44 years	39/57 (68.4)	62/78 (79.5)	−12.0 (−27.18, 3.14), .120
45–64 years	110/157 (70.1)	97/125 (77.6)	−6.3 (−16.40, 3.76), .219
☒65 years	41/58 (70.7)	51/68 (75.0)	−4.9 (−20.93, 11.18), .552
Enrolling region			
North America	55/66 (83.3)	46/58 (79.3)	5.5 (−8.37, 19.39), .437
Europe	99/159 (62.3)	131/174 (75.3)	−12.6 (−22.29, −3.00), .010
Asia	36/48 (75.0)	35/42 (83.3)	−8.3 (−25.68, 9.08), .349
Sex			
Male	106/148 (71.6)	129/165 (78.2)	−6.4 (−15.87, 2.99), .181
Female	84/125 (67.2)	83/109 (76.1)	−8.7 (−20.17, 2.74), .136
Use of T-cell depletion therapy			
Yes	82/127 (64.6)	113/141 (80.1)	−15.2 (−25.79, −4.54), .005
No	108/146 (74.0)	99/133 (74.4)	−1.2 (−11.57, 9.15), .819
CMV serostatus			
Donor +/recipient +	102/138 (73.9)	127/155 (81.9)	−9.6 (−19.03, −0.07), .048
Donor −/recipient +	61/98 (62.2)	55/83 (66.3)	−3.2 (−17.42, 10.94), .654
Donor −/recipient −	8/10 (80.0)	7/10 (70.0)	22.6 (−24.47, 69.63), .347
Donor +/recipient −	14/20 (70.0)	20/22 (90.9)	−22.4 (−48.64, 3.81), .094
History of CMV prophylaxis			
Yes	18/26 (69.2)	18/22 (81.8)	−13.2 (−38.29, 11.82), .301
No	172/247 (69.6)	194/252 (77.0)	−7.4 (−15.05, 0.34), .061



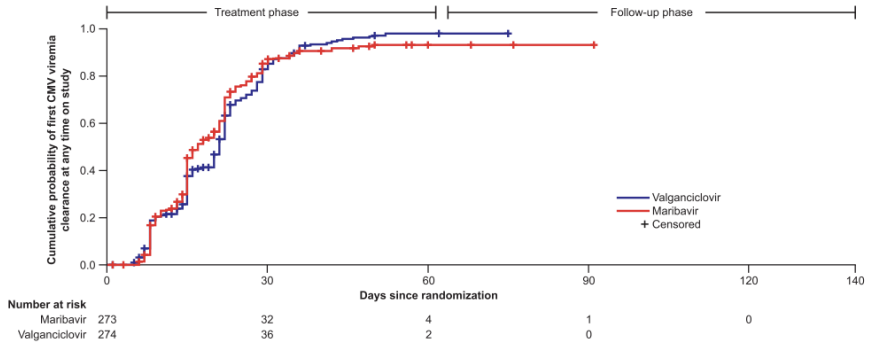


Figure 5. Cumulative probability of first CMV viremia clearance at any time on study by treatment arm (Modified Randomized Population). Abbreviation: CMV, cytomegalovirus.

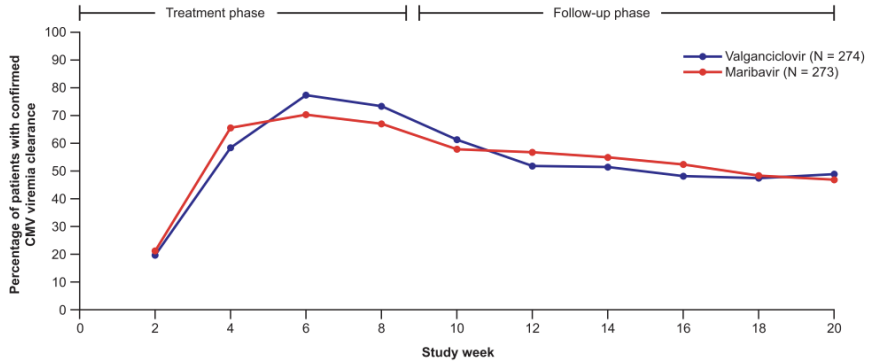


Figure 6. Percentage of patients with confirmed CMV viremia clearance by study week and treatment arm (Modified Randomized Population; post hoc analysis). A post hoc analysis of patients with confirmed CMV viremia clearance by study week for the 2 treatment arms was performed by calculating the proportion of patients with CMV DNA below the lower limit of quantification at that visit and consecutive prior visits spanning 5 days (ie, confirmed viremia clearance by central laboratory) for each treatment arm. Abbreviation: CMV, cytomegalovirus.

Maribavir: AURORA study (iii)

- **Treatment-emergent resistance** occurred in **8.8% and 2.9% of patients in the maribavir and valganciclovir arms**, respectively; 21 patients in the maribavir arm and 4 in the valganciclovir arm who developed treatment-emergent mutations did not achieve the primary endpoint.
- Of the 14 patients with CMV viremia recurrence on maribavir treatment, 12 (85.7%) had treatment-emergent resistance mutations. No patients treated with valganciclovir had a recurrence on treatment.

Supplementary Table 3. Identified Treatment-Emergent[a] Known or Suspected RASs to Maribavir[b]

	Valganciclovir (N=274) n (%)	Maribavir (N=273) n (%)
Single maribavir RAS in only pUL97		
T409M	0	12 (4.4)
H411Y	0	6 (2.2)
Multiple maribavir RASs in only pUL97		
T409M+H411Y	0	5 (1.8)
T409M+C480F	0	1 (0.4)
T409M+C480R	1 (0.4)	0

Maribavir resistance: real-life data in SOT

Table 1. Baseline Characteristics and Outcomes of Solid Organ Transplant Recipients Who Received Maribavir for Refractory/Resistant Cytomegalovirus Infection

Patient ID	Age, y	Sex	Race	SOT Type	CMV Infection Classification[a]	Reason for Change to MBV	Genotypic Resistance	CMV VL at MBV Start, IU/mL	CMV VL at MBV End, IU/mL	MBV Duration for Episode, d	MBV Outcome	Time to Relapse, d	MBV Resistance	Outcome up to 1 y
Successful treatment with MBV														
A	57	M	B	Lung	DNAemia	Prior refractory w/ resistance	Not performed	840	0	105	Success	…	…	CMV ppx
B	53	F	W	Lung	DNAemia	Refractory w/resistance	UL54 C539R, S290R	3598	<200	56	Success	…	…	CMV ppx
C	72	M	W	Lung	Disease (probable pneumonitis)	Refractory w/resistance	UL97 A594V	1145	0	104	Success	…	…	CMV ppx
D	58	M	B	Heart	DNAemia	Refractory w/resistance	UL97 L595S	1434	0	124	Success	…	…	Off CMV therapies
E	54	M	W	Liver	DNAemia	Refractory	None	101 237	0	61	Success	…	…	Off CMV therapies
F	59	M	B	Liver	Disease (proven GI)	Refractory	Not performed	<200	0	59	Success	…	…	Off CMV therapies
Treatment failure or CMV recurrence within 4 wk of completing MBV														
G	45	M	B	Kidney-Pancreas	DNAemia	Refractory w/resistance	UL97 H520Q	3150	0	118	Relapse	27	Not performed	Off CMV therapies
H	57	F	B	Kidney	DNAemia	Refractory w/resistance	UL97 M460V	773	13 200	88	Failure	0	UL97 C480F	Off CMV therapies
I	23	F	B	Kidney-Liver	DNAemia	Refractory	None	1724	10 018	61	Failure	0	UL97 C480F	CMV ppx
A	57	M	B	Lung	DNAemia	Refractory w/resistance	UL97 C603W	54 288	<137	77	Relapse	13	Not performed	CMV ppx
J	41	M	B	Heart	DNAemia	Refractory w/resistance	UL54 T700A	10 200	1420[b]	60	Relapse	1	Not performed	CMV treatment
J	41	M	B	Heart	DNAemia	Refractory w/resistance	UL97 L595S	842	11 300	49	Failure	0	UL97 T409M	CMV ppx
K	61	M	W	Heart	Disease (proven GI)	Refractory w/resistance	UL97 C603W	187 506	40 600	52	Failure[c]	0	UL97 F342Y	CMV ppx
Partial response														
L	65	M	B	Kidney	DNAemia	Refractory w/resistance	UL97 L595S; UL54 A834P, V715M	254 000	939	72	Other	…	…	Off CMV therapies
M	76	M	W	Lung	Disease (probable pneumonitis)	Refractory w/resistance	UL97 L595F	13 884	391	59	Other	…	…	Deceased (unrelated to CMV)

- The study corroborates the meaningful rate (31%) of CMV recurrence observed in a separate real-world cohort of SOT recipients treated with MBV
- **Treatment failure due to the emergence of MBV resistance or virological recurrence in 47% of treatment episodes**, similar to prior MBV clinical trial experience
- Patients who experienced **treatment failure or recurrence had higher CMV viral loads** than patients for whom MBV treatment was successful.

The “new weapons”: letermovir

480 mg EV/PO q24h
PO with/without food
EV infuse in 1 hour
Pills not crushable

- Inhibitor of the **CMV-DNA terminase complex** (targeting the subunit **pUL56**)
- **Not associated with cross-resistance** to other anti-CMV agents
- **Highly specific to CMV**, not active against HSV or VZV

- No dosage adjustment in pts with ClCr>10 mL/min
- No data for patients with ClCr<10 mL/min or dialysis

- No dosage adjustment in pts with mild/moderate hepatic function impairment (Child-Pugh class A/B)
- Not recommended for patients with severe impairments (Child-Pugh class C)

- No data in pts < 18 years of age
- No data in pregnancy/lactation

- Adverse events: diarrhoea, cough, peripheral oedema, headache

Approved by FDA/EMA for prophylaxis of CMV infection and disease in adult CMV-seropositive recipients of HSCT (2017)

Letermovir: drug-drug interactions

- Letermovr should be used with caution with medicinal products that are **CYP3A substrates** with narrow therapeutic ranges (e.g., alfentanil, fentanyl, and quinidine) as co-administration may result in **increases in the plasma concentrations** of CYP3A substrates
- Increased **monitoring** of **cyclosporine, tacrolimus, sirolimus** is generally recommended the **first 2 weeks after initiating and ending letermovi**r as well as after changing route of administration of letermovir
- Therapeutic drug **monitoring is recommended for voriconazole**. Apparently, no impact on other azoles concentration
- Concomitant **use of dabigatran should be avoided** due to risk of reduced dabigatran efficacy
- Letermovir may increase the plasma concentrations of medicinal products transported by OATP1B1/3 such as many of the **statins**

EMA. Letermovir, summary of product characteristics

JAMA | Original Investigation
Letermovir vs Valganciclovir for Prophylaxis of Cytomegalovirus in High-Risk Kidney Transplant Recipients
A Randomized Clinical Trial

Letermovir: primary prophylaxis in SOT (i)

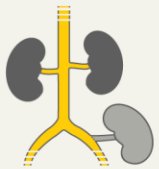
JAMA®

QUESTION Is letermovir noninferior to valganciclovir prophylaxis for cytomegalovirus (CMV) disease prevention in high-risk adult CMV-seronegative kidney transplant recipients who receive an organ from a CMV-seropositive donor?

CONCLUSION Letermovir was noninferior to valganciclovir for prophylaxis of CMV disease over 52 weeks among adult CMV-seronegative recipients who received an organ from a CMV-seropositive donor.

POPULATION

422 Men
167 Women



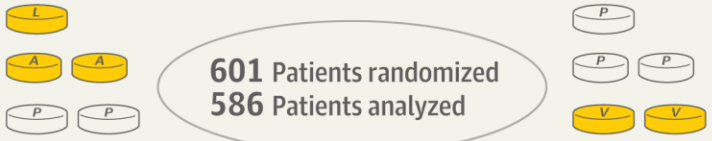
Adult CMV-seronegative kidney transplant recipients receiving an organ from a CMV-seropositive donor

Mean age: 50 years

LOCATIONS

94
Hospitals
worldwide

INTERVENTION



301
Letermovir
480 mg of letermovir orally daily, 400 mg of acyclovir twice daily, and a valganciclovir placebo

300
Valganciclovir
900 mg of valganciclovir orally daily with letermovir and acyclovir placebos

PRIMARY OUTCOME

CMV disease through 52 weeks after transplant

FINDINGS

Patients with committee-confirmed CMV through week 52

Letermovir
10.4% (30 of 289 patients)

Valganciclovir
11.8% (35 of 297 patients)

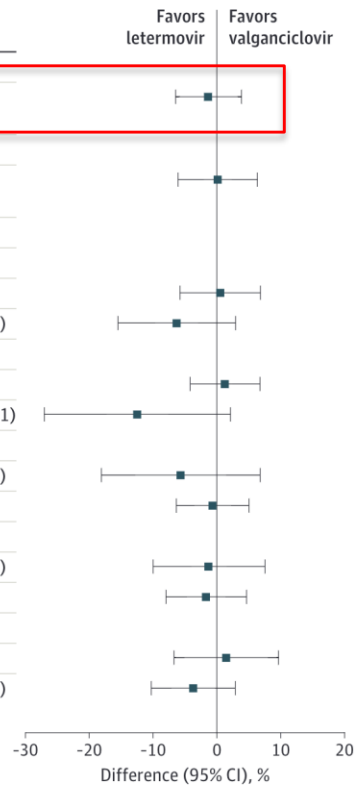
Letermovir was noninferior to valganciclovir:
Stratum-adjusted difference, −1.4%
(95% CI, −6.5% to 3.8%)

Limaye AP, Budde K, Humar A, et al. Letermovir vs valganciclovir for prophylaxis of cytomegalovirus in high-risk kidney transplant recipients: a randomized clinical trial. *JAMA*. Published online June 6, 2023. doi:10.1001/jama.2023.9106

JAMA | Original Investigation
Letermovir vs Valganciclovir for Prophylaxis of Cytomegalovirus in High-Risk Kidney Transplant Recipients
A Randomized Clinical Trial

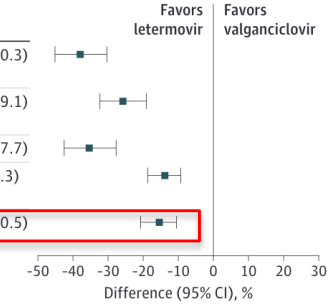
Letermovir: primary prophylaxis in SOT

	No./total No. (%)		Difference (95% CI), %[b]
	Letermovir[a]	Valganciclovir	
Primary outcome			
CMV disease[c]	30/289 (10.4)	35/297 (11.8)	-1.4 (-6.5 to 3.8) (noninferior)
Sensitivity analysis			
Investigator-reported CMV disease[d]	50/289 (17.3)	51/297 (17.2)	0.1 (-6.1 to 6.3)
Subgroup analysis			
Sex			
Men	25/210 (11.9)	24/209 (11.5)	0.5 (-5.8 to 6.8)
Women	5/79 (6.3)	11/88 (12.5)	-6.3 (-15.5 to 2.9)
Age, y			
<65	26/242 (10.7)	23/242 (9.5)	1.2 (-4.2 to 6.7)
≥65	4/47 (8.5)	12/55 (21.8)	-12.5 (-27.0 to 2.1)
Race[e]			
Non-White	2/37 (5.4)	6/53 (11.3)	-5.7 (-18.1 to 6.7)
White	28/250 (11.2)	29/243 (11.9)	-0.7 (-6.4 to 5.0)
Region			
US	15/118 (12.7)	16/116 (13.8)	-1.3 (-10.0 to 7.5)
Non-US	15/171 (8.8)	19/181 (10.5)	-1.7 (-8.0 to 4.6)
Lymphocyte-depleting induction immunosuppression			
Use	18/131 (13.7)	17/138 (12.3)	1.4 (-6.7 to 9.6)
Nonuse	12/158 (7.6)	18/159 (11.3)	-3.7 (-10.3 to 2.8)

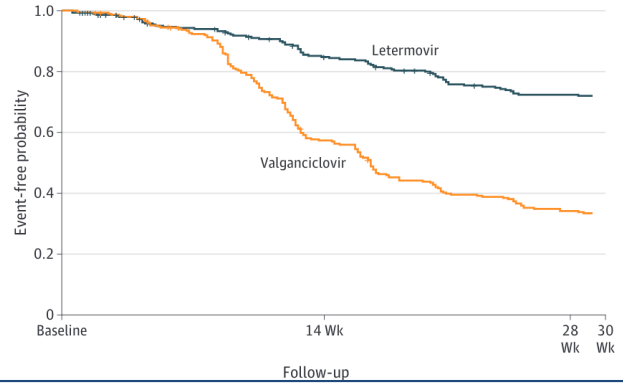


A Adverse events (AEs)

Events	No./total No. (%) Letermovir (n = 292)[a]	Valganciclovir (n = 297)	Difference (95% CI), %
≥1 leukopenia or neutropenia event[b]	76 (26.0)	190 (64.0)	-37.9 (-45.1 to -30.3)
Leukopenia reported as an AE	33 (11.3)	110 (37.0)	-25.7 (-32.3 to -19.1)
WBC count <3500 cells/μL	66 (22.6)	172 (57.9)	-35.3 (-42.5 to -27.7)
Neutropenia reported as an AE	8 (2.7)	49 (16.5)	-13.8 (-18.7 to -9.3)
ANC <1000 cells/μL	12 (4.1)	58 (19.5)	-15.4 (-20.7 to -10.5)



B Probability of no events of neutropenia or leukopenia



Resistance-associated substitutions: **none** (0/52) who received letermovir and **12.1%** (8/66) who received valganciclovir (participants evaluated for suspected CMV disease or CMV DNAemia)

Letermovir: secondary prophylaxis (i)

Case	Type of transplant	Age	Sex	CMV status	Immunosuppression (at time of letermovir initiation)	Ganciclovir resistance	Reason for (val) ganciclovir discontinuation	Outcome	Letermovir Resistance testing	Year published
1	Single lung transplant	69	M	D+/R−	Tacrolimus, prednisone	No	Leucopenia	Successful	No	2019 (Aryal)[11]
2	Bilateral lung transplant	60	M	D+/R+	Cyclosporine, prednisone	No	Leucopenia	Successful	No	2019 (Aryal)[11]
3	Single lung transplant	68	F	D+/R−	Tacrolimus, prednisone, mycofenolate mofetil	No	Leucopenia	Successful	No	2019 (Aryal)[11]
4	Bilateral lung transplant	59	F	D+/R−	Tacrolimus, prednisone	No	Leucopenia	Failure	No	2019 (Aryal)[11]
5	Bilateral lung transplant	63	F	D+/R−	Tacrolimus, prednisone	No	Leucopenia	Failure	No	2019 (Aryal)[11]
6	Single lung transplant	67	F	D+/R−	Tacrolimus, prednisone	Yes (UL97, not specified)	Resistance	Failure	No	2019 (Aryal)[11]
7	Heart transplant	60	M	D+/R−	Tacrolimus, prednisone	Yes (UL97 C603W)	Resistance	Successful	No	2018 (Chong)[12]

Letermovir: secondary prophylaxis (ii)

Study	Year	Patients	SOT	CMV serostatus	Immunosuppressors	Previous treatment(s)	Treatment duration (wks)	Outcome	Resistance
Hofman et al.	2018	2	KiTx	1) D+/R- 2) D+/R-	1) PDN MMF FK506 CYP 2) CYP AZA PDN	1) VCGV FOS 2) VCGV GCV FOS	1) 106 2) 98	1) Failure 2) Death	1) UL56 C325Y 2) UL56 C325Y

Column1	Age (Y)	Sex	Transplant Type	Underlying Disease	CMV Status	Induction Regimen	Applied IST[a]	Prior CMV Infection	Prior CMV Therapies	CMV Drug Resistance
Pt 5[b]	30	F	Kidney[c]	Congenital nephrotic syndrome	D+/R−	ATG	Tacrolimus, prednisone 5 mg, belatacept	DNAemia (max VL 158,060 IU/mL)	GCV	None
							Tacrolimus, prednisone 1250 mg	DNAemia (max VL 2150 IU/mL)	GCV, FOS, VAL, IVIG	None
							Prednisone 1250 mg	DNAemia (max VL 199 IU/mL)	GCV	NA
Pt 6	47	M	Kidney[c]	FSGS	D+/R−	ATG	Tacrolimus, prednisone 10 mg[d]	DNAemia (max VL 8282 IU/mL)	GCV, FOS, VAL	UL97 mutation at L595S and C603W
Pt 7	26	M	Kidney	FSGS	D+/R−	ATG	MMF, tacrolimus, prednisone 10 mg	DNAemia (max VL 1949 IU/mL)	VAL	UL97 mutation at A594V
Pt 8	28	M	Kidney	Nephronopthisis	D+/R-	Steroids	MMF, tacrolimus, prednisone 5 mg, ATG	DNAemia (max VL 13580 IU/mL)	GCV, FOS, VAL	UL97 mutation at L595F
Pt 9[‡]	35	F	Multivisceral[e]	Autoimmune hepatitis, ulcerative colitis	D+/R−	ATG	MMF, tacrolimus, prednisone 80 mg	DNAemia (max VL 1505 IU/mL)	GCV	NA
Pt 10	40	F	Kidney[f]	CNI toxicity	D+/R−	Basiliximab	Tacrolimus, prednisone 5 mg	DNAemia (max VL 1370 IU/mL)	GCV, VAL	None

	LTV Dosage (mg)	LTV Start Date (days Post-tx)	LTV Rationale	LTV Duration (days)	Reason for LTV Discontinuation	Details of csCMVi	LTV Resistance Testing
Pt 5	720	1576	Cytopenias	16	Breakthrough csCMVi, GI intolerance, fatigue	DNAemia (1369 IU/mL)	NA
	480	1735	Cytopenias, AKI	8	Breakthrough csCMVi	DNAemia (199 IU/mL)	None
	480	1765	Cytopenias	73[g]	NA, remains on therapy	NA	NA
Pt 6	720 -> 480[h]	165	Resistance	289[g]	NA, remains on therapy	NA[j]	NA
Pt 7	480	376	Resistance	128[g]	NA, remains on therapy	NA[k]	NA
Pt 8	480 -> 720[i]	172	Resistance	81	Breakthrough csCMVi	DNAemia (4753 IU/mL)	Positive, UL56 mutation at C325F
Pt 9	720 -> 480[h]	212	Cytopenias	230	Breakthrough csCMVi	CMV encephalitis/ ventriculitis	NA
Pt10	480	2572	Cytopenias	20	Breakthrough csCMVi	DNAemia (885 IU/mL)	None

Hofmann et al. *TID* 2021
Ibrahim et al. *J Pharm Practice* 2023

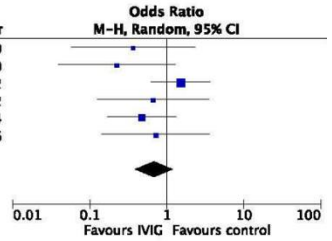
Immunoglobulins: polyclonal Ig

Kidney Tx

2a) CMV infection

Study or Subgroup	IVIG Events	IVIG Total	Control Events	Control Total	Weight	Odds Ratio M-H, Random, 95% CI	Year
Kasiske 1989	10	15	11	13	9.0%	0.36 [0.06, 2.31]	1989
Steinmuller 1990	2	16	7	18	9.9%	0.22 [0.04, 1.30]	1990
Stippel 1992	19	40	15	40	33.0%	1.51 [0.62, 3.68]	1992
McCune 1992	3	13	5	16	10.9%	0.66 [0.12, 3.50]	1992
Conti 1994	7	27	20	47	25.7%	0.47 [0.17, 1.33]	1994
Staak 2006	3	25	4	25	11.6%	0.72 [0.14, 3.59]	2006
Total (95% CI)		**136**		**159**	**100.0%**	**0.68 [0.39, 1.21]**	
Total events	44		62				

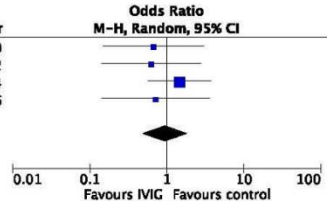
Heterogeneity: $Tau^2 = 0.05$; $Chi^2 = 5.49$, df = 5 (P = 0.36); $I^2 = 9\%$
Test for overall effect: Z = 1.31 (P = 0.19)



2b) Acute graft rejection

Study or Subgroup	IVIG Events	IVIG Total	Control Events	Control Total	Weight	Odds Ratio M-H, Random, 95% CI	Year
Steinmuller 1990	4	16	6	18	18.7%	0.67 [0.15, 2.98]	1990
McCune 1992	5	13	8	16	18.9%	0.63 [0.14, 2.76]	1992
Conti 1994	14	27	20	47	46.3%	1.45 [0.56, 3.76]	1994
Staak 2006	3	25	4	25	16.1%	0.72 [0.14, 3.59]	2006
Total (95% CI)		**81**		**106**	**100.0%**	**0.96 [0.50, 1.82]**	
Total events	26		38				

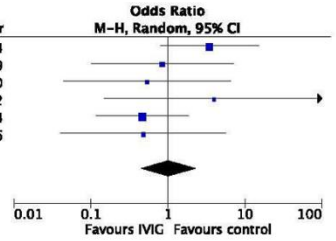
Heterogeneity: $Tau^2 = 0.00$; $Chi^2 = 1.41$, df = 3 (P = 0.70); $I^2 = 0\%$
Test for overall effect: Z = 0.14 (P = 0.89)



2c) Graft loss

Study or Subgroup	IVIG Events	IVIG Total	Control Events	Control Total	Weight	Odds Ratio M-H, Random, 95% CI	Year
Steiner 1984	8	25	3	25	28.1%	3.45 [0.79, 15.01]	1984
Kasiske 1989	2	15	2	13	14.0%	0.85 [0.10, 7.04]	1989
Steinmuller 1990	1	16	2	18	10.2%	0.53 [0.04, 6.51]	1990
McCune 1992	1	13	0	16	6.0%	3.96 [0.15, 105.65]	1992
Conti 1994	3	27	10	47	31.3%	0.46 [0.12, 1.85]	1994
Staak 2006	1	25	2	25	10.4%	0.48 [0.04, 5.65]	2006
Total (95% CI)		**121**		**144**	**100.0%**	**1.03 [0.46, 2.30]**	
Total events	16		19				

Heterogeneity: $Tau^2 = 0.04$; $Chi^2 = 5.19$, df = 5 (P = 0.39); $I^2 = 4\%$
Test for overall effect: Z = 0.06 (P = 0.95)

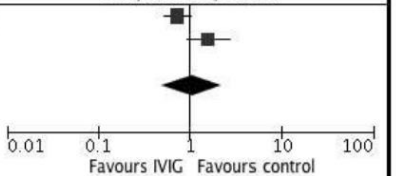


Lung Tx

Mortality

Study or Subgroup	IVIG Events	IVIG Total	Control Events	Control Total	Weight	Odds Ratio M-H, Random, 95% CI	Year
Tsuang 2014	82	265	125	330	53.6%	0.73 [0.52, 1.04]	2014
Lichvar 2015	146	216	43	76	46.4%	1.60 [0.94, 2.73]	2015
Total (95% CI)		**481**		**406**	**100.0%**	**1.05 [0.49, 2.26]**	
Total events	228		168				

Heterogeneity: $Tau^2 = 0.25$; $Chi^2 = 5.76$, df = 1 (P = 0.02); $I^2 = 83\%$
Test for overall effect: Z = 0.14 (P = 0.89)

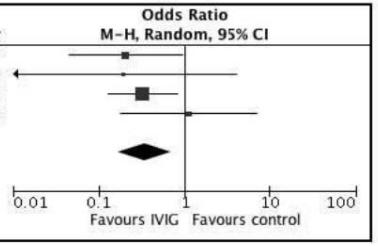


Heart Tx

Mortality

Study or Subgroup	IVIG Events	IVIG Total	Control Events	Control Total	Weight	Odds Ratio M-H, Random, 95% CI	Year
Carbone 2007	2	29	25	94	22.2%	0.20 [0.05, 0.92]	2007
Carbone 2012	0	55	2	55	5.4%	0.19 [0.01, 4.11]	2012
Carbone 2015	6	71	28	126	57.5%	0.32 [0.13, 0.82]	2015
Sarmiento 2016	3	12	3	13	14.9%	1.11 [0.18, 6.97]	2016
Total (95% CI)		**167**		**288**	**100.0%**	**0.34 [0.17, 0.69]**	
Total events	11		58				

Heterogeneity: $Tau^2 = 0.00$; $Chi^2 = 2.20$, df = 3 (P = 0.53); $I^2 = 0\%$
Test for overall effect: Z = 2.97 (P = 0.003)



Immunoglobulins: CMVIG

TABLE 2.
Comparative studies of CMVIG in heart transplantation

First author/year	Study design	Treatment groups	Antiviral therapy	No. patients	CMV outcome/s	Other outcomes
Prophylactic approach						
Potena et al/2006[18]	Prospective SC	D+/R–: CMVIG	IV GCV (10mg/kg per day x 2 wk, 6 mg/kg per day x 2wk) + (val)GCV (450-900 mg per day) for total GCV/(val)GCV mean 73 days	21	CMV infection: **73%** vs 94% $P = 0.038$	Reduced risk of AR ≥3A (RR [95% CI] 0.55 [0.26-0.96]; ($P = 0.03$), Slowed CAV progression: VVC ($P = 0.04$), LV ($P = 0.06$)
		R+: None	IV GCV (10mg/kg per day x 2 wk, 6 mg/kg per day x 2wk)	45		
Bonaros et al/2004[19]	Retrospective SC	D+/R–: CMVIG	IV GCV (10 mg/kg per day for 21 d)	111	CMV disease: 11.7% vs 32.3% ($P = 0.0003$)	CAV: 0.9% vs 7.3% ($P = 0.016$)
		D+/R–: CMVIG	None	96	CMV-related death: 0% vs 4.2% ($P = 0.033$) CMV infection: vs 66% vs 53% (P = n.s.)	Overall infection: 62.2% vs 70.8% ($P = 0.03$)
Valantine et al/2001[20]	Retrospective SC	D+/R–: CMVIG	IV GCV (10 mg/kg per day for 2 wk 6 mg/kg per day for 2 wk)	27	CMV disease: 24% vs 61% ($P = 0.002$)	Survival: 91% vs 63% ($P = 0.02$) AR: 66% vs 89% ($P < 0.05$)
		D+/R–: None		27		
Aguado et al/1995[21]	Prospective randomized SC	R+: CMVIG	None	15	CMV disease[a]: 40% vs 6% ($P = 0.03$)	Mortality rate by 6 mo: 13% vs 6% (P = n.s.)
		R+: None	IV GCV (10 mg/kg per day for 14 d)	16		
Response to hypogammaglobulinemia						
Yamani et al/2005[22]	Prospective randomized[b] SC	CMVIG	Both groups: D+ and D-/R+: (val). GCV 1800 mg/d for 2 wk, 900 mg/d for 2 wk) D–/R–: acyclovir (600 mg/d for 4 wk)	13	CMV infection: 15.4% vs 60.0% ($P = 0.039$)	No. AR (grade ≥2): 0.4 vs 1.4 ($P = 0.065$)
		Placebo		10		
Preemptive approach						
Vrtovec et al/2004[23]	Prospective randomized SC	R+ : CMVIG	None	14	CMV disease: 0% vs 0%	Mean number of AR: 0.52 vs 0.50 (P = n.s.)
		R+: none	IV GCV (10 mg/kg per day until negative CMV antigenemia; mean 12.3 d)	23		

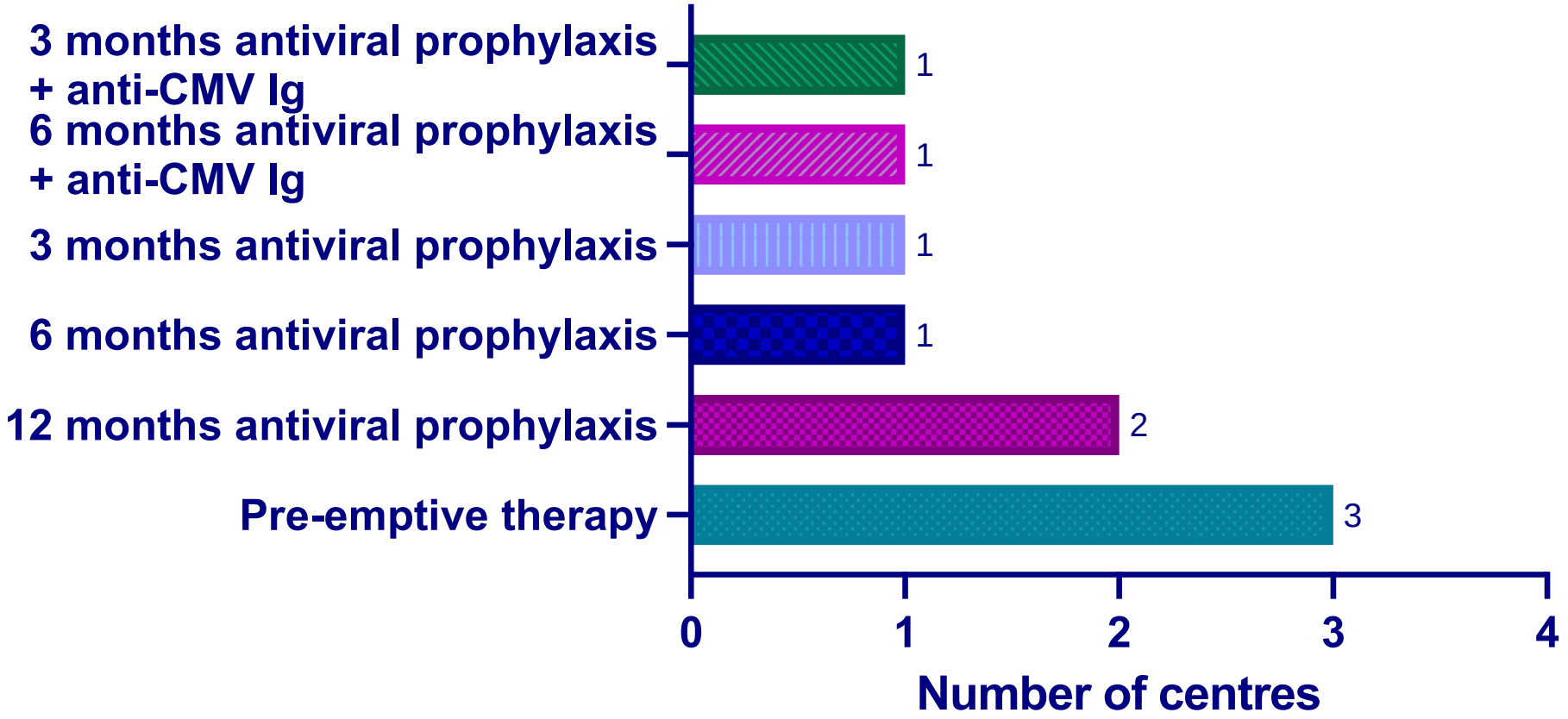
TABLE 3.
Comparative studies of CMVIG in lung and heart-lung transplantation

First author/year	Study design	Treatment groups	Antiviral therapy	No. patients	CMV outcome/s	Other outcomes
Solidoro et al/2011[34]	Retrospective SC unselected recipients	CMVIG	IV GCV (3 g/d) or (val)GCV (1.8 g/d) for 3 wk; IV GCV (10 mg/kg per day) for ≥1 mo if CMV infection was detected) Acyclovir (20 mg/kg per day); IV GCV (10 mg/kg per day) for ≥1 mo if CMV infection was detected)	33	CMV pneumonia (% of biopsies). Month 1: 9.1% vs 8.3% (P = n.s.). Month from 1 to 12: 1% vs 6.4% ($P = 0.048$). Month from 1 to 24:0.8% vs 6.5% ($P = 0.018$)	
		None		24		
Ranganathan et al/2009[35]	Retrospective MT unselected pediatric recipients	CMVIG	IV GCV (dose not stated: median 2.9 mo)	62	CMV infection: 8% vs 27%. CMV disease: 23% vs 23%. Multivariate analysis: high risk of CMV infection in recipients without CMVIG (HR, 3.4; 95% CI, 1.2-9.5)	No effect on AR/BOS/ survival
		None	IV GCV (dose not stated: median 1.6 mo)	267		
Solidoro et al/2008[36]	Retrospective SC unselected recipients	CMVIG + oral	GCV or (val)GCV (doses not stated for 3 wk) or if CMV infection was detected Acyclovir (dose not stated) for ≤12 mo) with GCV if CMV infection was detected	21	CMV pneumonia: 2% vs 7%, P = n.s.	LB 2% vs 11% ($P = 0.04$). AR 6% vs 17% ($P = 0.04$). OB 5% vs 5% (n.s.)
		None		25		
Ruttmann et al/2006[37]	Retrospective SC D+/R– or D+/R+	CMVIG	Both groups: IV GCV (10 mg/kg per day for 14 d) then oral GCV (3 g/d) or (val)GCV (1.8 g/d) to day 100	38	CMV infection: 18.5% vs 47.9% ($P = 0.027$). CMV-related death: 0% vs 16.7% ($P = 0.014$). CMV disease: 13.2% vs 43.3% ($P = 0.007$)	Survival: 71.5% vs 40% ($P = 0.013$) BOS: 18% vs 45.7% ($P = 0.024$)
		None		30		
Weill et al/2003[38]	Retrospective SC (excluded D-/R–)	CMVIG + IV/oral GCV	Both groups: R+: IV GCV (10 mg/kg per day) for 2 wk, oral GCV for 4 w; R–: IV GCV (10 mg/kg per day) for 6 wk, oral GCV for 6 wk	38	CMV disease 8% vs 33% ($P = 0.008$)	AR: 66% vs 79% (P = n.s.)
		IV/oral GCV		48		
Kruger/2003[33]	Prospective[#] Randomized R+	CMVIG	Both groups: none	22	CMV viremia: 73% vs 59% ($P = 0.19$) CMV pneumonitis: 50% vs 36% ($P = 0.54$)	Survival: 91% vs 82% ($P = 0.27$). AR[§]: 1.00 vs 1.09 ($P = 0.81$). BOS: 0% vs 9.1% (P = n.s.)
		No prophylaxis		22		

- Retrospective data suggest that addition of CMVIG to antiviral prophylaxis **may reduce rates of CMV-related events after heart transplantation**, including the incidence of acute rejection or chronic allograft vasculopathy
- In lung transplantation, addition of CMVIG in recipients of a CMV-positive graft **may offer an advantage in terms of CMV infection and disease**
- When CMVIG is used, it **should be administered with concomitant antiviral therapy**

Immunoglobulins: real-life data in LuTx (i)

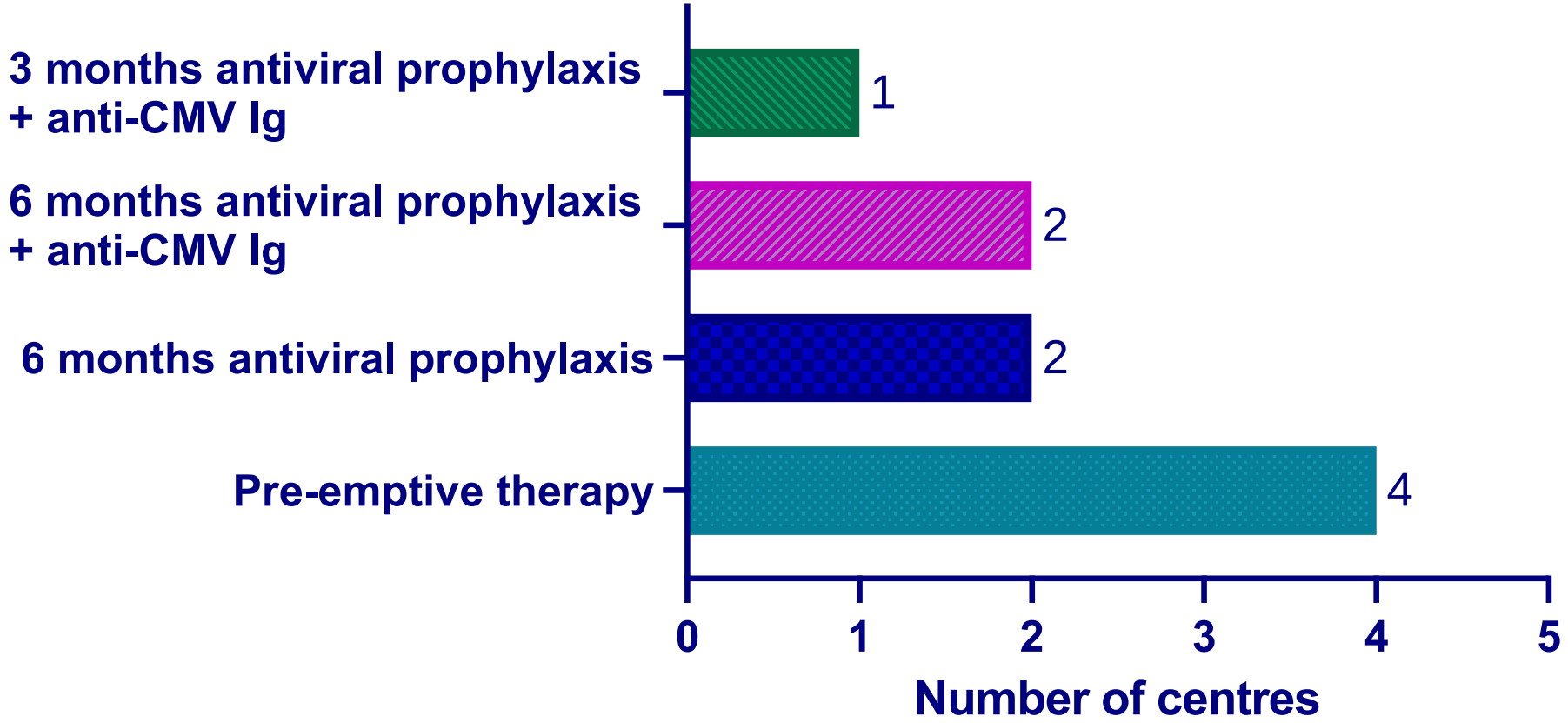
Prevention of CMV in D+/R-: which strategy?



Lombardi A, Personal data

Immunoglobulins: real-life data in LuTx (ii)

Prevention of CMV in R+: which strategy?



CMV-specific T-cell therapy (i)

Table 4. Clinical Responses After Adoptive T-cell Therapy

Patient Code	Organ	Timing of 1st Infusion Post-Transplant, d	Infusions, No.	Total T-cell Dose, $\times 10^6$ Cells	CMV Load, $\times 10^3$ Copies/mL: Peak Before Infusion	CMV Load, $\times 10^3$ Copies/mL: At 1st Infusion	CMV Load, $\times 10^3$ Copies/mL: After Infusion	Antiviral Therapy: Before Infusion	Antiviral Therapy: After Infusion	Clinical Symptoms/ Management After Infusion
1553PAH05	Kidney	411	1	45.25	1.4	0.32	0.32	VGCV, GCV, FOS, LEF	FOS, LEF[a]	DNAemia and CMV disease symptoms resolved
1553PAH06	Kidney	262	6	245	12	0.13	0.78	VGCV, GCV	None	DNAemia and CMV disease symptoms resolved
1553PAH08	Kidney	187	5	226	54	2.8	7.9	VGCV, GCV, FOS	VGCV, IVIG	Reduction in DNAemia and resolution of CMV disease symptoms
1553PAH09	Kidney	237	5	180	10	0	1.4	VGCV, GCV	VGCV	Diarrhea resolved and immunosuppression reduced
1553PCH01	Lung	3403	6	210	8	0	0.12	GCV, FOS	None	FOS stopped without viral reactivation
1553PCH02	Lung	724	3	108	48	0	2.3	VGCV, GCV, FOS, IVIG	None	Reduction in DNAemia
1553PCH03	Lung	1480	2	42	12	24	45	VGCV, GCV, FOS, IVIG	GCV	Died of multiorgan failure
1553PCH04	Lung	979	6	168	17	4.7	2.9	VGCV, GCV, FOS, IVIG, LEF	IVIG, LEF	Reduction in DNAemia
1553PCH05	Lung	1075	6	241	47	0	0	VGCV, GCV	VGCV	Reduction in DNAemia
1553RAH01	Lung	861	3	104	18.9	1.3	17.6	VGCV, GCV	GCV, FOS, IVIG	Ongoing elevated CMV PCR, however no end-organ disease
SASRAH01	Lung	266	4	120	344	0	1	VGCV, GCV, FOS	None	Drug-independent resolution of DNAemia
SASSVH01[b]	Lung	790	2 1	38.7 (cycle 1) 22.2 (cycle 2)	95.4	1.8	2.5	VGCV, GCV, FOS, CDV	CDV	Reduction in DNAemia
1553PCH06	Heart	637	6	204	1.5	0	0	VGCV	None	VGCV ceased after T-cell therapy

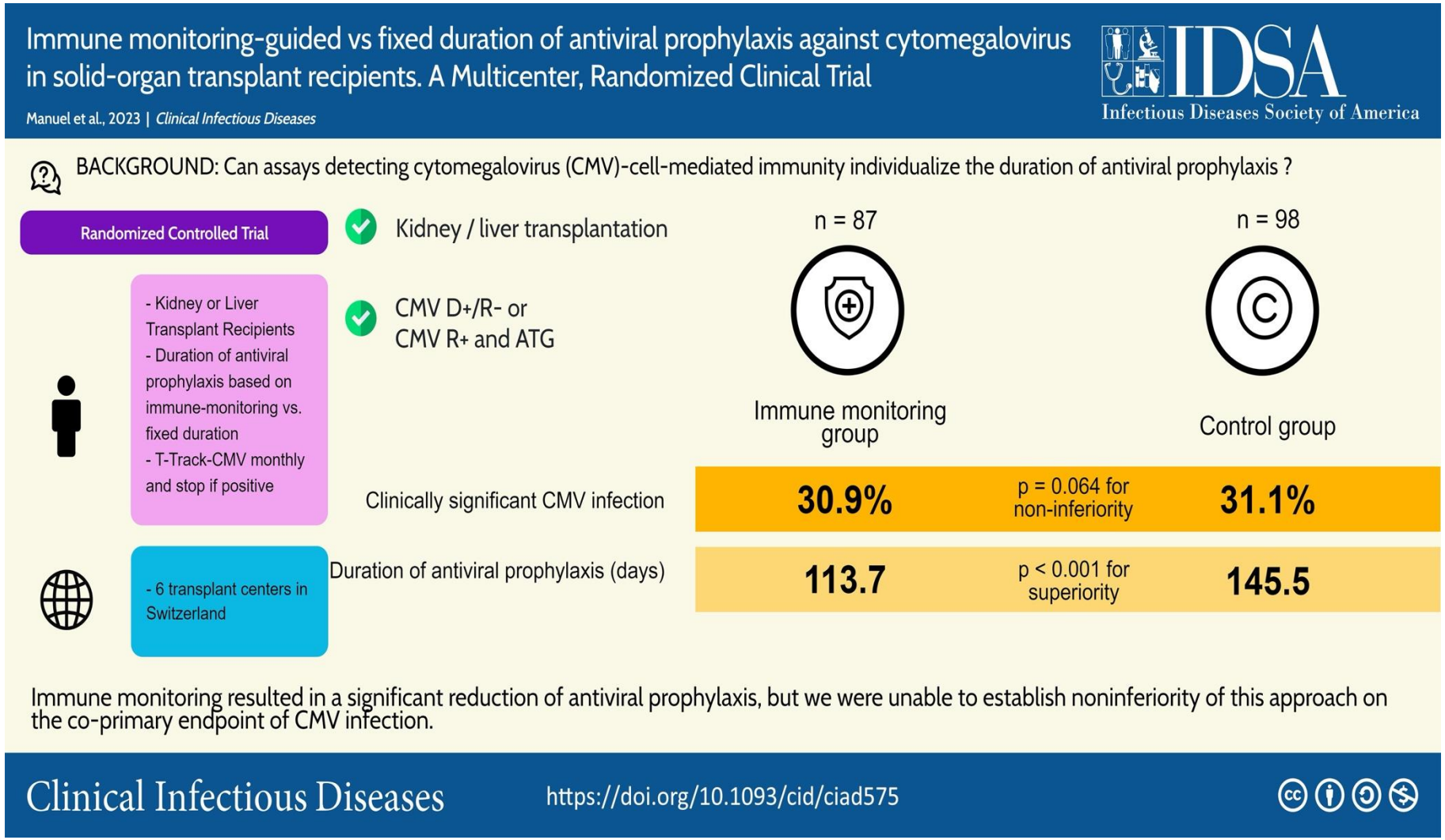
- 22 SOT recipients with with recurrent or ganciclovir-resistant CMV infection
- Autologous CMV-specific T-cell manufacture was successful in 20 patients
- The use of this adoptive immunotherapy was associated with **no therapy-related serious adverse events**
- Eleven (84%) of the 13 treated patients showed improvement in symptoms, including **complete resolution or reduction in DNAemia and CMV associated end-organ disease and/or the cessation or reduced use of antiviral drugs**
- Four of these patients showed coincident **increased frequency of CMV-specific T cells** in peripheral blood after completion of T-cell therapy

Smith et al., *CID* 2019

CMV-specific T-cell therapy (ii)

NCT Number	Study Title	Study URL	Conditions	Interventions
NCT03798301	Treatment of Cytomegalovirus (CMV) Infections With Viral-Specific T Cells	https://clinicaltrials.gov/study/NCT03798301	CMV Infection|Cytomegalovirus Infections|CMV Viremia|Opportunistic Infections	BIOLOGICAL: CMV-specific T-cells
NCT06453460	Prospect Eval of Efficacy of CMV-TCIP Direct Letermovir Prophylax After Allogen Hemato Cell Transpla	https://clinicaltrials.gov/study/NCT06453460	CMV|Allogeneic Stem Cell Transplantation	DRUG: Letermovir|DEVICE: CMV T Cell Immunity Panel (CMV-TCIP)|DIAGNOSTIC_TEST: CMV DNA PCR
NCT03266640	Virus Specific Cytotoxic T-Lymphocytes (CTLs) for Refractory Cytomegalovirus (CMV)	https://clinicaltrials.gov/study/NCT03266640	Cytomegalovirus Infections|Primary Immune Deficiency Disorder	DRUG: viral specific cytotoxic t-lymphocytes
NCT04056533	Prophylaxis of Cytomegalovirus Infection With Adoptive Cell Inmunotherapy	https://clinicaltrials.gov/study/NCT04056533	CMV	BIOLOGICAL: CMV CTLs
NCT04934527	Association of T Gamma Delta-CD16+ Cells and Anti-CMV Immunoglobulins in the Prevention of CMV Infection	https://clinicaltrials.gov/study/NCT04934527	Kidney Transplantation|CMV Infection	DRUG: Cytotect
NCT02982902	T Cell Therapy of Opportunistic Cytomegalovirus Infection	https://clinicaltrials.gov/study/NCT02982902	Cytomegalovirus Infections|Hematopoietic Stem Cell Transplant|Opportunistic Infections	BIOLOGICAL: CMV specific adoptive t-cells
NCT04832607	Multivirus-specific T-cell Transfer Post SCT vs AdV, CMV and EBV Infections	https://clinicaltrials.gov/study/NCT04832607	AdV Infection|EBV Infection|CMV Infection|Stem Cell Transplant Complications	OTHER: Multivirus (CMV, EBV, AdV)-specific T cells
NCT03665675	Donor Virus-Specific CMV or AdV CTL to Treat CMV or AdV Reactivation or Disease After Solid Organ or HCT	https://clinicaltrials.gov/study/NCT03665675	Allogeneic Hematopoietic Stem Cell Transplantation Recipient|Cytomegalovirus|Donor|Solid Organ Transplantation Recipient|Adenovirus	BIOLOGICAL: Allogeneic Cytomegalovirus-Specific Cytotoxic T lymphocytes|BIOLOGICAL: Allogeneic Adenovirus-specific Cytotoxic T Lymphocytes
NCT04013802	TETRAVI Multivirus CTL for Treatment of EBV, CMV, Adenovirus, and BK Infections Post Allogeneic SCT.	https://clinicaltrials.gov/study/NCT04013802	Viral Infection	BIOLOGICAL: HLA-matched VSTs
NCT02048332	Donor-Derived Viral Specific T-cells (VSTs)	https://clinicaltrials.gov/study/NCT02048332	Allogeneic Stem Cell Transplant|Viral Infection|Viral Reactivation	BIOLOGICAL: Viral specific VST Infusion
NCT02007356	A Study to Assess Safety and Feasibility of Direct Infusions of Donor-derived Virus-specific T-cells in Recipients of Hematopoietic Stem Cell Transplantation With Post-transplant Viral Infections Using the Cytokine Capture System®	https://clinicaltrials.gov/study/NCT02007356	Adenovirus Infection|EBV|Cytomegalovirus Infections|Cytokine Capture System|Allogenic Disease	BIOLOGICAL: IFN-γ positive selected T-cells

T cell responses to guide prophylaxis



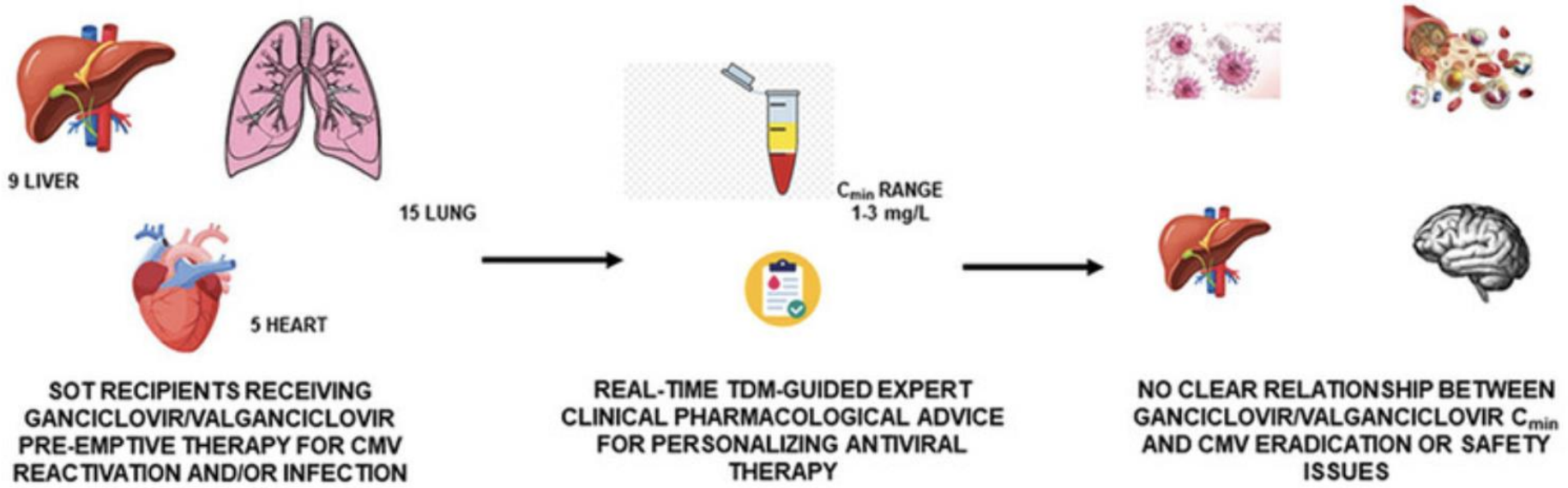
- Enrolled if they were **D+/R- or R+ receiving antithymocyte globulins**
- Control group were planned to receive **180 days (CMV-seronegative) or 90 days (CMV-seropositive) of valganciclovir**
- The duration of prophylaxis was shorter in the immune-monitoring group (adjusted difference, **−26.0 days**)

Oriol et al. *CID* 2023

TDM of antivirals

Does therapeutic drug monitoring (TDM) of trough concentrations suffice for optimizing preemptive therapy with ganciclovir of cytomegalovirus infections in non-renal solid organ transplant recipients?

Milo Gatti, Matteo Rinaldi, Luciano Potena, Elena Salvaterra, Maria Cristina Morelli, Maddalena Giannella, Pierluigi Viale, Federico Pea



Primary outcomes:

1. Reduced CMVviral load below the lower limit of quantification (LLQ) at 30 days
2. Occurrence of myelotoxicity

- Concentrations ranging from 0.13 to 1.6 mg/L allow CMV replication, **desired range of ganciclovir Cmin was set at 1.0–3.0 mg/L**
- No difference was found in the primary outcome between patients showing average Cmin below or above 1 mg/L (100.0% vs. 53.8%; p =.25) and/or 3 mg/L (65.2% vs. 33.3%; p = .20)
- ROC **analysis did not allow to identify an average Cmin cut-off predictive of clinical efficacy or toxicity**
- 24-h area under the concentration time curve (AUC24h) could be a better predictor of clinical outcome

Conclusions (i)

- After a long hiatus new drugs are available for treatment/prevention of CMV among SOT recipients
- Maribavir is an inhibitor of kinase UL97, do not co-administer with (val)ganciclovir
- Maribavir can pass the blood-retinal barrier but do not enter CSF
- Check for maribavir resistance if viremia relapse under treatment
- Maribavir is licensed (FDA/EMA) for treatment of resistant/refractory CMV infection
- Maribavir dosage is 400 mg q12h

Conclusions (ii)

- Letermovir is a CMV terminase complex inhibitor
- Letermovir is licensed for primary prophylaxis among HSCT, can be employed for primary prophylaxis in SOT (off-label use, RCT among KiTx)
- Letermovir has low genetic barrier, do not use it for treatment
- Letermovir resistance mutations frequent in secondary prophylaxis (UL96)
- Letermovir is ineffective against HSV and VZV, consider coadministration with acyclovir/valaciclovir
- Letermovir dosage is 480 mg q24h