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Long-Term Outcomes Among Lung Transplant Recipients With High-Risk Cytomegalovirus Mismatch Managed With a Multimodality Regimen

A long-term (up to 12 years) follow-up, retrospective, single-center cohort study based on real-world data

Banga N, Kanade R, Kappalayil A, Timofte I, Lawrence A, Bollineni S, Kaza V, Torres F.
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High-risk CMV mismatch (D+/R–) is an independent factor affecting post-transplant survival. It has historically been linked to increased CMV-related complications, highlighting the need for improved prevention strategies.

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CMV=cytomegalovirus.

In high-risk CMV-mismatch lung transplant recipients, long-term (8-year) overall survival was comparable to non–high-risk patients when CYTOGAM was part of the prophylactic regimen—suggesting a potential long-term benefit beyond the infusion period.

Background

High-risk CMV mismatch (D+/R−) has historically been associated with increased post-transplant complications and mortality in lung transplantation. Standard antiviral therapy may be insufficient due to both antiviral-related toxicities and the risk of post-prophylaxis CMV infection or disease. Adjunctive CMV immune globulin therapy (CYTOGAM) may offer additional protection against CMV.

ISHLT Registry Data

The ISHLT 2021 Registry Report identified cytomegalovirus (CMV) seropositive donor/seronegative recipient (D+/R–) mismatch as an independent predictor of increased mortality following lung transplantation.

CMV D+/R– mismatch independently increased mortality risk:

~10% higher at 1 year (HR, 1.105; 95% CI, 1.028–1.187; *P*<0.01; n=6,615[a])

~23% higher at 5 years (HR, 1.231; 95% CI, 1.163–1.302; *P*<0.01; n=4,142[b])

These findings provide important context for evaluating outcomes achieved with multimodality CMV prevention protocols.

CI, confidence interval; HR, hazard ratio; ISHLT, International Society for Heart & Lung Transplantation.
[a]Transplants from January 2000 through June 2017 (N=53,072).
[b]Transplants from January 1996 through June 2013 (N=35,214).

Source: Chambers DC, Perch M, Zuckermann A, et al. *J Heart Lung Transplant*. 2021;40(10):1060-1072. Data extracted from the published multivariable Cox regression model; only results pertaining to donor/recipient CMV antibody mismatch (D+/R–) shown.

IMPORTANT SAFETY INFORMATION FOR CYTOGAM (CONTINUED)

Immune Globulin Intravenous (Human) products have been reported to be associated with renal dysfunction, acute renal failure, osmotic nephrosis, and death. Patients predisposed to acute renal failure include patients with any degree of preexisting renal insuffciency, diabetes mellitus, age greater than 65, volume depletion, sepsis, paraproteinemia, or patients receiving known nephrotoxic drugs. Especially in such patients, IGIV products should be administered at the minimum concentrations available and the minimum rate of infusion practicable. Those containing sucrose as a stabilizer, like CYTOGAM, account for a disproportionate share of the total number of reports of renal dysfunction and acute renal failure when given at daily doses of 350 mg/kg or greater.

Objectives

Evaluate overall survival and chronic lung allograft dysfunction (CLAD)-free survival in high-risk CMV mismatch lung transplant recipients receiving combination prophylaxis with CYTOGAM and antiviral therapy.

Methods

This study, published in 2025, conducted at the University of Texas Southwestern Medical Center, evaluated lung transplants performed between 2012 and 2016. It assessed the impact of combination prophylaxis with CYTOGAM on overall and CLAD-free survival in high-risk CMV mismatch recipients. All recipients received CMV-prevention regimens tailored to donor/recipient CMV serostatus, with standardized CMV monitoring applied across groups.

Design: Retrospective, single-center cohort study with long-term follow-up (up to 12 years).

Population: 324 recipients: 83 D+/R– (high-risk), representing 25.6% of the study cohort. The remaining recipients (D+/R+, D−/R+, and D−/R−) constituted the non–high-risk group.

CMV-Prevention Protocols by Donor/Recipient Serostatus

Recipient CMV Serostatus	Prophylaxis Components
High-risk (D+/R–)	• Antiviral prophylaxis (ganciclovir/valganciclovir) • CMV immune globulin (CYTOGAM) administered at 150 mg/kg within 72 hours post–lung transplant, then at weeks 2, 4, 6, and 8, followed by 100 mg/kg at weeks 12 and 16 • CMV polymerase chain reaction (PCR) monitoring monthly for 6 months, then at 9 months, 1 year, and every 3 months thereafter
Non–high-risk (D+/R+, D–/R+, D–/R–)	• Antiviral prophylaxis (valganciclovir, duration per serostatus and protocol) • CMV PCR monitoring on a similar schedule • CYTOGAM not routinely used unless clinically indicated

IMPORTANT SAFETY INFORMATION FOR CYTOGAM (CONTINUED)

During administration, the patient's vital signs should be monitored continuously, and careful observation made for any symptoms throughout the infusion. Epinephrine and diphenhydramine should be available for the treatment of an acute and anaphylactic reactions.

Please see additional selected Important Safety Information throughout and full Prescribing Information enclosed in pocket.

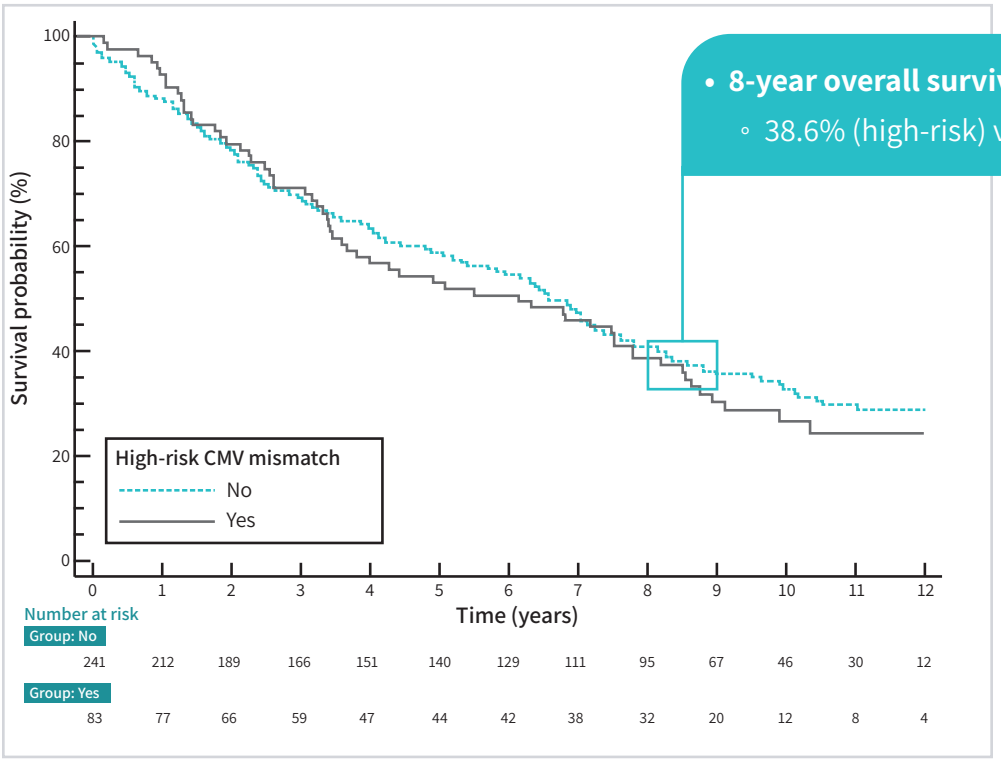
CYTOGAM®
Cytomegalovirus Immune Globulin Intravenous (Human) (CMV-IVIG)

Results

High-risk CMV-mismatch recipients receiving CYTOGAM plus antiviral therapy achieved similar overall survival to lower-risk patients. With CYTOGAM-based prophylaxis, CMV serostatus no longer predicted poorer mortality, with comparable survival through 8 years.

In this real-world cohort of high-risk CMV mismatch lung transplant recipients with follow-up to 8 years, combination prophylaxis with CYTOGAM achieved overall and CLAD-free survival comparable to non–high-risk patients (Figure 1).

Figure 1. Kaplan–Meier Survival by CMV Mismatch Risk Group



Survival curves among patients with and without high-risk CMV mismatch status (n=324) showing identical long-term survival (log rank *P*=0.539).

- **8-year overall survival:**
  - 38.6% (high-risk) vs 39.4% (non–high-risk); *P*=1.0
- **Kaplan–Meier survival analysis:**
  - Overlapping survival curves between groups (Figure 1)
    - No statistically significant difference in long-term survival (log-rank *P*=0.539)
- **CLAD-free survival:**
  - **1-year:** 75.9% (high-risk) vs 71.8% (non–high-risk); *P*=0.48
  - **2-year:** 53.0% (high-risk) vs 54.8% (non–high-risk); *P*=0.8
  - **3-year:** 39.7% (high-risk) vs 53.1% (non–high-risk); *P*=0.08
- **Safety and tolerability of CMV prophylaxis:** The CMV prophylaxis was well tolerated with no increased risk of non-CMV infections, venous thromboembolism, or renal dysfunction

IMPORTANT SAFETY INFORMATION FOR CYTOGAM (CONTINUED)

Increases in serum creatinine and blood urea nitrogen (BUN) have been observed as soon as one to two days following IGIV infusion. Progression to oliguria or anuria requiring dialysis has been observed.

Immune Globulin Intravenous (Human) products can contain blood group antibodies which may act as hemolysins and induce in vivo coating of red blood cells with immunoglobulin, causing a positive direct antiglobulin reaction and, rarely, hemolysis.

Thrombotic events have been reported in association with IGIV. Patients at risk may include those with a history of atherosclerosis, multiple cardiovascular risk factors, advanced age, impaired cardiac output, and/or known or suspected hyperviscosity. The potential risks and benefits of IGIV should be weighed against those of alternative therapies for all patients for whom IGIV administration is being considered.

Results (cont.)

- **CMV viremia:** The high-risk D+/R− group experienced significantly higher rates of CMV viremia and resistance compared to the non–high-risk group.

	High-risk CMV mismatch: No (n=241)	High-risk CMV mismatch: Yes (n=83)	OR (95% CI)	*P* value
Highest level of CMV viremia				
None	186 (77.2%)	50 (60.2%)	4.4 (2.34–8.13)[a]	**<0.001**
Detectable, non-quantifiable	31 (12.9%)	6 (7.2%)		
Quantifiable	24 (10%)	27 (32.5%)		
Highest CMV viral load (IU/mL)	518 (341–2073)	2050 (378–115500)		**0.03**
Resistant CMV viremia	2 (0.8%)	12 (14.4%)	20.2 (4.4–92.4)	**<0.001**

[a]Odds ratio (OR) based on 2 x 2 comparisons with estimated glomerular filtration rate (eGFR) cut-off of 60 and for CMV viremia based on the development of quantifiable CMV viremia.

Despite higher CMV viremia and resistance in high-risk recipients, 8-year survival (38.6% vs 39.4%; *P*=1.0) and CLAD-free outcomes were comparable to non–high-risk patients, suggesting a potential long-term protective effect of CYTOGAM.

IMPORTANT SAFETY INFORMATION FOR CYTOGAM (CONTINUED)

Baseline assessment of blood viscosity should be considered in patients at risk for hyperviscosity, including those with cryoglobulins, fasting chylomicronemia/markedly high triacylglycerols (triglycerides), or monoclonal gammopathies.

CYTOGAM is derived from human plasma. As with all plasma-derived products, the risk of transmission of infectious agents, including viruses and, theoretically, the Creutzfeldt-Jakob disease (CJD) agent, cannot be completely eliminated.

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CYTOGAM®
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Key Findings

- High-risk CMV mismatch recipients achieved survival similar to non–high-risk recipients. With CYTOGAM-based prophylaxis, CMV serostatus no longer predicted mortality, with comparable survival through 8 years
- Despite more frequent and severe CMV viremia, CLAD-free survival, a critical outcome in lung transplantation, was similar in high-risk CMV and non–high-risk groups
- Long-term survival and CLAD-free outcomes were similar to those of non–high-risk recipients, suggesting a potential long-term effect of CYTOGAM beyond the infusion period

Implications/Conclusion

A proactive multi-modal CMV prevention strategy using an antiviral in combination with CYTOGAM may mitigate the historically higher mortality risk associated with high-risk CMV mismatch.

In this study, CMV serostatus was no longer an independent predictor of mortality, and survival remained comparable across risk groups for up to 8 years.

- The addition of CYTOGAM to an antiviral for CMV prophylaxis may close the outcome gap between high-risk and non–high-risk patients
- CMV serostatus, typically a strong independent predictor of mortality in lung transplant recipients, no longer predicted mortality under this protocol—suggesting the potential for sustained benefit beyond the CYTOGAM infusion period
- These real-world findings support CMV immune globulin (CYTOGAM) alongside antiviral therapy to reduce CMV-related complications in high-risk patients post-transplant
- These results complement ISHLT registry data showing that CMV (D+/R−) mismatch historically confers higher post-transplant mortality, underscoring the importance of effective prevention strategies.

IMPORTANT SAFETY INFORMATION FOR CYTOGAM (CONTINUED)

Minor reactions, such as flushing, chills, muscle cramps, back pain, fever, nausea, vomiting, arthralgia, and wheezing, were the most frequent adverse reactions observed during the clinical trials for CYTOGAM.

Please see full Prescribing Information in the pocket for full prescribing details.

To report SUSPECTED ADVERSE REACTIONS, contact Kamada at pharmacovigilance@kamada.com or 1-(866)-916-0077 or FDA at 1-800-FDA-1088 or www.fda.gov/medwatch.

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Kamada Inc., 221 River St, Hoboken, NJ 07030
Tel. 1-833-779-2614

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