Presentación protocolo de profilaxis y tratamiento del CMV guiado por CMI en el paciente trasplantado renal

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Fundació Lluita contra les Infeccions

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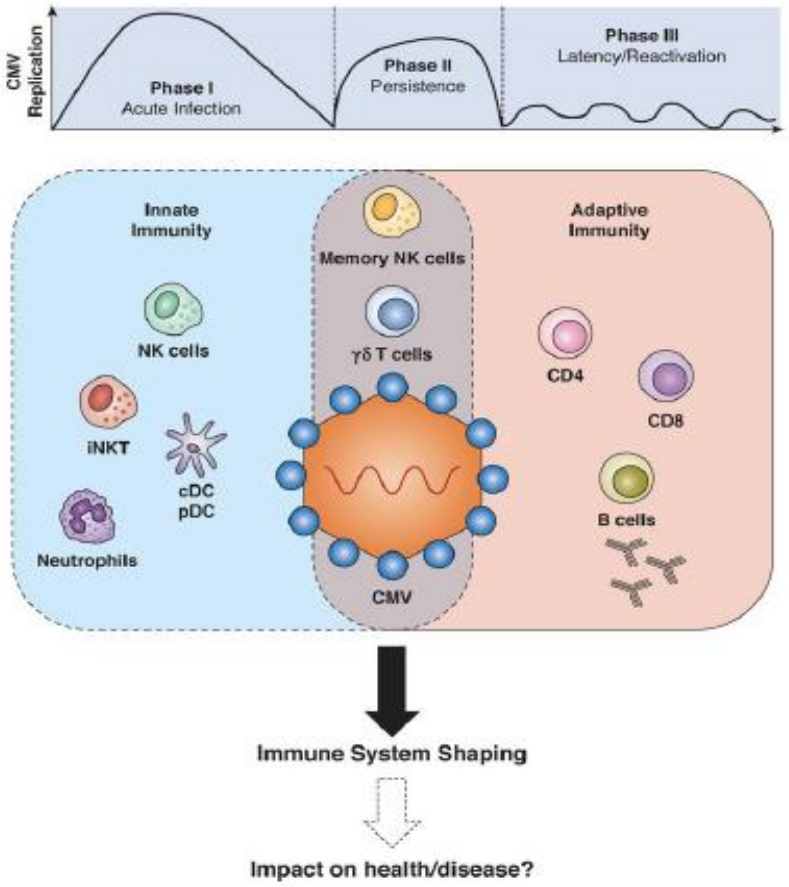
1. Introducción



Picarda g., et al., J inmunol 2018

El CMV es un herpes virus ubicuo presente en el 70% de la población.

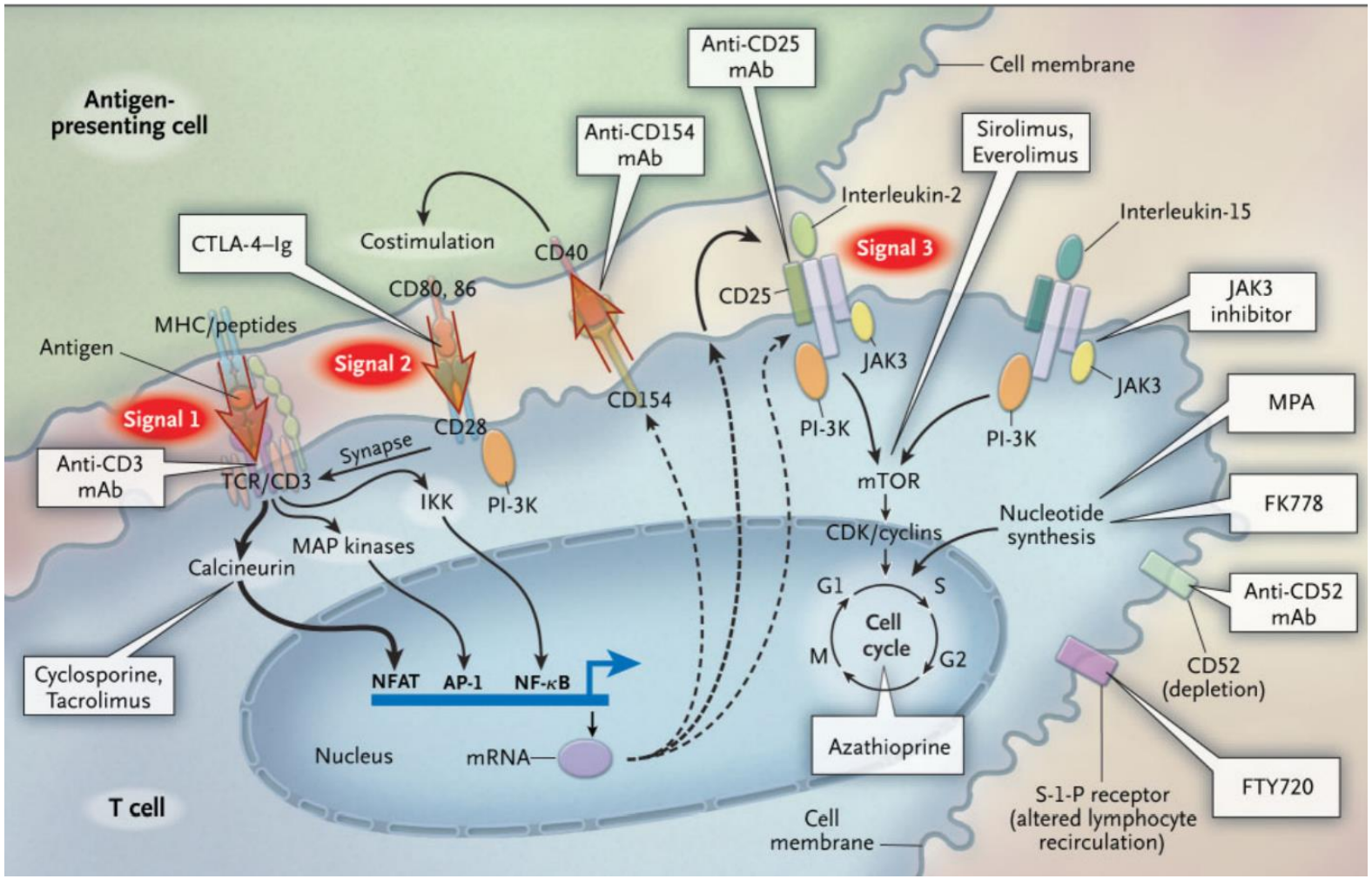
La infección por CMV es la infección oportunista más común en el trasplantado renal habiendo demostrado:

- un impacto negativo sobre la supervivencia de injerto y del paciente
- incidencia de rechazo
- coinfecciones víricas y fúngicas
- aumento del riesgo CV

1. Introducción

Glucocorticoides	Inmunoglobulinas Anti-linfocíticas	Inh calcineurina	Inh síntesis nucleótidos	Inh mTOR	Tto rechazo
	Timoglobulina/ATG	*Ciclosporina*	*Micofenolato*	*Sirolimus*	*Plasmaféresis* *Eculizumab*
	Basiliximab	*Tacrólimus*	*Azatioprina*	*Everolimus*	*Rituximab*
Herida qx **Bacterias** **Hongos**	**Virus** **Bacterias encapsuladas**	**Virus (herpes, gingivitis)** **Toxicidad NRL**	**Bacterias** **Víricas (CMV tardío, VPH)**	**Herida qx** **Toxicidad pulmonar** **Menor infección viral?**	**Bacterias Encapsuladas** **Virus (CMV)** **Hongos** **RTX - menor incidencia PTLD**

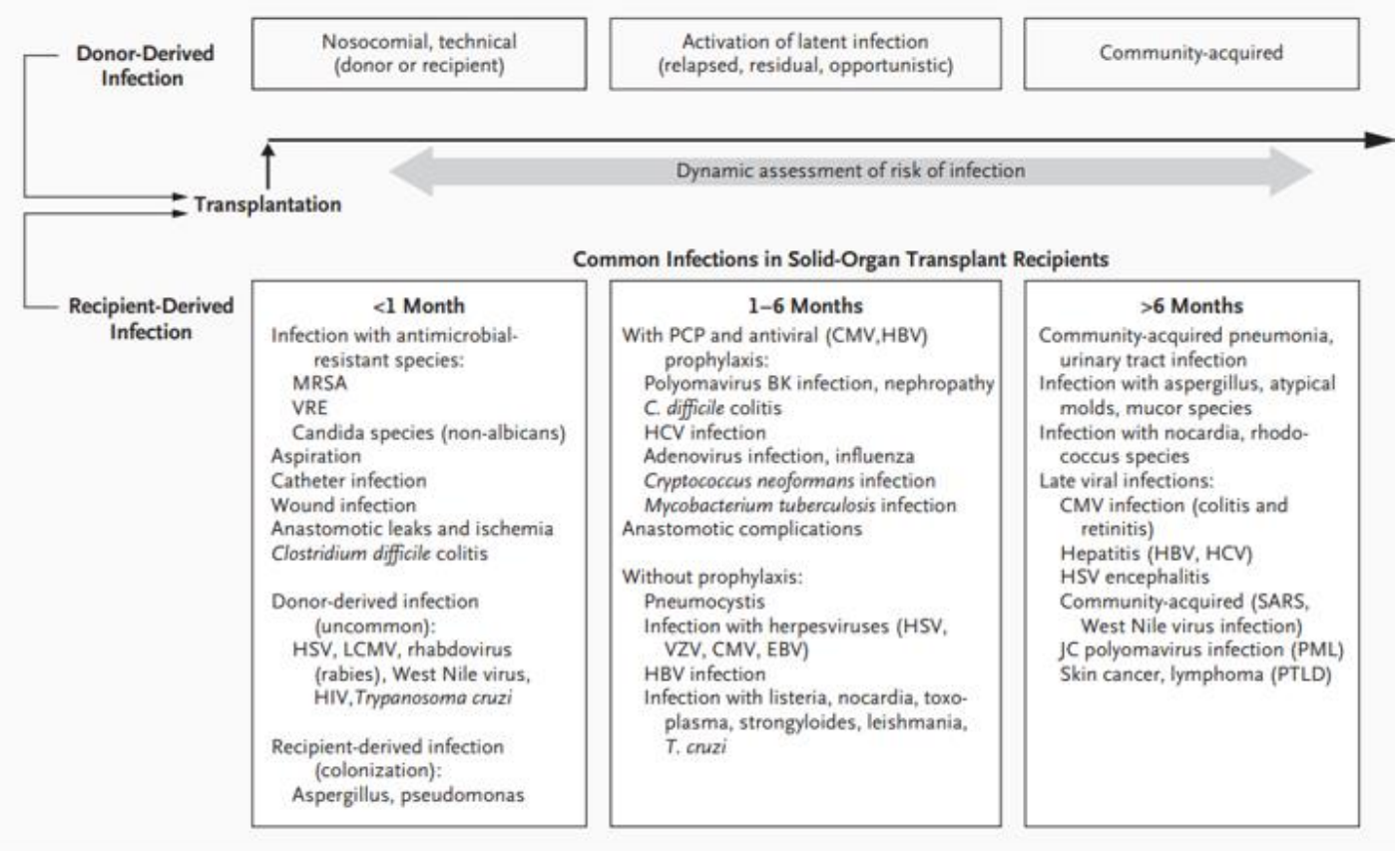
2. Mecanismo de acción IS



Halloran (2018)

3. La importancia del status serológico CMV

ALTO RIESGO (30%)		RIESGO MODERADO (50%)	RIESGO BAJO (20%)
D + R -	R+ ATG	R + que no recibe SAL	D - / R-



Fishman JA (2007)

4. Respuesta celular linfocitaria especifica frente a CMV

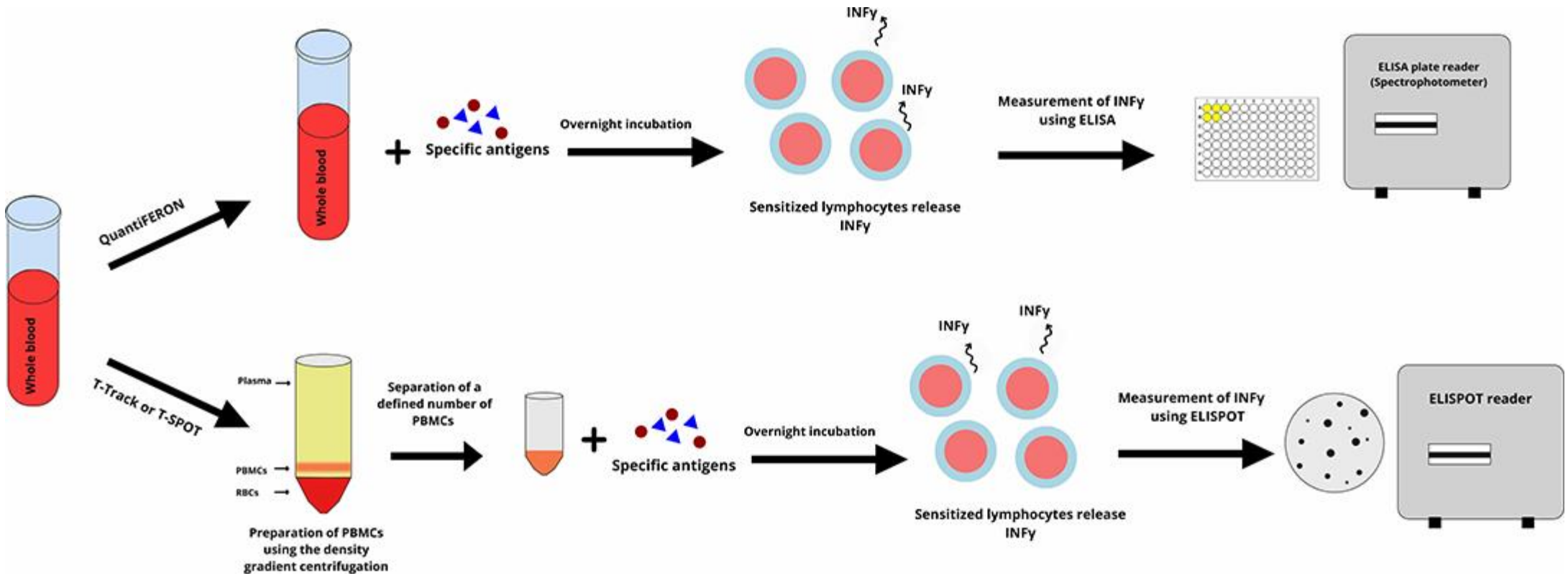
1. La infección por CMV activa múltiples respuestas inmunes, tanto innatas como adaptativas, aunque se ha demostrado que la inmunidad celular, **particularmente las células T memoria/efectoras**, es crucial para controlar la replicación.
2. La incorporación de la **monitorización de la CMI anti-CMV** es útil para ajustar la duración de la profilaxis pudiendo eventualmente servir de guía **para reducir el tiempo de profilaxis** con antivirales, y con ello, disminuir la aparición de **toxicidades** del fármaco y de posibles **resistencias** al antiviral.
3. Las **guías americanas** (Transplantation 2018), **europeas y Españolas** (Doc. Consenso GESITRA-SEIMC 2024) ya las han incorporado como herramienta para el ajuste de la profilaxis. Por esta razón hemos decido incorporarlo en nuestro protocolo actual.

TABLE 2.

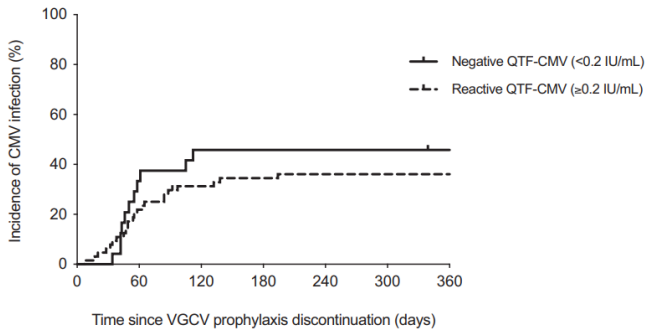
Advantages and limitations of various assays for immune monitoring of CMV

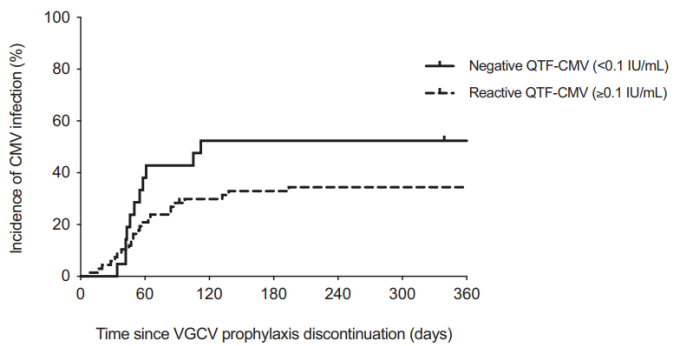
Assay	Advantages	Limitations	Comments	Predict viremia	Predict disease
ICS	Whole blood assay with low blood volume (1 mL) or PBMC Short incubation time Results available after 8 hours Identification of CD4+ and CD8+ T cells Knowledge of HLA not necessarily required Quantitative and qualitative characterization	Needs access to a flow cytometer Not standardized	Most data available with this technique Potential to freeze PBMCs and ship to reference lab for testing	Yes	Yes
QuantiFERON-CMV (Qiagen, USA)	Whole blood assay with low blood volume (3 mL) Simple to perform Results available after 30-40 hours Can be done in any center and stimulated plasma can be sent to reference lab	CD8+ responses only. Sensitive to lymphopenia. Rare patients whose HLA types are not covered in assay	Approved in Europe	Yes	Yes
ELISpot	Identifies both CD4+/CD8+ T cells Knowledge of HLA not necessarily required Results available after 30-40 hours	Need for purified PBMC from 10 mL blood (in reality 5-10 mL) Cannot differentiate CD4+ and CD8+ T cells Not standardized	Potential to freeze PBMCs and ship to reference lab for testing; Commercial availability (T-Track CMV, Lophius CE marked in Europe; T-SPOT.CMV is LDT in U.S.) and CE marked in Europe	Yes	Yes
MHC multimer staining	Fast assay (1-2 h) Whole blood assay with low blood volume (0.5-1 mL) or PBMC	CD8+ responses only Needs access to a flow cytometer HLA and epitope-specific. No information about function unless combined with ICS Not standardized	Unlikely to be used on a widespread basis	No, Only in combination with functional or phenotypical markers	No

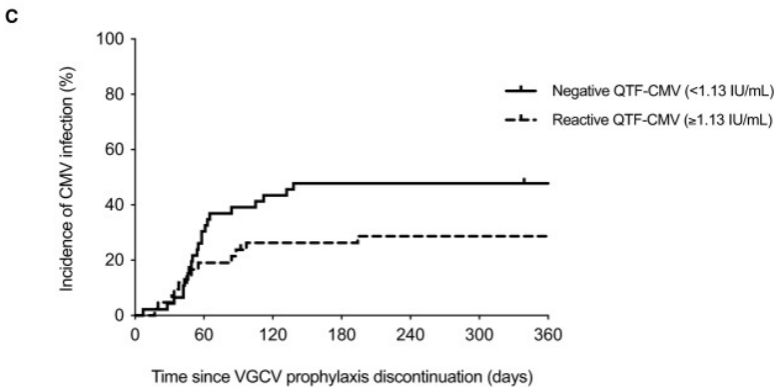
Kotton et al. Transplantation (2018)


Whole blood
QuantiFERON
Whole blood
Specific antigens
Overnight incubation
INFγ
INFγ
Sensitized lymphocytes release INFγ
Measurement of INFγ using ELISA
ELISA plate reader (Spectrophotometer)
Whole blood
T-Track or T-SPOT
Plasma
PBMCs
RBCs
Preparation of PBMCs using the density gradient centrifugation
Separation of a defined number of PBMCs
Specific antigens
Overnight incubation
INFγ
INFγ
Sensitized lymphocytes release INFγ
Measurement of INFγ using ELISPOT
ELISPOT reader

Antígeno de CMV menos Nil (UI/ml)	Mitogen menos Nil (UI/ml)	Resultado del ensayo QF-CMV	Interpretación del resultado de QF-CMV
<0,2	≥0,5	**No reactivo**	Inmunidad anti-CMV NO detectada
≥0,2	Cualquiera	**Reactivo**	Inmunidad anti-CMV detectada
<0,2	<0,5	**Indeterminado**	Resultado indeterminado respecto a la reactividad al CMV







Fernández-Ruiz (2020)

TABLE 3 Diagnostic accuracy of the QTF-CMV assay at different positivity thresholds for IFN-γ production at the time of discontinuation of VGCV prophylaxis to predict protect the subsequent development of CMV infection

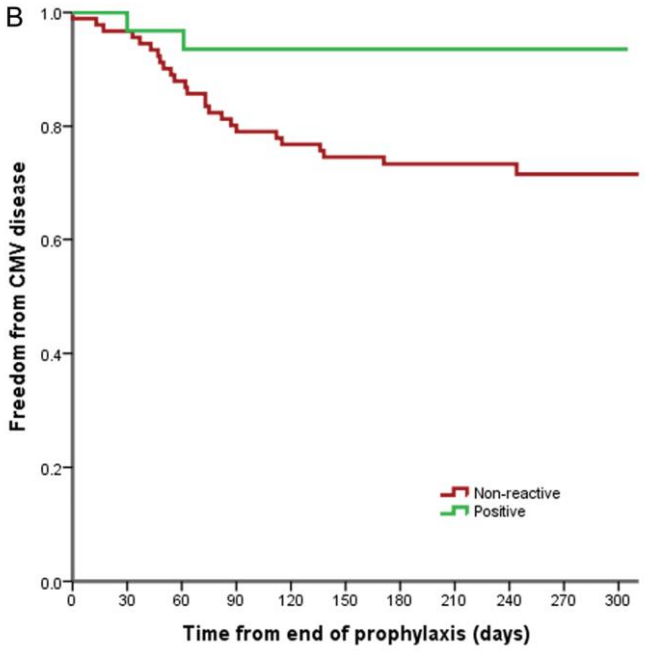
Threshold (CMV 4 minus nil) to define positivity of the QTF-CMV assay[a]	Proportion of patients (%)	Sensitivity (% [95% CI])	Specificity (% [95% CI])	PPV (% [95% CI])	NPV (% [95% CI])	PLR (95% CI)	NLR (95% CI)	Comments
IFN-γ ≥ 0.1 IU/mL	76.1	83.0 (70.2-91.9)	34.3 (19.1-52.2)	65.7 (59.4-71.5)	57.1 (38.6-73.9)	1.26 (0.97-1.65)	0.50 (0.23-1.05)	Cutoff value propos Kumar et al[18]
IFN-γ ≥ 0.2 IU/mL	72.7	77.4 (63.8-87.7)	34.3 (19.1-52.2)	64.1 (57.4-70.2)	50.0 (33.7-66.3)	1.18 (0.89-1.56)	0.66 (0.34-1.30)	Cutoff value propos manufacturer[16]
IFN-γ ≥ 0.5 IU/mL	60.2	64.2 (49.8-76.9)	45.7 (28.8-63.4)	64.2 (55.4-72.0)	45.7 (33.6-58.4)	1.18 (0.82-1.70)	0.78 (0.47-1.31)	
IFN-γ ≥ 1.0 IU/mL	50.0	56.6 (42.3-70.2)	60.0 (42.1-76.1)	68.2 (57.3-77.4)	47.7 (37.7-57.9)	1.42 (0.89-2.26)	0.72 (0.48-1.09)	
IFN-γ ≥ 1.13 IU/mL	47.7	56.6 (42.3-70.2)	65.7 (47.8-80.9)	71.4 (59.9-80.7)	50.0 (40.3-59.6)	1.65 (0.99-2.77)	0.66 (0.45-0.98)	Optimal cutoff value Youden's index[19]
IFN-γ ≥ 2.0 IU/mL	42.0	49.1 (35.1-63.2)	68.6 (50.7-83.2)	70.3 (57.4-80.6)	47.1 (38.6-55.7)	1.56 (0.89-2.74)	0.74 (0.53-1.05)	
IFN-γ ≥ 5.0 IU/mL	26.1	32.1 (19.9-46.3)	82.9 (66.4-93.4)	73.9 (55.3-86.6)	44.6 (38.8-50.6)	1.87 (0.82-4.28)	0.82 (0.65-1.04)	
IFN-γ ≥ 7.0 IU/mL	23.9	30.2 (18.3-44.3)	85.7 (69.7-95.2)	76.2 (56.3-88.8)	44.8 (39.4-50.3)	2.11 (0.85-5.24)	0.81 (0.65-1.02)	

Abbreviations: CI, confidence interval; CMV, cytomegalovirus; IFN-γ, interferon-γ; NLR, negative likelihood ratio; NPV, negative predictive value; PLR, positive likelihood ratio; PPV, positive pre value; QTF-CMV, QuantiFERON®-CMV; VGCV, valganciclovir.

[a]Nonreactive and indeterminate results were jointly considered as a "negative" (nonprotective) assay.

Fernández-Ruiz (2020)

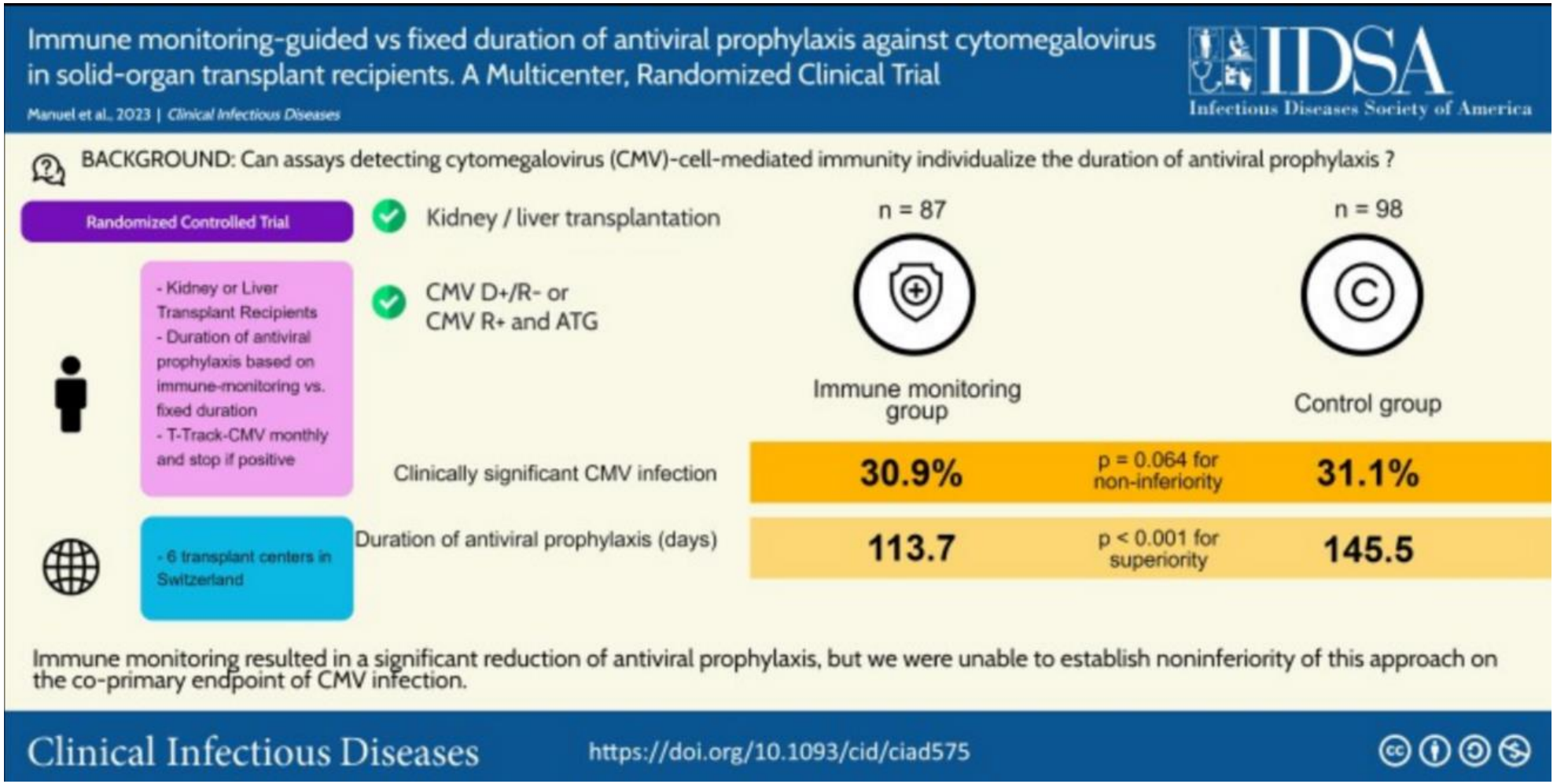
4. Escenarios clínicos potenciales de aplicación de la CMI



Clinical settings	Viral load	Immune monitoring result[a]	Action	Interpretation
Pretransplant				
Pretransplant R+		Neg	Prophylaxis or surveillance	Indicates low level protection
Pretransplant Seropositive patients with potential passive antibodies		Neg		Passive immunity; T cells are not transferred
		Pos		True Infection
Posttransplant prophylaxis				
End of prophylaxis		Pos	Stop prophylaxis	Indicates protection
		Neg	Continue prophylaxis or stop prophylaxis and do surveillance	Indicates lack of protection
Posttransplant preemptive therapy				
Asymptomatic R+ patients	Neg	Pos	Continue surveillance	Low risk, indicates protection
(>1 month posttransplant)	Neg	Neg	Close surveillance	Increased risk, indicates lack of protection
	Pos	Pos	No treatment; close monitoring	Low risk, indicates sufficient immunity
	Pos	Neg	Treatment	Indicates lack of protection
End of treatment	Neg	Pos	Stop treatment	Low risk of relapse, sufficient immunity
	Neg	Neg	Secondary Prophylaxis	High risk of relapse, lack of protection

[a] Positive (or Reactive) immune monitoring result suggests a threshold has been established; viral load negative means below lower limit of quantitation. Limited information in heart and lung transplant recipients and pediatric recipients.
Neg, negative; Pos, positive.

Kotton et al. Transplantation (2018)



Manuel O (2024)

Algoritmo de aplicación de la CMI según el riesgo

MUY ALTO RIESGO
D+/R-

	3 meses	3 meses	6-12 meses
	TX + Profilaxis universal obligatoria	Profilaxis universal opcional	Estrategia Anticipada
	VGCV oral ajustado a función renal No monitorización CMI No monitorización PCR	**Iniciar monitorización CMI** cuando CMI pos → STOP VGCV → iniciar Estrategia Anticipada si CMI neg → mantener VGCV 6 meses	**STOP VGCV** **Iniciar monitorización PCR CMV plasma** si PCR neg → seguir monitorizando si PCR pos → iniciar TRATAMIENTO **Monitorización CMI** no necesaria si ya es positiva Si CMI neg → vigilancia estrecha de la PCR CMV

	CMI pos	CMI neg
PCR CMV +	Iniciar TRATAMIENTO	Iniciar TRATAMIENTO
PCR CMV -	Replicación viral controlada	Monitorización estrecha PCR

Germans Trias i Pujol Hospital

Algoritmo de aplicación de la CMI según el riesgo

ALTO RIESGO
R+ con suero antilinfocitario

	3 meses	3-6 meses
	TX	Profilaxis universal obligatoria	Estrategia Anticipada

VGCV oral ajustado a función renal
No monitorización CMI
No monitorización PCR

STOP VGCV
monitorización CMI
monitorización PCR CMV plasma

	CMI pos	CMI neg
PCR CMV +	Monitorizar cinética viral*	Iniciar TRATAMIENTO
PCR CMV -	Replicación viral controlada	Monitorización estrecha PCR

** Ajustar tto IS y valorar si negativiza PCR CMV*

Germans Trias i Pujol Hospital

Algoritmo de aplicación de la CMI según el riesgo

RIESGO BAJO
D- / R -

0-6 meses

TOS | Estrategia Anticipada

No profilaxis VGCV
Monitorización PCR CMV plasma mensual
Serología IgG e IgM CMV a los 3, 6 y 12 meses post TR
si seroconversión → solicitar CMI

	CMI pos	CMI neg
PCR CMV +	Iniciar TRATAMIENTO	Iniciar TRATAMIENTO
PCR CMV -	Replicación viral controlada	Monitorización estrecha PCR

** Si PCR CMV positiva se manejará como un paciente de muy alto riesgo*

Germans Trias i Pujol Hospital

Monitorización de la PCR -CMV

- Tras finalizar la profilaxis antiviral específica.
- Tras iniciar o finalizar un tratamiento dirigido.
- Tras el trasplante cuando se inicie un tratamiento anticipado.

La frecuencia de determinación será máxima al principio y se espaciará progresivamente:

- Primer mes: semanal

- Segundo y tercer mes: quincenal

- A partir del cuarto mes: mensual hasta el mes 12.

IMPORTANTE: No está justificado monitorizar la PCR CMV en los pacientes que están bajo profilaxis con Ganciclovir/Valganciclovir

Germans Trias i Pujol
Hospital

CMV cell-mediated immunity in clinical practise: Does it help?

A. Romero[1], J. Ferrer[1], A. Sales[1] , M. Iglesias[2] , A. Casas[3], R. Benítez[1], C.Bracke[1], A. Peris[1], M.L. Pedro-Botet[1].

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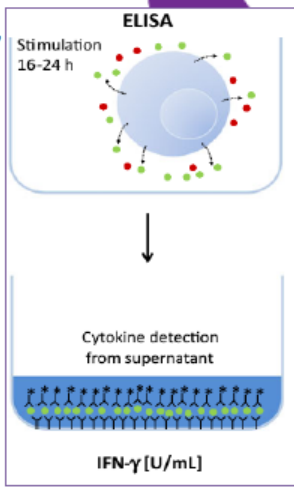
3) *Kidney Transplant Unit. Germans Trias i Pujol Hospital - Barcelona (Spain)*

INTRODUCTION

Cytomegalovirus (CMV) infection is the most prevalent viral infection after solid organ transplantation (SOT). CMV cell-mediated immunity (CMI) has demonstrated a high negative predictive value for the absence of CMV disease.

It has recently shown to reduce the duration of antiviral prophylaxis in high risk patients and algorithms have been proposed for intermediate-risk recipients to adjust the duration of universal prophylaxis.



Sester M, AST (2016)

METHODS

Objectives

To describe the relationship between **CMI and viral load in the different serogroups** at risk for CMV disease in our population.

Methods

We analized all **QuantiFERON-CMV ELISA** samples in our cohort of kidney transplant recipients during year 2023.

Patients were classified according to their pre-transplant serostatus (CMV-IgG) as: high risk (D+/R-), intermediate risk (R+) or low risk (D-/R-).

RESULTS

We had 30 samples collected, of which 17/30 (56%) patients tested positive 7/30 (23%) were considered borderline and 5/30 (16%) were negative.

Risk group	Frequency	CMI results	Comments
High risk (D+/R-)	6/30 (20%)	3/6 (50%) positive 2/6 (30%) borderline 1/6 (10%) negative	Those who tested positive were those who had presented a post prophylaxis higher peak of viremia (median of $3x10E^6$ IU/L) compared to those who did not (median of $3x10E^4$ UI/L).
Intermediate (R+ with or without ATG)	19/30 (63%)	10/19 (52%) positive 4/19 (21%) borderline 5/19 (26%) negative.	The maximum peak viremia in both positive and negative patients was an average of $10E^4$ IU/L.
Low risk (D-/R-)	4/30 (7%)	3/4 (75%) positive 1/4 (25%) borderline.	The median of the maximum peak viremia was $1x10E^4$ UI/L.

CONCLUSIONS

1) **50% of high-risk, 52% of intermediate-risk, and 75% of low-risk patients had positive CMI** against CMV
2) **Up to 50% of high-risk patients ended up testing positive for CMI**, at the expense of a **higher peak viremia than the intermediate or low-risk group.**
3) **A larger cohort study is ongoing that will establish negative predictive values in our center to open the door to start using CMI in clinical practise for adjusting CMV prophylaxis duration in high and intermediate risk groups.**

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34th ECCMID EUROPEAN CONGRESS OF CLINICAL MICROBIOLOGY AND INFECTIOUS DISEASES
Barcelona, Spain
27 – 30 April 2024

Estrategias terapéuticas de profilaxis y tratamiento antiviral

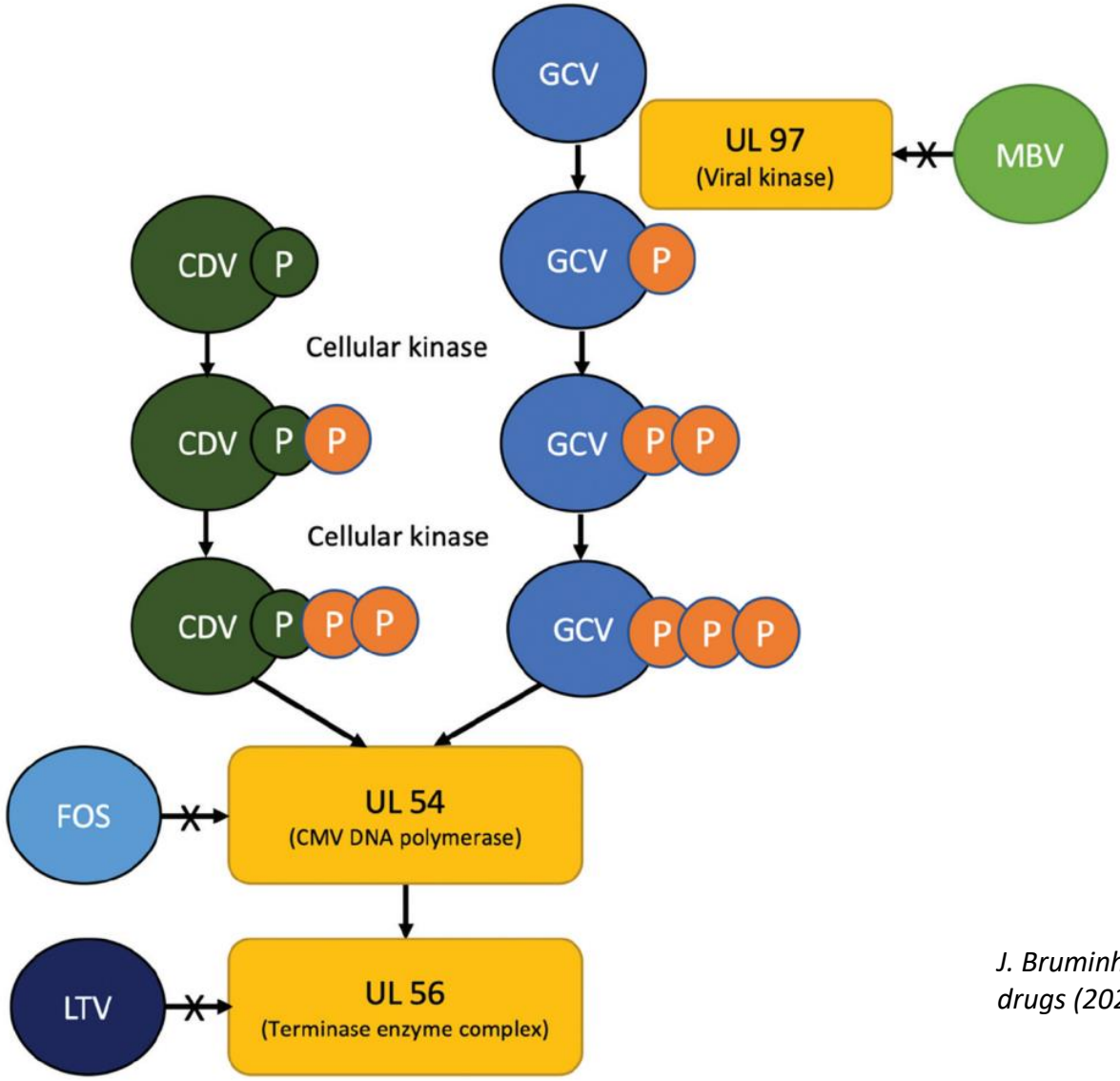
Fundació Lluita contra les Infeccions

Conceptos básicos del tratamiento de la infección por CMV

Infección por CMV refractaria	Incremento viremia >1Log10 ≥ 2 semanas de tto **a dosis adecuadas**
Enfermedad por CMV refractaria	Empeoramiento de los síntomas o signos de enfermedad ≥ 2 semanas de tto **a dosis adecuadas**
Infección Resistente	Alteración **genética** que disminuye la sensibilidad a uno o más antivirales

Bruminhent et al (2020)

Arsenal terapéutico anti-CMV



J. Bruminhent and RR. Razonable. Expert opinion on orphan drugs (2020)

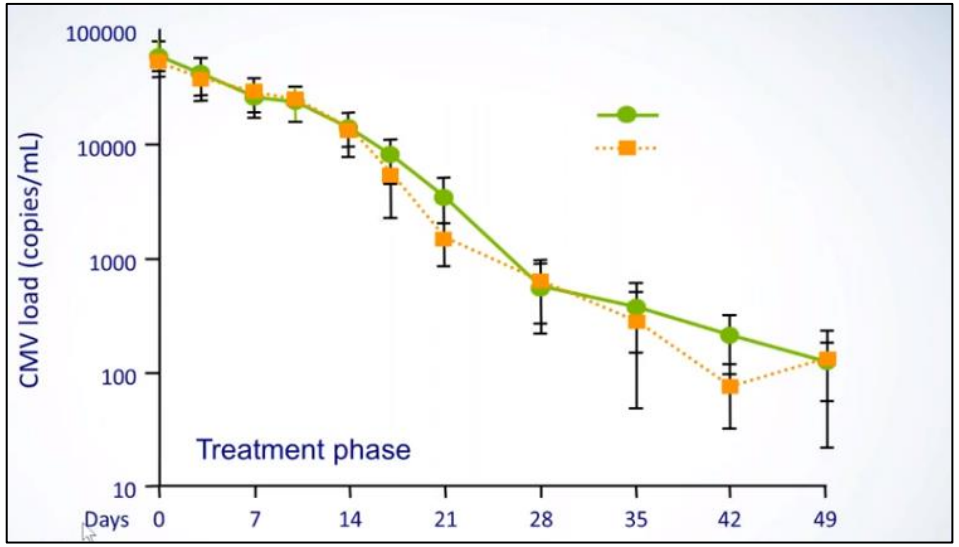
PAUTAS DE PROFILAXIS PARA CMV

- Ganciclovir / VGCV
- Letermovir

Ganciclovir / Valganciclovir

2.5mg/kg/12h por vía iv o Valganciclovir 900/24h v.o

- **Primera línea** de tratamiento y profilaxis
- Alta eficacia antiviral
- Alta barrera genética (R 2 -3.6%)
- Acción contra el resto de virus herpes (VHS-1/2, VHH-6, VHH-8)
- Equivalencia en forma oral o ev incluso con altas cargas virales.
- Eliminación **renal** – ajuste de dosis.
- **NO interacciona con los IS**

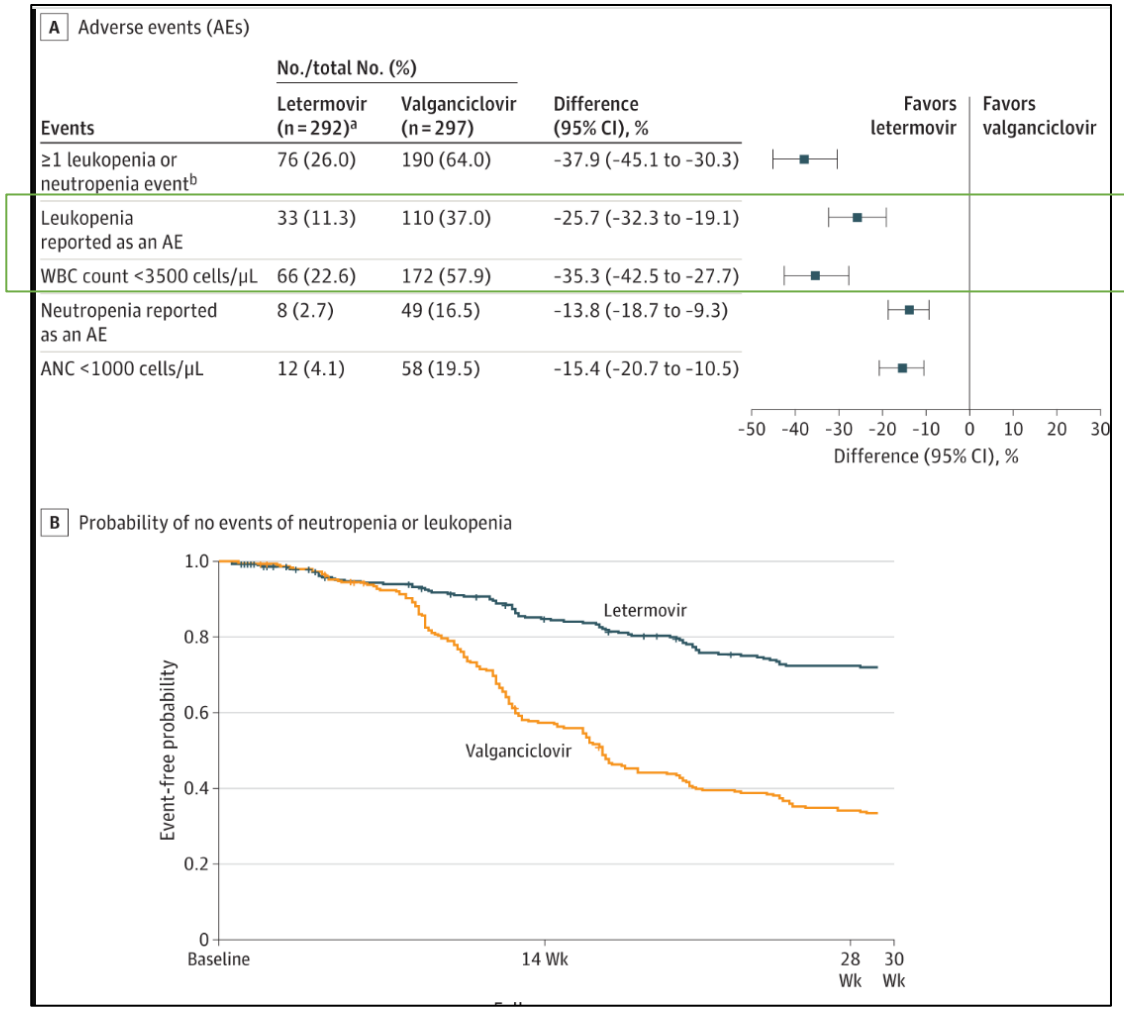


VICTOR study. Asberg, Humar et al (2007)

Letermovir

480mg/24h vo (240mg con CsA)

- Inhibe complejo terminasa UL56
- Indicación autorizada por la EMA (2023) para trasplante renal (no financiada)
- **No actividad contra otros herpesvirus**
- **Menor toxicidad medular**
- **Sin necesidad de ajuste por función renal**
- Aprobado por la EMA en profilaxis tx renal de alto riesgo (D+/R-) → indicación NO financiada → SUMSE
- **Interacción con IS** (ciclosporina)



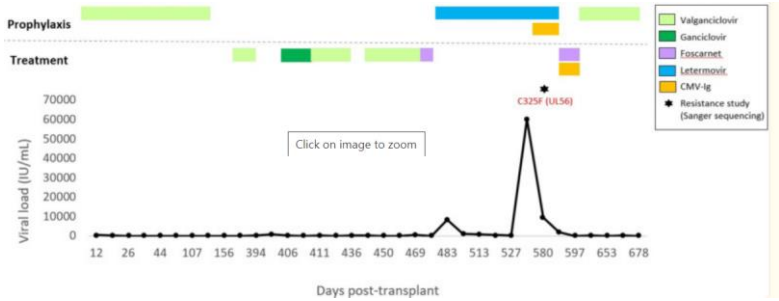
Limaye et al (2023)

Table 2. Adverse Events Through Week 28 in the Safety Population[a]

Adverse event	No. (%) Letermovir (n = 292)	Valganciclovir (n = 297)	Difference (95% CI), %[b]
Adverse event summary			
≥1 adverse event	271 (92.8)	276 (92.9)	−0.1 (−4.4 to 4.2)
Serious adverse events[c]	106 (36.3)	113 (38.0)	−1.7 (−9.5 to 6.1)
Drug-related adverse events[d]	58 (19.9)	104 (35.0)	−15.2 (−22.2 to −8.0)
Serious drug-related adverse events[c,d]	4 (1.4)	15 (5.1)	−3.7 (−7.0 to −0.9)
Death	2 (0.7)	1 (0.3)	0.3 (−1.3 to 2.2)
Discontinued due to adverse events	12 (4.1)	40 (13.5)	−9.4 (−14.1 to −4.9)
Discontinued due to serious adverse events[c]	6 (2.1)	14 (4.7)	−2.7 (−5.9 to 0.3)
Discontinued due to drug-related adverse events[d]	8 (2.7)	26 (8.8)	−6.0 (−10.1 to −2.4)
Discontinued due to serious drug-related adverse events[c,d]	2 (0.7)	7 (2.4)	−1.7 (−4.2 to 0.4)
Adverse events in ≥10% of participants			
Diarrhea	92 (31.5)	85 (28.6)	2.9 (−4.5 to 10.3)
Tremor	53 (18.2)	52 (17.5)	0.6 (−5.6 to 6.9)
Urinary tract infection	41 (14.0)	42 (14.1)	0.1 (−5.8 to 5.6)
Peripheral edema	39 (13.4)	38 (12.8)	0.6 (−4.9 to 6.1)
Hypomagnesemia	37 (12.7)	39 (13.1)	−0.5 (−5.9 to 5.0)
Leukopenia	33 (11.3)	110 (37.0)	−25.7 (−32.3 to −19.1)
Hypertension	33 (11.3)	36 (12.1)	−0.8 (−6.1 to 4.5)
Increased creatinine	30 (10.3)	41 (13.8)	−3.5 (−8.9 to 1.8)
Hypophosphatemia	30 (10.3)	35 (11.8)	−1.5 (−6.7 to 3.6)
Hyperkalemia	27 (9.2)	32 (10.8)	−1.5 (−6.5 to 3.4)
Nausea	25 (8.6)	33 (11.1)	−2.5 (−7.5 to 2.3)
Fatigue	18 (6.2)	32 (10.8)	−4.6 (−9.3 to −0.1)
Neutropenia	8 (2.7)	49 (16.5)	−13.8 (−18.7 to −9.3)

Limaye et al (2023)

… Y en profilaxis secundaria?
Real world experience



- RWE en TOS en profilaxis s2a
  - *Aryal S et al* (2019) (pulmón): 3/7 fracasos (42%)
  - *Ibrahim et al* (2024) (abdominales): 5/8 (62%)
  - *AB Pérez* (2023) (pulmón, hígado): 2/2 fracasos (100%)

- Revisión literatura:

  27 casos en profilaxis secundaria
  Éxito en 7/27
  Fracaso 8/27 (29%)-- > **resistencia UL56 en el 75%**
  Abandono (paliativos, falta financiación…) 3/27

AB Pérez (2023)

PAUTAS DE TRATAMIENTO PARA CMV

- Ganciclovir /Valganciclovir (5mg/kg/12h)
- Maribavir
- Foscarnet
- IGIV
- Terapia celular

Principios generales del tratamiento

- **Indicaciones**
  - Paciente **R- ó R+ con CMI negativa:** cualquier resultado de PCR.
  - Paciente **R+ con CMI positiva**
    - CV ≤5000 U/ml
      - se disminuirá la IS
      - se recomprobará la CMI-CMV
      - se repetirá una CV a las 48-72h
    - CV ≥5000 U/ml o > 1Log en 48h: iniciar tratamiento
  - Paciente **R+ sin CMI disponible / borderline:** ≥2000 U/ml

Maribavir

(400/12h x 8 semanas)

- Indicado por FDA y EMA para infección o enfermedad **refractaria con o sin resistencia**
- No necesario ajuste a FG
- **Antagonismo** con ganciclovir
- Resistencias cruzadas en mutaciones de la UL97

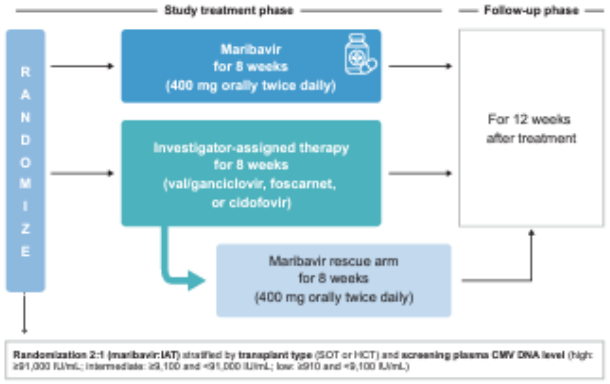
Maribavir for Refractory Cytomegalovirus Infections With or Without Resistance Post-Transplant: Results from a Phase 3 Randomized Clinical Trial

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

Avery RK et al (2022)

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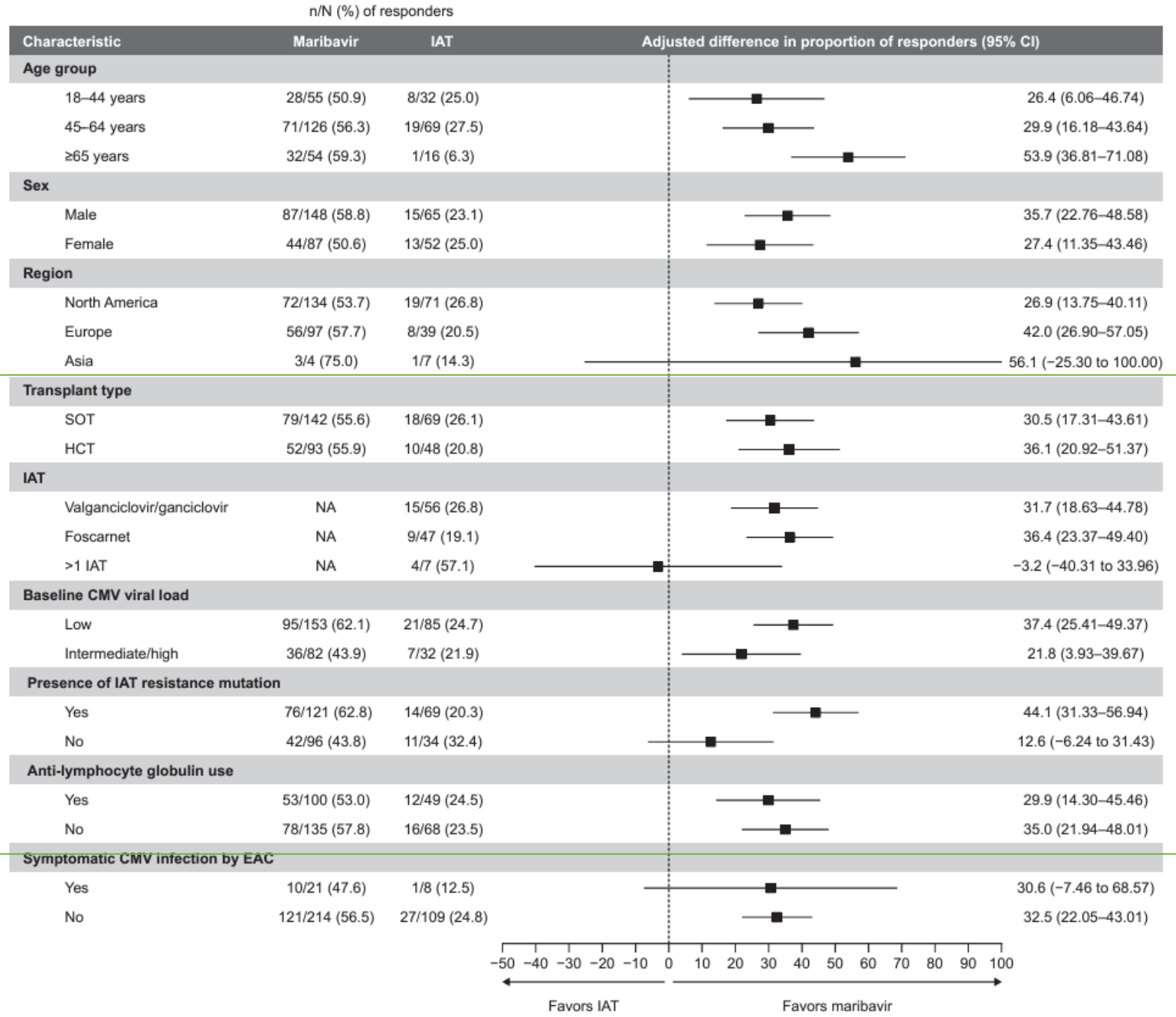


Characteristic	Maribavir	IAT	Adjusted difference in proportion of responders (95% CI)
Age group			
18–44 years	28/55 (50.9)	8/32 (25.0)	26.4 (6.06–46.74)
45–64 years	71/126 (56.3)	19/69 (27.5)	29.9 (16.18–43.64)
≥65 years	32/54 (59.3)	1/16 (6.3)	53.9 (36.81–71.08)
Sex			
Male	87/148 (58.8)	15/65 (23.1)	35.7 (22.76–48.58)
Female	44/87 (50.6)	13/52 (25.0)	27.4 (11.35–43.46)
Region			
North America	72/134 (53.7)	19/71 (26.8)	26.9 (13.75–40.11)
Europe	56/97 (57.7)	8/39 (20.5)	42.0 (26.90–57.05)
Asia	3/4 (75.0)	1/7 (14.3)	56.1 (−25.30 to 100.00)
Transplant type			
SOT	79/142 (55.6)	18/69 (26.1)	30.5 (17.31–43.61)
HCT	52/93 (55.9)	10/48 (20.8)	36.1 (20.92–51.37)
IAT			
Valganciclovir/ganciclovir	NA	15/56 (26.8)	31.7 (18.63–44.78)
Foscarnet	NA	9/47 (19.1)	36.4 (23.37–49.40)
>1 IAT	NA	4/7 (57.1)	−3.2 (−40.31 to 33.96)
Baseline CMV viral load			
Low	95/153 (62.1)	21/85 (24.7)	37.4 (25.41–49.37)
Intermediate/high	36/82 (43.9)	7/32 (21.9)	21.8 (3.93–39.67)
Presence of IAT resistance mutation			
Yes	76/121 (62.8)	14/69 (20.3)	44.1 (31.33–56.94)
No	42/96 (43.8)	11/34 (32.4)	12.6 (−6.24 to 31.43)
Anti-lymphocyte globulin use			
Yes	53/100 (53.0)	12/49 (24.5)	29.9 (14.30–45.46)
No	78/135 (57.8)	16/68 (23.5)	35.0 (21.94–48.01)
Symptomatic CMV infection by EAC			
Yes	10/21 (47.6)	1/8 (12.5)	30.6 (−7.46 to 68.57)
No	121/214 (56.5)	27/109 (24.8)	32.5 (22.05–43.01)

Diferencias ajustadas por grupos

Factores de riesgo de resistencia

- Profilaxis con VGCV subterapéutico
- Larga exposición a antivirales
- Replicación viral activa
  - Falta de inmunidad previa (D+/R-) o CMI negativa
  - Sobreinmunosupresión

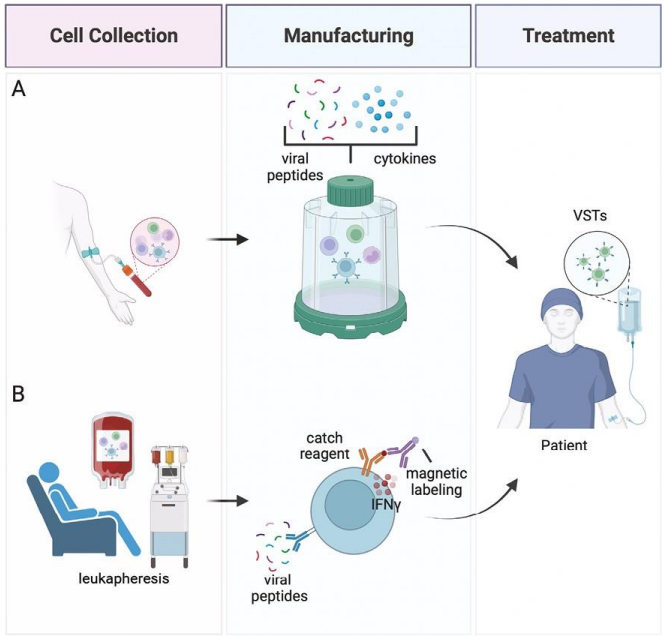
Foscarnet

60mg/kg/8h o 90mg/kg/12h

- En TR es una alternativa de segunda línea por su nefrotoxicidad
- Ajuste estricto a peso y función renal
- Riesgo de diselectrolitemia +++
- Indicación en enfermedad R/R
  - Con intolerancia oral
  - Resistencia genética a ganciclovir o maribavir (UL54, UL97)

Terapia celular con células T específicas (BST)

- **Células T específicas anti-CMV (CD4/CD8)**
  - Autólogas
  - Del donante
  - De un third party
- **Pools comerciales de células T específicas multi-virus** (posoleucel/tabelecleucel)
- Eficacia en SOT para CMV:
  - 40-70%. Menos eficaz en EOD y en profilaxis (30% reactivación)
  - Muy seguras. Matching HLA >4/10. Riesgo rechazo < 10%



Green et al (2023)

Virus	Study	Year	Method	Source	N=[a]	CR	PR
CMV	Smith [67]	2018	EVE	Auto	13	6 (46%)	5 (38%)
	Pierucci [68]	2016	EVE	Auto	1	0 (0%)	1 (100%)
	Macesic [69]	2015	EVE	3P	1	0 (0%)	1 (100%)
	Holmes-Liew [70]	2015	EVE	Auto	1	1 (100%)	0 (0%)
	Brestrich [71]	2009	GC	Auto	1	0 (0%)	1 (100%)

Clinical response
55 of 58 patients with CR/PR (95%)

CMV (n=24; incl. 4 with disease)
- CR 46%, PR 50%

AdV (n=12; incl. 10 with disease)
- CR 50%, PR 33%

HHV-6 (n=4)
- PR 75%

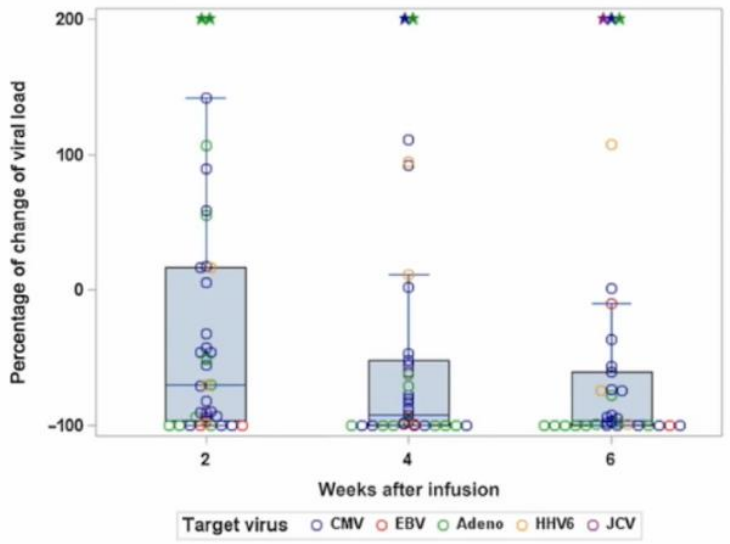
EBV (n=2)
- PR 100%

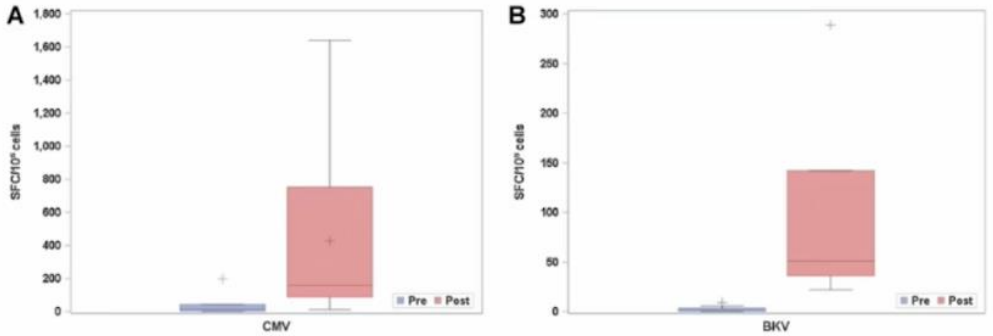
JC virus PML (n=1)
- Progressive disease

BKV (n=27)
- PR 100%

Clinical safety
- 22% with acute GVHD (3/12 > grade 1)

HLA Match
- No significant difference in clinical response and the degree of HLA matching between 1-2 HLA match versus 3-4 HLA match





Pfeiffer T. et al, Clin Cancer Res 2023;29:324–30

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Switzerland

Conclusiones

- El manejo de la infección CMV ha de ser **multidisciplinar.**
- Necesario un **abordaje integrativo a nivel inmunológico y virológico.**
- Reciente incorporación de estrategias de **monitorización inmune** ya publicadas en las **guías IDSA (2018)** y **GESITRA (2024)** e integradas en el **protocolo HGTIP de CMV en TR desde 2024.**
- **Es necesario establecer un adecuado punto de corte protector en vida real para las diferentes técnicas de CMI utilizadas.**