

The Next Frontier: Combination Therapy for Treatment of CMV

Camille Nelson Kotton MD, FIDSA, FAST
Clinical Director, Transplant and Immunocompromised Host Infectious Diseases
Infectious Diseases Division

Mass General Brigham Endowed Cancer Chair IV
Massachusetts General Hospital
Associate Professor, Harvard Medical School
Executive Committee, The Transplantation Society

Concepts Supporting Evaluation of CMV Combination Therapy

- While most CMV responds to treatment with valganciclovir, 5-10% develop resistant-refractory disease with significant morbidity and mortality
- Other viral infections use multiple agents, to avoid development of resistance
- Until present, we did not have options for multi-antiviral treatment w/o significant toxicity
- We are advancing transplant into higher risk recipients with higher risk of resistant-refractory disease
 - Highly sensitized, multi-transplant, comorbidities

	Ganciclo vir	Cidofovi r	Foscarn et	Maribavi r	Letermo vir	Zidovudi ne	Filociclo vir	Artesuna te	U0126 (MEK1/2 inhibitor)	Abemaci clib	Acyclovi r	Vidarabi ne	Sirolimu s	Interfero n-alpha	Ozonide OZ418	CDK7 Inhibitor
Ganciclo vir		Synergy	Synergy	Antagoni sm	Additive	Antagoni sm	Antagoni sm	Synergy						Synergy	Synergy	
Cidofovi r	Synergy		Synergy													
Foscarn et	Synergy	Synergy		Additive				Synergy								
Maribavi r	Antagoni sm		Additive					Synergy		Antagoni sm	Additive					Synergy
Letermo vir	Additive							Synergy					Additive			
Zidovudi ne	Antagoni sm															
Filociclo vir	Antagoni sm															
Artesuna te	Synergy		Synergy	Synergy	Synergy				Antagoni sm							
U0126 (MEK1/2 inhibitor)								Antagoni sm								
Abemaci clib				Antagoni sm												
Acyclovi r				Additive								Synergy		Synergy		
Vidarabi ne											Synergy					
Sirolimu s					Additive											
Interfero n-alpha	Synergy										Synergy					
Ozonide OZ418	Synergy															
CDK7 Inhibitor				Synergy												

Figure developed by Dr. Adam G. Stewart, Transplant ID fellow at MGH, future faculty at MDAnderson

Main Focus Areas for Combination Therapy

- Valganciclovir/ganciclovir + CMV immunoglobulin
- Valganciclovir/ganciclovir + artesunate for high CMV viral load
- Foscarnet + CMV immunoglobulin for resistant/refractory disease
- Maribavir + letermovir (+/- CMV Ig) for resistant/refractory disease

- GOAL: to expediate CMV clearance and avoid further resistance



Viral load kinetics and the clinical consequences of cytomegalovirus in kidney transplantation

Sabina Dobrer¹, Karen R. Sherwood¹, Ishan Hirji², James Lan^{1,3}, John Gill³, Nancy Matic¹ and Paul A. Keown^{1,3*} for the Genome Canada Transplant Consortium

¹Department of Pathology and Laboratory Medicine, University of British Columbia, Vancouver, BC, Canada, ²Global Evidence and Outcomes, Takeda Development Center Americas, Inc., Lexington, MA, United States, ³Department of Medicine, University of British Columbia, Vancouver, BC, Canada

OPEN ACCESS

EDITED BY
Stanislaw Stepkowski,
University of Toledo, United States

REVIEWED BY
Masako Shimamura,
The Research Institute at Nationwide
Children's Hospital, United States
Javier Carbone,
Gregorio Marañón Hospital, Spain
A. Raj Kumar Patro,
Kalinga Institute of Medical Sciences (KIMS),
India

*CORRESPONDENCE
Paul A. Keown
✉ paul.keown@ubc.ca

- British Columbia Transplant Program: 2510 sequential kidney transplant recipients
- January 1, 2008 -- December 31, 2018

- Patients with CMV infection were at significantly greater risk of graft loss ($p=0.0041$) and death ($p=0.0056$) than those without.
- **Peak viral load** ranged from 2.9 to 7.0 (median: 3.5) $\log_{10}$ IU/mL, the **duration of viremia** from 2 to 100 (15) days, and the **viral load area under the curve** from 9.4 to 579.8 (59.7) $\log_{10}$ IU/mL x days.
- **All three parameters were closely inter-related and were significantly increased in patients with more severe clinical disease or with graft loss** ($p=0.001$).
- *(no specific mention of resistant infection)*
- Duration of the first CMV viremic episode greater than 15 days or a peak viral load $\geq 4.0 \log_{10}$ IU/mL offered simple predictors of clinical risk with a 3-fold risk of transplant failure.

4th International CMV and Solid Organ Transplant Consensus Guidelines Meeting

June 20-23, 2024
Montreal, Canada



The
Transplantation
Society



The Fourth International Consensus Guidelines on the Management of Cytomegalovirus in Solid Organ Transplantation

Camille N. Kotton, MD,¹ Deepali Kumar, MD,² Oriol Manuel, MD,³ Sunwen Chou, MD,⁴ Randall T. Hayden, MD,⁵ Lara Danziger-Isakov, MD, MPH,⁶ Anders Asberg, PhD,⁷ Helio Tedesco-Silva, MD,⁸ and Atul Humar, MD²; on behalf of The Transplantation Society International CMV Consensus Group*

- **Prevention:** Although CMVIG or IVIG is not recommended routinely for the prevention of CMV infection, it **can be considered in combination with antiviral agents** in specific circumstances, including thoracic organ transplantation, D+/R– serostatus, and severe IgG hypogammaglobulinemia (IgG <400 mg/dL; weak, low).
- **Treatment of resistant/refractory disease:** If the chosen salvage treatment does not work after several weeks, options are to switch drugs among available approved therapies or try empiric combinations, except that the combination of maribavir and ganciclovir is strongly antagonistic in vitro. There is no solid evidence base to determine the best treatment options, which involve a tradeoff of viral and disease burden, antiviral toxicities and potency, logistical complexity, cost, and risk of drug resistance. **Foscarnet may be used in combination with ganciclovir or maribavir as tolerated or switched to maribavir after the viral load reaches a low level (optimally <3.7 log₁₀ IU/mL).**
- **Future directions:** New therapeutic options are needed, with improved safety, potency, and avoidance of cross-resistance, including drug combinations directed at different viral targets.

Recommendations from the 10th European Conference on
Infections in Leukaemia for the management of *Lancet Infect Dis 2025*
cytomegalovirus in patients after allogeneic haematopoietic
cell transplantation and other T-cell-engaging therapies

*Per Ljungman, Sophie Alain, Roy F Chemaly, Hermann Einsele, Federica Galaverna, Hans H Hirsch, Alicja Sadowska-Klasa, David Navarro,
Jan Styczynski, Rafael de la Camara*

“**Combination therapy** for resistant or refractory CMV infections has not been systematically studied but **could be considered in patients with difficult-to-manage infection**. However, the combination of maribavir with valganciclovir or ganciclovir should not be used due to their antagonistic mechanism of action.”

“Future directions: New treatment options have emerged but are associated with an increased rate of antiviral resistance. Patients with resistant or refractory infections represent an unmet **medical need and require other therapeutic options**. Combination therapies and future studies of adoptive virus-specific T-cell therapies are possible ways to address this gap.”



• + ○ Ongoing Clinical Trials



Study Evaluating the Efficacy and Safety of Artesunate

ClinicalTrials.gov ID ⓘ **NCT06853184**

Sponsor ⓘ Amivas (US), LLC

Information provided by ⓘ Amivas (US), LLC (Responsible Party)

Last Update Posted ⓘ 2025-02-28



+ Expand all content

— Collapse all content

Study Details

Researcher View

No Results Posted

Record History

On this page

Study Overview

Contacts and Locations

Participation Criteria

Study Plan

Collaborators and Investigators

Study Record Dates

More Information

Study Overview

Brief Summary

This study is a randomized, open-label, active comparator-controlled, dose-ranging trial of the efficacy and safety of IV artesunate in combination with IV GCV or oral VGCV and SOC treatment compared to GCV or VGCV monotherapy and SOC treatment in SOT recipients with clinically significant CMV infection.

Official Title

Phase 2, Randomized, Open-label, Active Comparator, Dose-ranging Study Evaluating the Efficacy and Safety of Artesunate for Injection in Combination With Ganciclovir or Valganciclovir for the Treatment of Cytomegalovirus Infection in Solid Organ Transplant Recipients

Study Start (Estimated) ⓘ

2025-05-01

Primary Completion (Estimated) ⓘ

2028-05-31

Study Completion (Estimated) ⓘ

2028-06-30

Exploratory use of CMV
immunoglobulin in high
risk (D+R-) transplant
recipients at the end of
antiviral prophylaxis to
decrease the risk of late
CMV infection

- We are conducting a randomized placebo controlled trial giving CMVIG monthly vs nothing (standard of care) at the end of prophylaxis x 3 months to high-risk transplant recipients
 - Massachusetts General Hospital, Camille Kotton
 - University of Texas Southwestern, David Wojciechowski
- Funded by Kamada
- Optimizes modern prophylaxis practice with use of immunoglobulins
- SHIELD – Strategic Help with Immunoglobulin to Enhance protection against Late Disease (CMV)
- Hypothesis: CMVIG may attenuate (or even eliminate) the risk of late CMV after the end of prophylaxis (Achilles heel!)
 - Does this prevent clinically meaningful CMV?
 - Does this improve outcomes and patient experience?

Main Focus Areas for Combination Therapy

✓ Valganciclovir/ganciclovir + CMV immunoglobulin

more can be done

✓ Valganciclovir/ganciclovir + artesunate for high CMV viral load

- Foscarnet + CMV immunoglobulin for resistant/refractory disease
- Maribavir + letermovir (+/- CMV Ig) for resistant/refractory disease

There are many interesting aspects of combination therapy for
CMV treatment.

Based on what you have learned today, do you think further
study is an appropriate allocation of resources for TAVI?

Strongly Disagree

Disagree

Neutral

Agree

Strongly Agree

In Which Areas in Combination Therapy Should TAVI Focus?

- Valganciclovir/ganciclovir + CMV immunoglobulin
- Valganciclovir/ganciclovir + artesunate for high CMV viral load
- Foscarnet + CMV immunoglobulin for resistant/refractory disease
- Maribavir + letermovir (+/- CMV Ig) for resistant/refractory disease

Questions? ckotton@mgh.harvard.edu

My office – come visit!

*Twitter/X @KottonNelson
BlueSky @KottonNelson.bsky.social*



MASSACHUSETTS
GENERAL HOSPITAL
TRANSPLANT CENTER