New challenges in infectious diseases in solid organ trasplantation

Cytomegalovirus infection

Julián de la Torre-Cisneros.

Hospital Universitario Reina Sofía-IMIBIC,
University of Córdoba.
Córdoba, Spain.

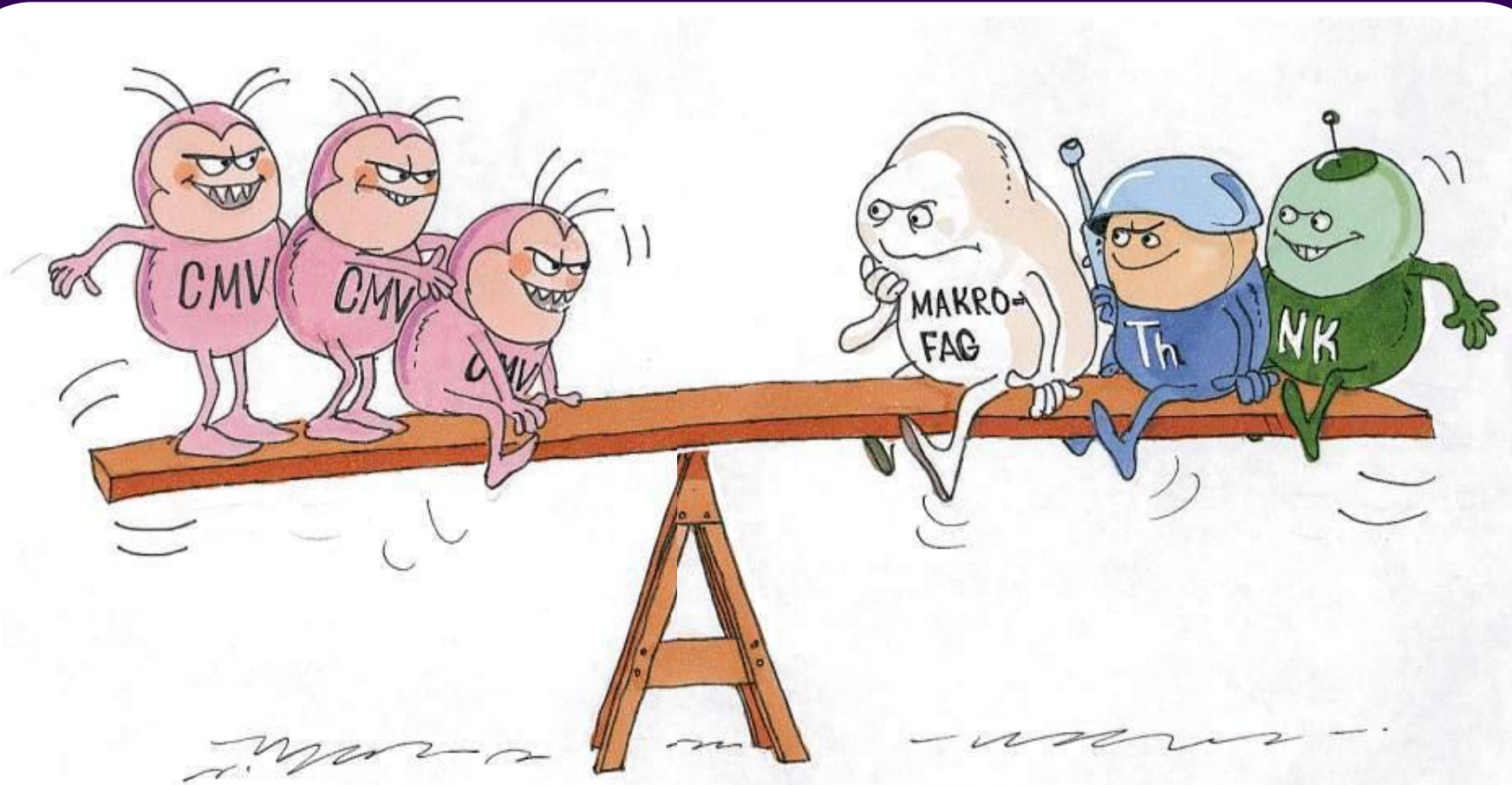
Julian Torre-Cisneros

Reina Sofia University Hospital-IMIBIC, University of Córdoba, Spain

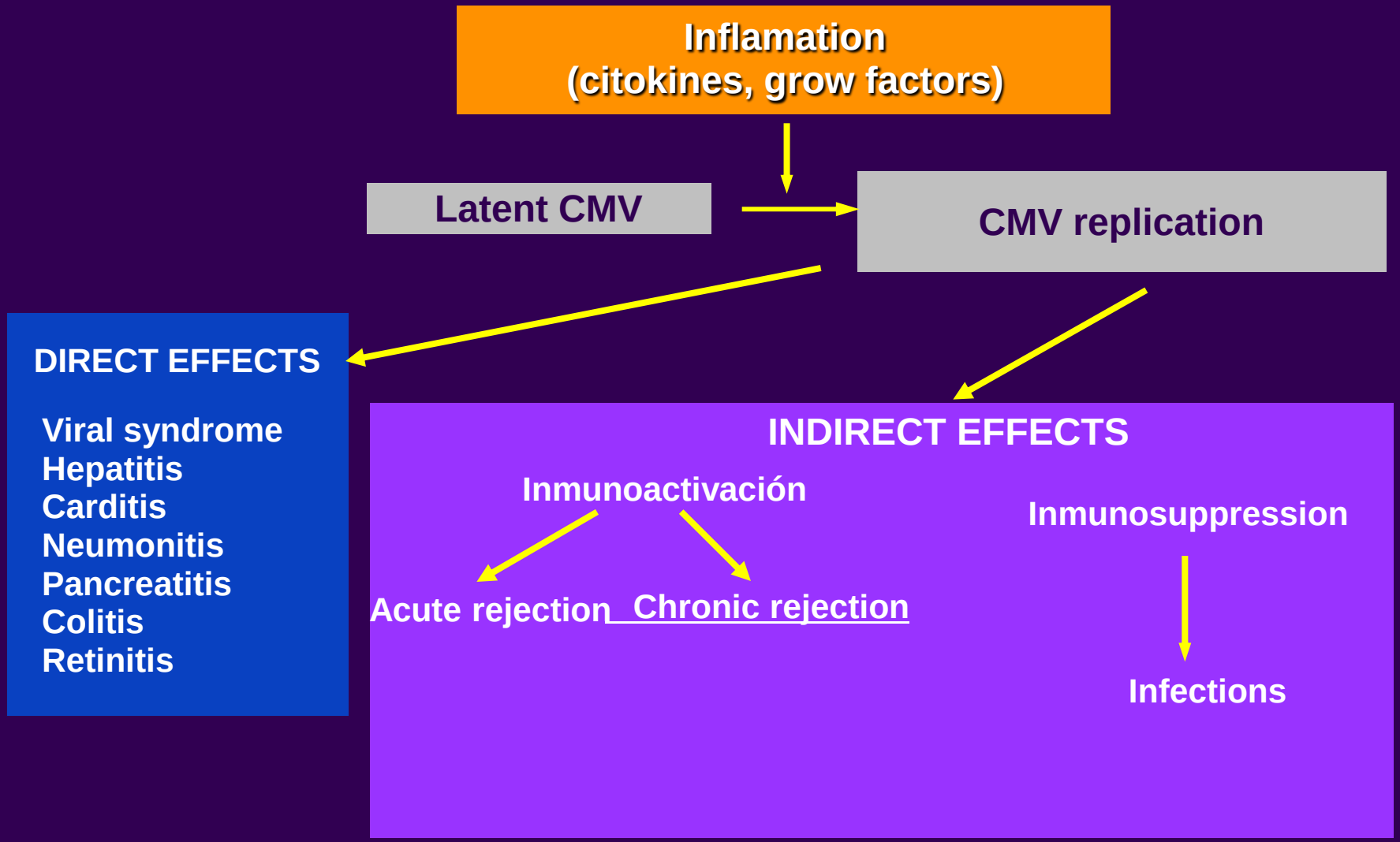
Disclosure

–Consulting – Astellas, Roche

–Research support – Roche


CMV
CMV
CMV
MAKRO-
FAG
Th
NK

Effects of CMV



Fishman JA & Rubin RH N Engl J Med 1998; 338: 1741

Guidelines to be reviewed

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

Camille N Kotton,[1,10] Deepali Kumar,[2] Angela M. Caliendo,[3] Anders Åsberg,[4] Sunwen Chou,[5] David R. Snydman,[6] Upton Allen,[7] and Atul Humar[2]; on behalf of The Transplantation Society International CMV Consensus Group[9]

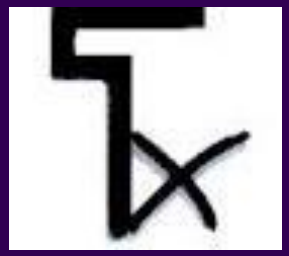
Summary of the British Transplantation Society Guidelines for the Prevention and Management of CMV Disease After Solid Organ Transplantation

Peter A. Andrews,[1,4] Vincent C. Emery,[2] and Chas Newstead[3]

Consensus document

GESITRA-SEIMC/REIPI recommendations for the management of cytomegalovirus infection in solid-organ transplant patients

Julian de la Torre-Cisneros[a,*], Mª. Carmen Fariñas[b], Juan José Castón[c], José María Aguado[d], Sara Cantisán[a], Jordi Carratalá[e], Carlos Cervera[f], José Miguel Cisneros[g], Elisa Cordero[g], Maria G. Crespo-Leiro[h], Jesús Fortún[i], Esteban Frauca[j], Joan Gavaldá[k], Salvador Gil-Vernet[l], Mercé Gurguí[m], Oscar Len[k], Carlos Lumbreras[d], María Ãngeles Marcos[n], Pilar Martín-Dávila[i], Victor Monforte[o], Miguel Montejo[p], Asunción Moreno[f], Patricia Muñoz[q], David Navarro[r], Albert Pahissa[k], José Luis Pérez[s], Alberto Rodriguez-Bernot[t], José Rumbao[u], Rafael San Juan[d], Francisco Santos[v], Evaristo Varo[w], Felipe Zurbano[x]



Indirect effects

- The GESITRA panel of experts considers that that an association relationship exits between CMV infection and :
  - Acute rejection in renal transplantation (BII),
  - Opportunistic bacterial and fungal infecctions, PTLD (CIII).

- The panel did not reach consensus on the role of CMV in the rest of indirect effects.

Updated International Consensus Guidelines on the Management of Cytomegalovirus in Solid-Organ Transplantation

Camille N. Kotton,[1,2] Deepali Kumar,[2] Angela M. Caliendo,[3] Anders Åsberg,[4] Sunwen Chou,[5] Lara Danziger-Isakov,[6] and Atul Humar,[7] on behalf of The Transplantation Society International CMV Consensus Group

Cytomegalovirus (CMV) continues to be one of the most common infections after solid organ transplantation, resulting in significant morbidity, graft loss, and adverse outcomes. Management of CMV varies considerably among transplant centers but has been become more standardized by publication of consensus guidelines by the Infectious Diseases Section of The Transplantation Society. An international panel of experts was reconvened in October 2012 to review and expand evidence and expert opinion based consensus guidelines on CMV management, including diagnostics, immunology, prevention, treatment, drug resistance, and pediatric issues. The following report summarizes the recommendations.

Keywords: Cytomegalovirus, CMV, Ganciclovir, Prevention, Prophylaxis, Resistance, Treatment, Valganciclovir.

(Transplantation 2013;96: 333–360)

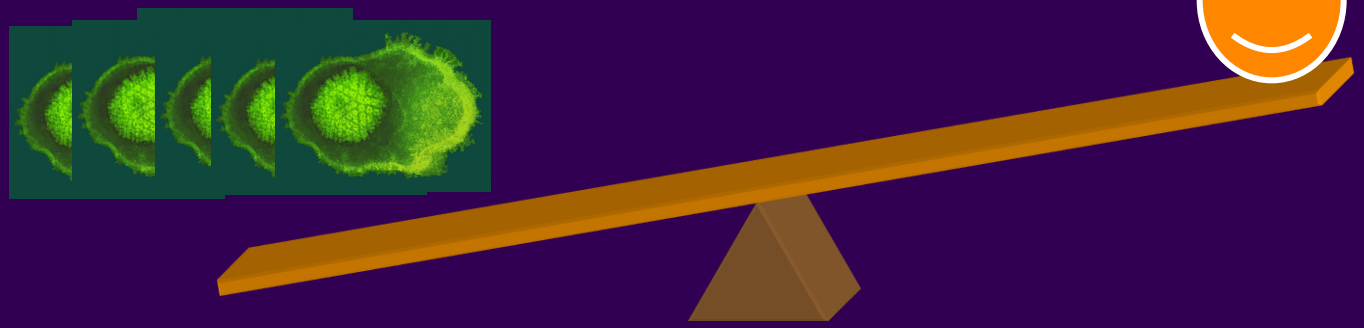
TABLE 1. Possible indirect effects of CMV

Transplant-specific indirect effects
Chronic allograft nephropathy and/or allograft loss after renal transplantation (*144, 246, 247*)
Accelerated hepatitis C virus recurrence after liver transplantation (*248*)
Hepatic artery thrombosis after liver transplantation (*249–251*)
Allograft vasculopathy after cardiac transplantation (*252, 253*)
Bronchiolitis obliterans after lung transplantation (*131, 254, 255*)
General indirect effects—elevated risks
Bacterial infections (*144, 256, 257*)
Fungal infection (*144, 148*)
Viral infections (summarized in (*258*))
Posttransplantation lymphoproliferative disorder (*259*)
Cardiovascular events (*260*)
New onset diabetes mellitus after transplantation (*261, 262*)
Immunosenescence (*263*)
Acute rejection (*131, 257, 264*)
Mortality (*144, 251, 254–256, 265*)

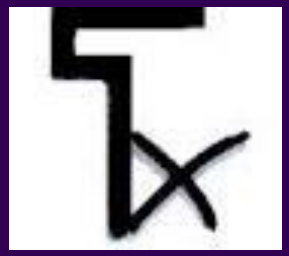
The association between CMV disease and these indirect effects has not been demonstrated in all studies. References listed here are examples supporting these statements and are not meant to include all references on this topic. Additional references can be found in the comprehensive review by Freeman; (*266*) table modified from Kotton (*267*).

T-CELL MEDIATED IMMUNITY

VIRUS



High level of viral replicartion



Risk factors

- Main risk factors.
  - D+/R-
  - Organ: lung, pancreas, bowel.
- Basal immunosuppression: recommedations are not available.
  - MMF and gastrointestial disease.
- Induction treatment, high dose steroids.
- mTOR inhibitors can reduce the risk of CMV: no recommendations to avoid CMV risk.

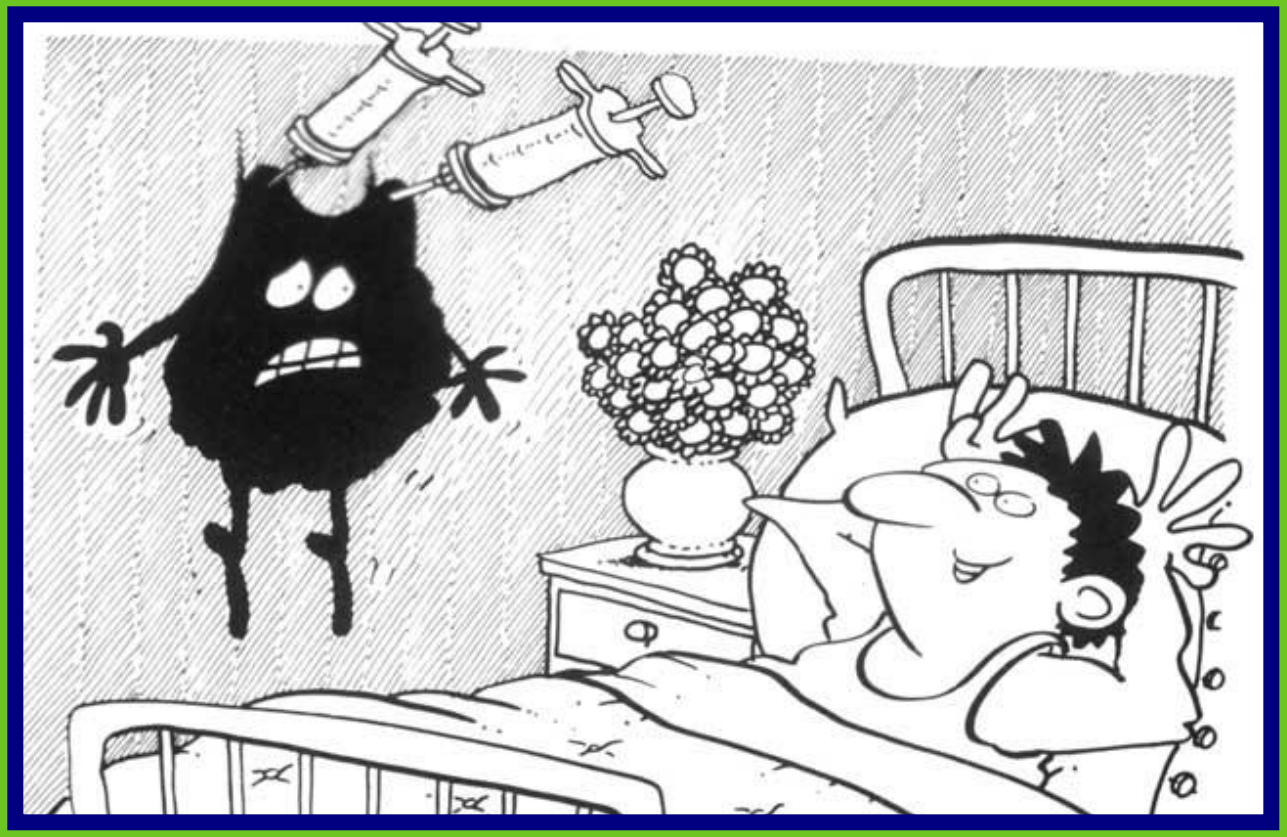
¿Mechanism?

CMV Late Phase-Induced mTOR Activation Is Essential for Efficient Virus Replication in Polarized Human Macrophages

Poglistch M. Am J Transplant 2012;12:1458-68

- mTOR activation is essential for CMV replication.
- mTOR inhibition can reduce CMV replication.

With the available evidences
¿what to do?
¿universal prophylaxis or preemptive therapy?



A open discussion….

	PROS	CON
Preemptive therapy	Increase CMI. Reduce antiviral use	Logistics problems CMV replication Indirects effects
Universal prophylaxis	Reduce CMV replication Reduce indirect effects	CMI (D+/R-) Late MV disease Resistant CMV Toxicity, expensive

• CID 2009:49 (15 October) • EDITORIAL COMMENTARY

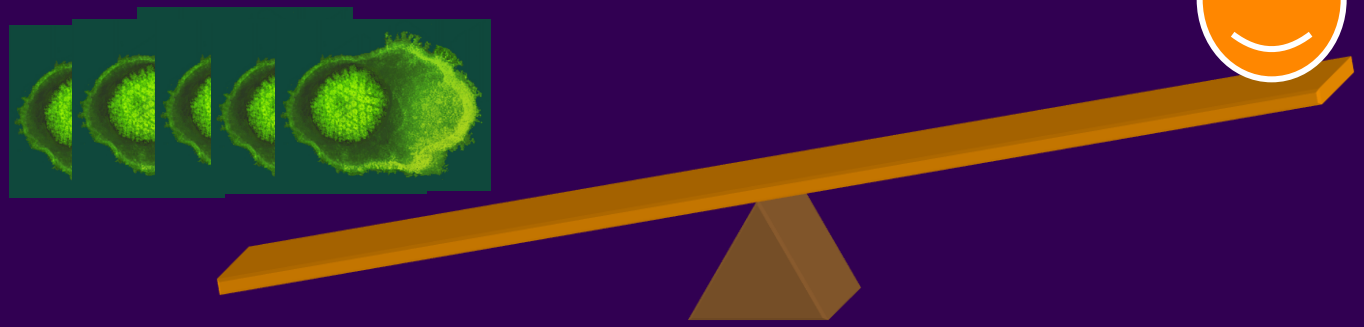
EDITORIAL COMMENTARY

Toward the Individualization of Cytomegalovirus Control after Solid-Organ Transplantation: The Importance of the "Individual Pathogenic Balance"

Julian Torre-Cisneros
Instituto Maimonides de Investigación Biomédica de Córdoba (IMIBIC)–Reina Sofia University Hospital, University of Córdoba, Córdoba, Spain

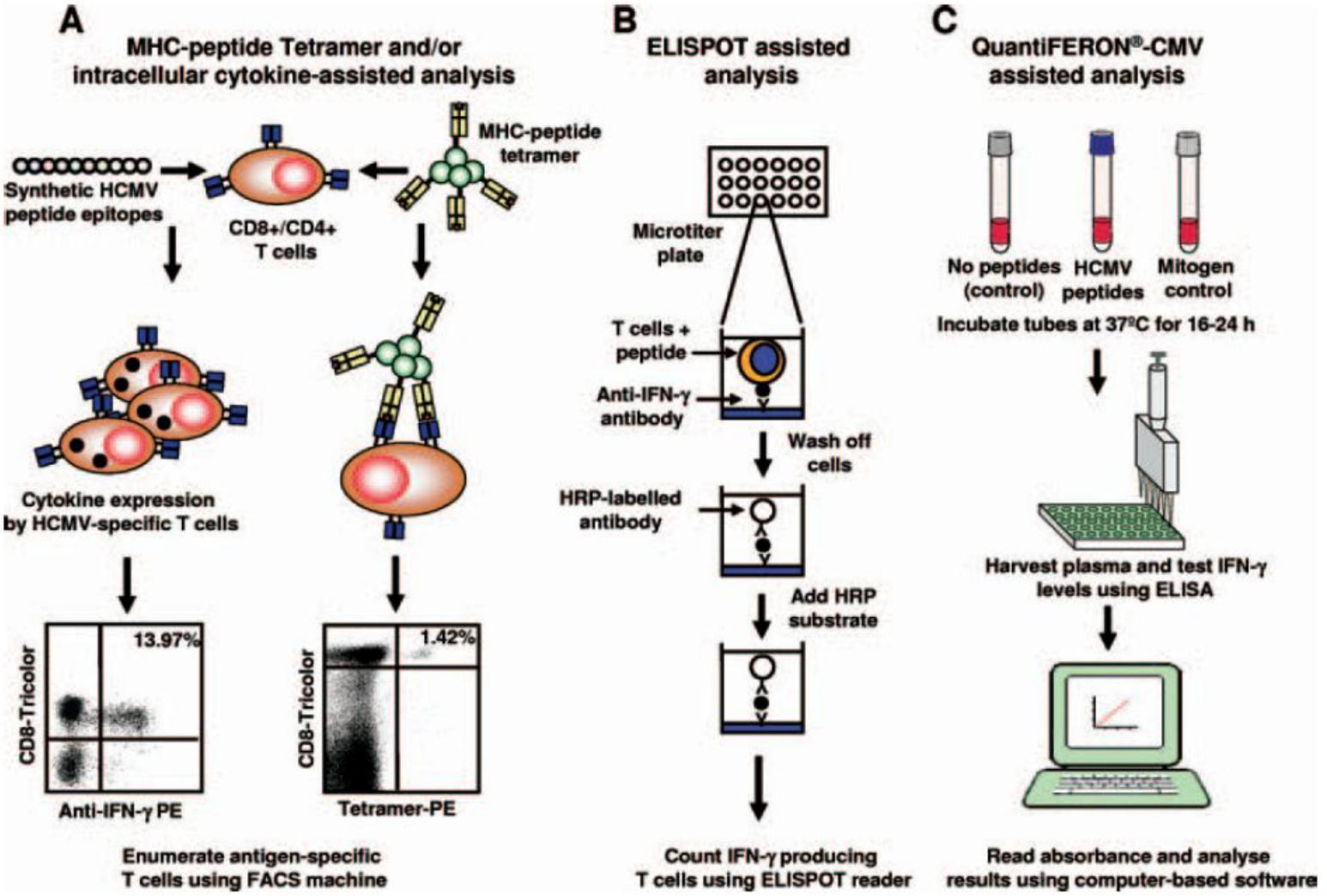
T-CELL MEDIATED IMMUNITY

VIRUS



CMV-specific cell-mediated immunity

Monitoring of CMV-specific T-cell mediated inmmunity.



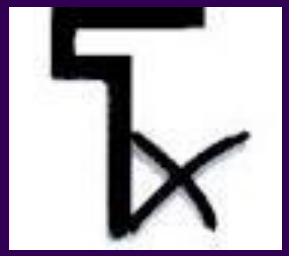
Gandhi MK, Khanna R. *Lancet Infect Dis* 2004; **4:** 725–38

State-of-the-Art Monitoring of Cytomegalovirus-Specific Cell-Mediated Immunity After Organ Transplant: A Primer for the Clinician

Adrian Egli, Atul Humar, and Deepali Kumar

Transplant Infectious Diseases, Alberta Transplant Institute, University of Alberta, Edmonton, Canada

CID 2012



Monitoring of T-cell mediated immunity (CMI)

- Potentially useful: can predict the risk of CMV replication.
  - Many post-transplant studies.
  - Manuel O. Clin Infect Dis 2013: D+/R-
  - Cantisán S. Am J Transplant 2013: pretrasplant.
- It is not recommended for clinical use (only research): interventional studies must be performed.

TABLE 4. Potential clinical scenarios for the use of immune-based assays

Clinical scenarios	Assays studied	Potential clinical management[a]
CMV D+/R- and R+ at the end of prophylaxis	QFT, ELISpot, ICS	For negative assay, prolong prophylaxis; for positive assay, no further prophylaxis
CMV D+/R- and R+ during preemptive strategy	QFT, ELISpot, ICS	Result may help guide frequency of viral load monitoring and thresholds for initiating antiviral therapy
Posttherapy for acute rejection	ICS (small number, not predictive)	For negative assay, restart prophylaxis or viral load monitoring; for positive assay, no further intervention
Recent completion of therapy for CMV disease or viremia (prediction of relapse)	No studies	For negative assay, secondary prophylaxis; for positive assay, no further therapy
Risk stratification in patients before transplantation	ICS, QFT	For positive assay, assume true positive CMV status

[a] No formal studies of clinical management have been published to date.

American Journal of Transplantation
Wiley Periodicals Inc.

doi: 10.1111/ajt.12049

Pretransplant Interferon-γ Secretion by CMV-Specific CD8+ T Cells Informs the Risk of CMV Replication After Transplantation

S. Cantisán[a,*], R. Lara[a], M. Montejo[b], J. Redel[c], A. Rodríguez-Benot[d], J. Gutiérrez-Aroca[e], M. González-Padilla[a], L. Bueno[f], A. Rivero[a], R. Solana[a] and J. Torre-Cisneros[a]

Key words: Cytomegalovirus replication, CD8+ T cells, interferon-γ, solid organ transplantation

Received 16 July 2012, revised 30 October 2012 and accepted for publication 02 November 2012

American Journal of Transplantation 2014; XX: 1–8
Wiley Periodicals Inc.

doi: 10.1111/ajt.13012

Factors Related to the Development of CMV-Specific CD8+ T cell Response in CMV-Seropositive Solid Organ Transplant Candidates

S. Cantisán[1,2,*], C. Rodelo-Haad[3], A. Páez-Vega[1,2], A. Nieto[4], J. M. Vaquero[2,5], A. Poyato[6], M. Montejo[2,7], C. Fariñas[2,8], A. Rivero[1,9], R. Solana[1,2,10], A. Martín-Malo[1,3] and J. Torre-Cisneros[1,2,9]

Table 2. Factors related to the development of CMV-specific CD8+ response (QuantiFERON-CMV Reactive) in CMV-seropositive solid organ transplant candidates.

	Multivariate		
Variable	**Adjusted OR**	**95% CI**	**p**
Age, mean (SD)			
Age, n (%) [a]			
≤50	1		
>50	6.3	1.9-20.7	0.002
Sex, n (%)			
Male			
Female			
Organ to be transplanted, n (%)			
Lung	1		
Liver	1.8	0.5-7.1	0.388
Kidney	8.8	2.2-34.9	0.002
HLA class I alleles, n (%)			
non-HLA-A1/non-HLA-A2	1		
HLA-A1 and/or HLA-A2	10.9	3.4-35.8	<0.001

[a] Age stratified as binary variable (younger and older than 50)
[b] QF-CMV (QuantiFERON-CMV) Reactive: ≥0.2IU/mL IFNγ

Assessment of Cytomegalovirus-Specific Cell-Mediated Immunity for the Prediction of Cytomegalovirus Disease in High-Risk Solid-Organ Transplant Recipients: A Multicenter Cohort Study

Oriol Manuel,[1] Shahid Husain,[2] Deepali Kumar,[3] Carlos Zayas,[4] Steve Mawhorter,[5] Marilyn E. Levi,[6] Jayant Kalpoe,[7] Luiz Lisboa,[3] Leticia Ely,[3] Daniel R. Kaul,[8] Brian S. Schwartz,[9] Michele I. Morris,[10] Michael G. Ison,[11] Belinda Yen-Lieberman,[12] Anthony Sebastian,[13] Maha Assi,[14] and Atul Humar[3]

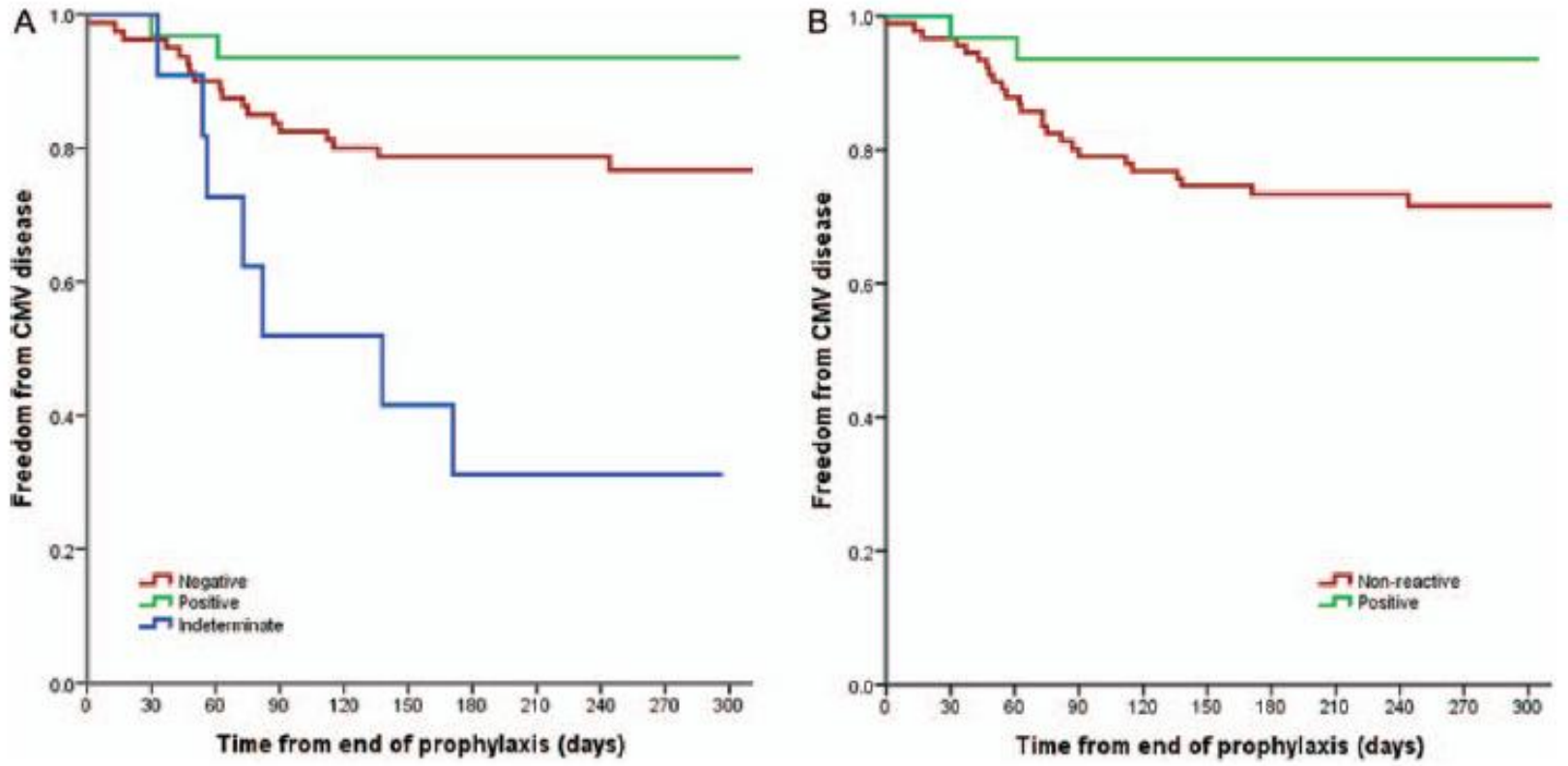
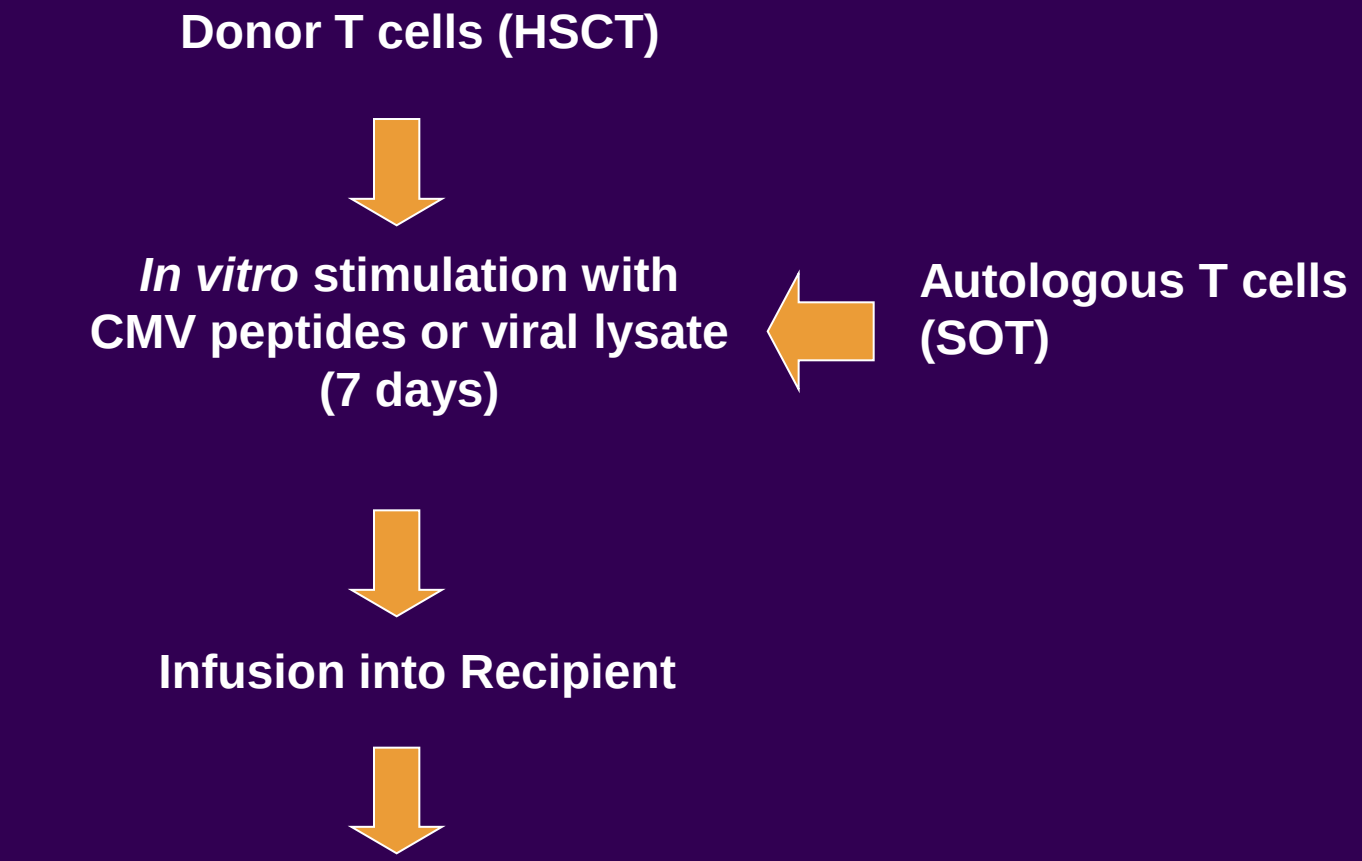


Figure 2. Kaplan-Meier curves of the incidence of cytomegalovirus (CMV) disease according to the result of the Quantiferon-CMV assay. *A*, Positive vs negative vs indeterminate result of the assay (log-rank test, $P < .001$). *B*, Positive vs nonreactive result of the assay (log-rank test, $P = .024$). Abbreviation: CMV, cytomegalovirus.

Adoptive Immunotherapy highlights the importance of CMI

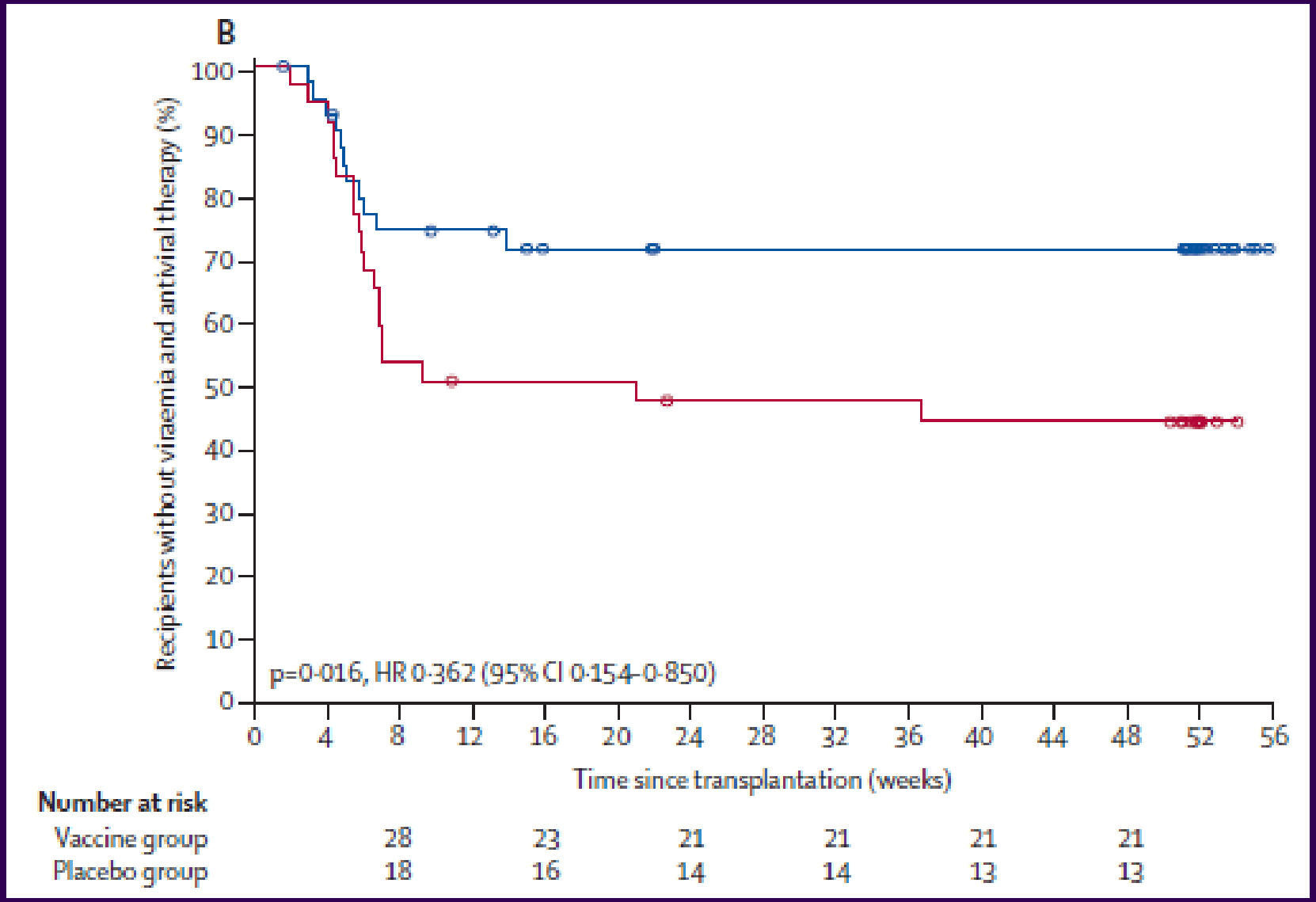


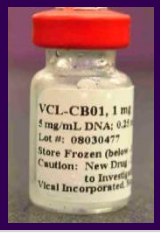
Einsele H et al. Blood 2002;
Brestrich G et al. Am J Transplant 2009.

CMV Therapeutic DNA Vaccine

- DNA vaccine;
- Two plasmids: gB + pp65
- RCT Vaccine *vs*. Placebo before conditioning and at 1,3 and 6 months post HSCT [in a subgroup with paired donors – vaccine also given to donors]

Lancet Infect Dis 2012; 12: 290-99.


B
Recipients without viraemia and antiviral therapy (%)
100
90
80
70
60
50
40
30
20
10
0
p=0·016, HR 0·362 (95% CI 0·154–0·850)
0
4
8
12
16
20
24
28
32
36
40
44
48
52
56
Time since transplantation (weeks)
Number at risk
Vaccine group 28 23 21 21 21 21
Placebo group 18 16 14 14 13 13



Administer Vaccine

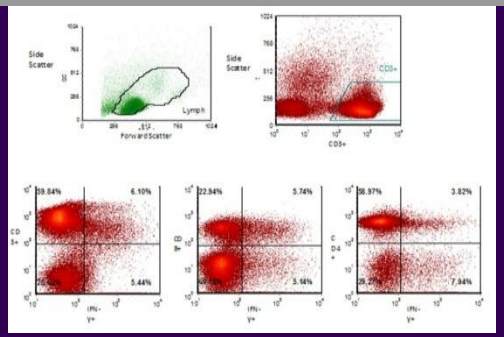
SOT
CMV D+/R-
CMV R+/QFnr

Time Post-Transplant

Measure Vaccine Response [CMI]

\+ → **No need for prophylaxis**

CMV viral lysate – 2x10^6 PBMCs stimulated with viral lysate showing significant IFN-γ production in CD8+ and CD4+ T cells in a CMV-seropositive renal transplant recipient



\- → **Give prophylaxis**

reipi

RED ESPAÑOLA DE INVESTIGACIÓN EN PATOLOGÍA INFECCIOSA

seimc

GESITRA

Sociedad Española de enfermedades infeccionas y Microbiologica Clinica