Bol Med Hosp Infant Mex. 2016;73(1):4–9

Boletín Médico del
Hospital Infantil de México

www.elsevier.es/bmhim

RESEARCH ARTICLE

# Correlation between viral load of cytomegalovirus and tacrolimus and sirolimus levels in transplanted pediatric patients

**Herlinda Reyes-Pérez[a], José Luis Sánchez-Huerta[a], Gustavo Varela-Fascinetto[b], José Carlos Romo-Vázquez[c], Abigail Morales-Sánchez[d], Ezequiel M. Fuentes-Pananá[d], Israel Parra-Ortega[a], Graciela Ramírez-Ramírez[a], Briceida López-Martínez[e,*]**

[a] *Departamento de Laboratorio Clínico, Hospital Infantil de México Federico Gómez, México, D.F., México*
[b] *Departamento de Trasplantes, Hospital Infantil de México Federico Gómez, México, D.F., México*
[c] *Departamento de Nefrología, Hospital Infantil de México Federico Gómez, México, D.F., México*
[d] *Unidad de Investigación en Virología y Cáncer, Hospital Infantil de México Federico Gómez, México, D.F., México*
[e] *Subdirección de Servicios Auxiliares de Diagnóstico, Hospital Infantil de México Federico Gómez, México, D.F., México*

Received 4 December 2015; accepted 7 December 2015
Available online 26 February 2016

**KEYWORDS**
Transplant;
Cytomegalovirus;
Sirolimus;
Tacrolimus

**Abstract**
*Introduction:* Survival of transplant patients and grafts depends largely on the use of immunosuppressive drugs. However, a balance remains to be established among immunosuppression, transplant rejection and cytomegalovirus (CMV) infection, which results in a high rate of morbidity and mortality. The aim of this study was to define a better strategy for monitoring transplanted patients based on the analysis of the blood concentration of sirolimus and tacrolimus and the burden of CMV.
*Methods:* Fifty five post-transplant (kidney and liver) pediatric patients, nine treated with sirolimus and 46 treated with tacrolimus, were included. A total of 541 measurements were obtained. In each measurement the concentration of immunosuppressant in whole blood and CMV viral load in plasma and whole blood was quantified by real-time PCR. Pearson correlation coefficient (r) was estimated.
*Results:* Values of $r \leq 0.0747$ were found for the relationship between dose and concentration of immunosuppressant; $r = 0.9406$ for the relationship between viral load in whole blood and plasma, and $r \leq 0.4616$ for the relationship between concentration of immunosuppressant and viral load.

* Corresponding author.
*E-mail address:* brisalm@yahoo.com.mx (B. López-Martínez).

http://dx.doi.org/10.1016/j.bmhimx.2015.12.006

*Conclusions:* These data support that the doses of immunosuppressive drugs do not correlate with the levels of the same in whole blood. Therefore, systemic levels of immunosuppressant should be constantly monitored together with CMV load. Meanwhile, a high correlation between viral load measured in whole blood and plasma was found.


**PALABRAS CLAVE**
Trasplante;
Citomegalovirus;
Sirolimus;
Tacrolimus

**Correlación entre la carga viral de citomegalovirus y los niveles de tacrolimus y sirolimus en pacientes pediátricos trasplantados**

**Resumen**
*Introducción:* La supervivencia de pacientes trasplantados y de los injertos depende en gran medida del uso de fármacos inmunosupresores. Sin embargo, aún no se ha logrado establecer un balance entre la inmunosupresión, el rechazo al trasplante y la infección por citomegalovirus (CMV), lo cual deriva en una alta tasa de morbilidad y mortalidad. El objetivo de este trabajo fue definir una mejor estrategia de seguimiento de los pacientes trasplantados a partir del análisis de la concentración en sangre de sirolimus y tacrolimus y la carga de CMV.
*Métodos:* Se incluyeron 55 pacientes pediátricos post-trasplante (riñón e hígado), nueve en tratamiento con sirolimus y 46 en tratamiento con tacrolimus. Se obtuvieron 541 mediciones en total. En cada medición se cuantificó la concentración de inmunosupresor en sangre total y la carga viral de CMV en plasma y sangre total mediante PCR en tiempo real. Se calculó el coeficiente de correlación de Pearson (r).
*Resultados:* Se encontraron valores de $r \leq 0.0747$ para la relación entre dosis y concentración del inmunosupresor; de $r = 0.9406$ para la relación de la carga viral entre suero y sangre total y de $r \leq 0.4616$ para la relación entre concentración de inmunosupresor y carga viral.
*Conclusiones:* Estos datos apoyan que la dosis de los fármacos inmunosupresores no correlaciona con los niveles de los mismos en sangre total. Por ello, deben ser constantemente monitoreados junto con la carga viral. Por su parte, se encontró alta correlación entre la carga viral medida en sangre total y plasma.


## 1. Introduction

Solid organ transplant (SOT) is a viable option for the treatment of childhood diseases that result in end organ failure. According to the Organ Procurement and Transplantation Network (OPTN) in the U.S. in 2008, almost 2000 pediatric patients (<18 years) received an organ transplant, representing 7.6% of all transplants performed. The majority of those transplants were kidney followed by liver. Among the principal problems associated with the transplant are graft rejection and infection due to cytomegalovirus (CMV).[1,2]

CMV or human herpesvirus 5 was initially isolated from the salivary glands and kidneys of children.[3] It received the name of cytomegalovirus because it produces typical cytomegalic inclusions in the affected cells.[4,5] In 1965 it was isolated in a kidney transplant recipient.[6] Infection caused by CMV is present in 90% of the world population, usually since childhood.[7] In patients who are immunocompromised, such as patients with SOT, CMV is one of the principal causes of morbidity and mortality because it causes clinical effects such as viral syndrome by CMV, fatigue, organ failure and graft rejection.[8] In addition, these effects are associated with an increase in hospitalization costs.[8–12]

Despite advances in the development of immunosuppressive agents, a balance between therapy to prevent rejection and, at the same time, preserve the ability of the immune system to control or prevent infectious processes has not been found. Two of the most commonly used immunosuppressants are tacrolimus and sirolimus. Currently, for management of patients with SOT, the best strategy to prevent rejection associated with insufficient concentrations of immunosuppressant and CMV disease is to individualize therapy. Preventing rejection is achieved by routinely quantifying the immunosuppressant levels in blood to keep them within the therapeutic range. In regard to CMV disease, prevention is carried out by monitoring the viral load in whole blood and/or plasma.[13–16] The solid organ transplant program of the Hospital Infantil de México Federico Gómez (HIMFG) is one of the main programs in Mexico. In that institution no studies have been carried out that document the quantitative relationship between the dose and the blood levels of the immunosupresant or that show the