مستشفى الملك فيصل التخصصي ومركز الأبحاث
King Faisal Specialist Hospital & Research Centre
Gen. Org. مؤسسة عامة

Optimizing Immunosuppression in spontaneous pancreatic-kidney transplant

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Section Head , Nephrology Section
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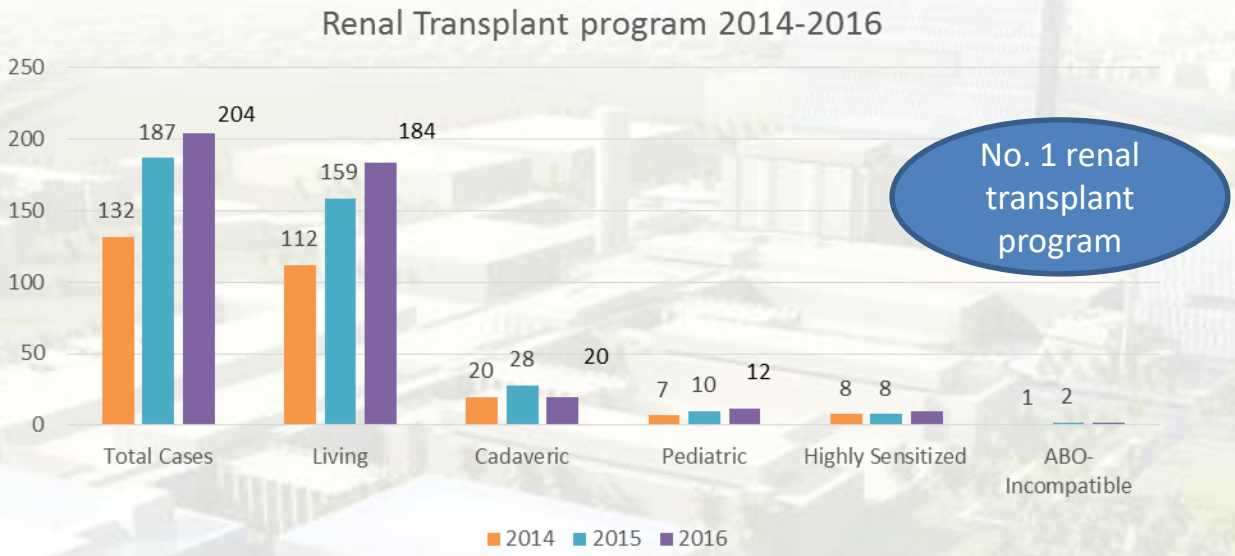
Department of Medicine

Renal transplant at KFSH&RC-Jeddah

Renal transplant program-KFSH&RC-Jeddah

- In the last three years:



Renal transplant program-KFSHRC Jeddah

- Outcome

	KFSHRC-Jeddah	Mayo clinic	Johns Hopkins	NY-Presbetirian
Patients survival	98.5%	99.6%	97.02%	95.7%
Graft survival	99.5%	98.8%	95.2%	94%

KFSH-RC-Jeddah	One year	Three years
Graft survival	98	97
patients survival	99	98.2

Renal Transplant 2016 n=204	Percentage %	Frequency
Adult	93.1	190
Pediatric	6.9	14
ATN	10.3	21
Acute Rejection-Free Survival CI (46.8-48.9)	98	4
Graft -Free Survival CI (49.8-51.2)	99	2
patient survival CI (15.6-24.4)		

Our protocol

- We use triple therapy (TAC/MMF and steroids)
- Induction agent :
  - Thymoglobulin
  - Basiliximab
- We use mTOR in certain cases

Pancreatic transplant protocol

- About 75% of pancreas transplantations are performed simultaneously with a kidney transplantation from the same deceased donor.
- About 15% of pancreas transplantations are performed after a previously successful kidney transplantation from a living or deceased donor.
- The remaining 10% of cases are performed as pancreas transplantation alone in patients who have normal renal function, but with very labile and problematic diabetes, such as patients with life-threatening hypoglycemic attacks.

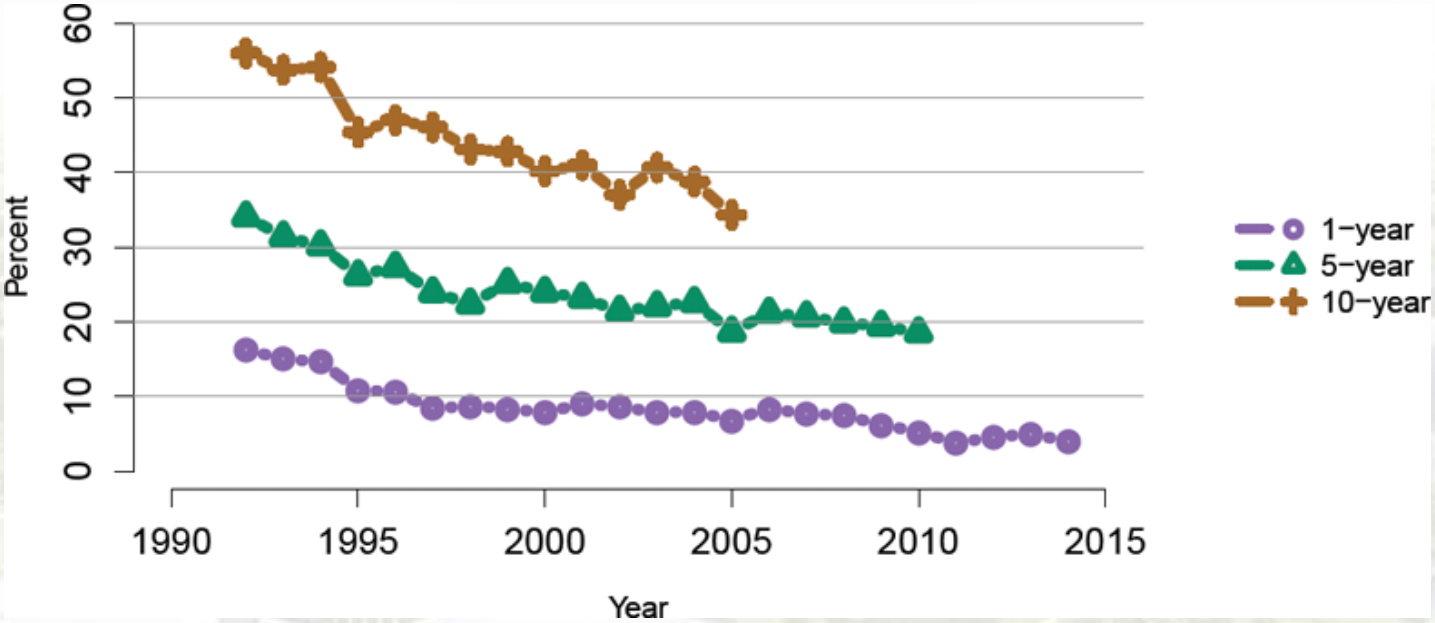
Goals of immunosuppression in pancreas transplantation

- Primary goal is maintaining a functioning transplant, which optimizes patient survival
- Optimize graft survival by minimizing rejection, drug toxicity and immunoseficient complication
- Availability of new immunosuppressive agents has prompted an evolution in drug combinations, thus permitting dosing flexibility and tailored, individualized therapy

Pancreatic transplant in the new millennium

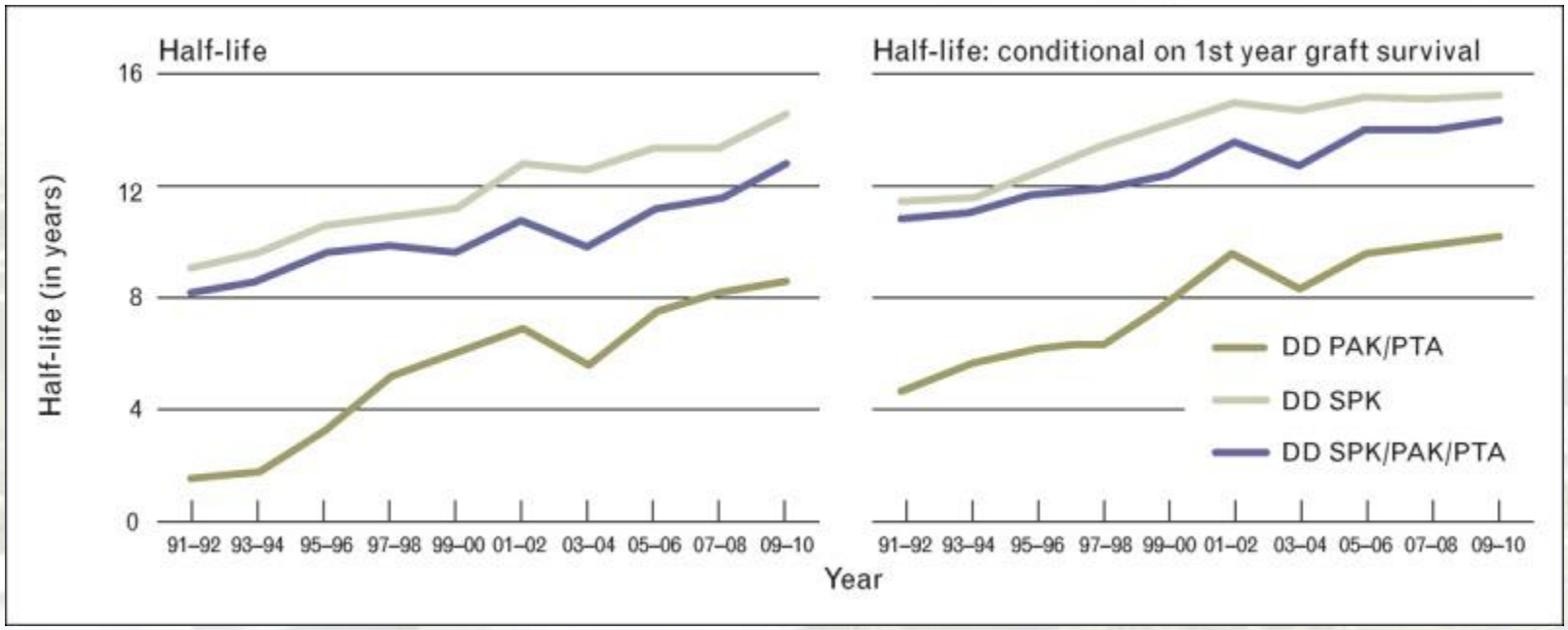
- Better result due to the advanced in immunosuppression
- 1-year graft survival(pancreas) in patients receiving TAC/MMF are 86% in SPKT, 80% in PAK and 78% in PA recipients(**2011 Update on Pancreas Transplantation: Comprehensive Trend Analysis of 25,000 Cases Followed Up Over the Course of Twenty-Four Years at the International Pancreas Transplant Registry (IPTR)**
- Rate of rejection decreased from range of 50-80% to a range of 10-30%

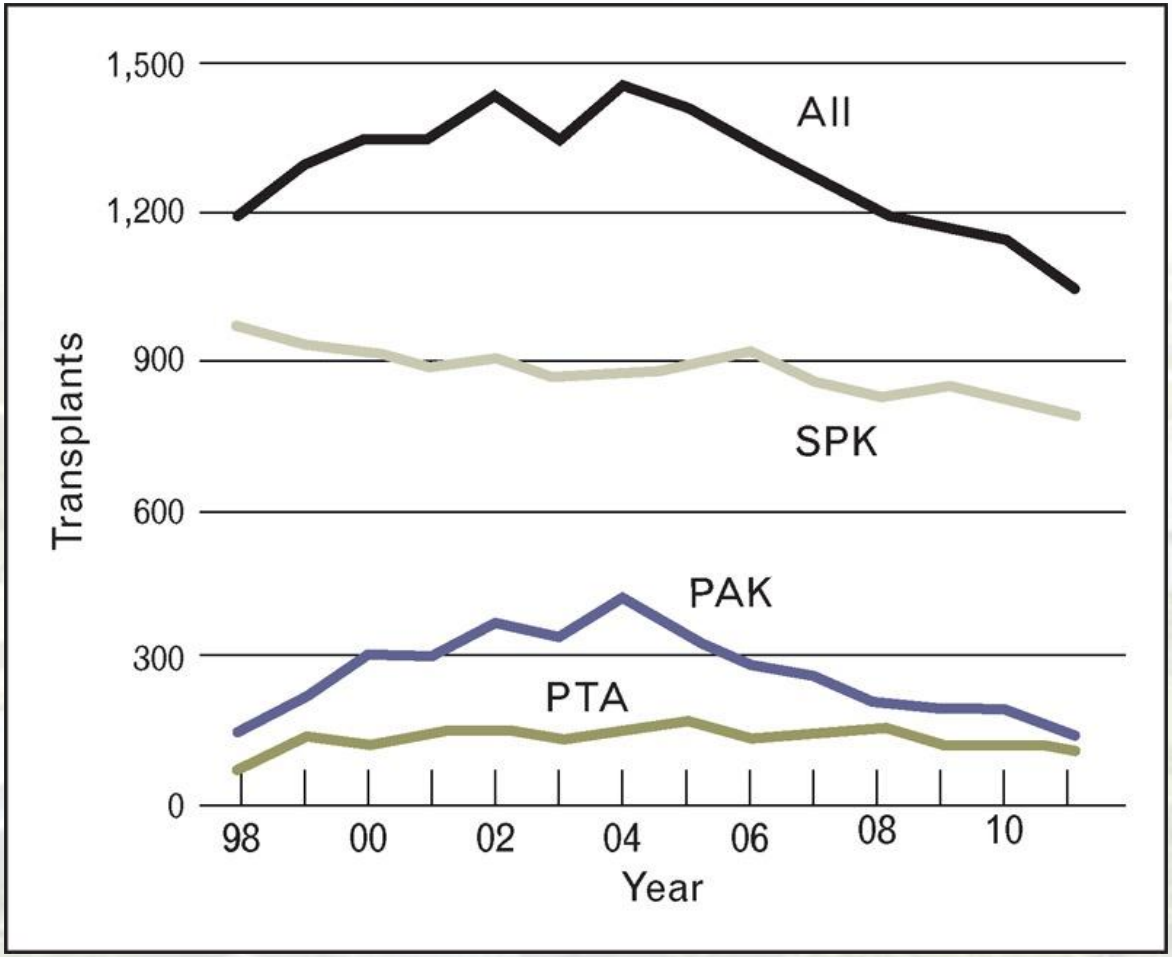
OPTN/SRTR 2015 Annual Data Report: Pancreas



American Journal of Transplantation
pages 117-173, 3 JAN 2017 DOI: 10.1111/ajt.14125
http://onlinelibrary.wiley.com/doi/10.1111/ajt.14125/full#ajt14125-fig-0050

Outcome

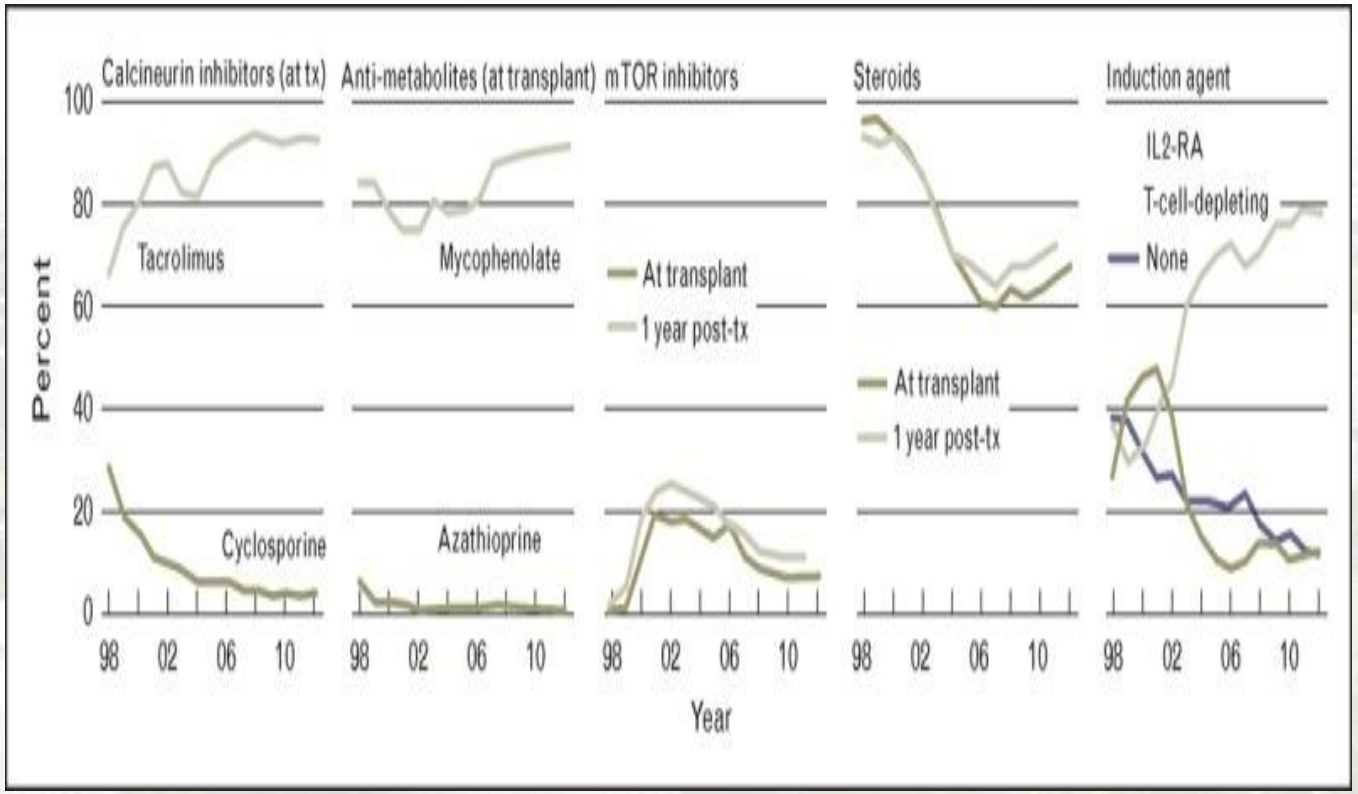

Half-life
Half-life: conditional on 1st year graft survival
Half-life (in years)
16
12
8
4
0
91–92 93–94 95–96 97–98 99–00 01–02 03–04 05–06 07–08 09–10
Year
DD PAK/PTA
DD SPK
DD SPK/PAK/PTA


1,500
1,200
900
600
300
0
Transplants
All
SPK
PAK
PTA
98
00
02
04
06
08
10
Year

Immunosuppression in pancreas Transplantation

- No data to support any specific immunosuppressive(IS) regimen in diabetic recipients for improved outcomes
- Steroids induce insulin resistance; calcineurin inhibtors(CNI) are islet toxic; insulin sensitivity reduced by 25% to 50%
- Patients with gastroparesis may not tolerate MMF;SRL may induce sever dyslipidemia
- Cardiovascular and infectious complication have greatest impact on long term outcomes

Trends in SPK immunosuppression



OPTN/SRTR 2011 annual data report: pancreas. Am J Transplant 2013; 13 (Suppl 1):47–72

Trends in SPK immunosuppression

- Induction therapy:
  - From OKT3 to basiliximab/daclizumab, rATG, Campath-1H
- Maintenance therapy:
  - From CsA to TAC-based therapy
  - From AZA to MMF or SRL maintenance therapy
  - From high dose to low dose steroids or steroid withdrawal or avoidance

Induction therapy

Induction therapy

- Commonly used :
  - antithymocyte globulin
  - interleukin 2 receptor
  - alemtuzumab

Induction therapy

- Reduces the incidence of acute rejection
- Allows for steroids minimization
- Allows for CNI minimization

Induction therapy

Author			induction	maintence	Graft survival	AR	strength	weakness
Stratta	SPK (*n* = 303)	Study	Daclizumab 1 mg/kg every other week ×5	CS, TAC, MMF	92% and 85% 6 month and 3 year kidney	21% and 25% 6 month and 3 year kidney	Large study	Daclizumab is no longer available
					86% and 77% 6 month and 3 year pancreas	4% and 10% 6 month and 3 year pancreas	3 year follow-up	
Kaufman	SPK	Study	Basiliximab, daclizumab, OKT-3, thymoglobulin, or ATG (*n* = 87)	CS, TAC, MMF	96.6% kidney, 83.9% pancreas 1 year	25% 1 year, BPAR 13% 1 year	Good-sized study	Variable induction
		Control	None (*n* = 87)	CS, TAC, MMF	92% kidney, 85.1% pancreas 1 year	31% 1 year (*P* = NS), BPAR 21% 1 year (*P* = NS)		

Randomized comparison of triple therapy and antithymocyte globulin induction treatment after simultaneous pancreas-kidney transplantation

Diego Cantarovich, Georges Karam, Magali Giral-Classe, Maryvonne Hourmant, Jacques Dantal, Gilles Blancho, Loïc Le Normand, Jean-Paul Soulillou

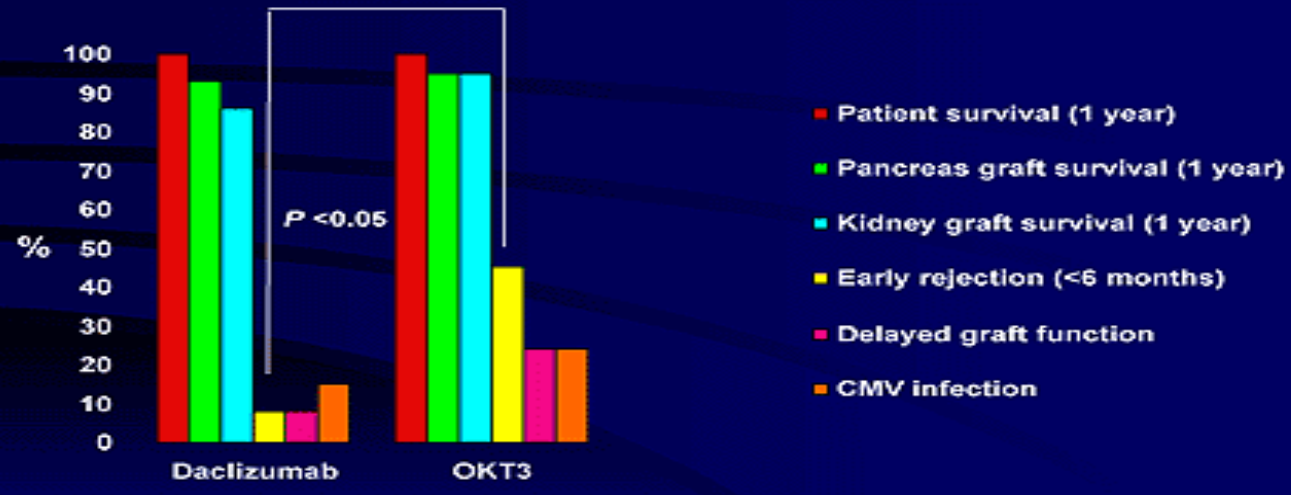
Kidney International
Volume 54, Issue 4, Pages 1351-1356 (October 1998)
DOI: 10.1046/j.1523-1755.1998.00094.x

	Non-ATG group (N=25)	ATG group (N=25)	P value
Number of rejection episodes	29	13	<0.05
Patients with acute rejection	19 (76%)	9 (36%)	<0.01
First rejection <15 days	9	1	<0.002
First rejection 16–90 days	9	8	<0.002
First rejection 91–180 days	1	0	<0.002
Borderline rejections	7	3	NS
Grade 1 rejections	20	5	NS
Grade 3 rejections	1	5	NS

Abbreviation ATG is antithymocyte globulin. Rejection episodes were restricted to the kidney transplant and were all histologically confirmed and graded according to the Banff classification. NS denotes not significant.

Kidney International 1998 54, 1351-1356DOI: (10.1046/j.1523-1755.1998.00094.x)

Two-dose Daclizumab in Simultaneous Kidney/Pancreas Transplant Recipients



Van der Werf WJ et al. *Am J Transplant*. 2001;1(suppl):430. Abstract 1165.

Induction therapy

- **5-Year Results of a Prospective, Randomized, Single-Center Study of Alemtuzumab Compared With Rabbit Antithymocyte Globulin Induction in Simultaneous Kidney–Pancreas Transplantation**

- From February 2005 through October 2008, a total of 46 SKPTs (45 portal-enteric drainage) were prospectively randomized to receive either single-dose ALEM (30 mg intraoperatively) or multiple-dose rATG antibody induction

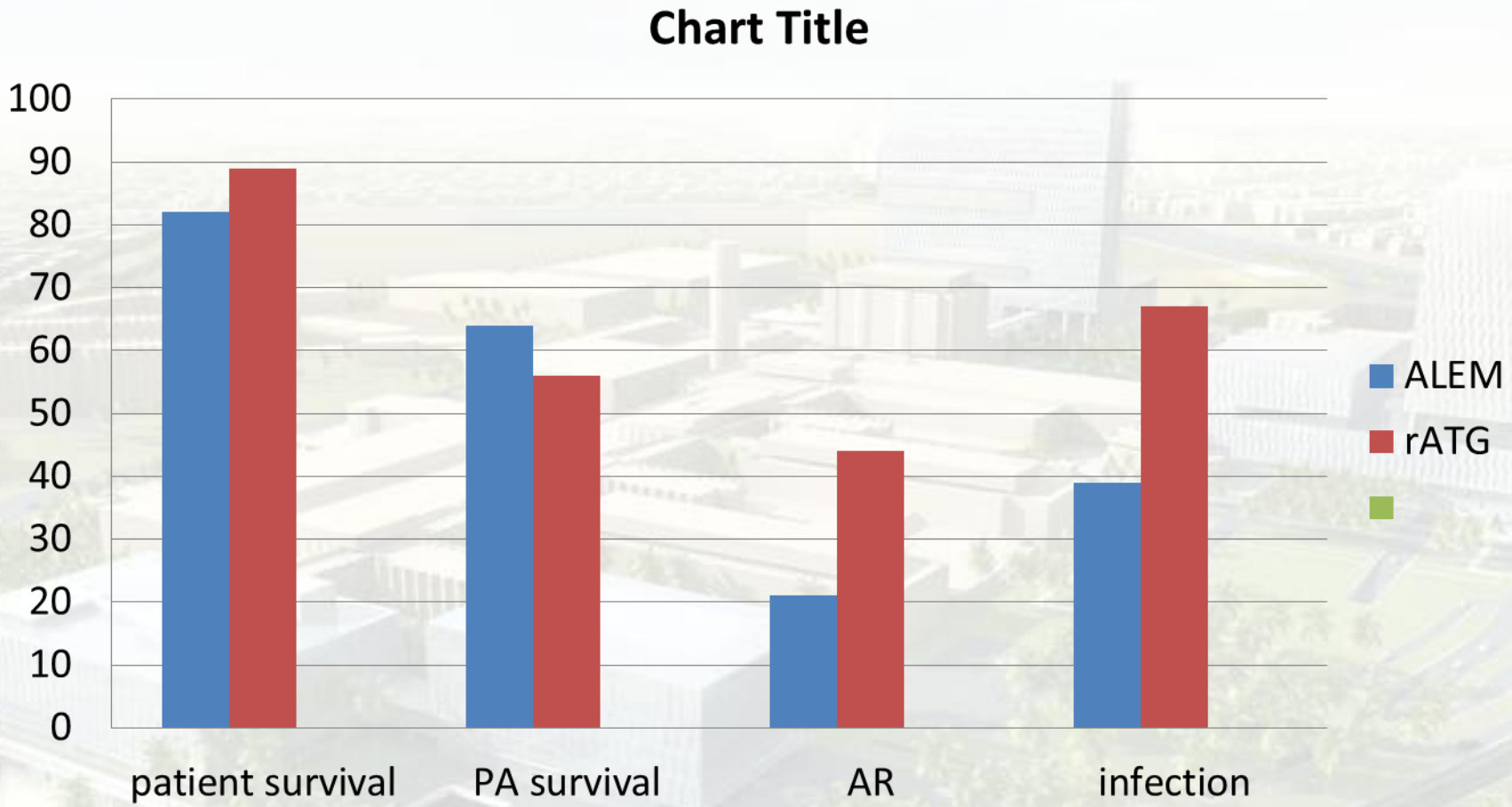
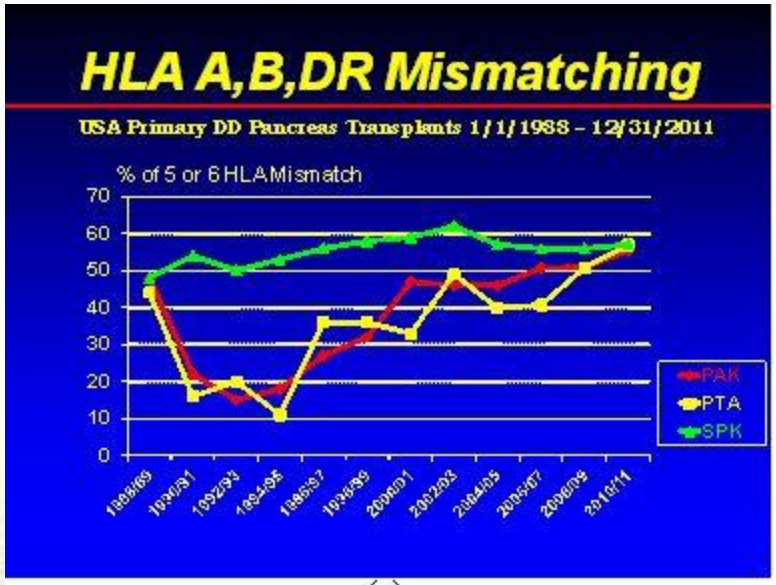
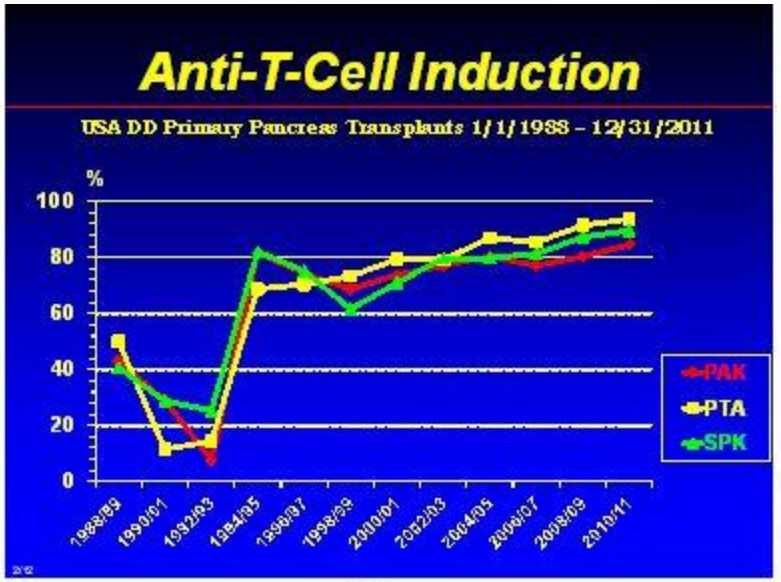


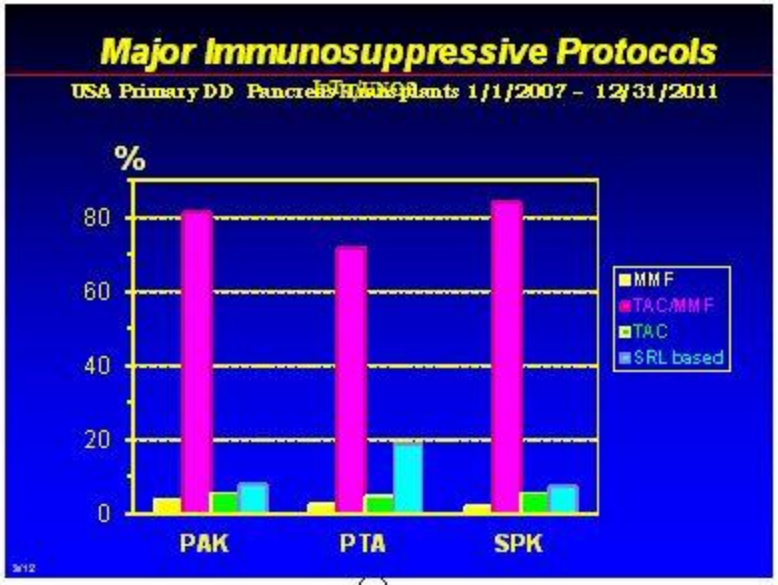
Chart Title
100
90
80
70
60
50
40
30
20
10
0
patient survival
PA survival
AR
infection
ALEM
rATG


HLA A,B,DR Mismatching
USA Primary DD Pancreas Transplants 1/1/1988 – 12/31/2011
% of 5 or 6 HLA Mismatch
70
60
50
40
30
20
10
0
1988/89
1990/91
1992/93
1994/95
1996/97
1998/99
2000/01
2002/03
2004/05
2006/07
2008/09
2010/11
PAK
PTA
SPK

(a)


Anti-T-Cell Induction
USA DD Primary Pancreas Transplants 1/1/1988 – 12/31/2011
%
100
80
60
40
20
0
1988/89
1990/91
1992/93
1994/95
1996/97
1998/99
2000/01
2002/03
2004/05
2006/07
2008/09
2010/11
PAK
PTA
SPK

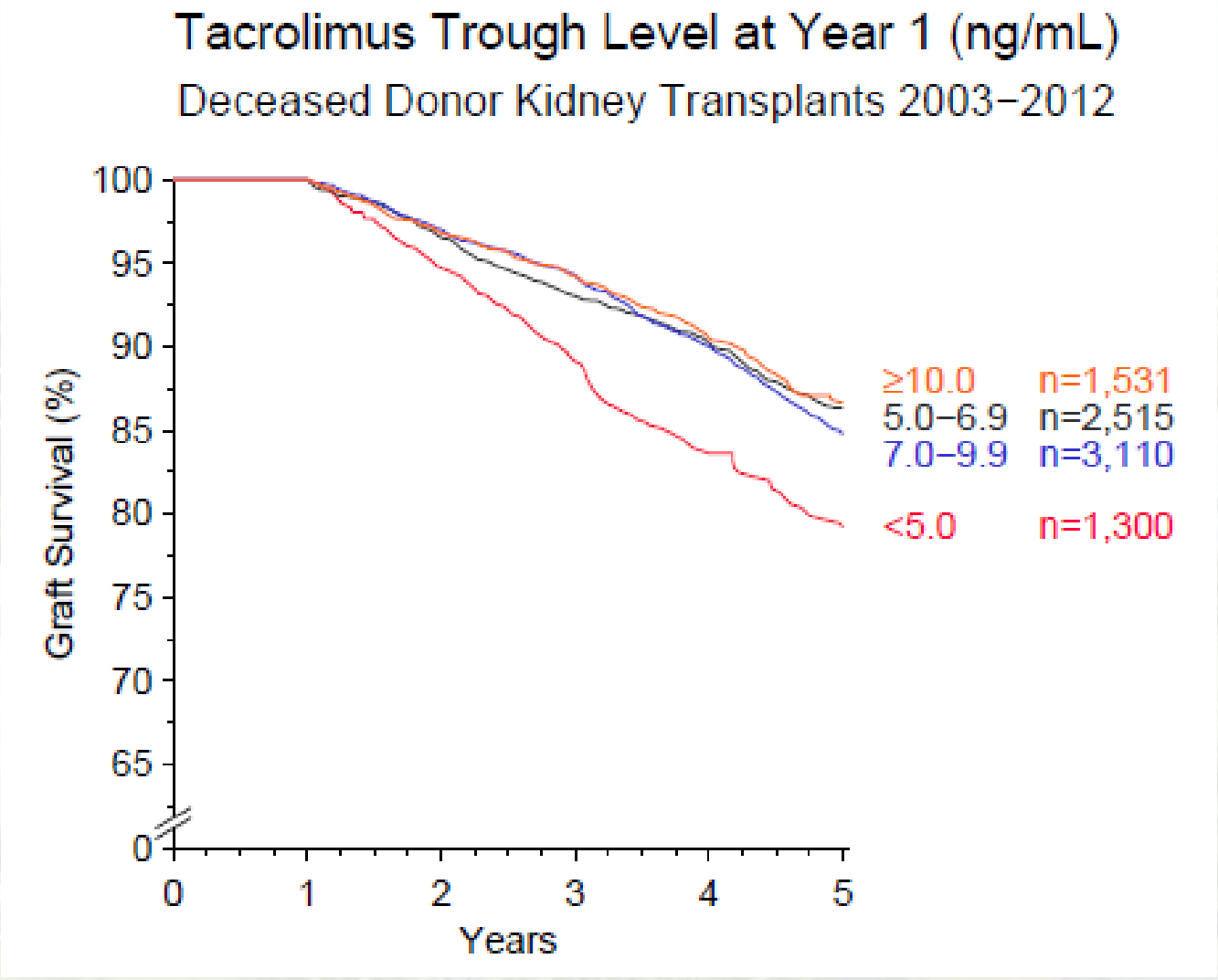
(b)


Major Immunosuppressive Protocols
USA Primary DD Pancreas Transplants 1/1/2007 – 12/31/2011
%
80
60
40
20
0
MMF
TAC/MMF
TAC
SRL based
PAK
PTA
SPK

(c)

What tacrolimus target to aim for?

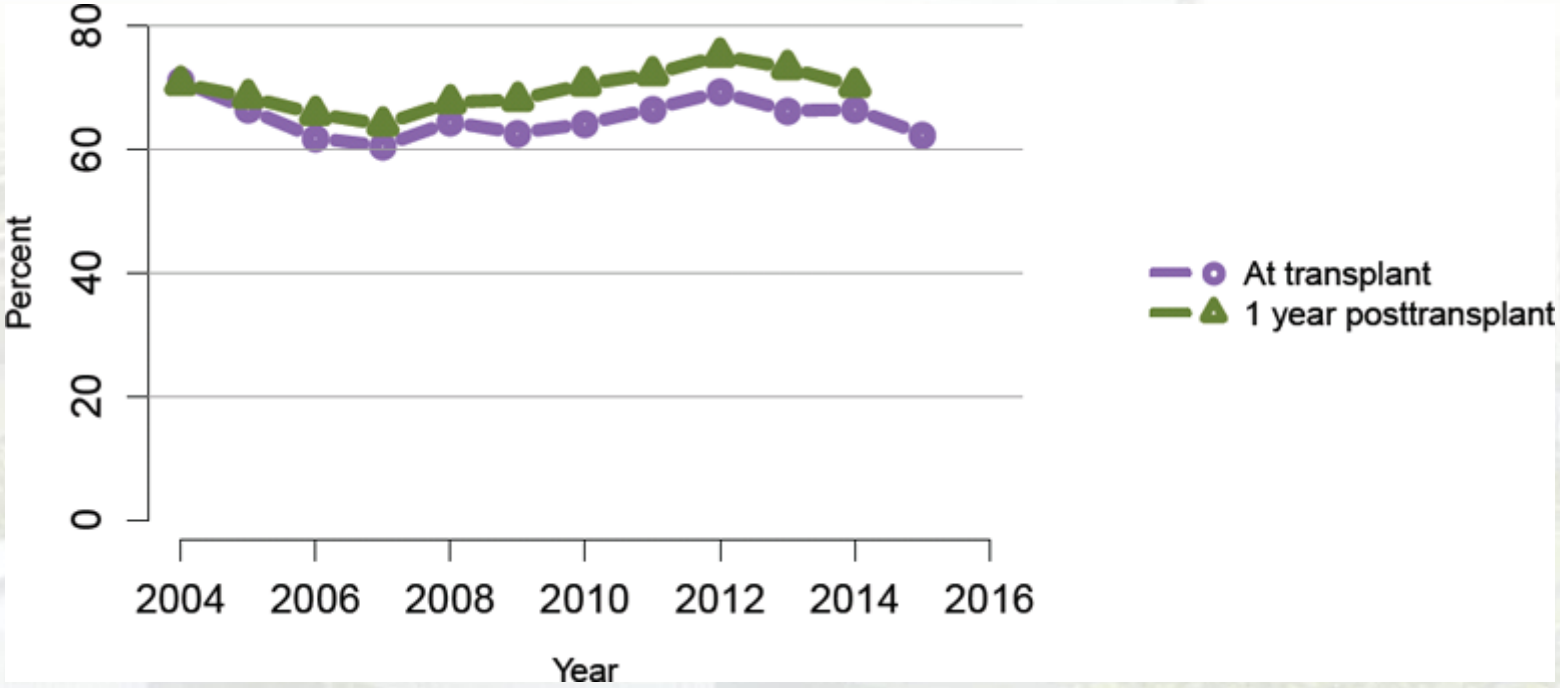
Long-term tacrolimus exposure and graft survival



Opelz, CTS newsletter 2014:1

steroids

- Steroids based
- Steroids avoidance
- Steroids withdrawal


Percent
0
20
40
60
80
2004
2006
2008
2010
2012
2014
2016
Year
At transplant
1 year posttransplant

The New England
Journal of Medicine

VOLUME 343 JULY 27, 2000 NUMBER 4

ISLET TRANSPLANTATION IN SEVEN PATIENTS WITH TYPE 1 DIABETES MELLITUS USING A GLUCOCORTICOID-FREE IMMUNOSUPPRESSIVE REGIMEN

A.M. JAMES SHAPIRO, M.B., B.S., JONATHAN R.T. LAKEY, PH.D., EDMOND A. RYAN, M.D., GREGORY S. KORBUTT, PH.D., ELLEN TOTH, M.D., GARTH L. WARNOCK, M.D., NORMAN M. KNETEMAN, M.D., AND RAY V. RAJOTTE, PH.D.

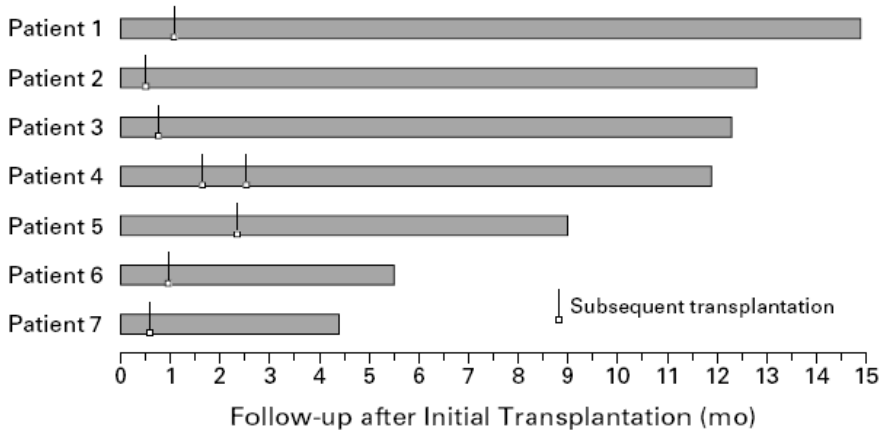
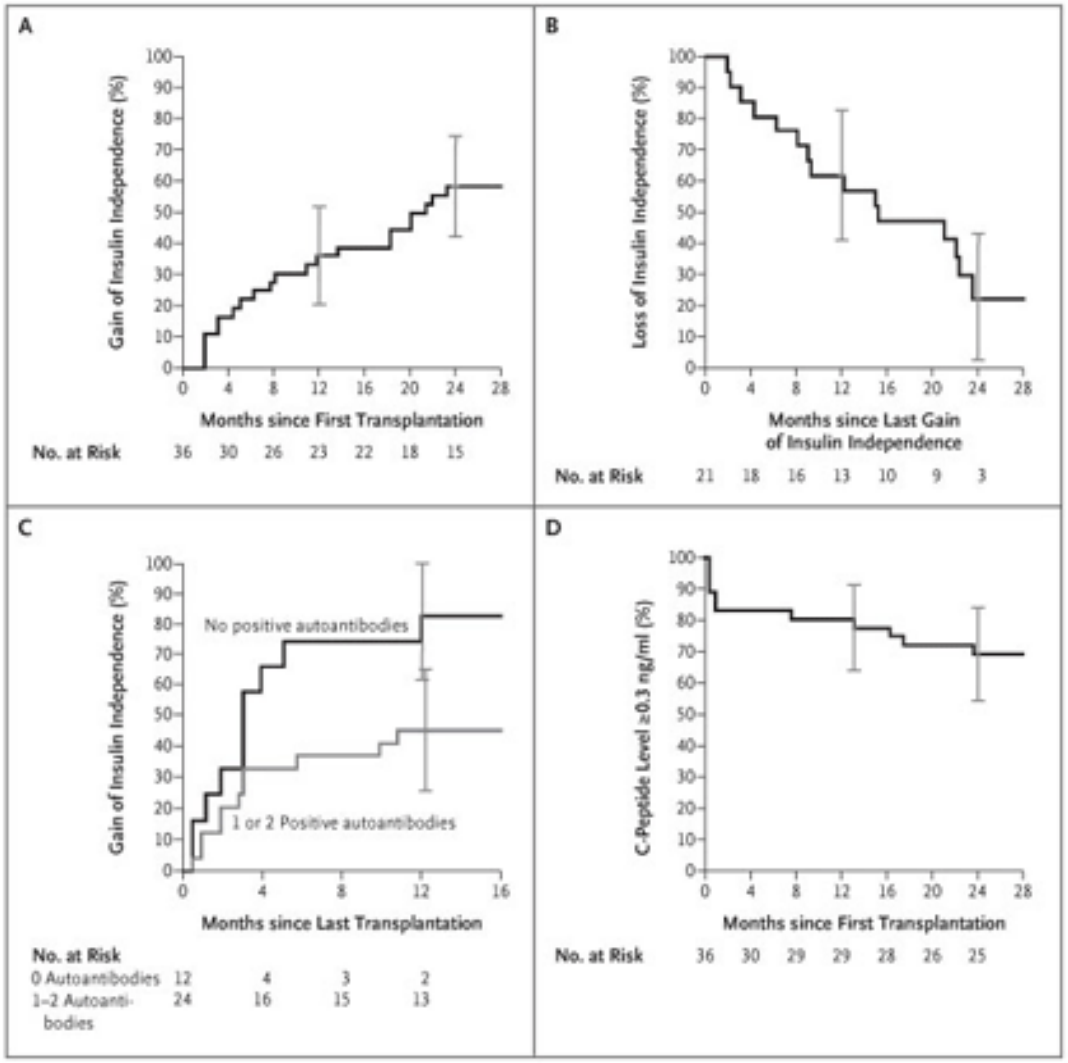


Figure 1. Length of Follow-up after the Initial Islet Transplantation and the Time at Which Subsequent Transplantations Were Performed.

- ***Efficient Isolation Procedure***
- ***Reliable Collagenase***
- ***Steroid Free Immunosuppressive Protocol***
  - ***IL-2R Blockade***
  - ***Tacrolimus***
  - ***Sirolimus***



ORIGINAL ARTICLE

International Trial of the Edmonton Protocol for Islet Transplantation

A.M. James Shapiro, M.D., Ph.D., Camillo Ricordi, M.D., Bernhard J. Hering, M.D., Hugh Auchincloss, M.D., Robert Lindblad, M.D., R. Paul Robertson, M.D., Antonio Secchi, M.D., Mathias D. Brendel, M.D., Thierry Berney, M.D., Daniel C. Brennan, M.D., Enrico Cagliero, M.D., Rodolfo Alejandro, M.D., Edmond A. Ryan, M.D., Barbara DiMercurio, R.N., Philippe Morel, M.D., Kenneth S. Polonsky, M.D., Jo-Anna Reems, Ph.D., Reinhard G. Bretzel, M.D., Federico Bertuzzi, M.D., Tatiana Froud, M.D., Raja Kandaswamy, M.D., David E.R. Sutherland, M.D., Ph.D., George Eisenbarth, M.D., Ph.D., Miriam Segal, Ph.D., Jutta Preiksaitis, M.D., Gregory S. Korbutt, Ph.D., Franca B. Barton, M.S., Lisa Viviano, R.N., Vicki Seyfert-Margolis, Ph.D., Jeffrey Bluestone, Ph.D., and Jonathan R.T. Lakey, Ph.D.

Only 31% remained insulin independent at 2 years

N Engl J Med 2006;355:1318-30.

In retrospective analysis of UNOS database data on pancreas and kidney-pancreas transplant recipients(27000), the use of maintenance steroids increased the risk of infectious complications but did not decrease the rate of patient death or graft loss.

Steroid Withdrawal in Simultaneous Pancreas-Kidney Transplantation: A 7-Year Report

J. Malheiro, L. Martins, I. Fonseca, A.M. Gomes, J. Santos, L. Dias, J. Dores, F. Oliveira, R. Seca,
R. Almeida, A. Henriques, A. Cabrita, and M. Teixeira

	2 years	5years
Steroid free(n=42)		
Patient	100	98
Kidney	98	98
pancreas	95	90
Steroid based(n=12)		
patient	92	83
kidney	92	83
pancreas	83	75

	Patient		Kidney		Pancreas	
	Av.	With.	Av.	With.	Av.	With.
1-year (n = 49)	96	100	96	100	88	88
2-year (n = 46)	96	96	92	96	88	84
3-year (n = 35)	92	96	88	96	80	76
4-year (n = 25)	92	96	88	96	80	76
5-year (n = 6)	92	96	88	96	80	76

Cantarovich D, Karam G, Hourmant M, et al. Steroid avoidance versus steroid withdrawal after simultaneous pancreas-kidney transplantation. Am J Transplant. 2005;5:1332–8.

A recent Cochran review evaluated steroid avoidance and steroid withdrawal protocols in pancreas transplant recipients

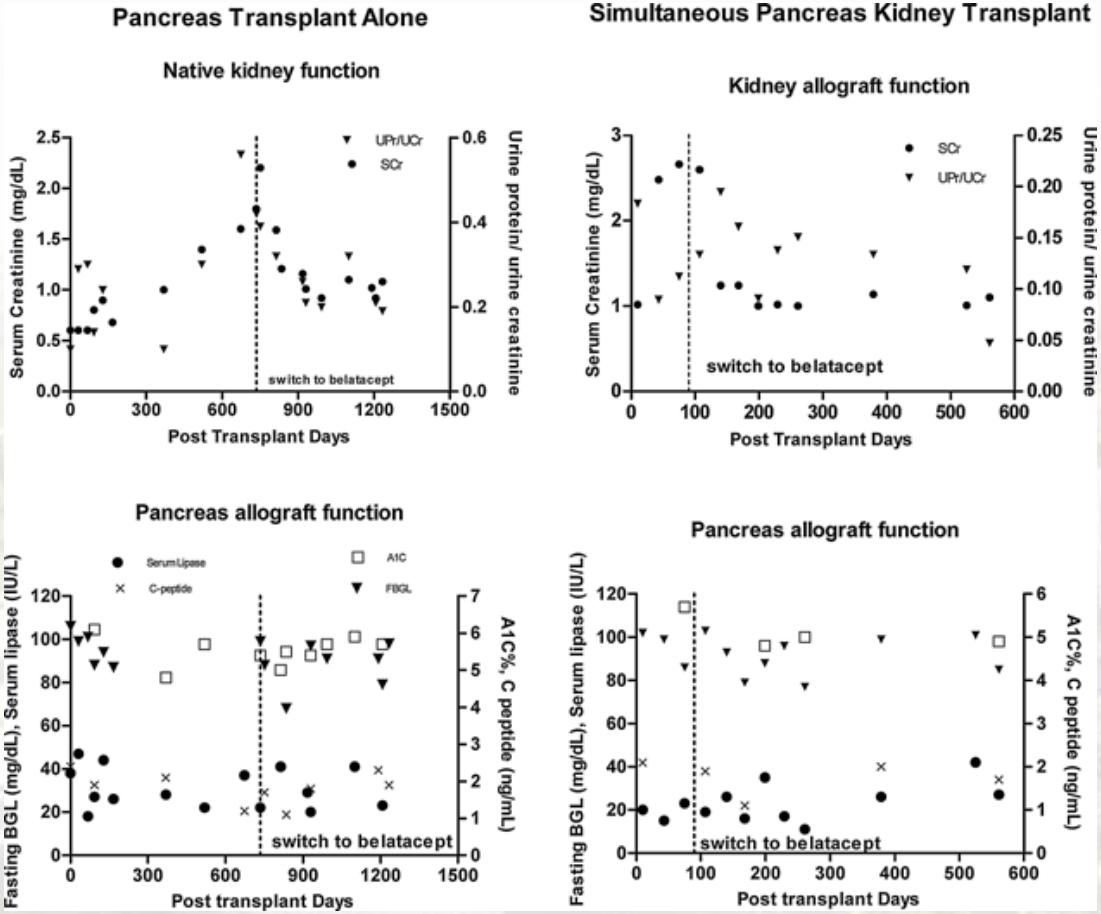
- **AUTHORS' CONCLUSIONS:**
- There is currently insufficient evidence for the benefits and harms of steroid withdrawal in pancreas transplantation in the three RCTs (144 patients) identified. The results showed uncertain results for short-term risk of rejection, mortality, or graft survival in steroid-sparing strategies in a very small number of patients over a short period of follow-up. Overall the data was sparse, so no firm conclusions are possible. Moreover, the 13 observational studies findings generally concur with the evidence found in the RCTs.

- Conclusion :
  - The data is contraverial
  - 60% of the programs still using steroids
  - There is probably little long-term benefit and a small, although clear risk observed in patients withdrawn from low doses (5 mg) of steroids

New agents

- Mirroring larger experiences in kidney transplantation , **belatacept** may prove an important strategy for preservation of renal and pancreatic function after SPK transplantation, either as a first-line or rescue therapy.

Conversion From Tacrolimus to Belatacept to Prevent the Progression of Chronic Kidney Disease in Pancreas Transplantation: Case Report of Two Patients



American Journal of Transplantation
Volume 14, Issue 11, pages 2657-2661, 1 SEP 2014 DOI: 10.1111/ajt.12863
http://onlinelibrary.wiley.com/doi/10.1111/ajt.12863/full#ajt12863-fig-0002

- there is an ongoing belatacept induction and maintenance trial in primary SPK transplantation using maintenance MMF, early steroid withdrawal and CNI minimization with possible weaning (CTOT-15;NCT01790594).

Optimal protocol

Rejection After SKPT With Contemporary Immunosuppression

Immunosuppressive Regimen	Incidence of Rejection
TAC/MMF/PRED + no antibody induction or CSA (modified)/ MMF/PRED + daclizumab or basiliximab	30% to 35%
TAC/MMF/PRED + daclizumab or basiliximab	20% to 25%
TAC/MMF/PRED + rATG induction	10% to 15%
TAC/MMF or TAC/SRL + rATG/Dac or Campath-1H ± PRED withdrawal	5% to 10%

Thank you