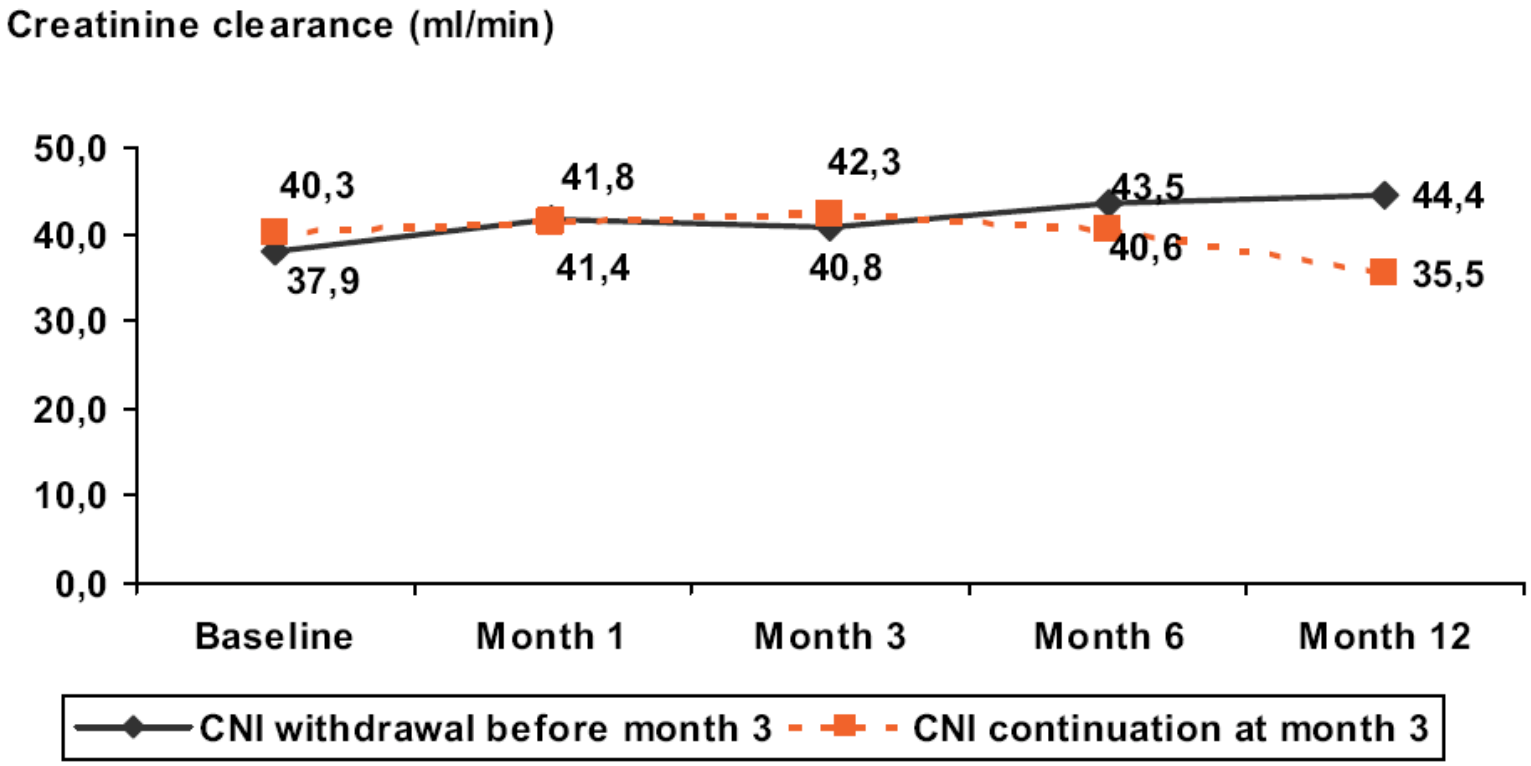
Controversia en inmunosupresión: ¿anticalcineurínico si o no? Trasplante cardiaco

Juan F. Delgado

17.03.2011

Retirada tardía del CNI

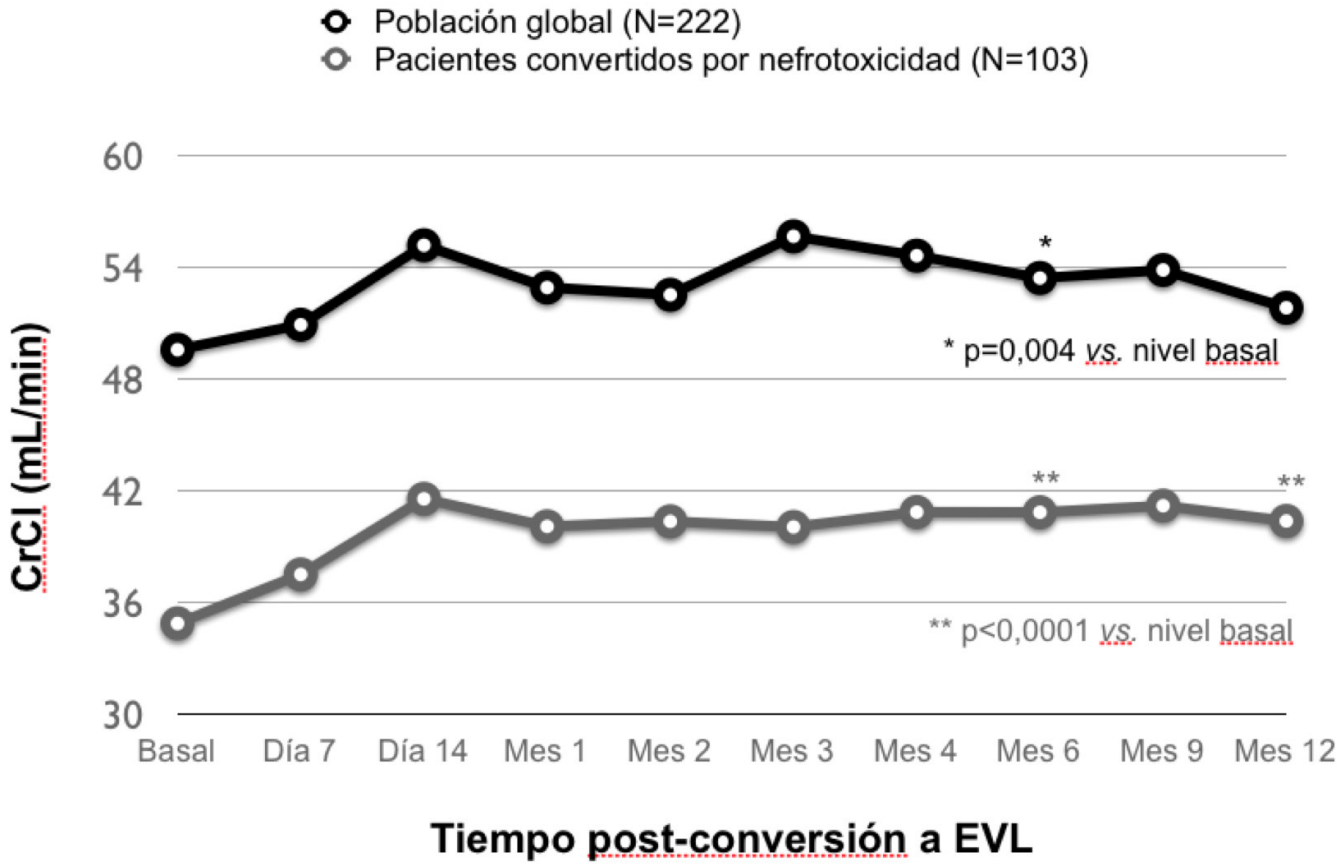
RAPACOR: n 97 con C > 1.5 ó CCl < 50 mil/min, 33% sin CNI y 1 RA



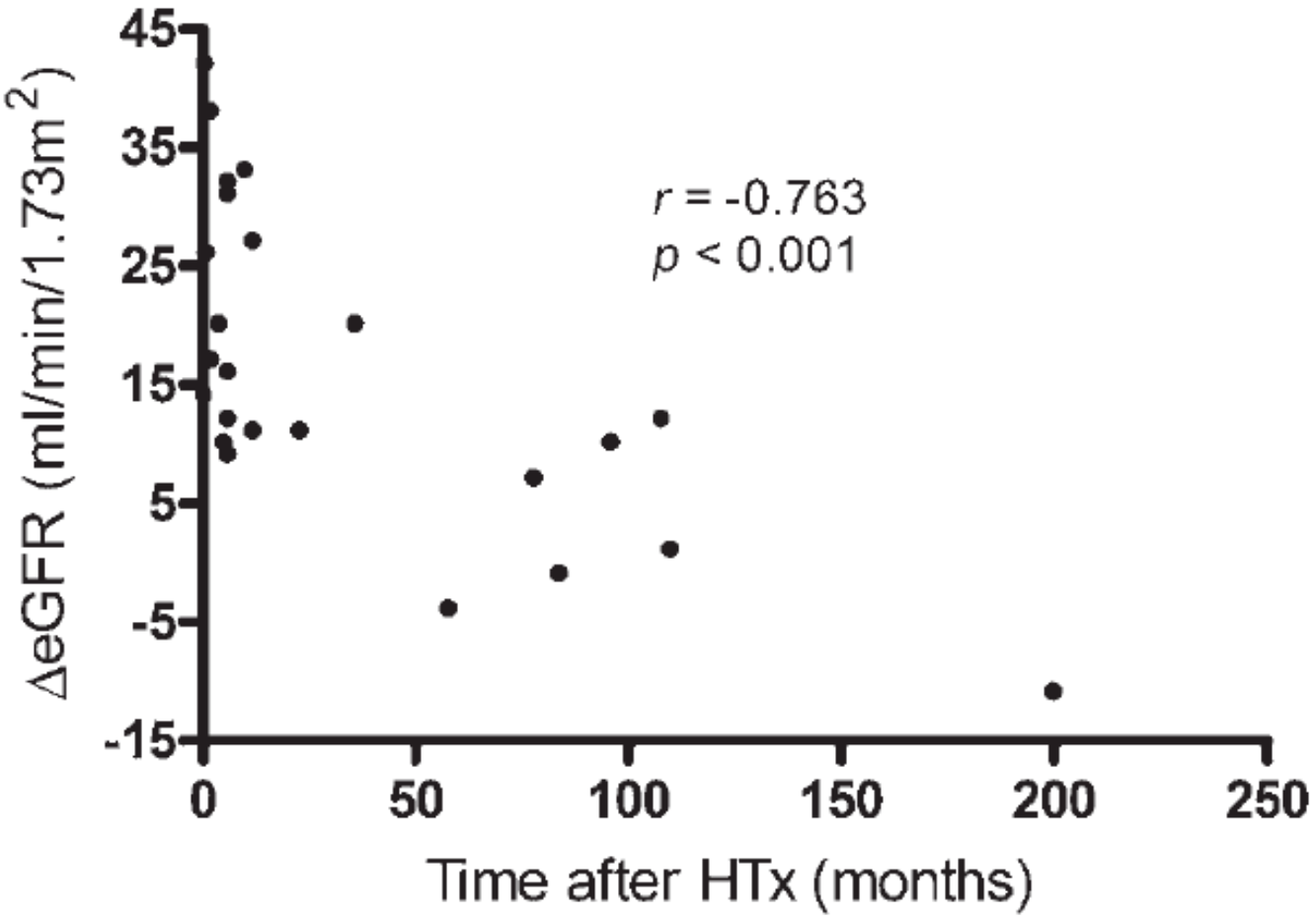
JF Delgado et al. Transp Proc 2009

Retirada tardía del CNI

Everodata: n 103, C > 1.5 ó CCI < 50, 35% sin CNI y 10% RA



Relación entre mejoría de función renal y momento de retirada de CNI



Gude, J Heart Lung Transplant 2010

Probablemente necesitamos retirar el CNI y hacerlo precozmente

¿Pero es seguro?

Inmunosupresión sin CNI

American Journal of Transplantation 2005; 5: 827–831
Blackwell Munksgaard

doi: 10.1111/j.1600-6143.2005.00757.x

Brief Communication

First Experience with *de novo* Calcineurin-Inhibitor-Free Immunosuppression Following Cardiac Transplantation

Bruno Meiser*,†, Bruno Reichart†, Ioannis Adamidis, Peter Überfuhr and Ingo Kaczmarek

transplantation (HTx) (1–5). All of these strategies have been based on the use of calcineurin inhibitors (CNIs) (cyclosporine or tacrolimus) as primary immunosuppressants.

- Estudio piloto, 8 pacientes.
- Sirolimus + MMF + esteroides (se retiran 6º mes).
- Supervivencia 1 año 100% y 25% RA.

Inmunosupresión sin CNI

Avoidance of Calcineurin Inhibitors With Use of Proliferation Signal Inhibitors in De Novo Heart Transplantation With Renal Failure

Francisco González-Vílchez, MD, José Antonio Vázquez de Prada, MD, Víctor Expósito, MD, Tamara García-Camarero, MD, Leticia Fernández-Friera, MD, Miguel Llano, MD, Javier Ruano, MD, and Rafael Martín-Durán, MD

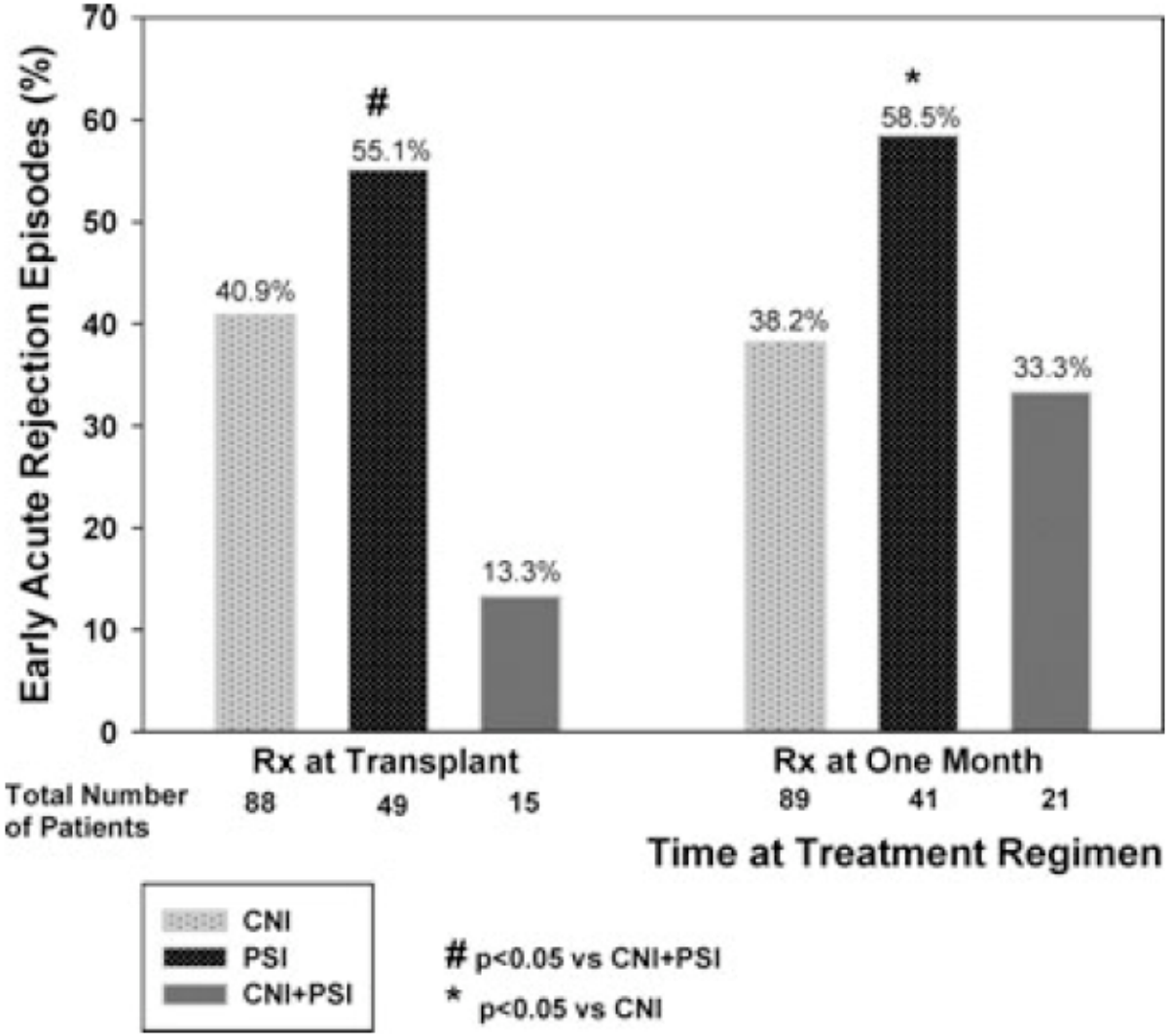
Background: This study describes our experience with proliferation signal inhibitors in de novo heart transplant recipients with significant renal impairment. To circumvent further nephrotoxicity, calcineurin inhibitors were avoided in the peri-operative period.

Methods: Immunosuppression in 20 patients was with a proliferation signal inhibitor (sirolimus, 14; everolimus, 6), an anti-mitotic drug, and corticosteroids from the time of transplantation. Induction was used in 9 patients (45%). All patients had preoperative significant renal dysfunction (mean glomerular filtration rate <30 ml/min/1.73 m^2), and 4 patients required dialysis.

Results: Post-operatively, the glomerular filtration rate significantly increased (>65 ml/min/1.73 m^2 at Month 1, remaining stable thereafter). No patients required dialysis after the first month of transplantation. Mean follow-up was 500 days. Rejection episodes occurred in 11 patients (55%), and 4 patients died (2 of rejection, although 1 death occurred 48 days after conversion to conventional treatment with tacrolimus). Half of the patients were eventually converted to conventional calcineurin-inhibitor therapy because of proliferation signal inhibitor adverse events.

Conclusion: Although this immunosuppressive approach was associated with a somewhat high rate of rejection and frequent side effects, it represents an attractive alternative in the complicated peri-operative setting of patients with significant renal impairment. This approach could serve as a temporary bridge to a conventional treatment. J Heart Lung Transplant 2008;27:1135-41. Copyright © 2008 by the International Society for Heart and Lung Transplantation.

Inmunosupresión sin CNI



Leet, Am J Transplant 2009

Heart Spare The Nephron (STN)

Roche

Pharmaceuticals

IMPORTANT SAFETY INFORMATION

February 1, 2007

Subject: **Higher than expected incidence of acute rejection in cardiac transplant patients switched from calcineurin inhibitors in combination with CellCept® (mycophenolate mofetil) to Rapamune® (sirolimus) in combination with CellCept® at 12 weeks post heart transplantation**

SCHEDULE TRIAL

Scandinavian Heart Transplant de Novo Study With Early Calcineurin Inhibitor (CNI) Avoidance (SCHEDULE)

This study is currently recruiting participants.
Verified by Novartis, December 2010

First Received: August 9, 2010 Last Updated: December 22, 2010 History of Changes

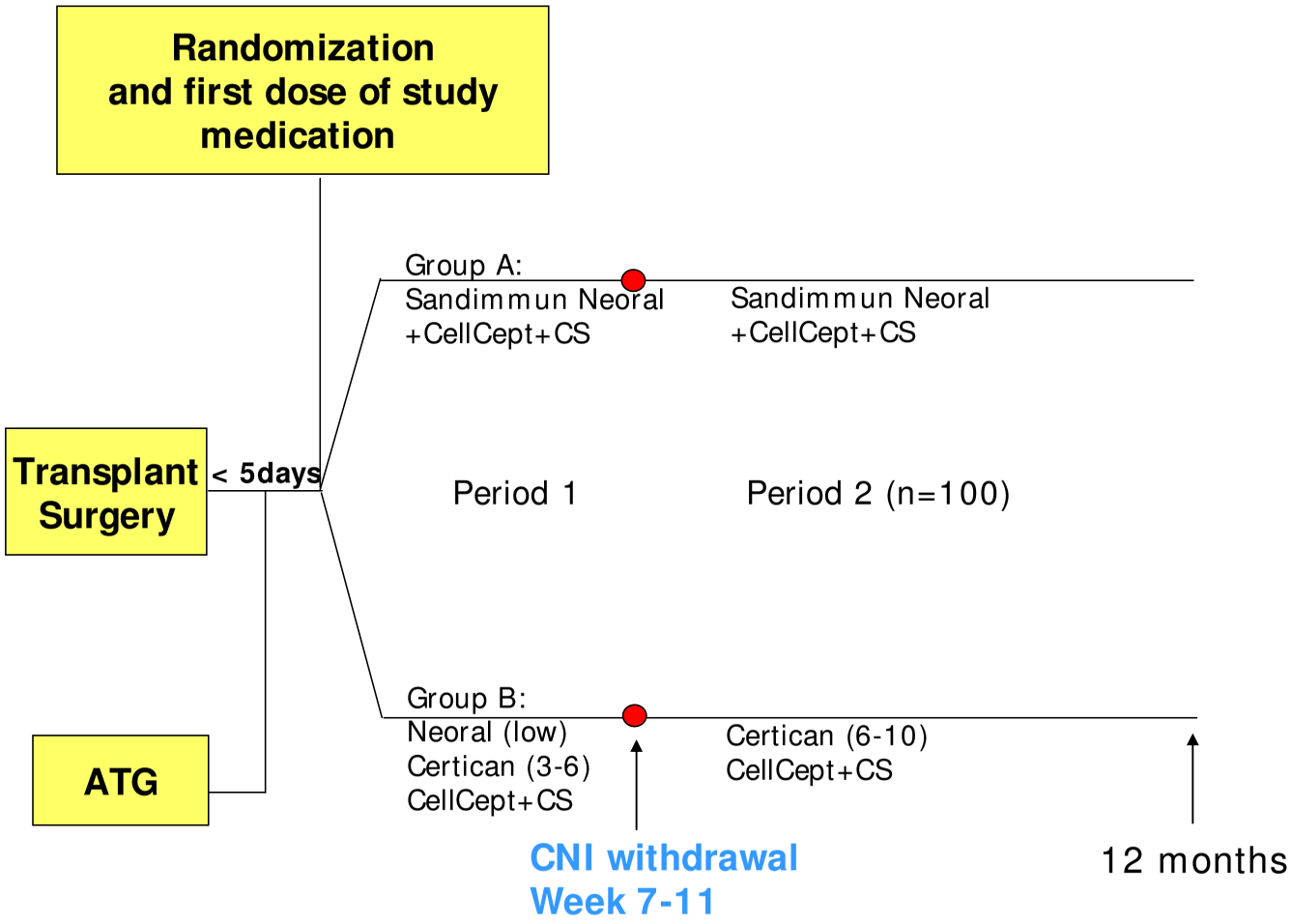
Sponsor:	Novartis Pharmaceuticals
Information provided by:	Novartis
ClinicalTrials.gov Identifier:	NCT01266148

Purpose

The study population will consist of a representative group 100 de novo heart transplant patients who fulfills the requirements of entering period 2 of the study (patients will continue into period 2 of the study after the completion of period 1 (7-11 weeks after transplantation -TX-), The patients will be randomized at transplantation to receive a standard immunosuppressive protocol of cyclosporine, mycophenolate mofetil (MMF) and corticosteroids (CS)- Group A, or a combination of reduced dose cyclosporine, low dose everolimus, reduced dose MMF and CS- Group B. After 7-11 weeks patients fulfilling the inclusion/exclusion criteria for period 2 will continue in the study for a total of 12 months. In Group A patients will continue with unchanged medication. In Group B cyclosporine will be abruptly withdrawn and the everolimus dose increased. Enrollment will continue until the required sample size (N=100) has entered period 2. An anticipated withdrawal rate in period 1 of about 15% means that about 120 patients need to be randomized. The patients will be recruited from all 5 Scandinavian centers for heart transplantation in Oslo, Gothenburg, Lund, Copenhagen and Aarhus

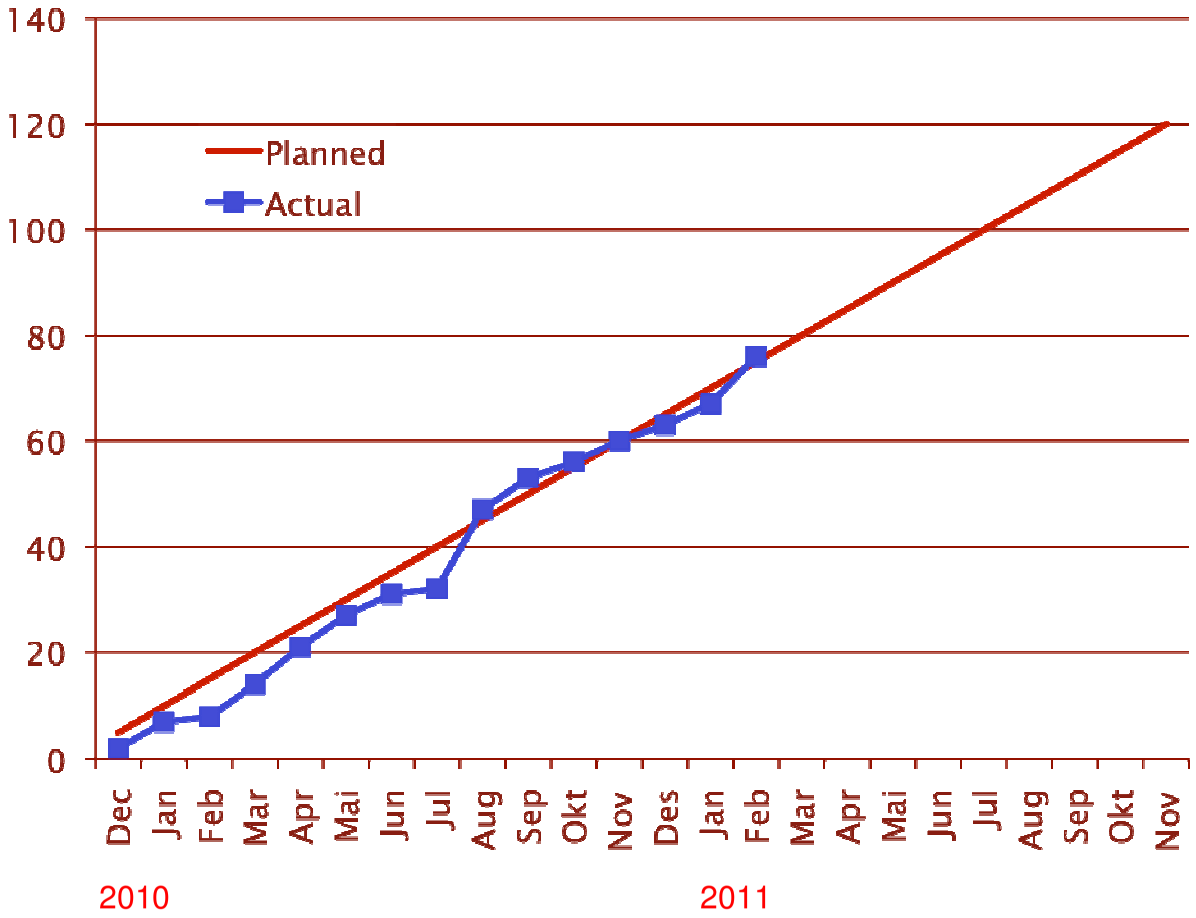
Condition	Intervention	Phase
Renal Function	Drug: Everolimus Drug: Cyclosporine A	Phase IV

SCHEDULE - study design



Primary endpoint: mGFR (Cr EDTA clearance) at month 12.

SCHEDULE trial
Patient recruitment February 28, 2011



Ensayos clínicos de inmunosupresión en Trasplante Cardiaco

Author (year)	Study	No.	Follow-up	Survival	Rejection	CAV by IVUS
Kobashigawa[137] (1998)	MMF vs. AZA	650	3 years	MMF = higher survival[a]	MMF = less rejection	NS; MMF = less CAV at 1 year[b]
Reichart[148] (1998)	TAC vs. CYA	82	1 year	NS	NS	. . .
Taylor[139] (1999)	TAC vs. CYA	85	1 year	NS	NS	. . .
Eisen[140] (2003)	EVL vs. AZA	634	1 year	NS	EVL groups = less rejection	EVL groups = less CAV
Keogh[141] (2004)	SRL vs. AZA	136	2 years	NS	SRL groups = less rejection at 6 months	SRL groups = less CAV
Grimm[142] (2006)	TAC vs. CYA	314	1.5 year	NS	TAC = less rejection at 6 months	. . .
Kobashigawa[143] (2006)	TAC/MMF vs. TAC/SRL vs. CYA/MMF	343	1 year	NS	NS; TAC groups = lower any treated rejection	. . .
Baran[144] (2007)	TAC/MMF vs. TAC	58	1 year	NS	NS	NS
Lehmkuhl[145] (2008)	EVL/rd-CYA vs. MMFsd-CYA	176	1 year	NS	NS	. . .

Guías de práctica clínica en trasplante cardiaco

Class IIa:

1. Calcineurin inhibitor-based therapy remains the standard in immunosuppressive protocols used after HT.

Level of Evidence: B.

Guidelines ISHLT 2010

La pregunta: ¿CNI si o no?

- La retirada tardía, en pacientes seleccionados, parece segura aunque de beneficio limitado.

- Inmunosupresión de inicio sin CNI: es una opción no despreciable en pacientes con disfunción renal peritrasplante.

- La retirada precoz, no seleccionada, (antes de los 6 meses) se está evaluando.