Proyecto Prometeo II

LA FUNCIÓN RENAL POSTRASPLANTE COMO MARCADOR DE SUPERVIVENCIA: ANÁLISIS DE LA EVIDENCIA

SET
SOCIEDAD ESPAÑOLA DE TRASPLANTE

NOVARTIS

Proyecto Prometeo II

INTRODUCCIÓN

Manuel Arias
Josep María Campistol

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Causes of log-term Graft losses

IMMUNOSUPPRESSION NON-RELATED

- Increased donor and recipient age
- Suboptimal kidneys

IMMUNOSUPPRESSION RELATED

- Chronic allograft nephropathy
- Death with functioning graft
  - Cardiovascular disease
  - Cancer
  - Infections

Proyecto Prometeo

El **Proyecto Prometeo**, consiste en un programa de **formación continuada** en trastornos metabólicos del paciente **trasplantado renal** con el fin de elaborar **protocolos de diagnóstico y seguimiento** que poste te pu r impl s en las unidades de trasplante renal de nuestro país.

Propósito del proyecto

El propósito de este proyecto consiste en la **constitución de un grupo estable**, formado por un **especialista de cada una de las unidades de trasplante nacionales** que se reunirán anualmente con **expertos** en cada uno de los temas a tratar (hipertensión arterial, diabetes, trastornos de los lípidos, osteodistrofia renal, anemia…)

Sin duda, todo este esfuerzo, redundará en la formación de los facultativos de trasplante y en definitiva, en beneficio de los **pacientes** de nuestro país.

Proyecto Prometeo II

Coordinadores

- **Dr. Manuel Arias**

Hospital Univ. Marqués de Valdecilla, Santander

- **Dr. Josep M. Campistol**

Hospital Clínic, Barcelona

Grupo de trabajo Prometeo

- Grupo de trabajo Prometeo: **1 persona x Unidad de TR**

Proyecto Prometeo II

Organización del Trabajo

- División en 3 Grupos de Trabajo
- Búsqueda bibliográfica
- Revisión de +/- 1-2 artículos/persona

- Presentación a cada unidad por cada miembro del grupo Prometeo

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Suplementos en Nefrología

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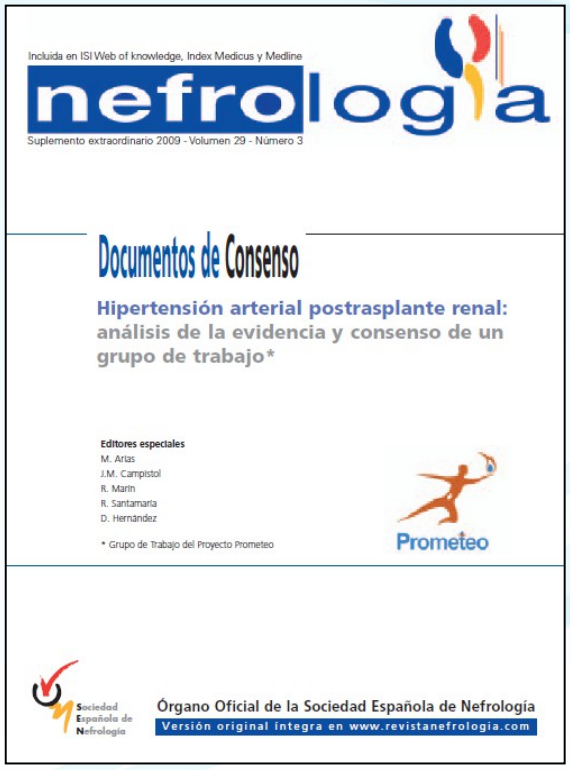
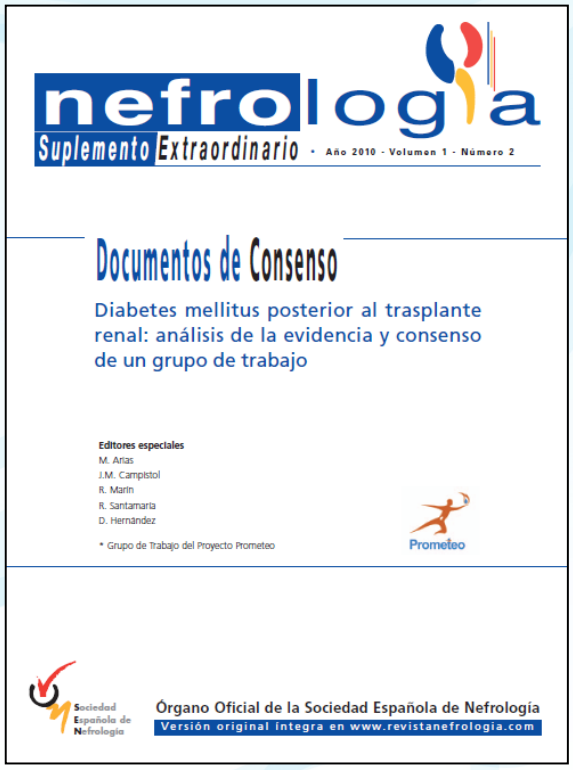
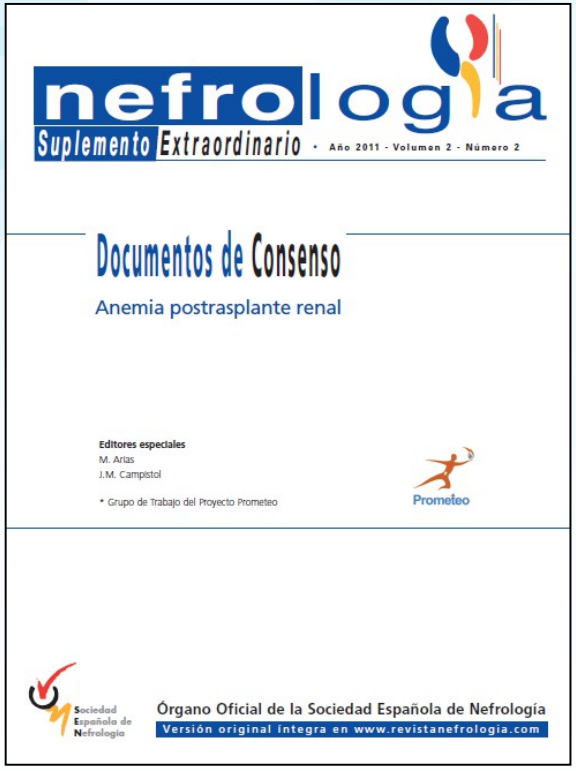
I. Hipertensión Arterial



II. Diabetes



III. Anemia



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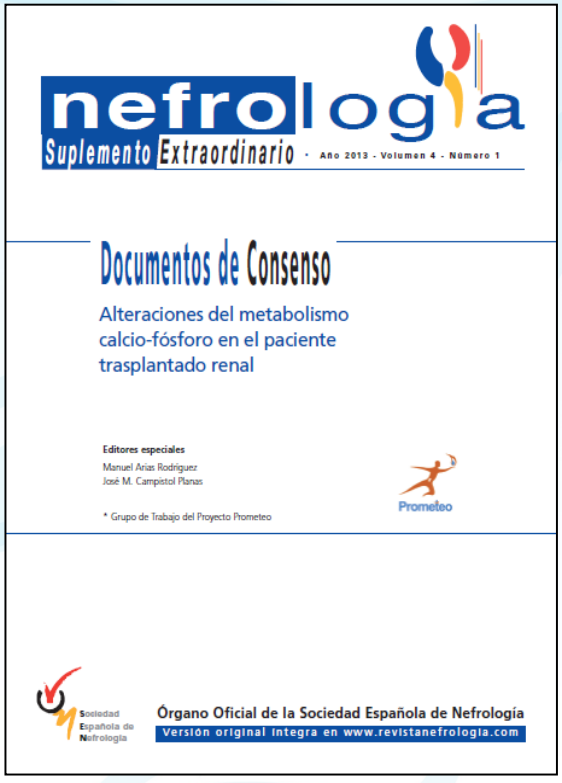
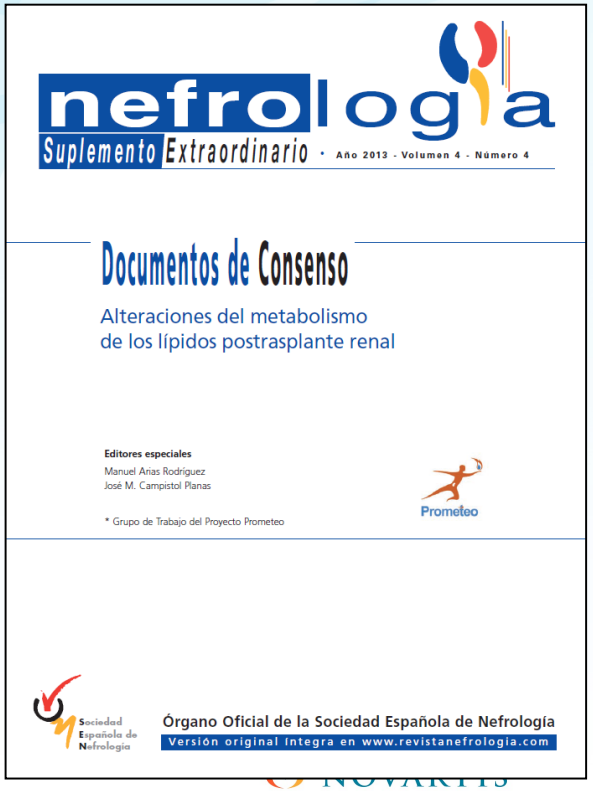
IV. CMV

V. METABOLISMO CALCIO-FÓSFORO



VI. ALTERACIONES DE LOS LÍPIDOS POSTRASPLANTE RENAL



Proyecto Prometeo II

En breve …

Evaluación Global de los Factores de Riesgo CV en Postrasplante Renal

- **Índice**:

  - **Introducción** – *Manuel Arias, José M. Campistol*

  - Artículos Especiales

    Mortalidad cardiovascular: ¿cómo prevenirla? - *Ramón Estruch*

    Predictores de riesgo cardiovascular en el trasplante renal – *Domingo Hernández*

  - **Grupo 1: Papel de la hipertensión en el riesgo cardiovascular postrasplante** - *Ángel Alonso*

  - **Grupo 2: Diabetes mellitus de novo post-trasplante (DMNPT)** - *Francesc Moreso*

Proyecto Prometeo II

Estudios Observacionales

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Prometeo
PROMETEO HTA
PROMETEO CMV
Retenal
Estudio Opera

Proyecto Prometeo II

ELSEVIER

Ambulatory Blood Pressure Monitoring in Kidney Transplant Patients: RETENAL Study

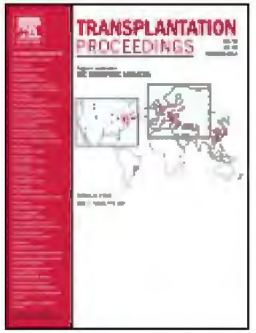
G. Fernandez Fresnedo, A. Franco Esteve, E. Gómez Huertas, V. Cabello Chaves, J.M. Díz Gómez, J.M. Osorio Moratalla, R. Gallego Samper, E. Gallego Valcárcel, J.M. Campistol Plana, R. Marín Iranzo, and M. Arias Rodríguez, RETENAL Group

ABSTRACT

Hypertension is common following renal transplantation, affecting up to 80% of transplant recipients. It is generally accepted that hypertension is associated with poor graft survival and reduced life expectancy, contributing to increased cardiovascular risk factors and mortality rates. The aim of the study was to compare the blood pressure (BP) control in kidney transplant patients through the use of ambulatory BP monitoring (ABMP) versus office BP measurements (oBP). A multicenter, cross-sectional, observational study was conducted in 30 nephrology/kidney transplant units. Eligible patients included hypertensive cadaveric kidney transplant recipients aged <70 years, with a functioning kidney for at least 1 year and with an estimated glomerular filtration ≥30 mL/min/1.73 m^2 and a serum creatinine < 2.5 mg/dL. Recorded data included demographic characteristics, oBP, and ABPM and labroatory investigations. The 868 patients showed a mean recipient age of was 53.2 ± 11.6 years and mean follow-up after transplantation, 5.5 ± 2.8 years. Mean systolic and diastolic oBP were 140.2 ± 18 and 80.4 ± 10 mm Hg, respectively. Seventy-six percent of patients had oBP higher than or equal to 130/80 mm Hg. Mean 24 hour ABPM were 131.5 ± 14 and 77.4 ± 8.7 mm Hg for systolic and diastolic BP, respectively. Using the ABPM, we observed that 36.5% of subjects were controlled (mean 24-hour BP < 130/85 mm Hg). The two methods (oBP and ABPM) showed significant agreement. After ABPM, 65% patients diagnosed as true controlled hypertension were considered to have white-coat RH. In clinical practice ABPM may help for better adjustment of drugs for adequate BP control.

CONGRESO SOCIEDAD ESPAÑOLA DE TRASPLANTE PALACIO DE CONGRESOS MADRID 2012 23 26 JUNIO

Transplantation Proceedings



CÁTEDRA DE TRASPLANTE UAM-ROCHE

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RE: JH-D-13-00846R2, entitled "Prevalence and Clinical Characteristics of Renal Transplant Patients With True Resistant Hypertension"

Dear Dr Fernandez,

The revised version of your manuscript has been further evaluated by referees 1 and 3 in charge of judging the previous versions. **While referee 1 is satisfied of the revised version, referee 3 (see enclosure) still raises important criticisms** that need to be properly addressed before the paper can be further evaluated.

If you can deal with referee's comments and modify the paper according to the suggestions the Editorial Board may reconsider your work. Yet, bear in mind that the revised version of your paper will be sent out for further scrutiny to referee 3 and that its final acceptance is not guaranteed. For your convenience we want to inform you that the rate of acceptance of the revised papers is below 30%.

With kind regards,

Prof. Guido Grassi
Executive Editor
Journal of Hypertension

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Reviewer	Comments:
Reviewer #1:	
No further objection. The manuscript still requires language improvement but I am sure this will be done by the Journal.	

Reviewer #3:

The authors still do not take my remarks seriously: Although they state in their point-to-point reply that they have done a **sensitivity analysis**, I see **nothing of it in the paper**. So, we do not know how they did it and what it showed.
The flow chart that I asked for is now in the manuscript but is wrong. According to the protocol only patients that had a transplant **for less than 10 years** were included. Yet, the flowchart shows that from all patients who fulfilled the inclusion criteria, a number was excluded because they had a transplant for more than 10 years. One should either mention all the patients who were excluded on the basis of exclusion criteria (there must have been some) or limit the table to those who were truly eligible. Moreover, **we need to know whether there was inclusion bias** so the characteristics of the final population should be compared with those in the original population.

Apparently, the authors do not know what **'floating numbers'** mean. It can be found in any book on mathematics. For instance, writing that the number of patients was 28.9 (page 4) is meaningless. I myself know only entire patients (or 'integer' to put it mathematically), not tenths of patients.

Proyecto Prometeo II

Estudio Opera+

“Estudio observacional epidemiológico prospectivo multicéntrico para evaluar la incidencia de enfermedad por CMV y los factores de riesgo asociados en pacientes trasplantados Renales Receptor +”

Promotor: SET

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Proyecto Prometeo II

ATC 2013
Poster

Poster Board Number: A580
"CMV, Respiratory and Other Viruses"
Date: Saturday, May 18, 2013

Epidemiology and Prevention Approaches for Cytomegalovirus (CMV) Disease in CMV-Seropositive Kidney Transplant (KT) Recipients: Results from a Multicenter, Prospective, Cohort Study

2013 AMERICAN TRANSPLANT CONGRESS

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José María AGUADO[a], Mario FERNÁNDEZ-RUIZ[a], Manuel ARIAS[b], José María CAMPISTOL[c], on behalf of the OPERA Study

[a] Unit of Infectious Diseases, Instituto de Investigación Hospital "12 de Octubre" (i+12), Hospital Universitario "12 de Octubre", Madrid, Spain. [b] Department of Nephrology, Hospital Universitario "Marqués de Valdecilla", Santander, Spain. [c] Department of Nephrology, Hospital Clinic-IDIBAPS, Barcelona, Spain.

Transparency declaration
All authors: The authors have no conflicts of interest.

ABSTRACT

Background: Although much is known about the incidence, risk factors, and prevention strategies in CMV-seronegative KT recipients, there is comparatively little information on these issues in CMV-seropositive patients.

Methods: From May 2011 to April 2012 a total of 287 CMV-seropositive KT recipients (170 males; age: 53.5 ± 12.2 years) were included in a multicenter, prospective, cohort study conducted in 21 Spanish transplant centers. The minimum follow-up period was 6 months. The primary study outcome was the incidence of CMV disease (viral syndrome or tissue-invasive disease) at months 3 and 6. A number of pre-transplant, perioperative, and post-transplant variables were prospectively recorded in a computerized database. Monitoring of CMV infection was performed according to local practice at each institution. We specifically analyzed the incidence of CMV disease in different groups: preemptive treatment (PT) or prophylaxis (ganciclovir or valganciclovir).

Results: At baseline, 126 patients (43.9%) were managed by PT, 124 (43.2%) by prophylaxis, and 37 (12.9%) underwent no specific prevention approach. Seven centers (33.3%) did not use PT, and one center (4.7%) did not perform any strategy. On multivariate regression model, the use of prophylaxis was associated with induction with polyclonal antibodies (odds ratio [OR]: 38.33; 95% confidence interval [CI]: 10.99-133.63), previous KT (OR: 6.04; 95%CI: 1.22-30.29) and recipient age ≥65 years (OR: 6.60; 95%CI: 2.66-16.39). Prophylaxis were administered for <3 (17.7%), 3 (59.7%) or 6 months (22.6%). Cumulative incidences of CMV disease at months 3 and 6 were 2.4% (7 patients) and 4.2% (12 patients), respectively. According to the baseline strategy, cumulative incidences at month 3 in the prophylaxis and PT groups were 0% and 4.0%, respectively (unadjusted OR [uOR]: 0.45; 95%CI: 0.43-0.56). Cumulative incidences at month 6 in the prophylaxis and PT groups were 1.6% and 5.3% (*P* = 0.112). There were no significant differences according to the duration of prophylaxis (3- or 6-month regimens). Diabetic nephropathy was associated with CMV disease at month 6 (uOR: 5.23; 95%CI: 1.47-18.64). Among the 70 patients receiving polyclonal antibodies within first 15-days, 62 (89.9%) were managed by prophylaxis and 7 (10.1%) by PT, with only one case of CMV disease (1.4%) in the prophylaxis group.

Conclusion: Prophylaxis strategy was associated with a lower incidence of CMV disease in a large prospective cohort of CMV-seropositive KT recipients.

INTRODUCTION

- CMV remains the most important serious viral infection complicating KT. To date, two approaches to CMV prevention (universal prophylaxis or preemptive therapy) are routinely used, aiming to minimize the acute complications of CMV (symptomatic CMV disease).
- Patients with CMV serologic mismatch (R+/D-) represent the highest risk and the use of universal prophylaxis has been long recommended for this group.
- Overall, CMV-seropositive recipients (R+) have moderate risk of infection. There is considerable variation in the type and duration of prevention in this population among different transplant centers, as the current guidelines acknowledge the use of both universal prophylaxis or preemptive therapy.
- The present study was aimed at assessing the incidence of CMV disease in a prospective, multicenter cohort of CMV-seropositive recipients according to the type of prevention approach used.

METHODS

- From May 2011 to April 2012 a total of **287 CMV-seropositive recipients** were included in a **multicenter, prospective, cohort study** conducted in 21 Spanish transplant centers (the OPERA Study).
- **The minimum follow-up period was 6 months.**
- The primary study outcome was the incidence of CMV disease (viral syndrome or tissue-invasive disease) at months 3 and 6.
- Pre-transplant, perioperative, and post-transplant variables were prospectively recorded in a computerized database.
- Monitoring of CMV infection was performed according to local practice at each institution.
- We compared the **cumulative incidence of CMV disease** (at months 3 and 6) in two different groups: preemptive treatment or universal prophylaxis.

Figure 1. Type of initial CMV prevention strategy per patient (n = 287).

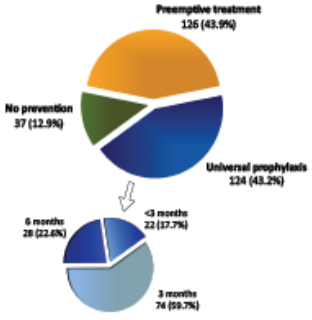
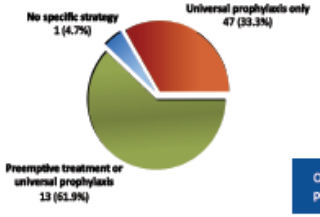


Figure 2. Type of CMV prevention strategy per center (n = 21).



RESULTS

Table 1. Clinical characteristics according to the type of prevention strategy [n (%) or mean ± SD].

	Universal prophylaxis (n = 124)	Preemptive therapy (n = 126)	*P*-value	Adjusted OR (95% CI)		*P*-value
Recipient age, years	54.9 ± 12.9	52.0 ± 11.6	0.065	-	-	-
≥65 years	33 (26.6)	17 (13.5)	0.010	7.92	(1.36-46.08)	0.021
Pre-transplant renal replacement therapy			0.086			
Hemodialysis	91 (79.8)	76 (67.3)		-	-	-
CAPD	12 (10.5)	22 (19.5)		-	-	-
None	11 (9.6)	15 (13.3)		-	-	-
Dialysis vintage, years	3.6 ± 2.6	2.9 ± 2.1	0.057	1.37	(1.07-1.75)	0.013
Donor age, years	56.4 ± 14.4	54.1 ± 14.7	0.197	-	-	-
Cold ischemia, hours	14.6 ± 6.5	12.5 ± 6.9	0.081	-	-	-
CMV serologic status			0.214			
D+/R+	96 (90.6)	103 (85.1)		-	-	-
D-/R+	10 (9.4)	18 (14.9)		-	-	-
Previous KT	10 (8.1)	3 (2.4)	0.045	-	-	-
Induction therapy			0.000			
None	14 (12.2)	50 (40.7)		-	-	-
Basiliximab	44 (38.3)	67 (54.5)		1.56	(0.42-5.73)	0.504
ATG	57 (49.6)	6 (4.9)		31.86	(5.24-193.9)	0.000

Table 2. Risk factors for CMV disease at month 6 (other than prevention strategy).

	No CMV disease (n = 275)	CMV disease (n = 12)	*P*-value
Diabetic nephropathy	8 (3.1)	4 (14.3)	0.021
Induction therapy			0.346
None	70 (27.2)	5 (41.7)	
Basiliximab	124 (48.2)	6 (30.0)	
ATG	63 (24.5)	1 (8.3)	
Acute graft rejection	11 (3.9)	1 (14.3)	0.379

Figure 3. Cumulative incidence of CMV disease according to prevention strategy at months 3 (a) and 6 (b).

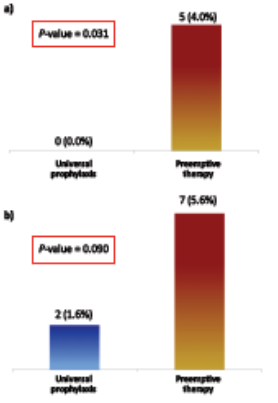
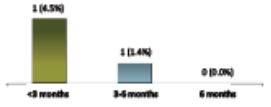


Figure 4. Cumulative incidence of CMV disease at month 6 according to the duration of prophylaxis.



CONCLUSIONS

Overall, the cumulative incidence of CMV disease at months 3 and 6 in a large cohort of CMV-seropositive KT recipients was low. A CMV prevention approach based on universal prophylaxis was associated with a lower incidence of CMV disease in our study. Further studies are needed to clarify the optimal prevention strategy in intermediate-risk KT recipients.

Proyecto Prometeo II

ESOT 2013
Comunicación Oral al Congreso

CYTOMEGALOVIRUS (CMV) PREVENTION STRATEGIES IN SEROPOSITIVE KIDNEY TRANSPLANT (KT) RECIPIENTS RECEIVING ANTILYMPHOCYTE INDUCTION THERAPIES: DATA FROM A MULTICENTER COHORT STUDY.

José María AGUADO, Mario FERNÁNDEZ-RUIZ, Manuel ARIAS, José María CAMPISTOL, on behalf of the OPERA Study.

Background: Induction therapy with antilymphocyte antibodies increases the risk of CMV reactivation in seropositive KT recipients. The optimal duration of universal prophylaxis with valganciclovir (VGCV) in this population remains to be assessed.

Methods: From May 2011 to April 2012 a total of 287 CMV-seropositive KT recipients were included in a multicenter cohort study conducted in 21 Spanish centers. The minimum follow-up period was 6 months. The primary study outcome was the incidence of CMV disease (viral syndrome or tissue-invasive disease) at months 3 and 6. A number of pre-transplant, perioperative, and post-transplant variables were prospectively recorded.

Results: Seventy patients (24.4% of the overall cohort) received antilymphocyte induction therapy (either antithymocyte [68 patients] or antilymphocyte globulin [2 patients]). The CMV prevention strategies consisted of universal prophylaxis in 63 patients (90.0%), preemptive therapy in 6 (8.6%), and no specific approach in one (1.4%). VGCV prophylaxis was used for <100 (14 patients), 100 (41 patients) or 200 days (8 patients). Cumulative incidences of CMV disease at months 3 and 6 were 0.0% and 1.4% (1 patient), respectively. According to the duration of VGCV prophylaxis the cumulative incidences of CMV disease at month 6 were 7.1% (<100 days) and 0.0% (≥100 days) (*P*-value = 0.222).

Conclusions: Universal prophylaxis with VGCV for ≥100 days, compared to shorter regimens, was associated with a lower incidence of CMV disease in seropositive KT recipients receiving antilymphocyte induction therapy.

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Proyecto Prometeo II

SEIMC 2014
Comunicación Oral al Congreso

370. IMPACTO DE LA ESTRATEGIA DE PREVENCIÓN SOBRE LA INCIDENCIA DE ENFERMEDAD POR CITOMEGALOVIRUS EN RECEPTORES SEROPOSITIVOS DE TRASPLANTE RENAL: RESULTADOS DE UN ESTUDIO MULTICÉNTRICO

J.M. Aguado[1], M. Fernández-Ruiz[1], M. Arias[2] y J.M. Campistol[3]

[1]Hospital Universitario 12 de Octubre. Madrid. [2]Hospital Universitario Marqués de Valdecilla. Santander. [3]Hospital Clínic de Barcelona. Barcelona.

Introducción: Si bien la epidemiología y factores de riesgo de la enfermedad por citomegalovirus (CMV) en la población de receptores de trasplante renal (TR) de alto riesgo (receptores seronegativos de un órgano de un donante seropositivo [D+/R-]) han sido ampliamente estudiados, la información disponible respecto a la población de riesgo intermedio (receptores seropositivos) es comparativamente menor.

Material y método: Entre mayo de 2011 y abril de 2012 fueron incluidos 287 receptores de TR seropositivos para CMV (170 varones; edad: 53,5 ± 12,2 años) en un estudio prospectivo y multicéntrico llevado a cabo en 21 centros españoles (estudio OPERA). El seguimiento mínimo de la cohorte fue de 12 meses. La monitorización de la viremia por CMV y la estrategia de prevención fueron establecidas según las prácticas locales de cada centro. El objetivo primario del estudio fue la incidencia acumulada de enfermedad por CMV (síndrome viral o enfermedad orgánica) en los meses 3 y 12 post-trasplante en tres grupos diferentes según el tipo de prevención aplicado: profilaxis universal, terapia anticipada o ausencia de estrategia específica. Analizamos igualmente los factores asociados al empleo de profilaxis universal.

Resultados: En la evaluación basal, 124 (43,2%) pacientes recibieron profilaxis universal, 126 (43,9%) recibieron terapia anticipada, y 37 (12,9%) no fueron sometidos a ninguna estrategia de prevención. Siete centros (33,3%) no llevaron a cabo terapia anticipada en ninguno de sus pacientes. En el análisis multivariante el uso de profilaxis universal se asoció al tratamiento de inducción con anticuerpos antilinfocíticos policlonales (*odds ratio* [OR]: 38,33; intervalo de confianza [IC] del 95%: 10,99-133,63), el TR previo (OR: 6,84; IC95%: 1,22-38,29) y la edad del receptor ≥ 65 años (OR: 6,60; IC95%: 2,66-16,39). La profilaxis antiviral (fundamentalmente valganciclovir) fue administrada durante < 3 meses (17,7%), 3 meses (59,7%) o 6 meses (22,6%). Las incidencias acumuladas de enfermedad por CMV al mes 3 post-trasplante fueron: 0% (grupo de profilaxis universal), 5,2% (grupo de terapia anticipada) y 7,1% (grupo sin estrategia de prevención) (p = 0,004). En el mes 12 post-trasplante, las incidencias acumuladas en cada uno de los grupos fueron: 1,3%, 5,2% y 7,1%, respectivamente (p = 0,057). Entre los 70 pacientes que recibieron tratamiento de inducción con anticuerpos antilinfocíticos policlonales, 62 (89,9%) fueron sometidos a profilaxis y 7 (10,1%) a terapia anticipada, con tan sólo un caso de enfermedad por CMV (1,4%) en el grupo de profilaxis.

Conclusiones: En el presente estudio multicéntrico la incidencia de enfermedad por CMV en receptores seropositivos de TR fue baja (3,9% a los 12 meses), si bien comparable a la de otras series recientes. Un número elevado de pacientes (43,2%) fueron sometidos a profilaxis universal, particularmente en receptores de mayor riesgo inmunológico que recibieron tratamiento de inducción con anticuerpos antilinfocíticos. El empleo de profilaxis universal se asoció a una menor incidencia de enfermedad por CMV, si bien el coste-efectividad de esta estrategia de prevención en una población de riesgo intermedio debe ser analizado en el futuro.

XVIII CONGRESO NACIONAL DE LA SOCIEDAD ESPAÑOLA DE ENFERMEDADES INFECCIOSAS Y MICROBIOLOGÍA CLÍNICA

seimc 2014 Valencia 9-11 ABRIL 2014 Palacio de Congresos de Valencia

SET SOCIEDAD ESPAÑOLA DE TRASPLANTE

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Proyecto Prometeo II

SET 2014
Comunicación Oral al Congreso

09:50 O134/ Impacto de las diferentes estrategias de prevención en el riesgo de infección por CMV en receptores seropositivos de trasplante renal: Resultados de un estudio multicéntrico

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1Hospital Universitario 12 de Octubre, Madrid 2Hospital Universitario Marqués de Valdecilla, Santander 3Hospital Clinic-IDIBAPS, Barcelona

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III CONGRESO
DE LA SOCIEDAD ESPAÑOLA
DE TRASPLANTE

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La Junta Directiva y el Comité Científico de la Sociedad Española de Trasplante han decidido otorgar el Premio de Accesit a la Mejor Comunicación ORAL, presentada en el **III Congreso de la Sociedad Española de Trasplante,** al trabajo titulado:

Efecto de polimorfismos de un solo nucleótido localizados en genes involucrados en la respuesta inmune sobre el riesgo de infección por CMV en receptores seropositivos de trasplante renal

Presentado por los autores:

David Navarro[1], Mario Fernández Ruiz[2], Isabel Corrales[1], Estela Giménez[1], Manuel Arias[3], Josep Maria Campistol[4], José María Aguado[2]

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Valencia, a 10 de Junio de 2014

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Presidente del Comité Organizador

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SOCIEDAD ESPAÑOLA DE TRASPLANTE

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Proyecto Prometeo II

WTC 2014
Poster

Impact of Different Prevention Strategies on the Risk of Cytomegalovirus (CMV) Infection and Disease in Seropositive Kidney Transplant (KT) Recipients

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INTRODUCTION

- Human cytomegalovirus (CMV) remains as one of the major causes of infection-related morbidity in KT recipients.
- The combination of donor (D) and recipient (R) CMV serostatus plays a definitive role in defining the risk of post-transplant CMV infection and disease.
- CMV-seropositive patients constitute by far the most common risk group among the solid organ transplant population.
- However, most of large randomized clinical trials have been historically focused on the highest-risk category (D+/R- recipients), whereas only a few studies have examined the optimal prevention approach (i.e., antiviral prophylaxis or preemptive therapy) in CMV-seropositive recipients.
- Although there is some evidence of the superiority of antiviral prophylaxis in CMV-seropositive KT recipients, current guidelines contemplate both approaches —with different strength of recommendation— as potentially effective.
- Such relative scarcity of evidence might explain the notable heterogeneity across centers regarding management strategies among CMV-seropositive recipients.

METHODS

- **Study design:** We performed a prospective, observational, cohort study at 26 transplant centers in Spain (The OPERA Study) between March 2011 and December 2013. The choice and implementation of the CMV prevention strategy (i.e., antiviral prophylaxis or preemptive therapy) were not standardized, but rather based on local institutional protocols.
- **Study population:** Eligibility criteria included patients aged ≥18 years that underwent single KT at one of the participating institutions during the recruitment period and were CMV-seropositive before transplantation. Recipients of a double or combined transplant were excluded. Participants were enrolled at the time of transplantation and followed-up for at least 12 months, unless death or graft loss occurred earlier. Scheduled follow-up visits were carried out at baseline, week 2, and months 1, 3, 6, 9 and 12. Further visits were additionally performed depending on local practices at each center.
- **Study outcomes:** The primary outcome was the 12-month incidence of CMV disease. Secondary outcomes included the 12-month incidence of asymptomatic CMV infection, the 6- and 12-month cumulative incidences of biopsy-proven acute rejection (BPAR), non-CMV infection, graft loss and all-cause mortality, and the evolution of graft function at months 3, 6 and 12 after transplantation.
- **Statistical analysis:** Associations were expressed as odds ratios (ORs) with 95% confidence intervals (CIs). Survival probabilities were estimated by the Kaplan-Meier method with CMV infection and disease as events, and differences between strategy groups were compared by the log-rank test. Univariate and multivariate Cox regression models were used to evaluate the association between the prevention strategy and outcomes, with results expressed as hazard ratios (HRs). Patients not receiving any specific intervention were excluded from these analyses.

Table 1. Demographics and clinical characteristics of both study groups.

Variable		
Recipient age, years (mean ± SD)	53.4 ± 12.4	
Recipient gender (male) [n (%)]	224	(57.0)
Race [n (%)]		
Caucasian	358	(91.1)
Black	24	(6.1)
Asian	5	(1.3)
Body-mass index at transplantation, Kg/m² (mean ± SD)	26.1 ± 4.4	
Etiology of underlying ESRD [n (%)]		
Glomerulonephritis	167	(17.6)
Diabetic nephropathy	98	(9.8)
Nephrosclerosis	99	(9.9)
Polycystic renal disease	88	(11.1)
Chronic interstitial nephropathy	97	(9.5)
Congenital nephropathy	7	(1.4)
Ischemic vasculitis	7	(1.3)
Unknown	70	(14.0)
Others	28	(3.2)
Pre-transplant renal replacement therapy [n (%)]	338	(87.3)
Type of therapy [n (%)]*		
Hemodialysis	242	(69.0)
Continuous ambulatory peritoneal dialysis	57	(19.1)
Dialysis vintage, years (median [IQR])	2.3	(1 - 3.7)
Previous kidney transplantation [n (%)]	27	(7.0)
≥2 previous transplants	11	(2.8)
Donor age, years (mean ± SD)	55.2 ± 14.5	
Donor gender (male) [n (%)]	203	(57.6)
Type of donor [n (%)]		
Donation after brain death	308	(79.6)
Donation after circulatory death	26	(6.7)
Living donation	53	(13.7)
Donor cause of death [n (%)]		
Cerebrovascular accident	267	(65.5)
Head trauma	47	(14.9)
Anoxia	34	(13.0)
Others	28	(8.6)
Baseline immunological risk [n (%)]		
Peak PRA >10%	35	(10.0)
Peak PRA >50%	18	(5.0)
HLA mismatches, number (median [IQR])	4	(2 - 5)
Donor and recipient CMV serostatus [n (%)]		
D+/R+	301	(76.8)
D+/R-	57	(14.7)
R+ (donor serostatus unknown)	26	(6.5)
Cold ischemia time, hours (mean ± SD)	13.3 ± 7.3	

RESULTS

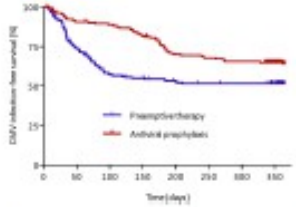

Table 2. Risk factors for the occurrence of CMV infection (follow-up truncated at one year).

	Univariate analysis			Multivariate analysis		
	HR	95% CI	P value	HR	95% CI	P value
Recipient age, years*	1.03	1.01 - 1.04	0.001	1.01	1.00 - 1.04	0.017
Donor age, years*	1.03	1.01 - 1.05	0.001	-	-	-
CMV serostatus (to/fr. versus D-/R+)	3.83	1.51 - 9.71	0.005	2.42	1.00 - 4.45	0.005
Graft function (eGFR) at month 1, mL/min	0.98	0.97 - 0.99	0.002	0.99	0.98 - 0.99	0.008
Antiviral prophylaxis (versus preemptive therapy)	0.41	0.41 - 0.83	0.002	0.62	0.41 - 0.90	0.004

*Per unitary increment.

Table 3. Risk factors for the occurrence of CMV disease (follow-up truncated at one year).

	Univariate analysis			Multivariate analysis		
	HR	95% CI	P value	HR	95% CI	P value
Dialysis vintage, years*	0.57	0.35 - 0.93	0.024	-	-	-
Diabetic nephropathy as underlying ESRD	3.79	1.19 - 12.09	0.024	4.86	1.19 - 13.32	0.025
Antiviral prophylaxis (versus preemptive therapy)	0.17	0.06 - 0.76	0.019	0.19	0.06 - 0.91	0.037

*Per unitary increment.

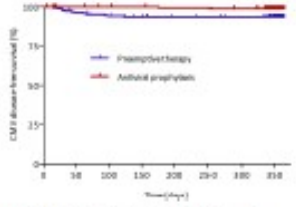

Table 4. Impact on graft and recipient outcome of the CMV prevention strategy.

	Antiviral prophylaxis (n = 183)	Preemptive therapy (n = 190)	P value
Cumulative incidence of BPAR [n (%)]			
At month 6	11 (11.4)	22 (11.6)	0.945
At month 12	11 (11.4)	26 (12.6)	0.827
Cumulative incidence of non-CMV infection [n (%)]			
At month 3	46 (24.9)	46 (23.2)	0.699
At month 6	54 (29.2)	50 (26.9)	0.594
Graft function (eGFR), mL/min (mean ± SD)			
At month 6	52.1 ± 16.7	51.3 ± 18.7	0.665
At month 12	53.4 ± 19.9	54.3 ± 18.7	0.667
Total WBC count, x 10^3/mm^3 (mean ± SD)			
At month 3	6.1 ± 2.4	6.8 ± 2.5	0.001
At month 6	6.4 ± 3.3	6.8 ± 4.7	0.183
At month 12	6.8 ± 2.2	7.1 ± 2.4	0.278
Leukopenia within the first 3 months [n (%)]	41 (22.3)	21 (11.1)	0.004
Graft loss [n (%)]	6 (3.2)	5 (2.6)	0.726
All-cause mortality [n (%)]	4 (2.2)	2 (1.1)	0.339

CONCLUSIONS

In this large multicenter cohort study, antiviral prophylaxis was associated with a lower incidence of CMV infection and disease in CMV-seropositive KT recipients, although such a benefit should be balanced with the risk of late-onset disease and hematological toxicity.

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Proyecto Prometeo II

Complete title: Impact of antiviral prophylaxis on the incidence of cytomegalovirus disease in seropositive kidney transplant recipients.

Running title: CMV disease in seropositive KT recipients.

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* A full listing of the members of the OPERA Study Group is provided in the Acknowledgements

Respuesta: **Although the subject is of interest, the reviewers did not assign this manuscript sufficient priority for publication in AJT**

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Proyecto Prometeo II

Revised paper (AJT-O-14-01197.R1) [marked version]
Original article
Title page

Aceptado

Complete title: Individual and combined associations of single-nucleotide polymorphisms in genes involved in the innate immunity and risk of CMV infection in seropositive kidney transplant recipients.

Running title: SNPs and CMV infection in R+ KT recipients.

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VIERNES 24 OCTUBRE

11:00-11:15 h. | **Introducción y Bienvenida**
Manuel Arias
Catedrático de Medicina
Jefe del Servicio de Nefrología
Hospital Univ. Marqués de Valdecilla, Santander

Josep Mª Campistol
Director del Instituto Clínico de Nefrología y Urología
Hospital Clínic, Barcelona

Sesión de expertos

11:15-12:15 h. (incluido discusión) | **Medida de la función renal: validez de las fórmulas de estimación en trasplante renal**
Emilio Rodrigo
Médico Especialista en Nefrología
Servicio de Nefrología
Hospital Univ. Marqués de Valdecilla, Santander

12:15-13:15 h. (incluido discusión) | **Biopsia del implante renal: tiene valor pronóstico?**
Raimundo García del Moral
Catedrático de Anatomía Patológica
Facultad de Medicina
Universidad de Granada

13:15-14:15 h. (incluido discusión) | **La supervivencia del injerto a largo plazo: Métodos estadísticos de medida**
Víctor Abraira
Unidad de Bioestadística Clínica
CIBER de Epidemiología y Salud Pública (CIBERESP)
Hospital Ramón y Cajal, Madrid

14:15-15:45 h. | Comida

16:00-17:00 h. | **¿Mejora la supervivencia del injerto a largo plazo en el trasplante renal?**
Fernando G. Cosio
Department of Nephrology and Hypertension, Transplant Center,
Mayo Clinic, Rochester, USA

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17:00-19:00 h. | **Trabajo en Grupos**

19:00-20:00 h. | **Reunión de Portavoces y Coordinadores**

SÁBADO 25 OCTUBRE

09:00-10:00 h. | **Marcadores de supervivencia pretrasplante del donante y del receptor**
Enrique Luna
Servicio de Nefrología
Hospital Infanta Cristina, Badajoz

10:00-11:00 h. | **Función renal inicial como marcador de supervivencia a largo plazo**
Isabel Beneyto
Servicio de Nefrología
Hospital La Fé, Valencia

11:00-12:00 h. | **Inmunosupresión y función renal a largo plazo: hay evidencias?**
José Francisco Crespo
Servicio de Nefrología
Hospital Universitario Dr. Peset, Valencia

12:00-12:30 h. | **Resumen y Conclusiones**
Manuel Arias
Catedrático de Medicina
Jefe del Servicio de Nefrología
Hospital Univ. Marqués de Valdecilla, Santander

Josep Mª Campistol
Director del Instituto Clínico de Nefrología y Urología
Hospital Clínic, Barcelona

12:30-13:15 h. | **Comida**

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Acreditación

- Esta actividad docente está acreditada por la Comisión de Formación Continuada de las Profesiones Sanitarias de Cantabria con

14,3 créditos.

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