Overview of New Approaches to Immunosuppression in Renal Transplantation

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Immunosuppression in the 1950's

- Nothing

Successful Transplantation Limited to Identical Twins

Immunosuppression in the 1960's and 1970's

- Azathioprine
- Steroids
- Anti-Lymphocyte Preparations – Polyclonal

Success – 50%

Immunosuppression in the 1980's

- Cyclosporine
- Azathioprine
- Steroids
- Anti-Lymphocyte Preparations – Polyclonal

Success – 75 to 85%

Side Effects of Cyclosporine

- Nephrotoxicity
- Hypertension
- Hirsutism
- Gum Hyperplasia
- Hyperuricemia
- Diabetes
- Neurologic Side Effects
- Hepatotoxicity

Side Effects of Steroids

- Infections
- Weight Gain
- Cushingoid Changes
- Joint Destruction – Avascular Necrosis
- Osteoporosis
- Diabetes
- Cataracts
- Growth Retardation
- Muscle Wasting
- Upper Gastrointestinal Bleeding

Side Effects of Azathioprine

- Bone Marrow Suppression
- Hepatotoxicity
- Malignancy

Side Effects of Anti-Lymphocyte Preparations

- Viral Infections
- Post-Transplant Lymphoproliferative Disorder

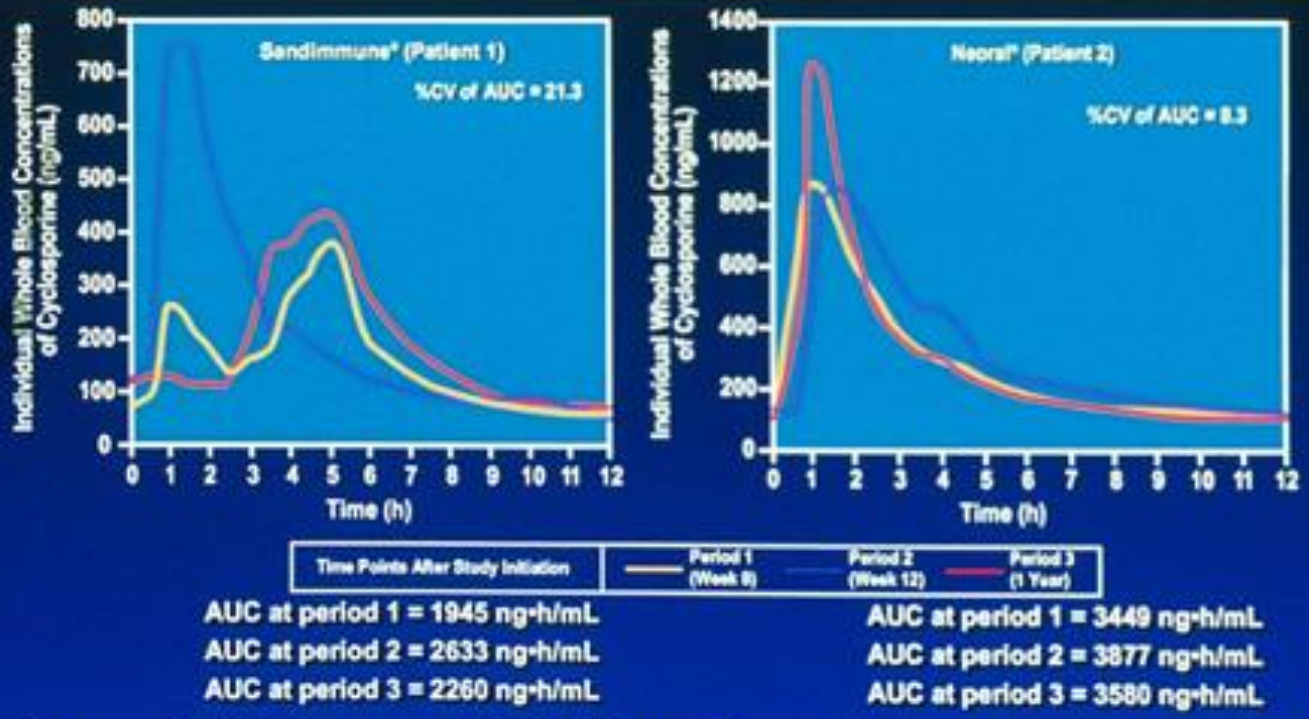
New Immunosuppressive Agents Since 1994

- Cyclosporine (Micro emulsion)
- Tacrolimus
- Mycophenolate Mofetil
- Sirolimus
- Daclizumab
- Basiliximab
- Thymoglobulin
- Alemtuzumab
- Belatacept

Cyclosporine (Micro emulsion)

- Less Variability
- ? ⬆ Efficacy

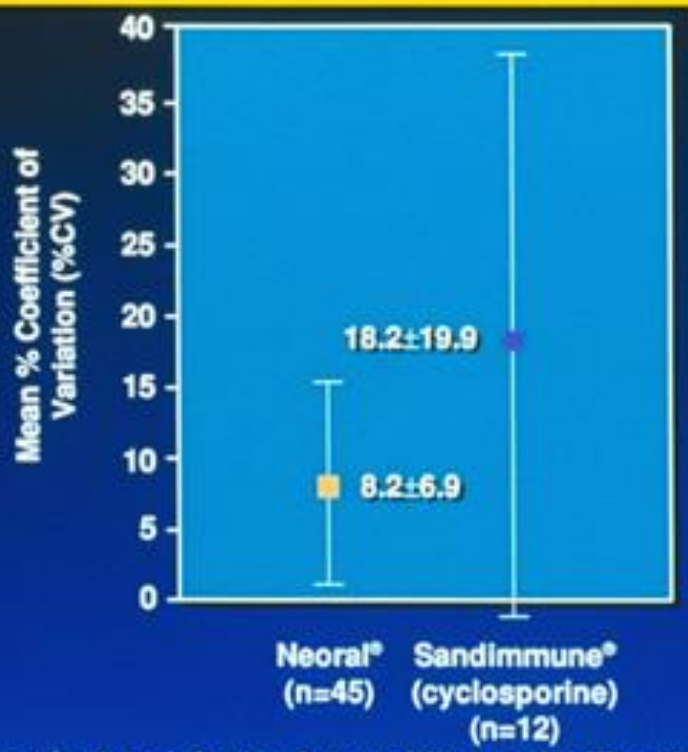
NEORAL® (cyclosporine capsules and oral solution for microemulsion) SHOWS LESS INTRASUBJECT VARIABILITY IN CYCLOSPORINE EXPOSURE THAN SANDIMMUNE® (cyclosporine)



Blood concentration-time curves (AUCs) in a maintenance renal transplant recipient receiving Sandimmune vs a patient receiving Neoral.*† Average time posttransplantation of patients in the study was 4.7 years (range 3.5 months–12.6 years).

*From Sandoz Study OLM102. Data from an average patient (closest to the mean %CV of AUC) in the relevant study arm.
†Intrasubject variability (%CV) of the AUC in individual studies of maintenance and de novo renal transplant recipients was 9% to 21% for Neoral and 19% to 26% for Sandimmune.

NEORAL® (cyclosporine capsules and oral solution for microemulsion) REDUCES VARIABILITY IN CYCLOSPORINE EXPOSURE

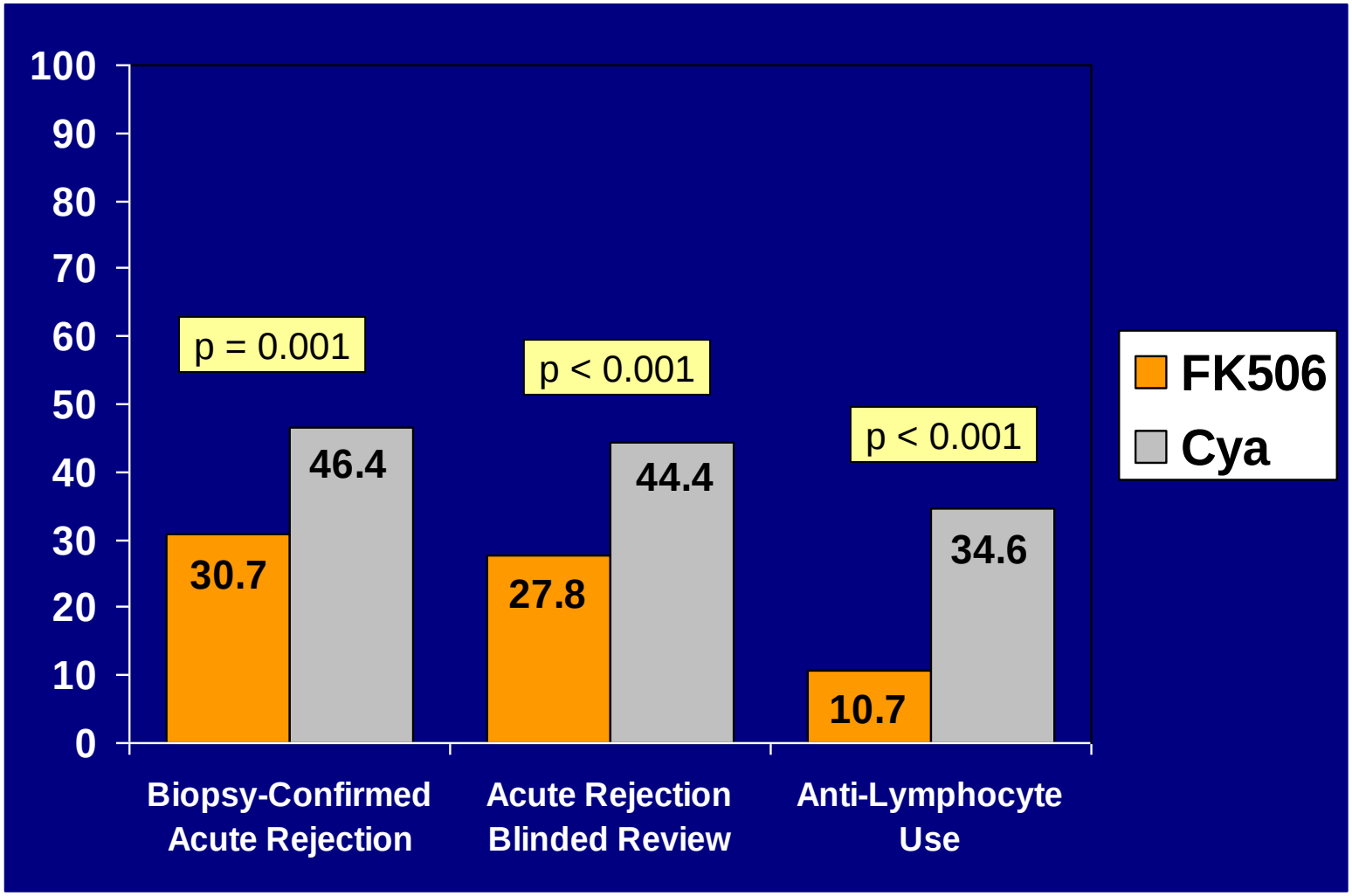


In maintenance renal transplant recipients: Intrasubject variability of drug exposure of Neoral vs Sandimmune®.*

*From Sandoz Study OLM102. In individual studies of both maintenance and de novo renal transplant recipients, the intrapatient variability of the area under the concentration-vs-time curve (AUC), as measured by percent coefficient of variation (%CV), has ranged from 9% to 21% for Neoral vs 19% to 26% for Sandimmune.

FK506 – Tacrolimus (Prograf®)

Acute Rejection



Biopsy-proven Acute Rejection

	Tacrolimus N=286		CyA-ME N=271		
Acute Rejection	56	19.6%	101	37.3%	*
Steroid-sensitive	30	10.5%	54	19.9%	
Steroid-resistant	27	9.4%	57	21.0%	*
Antibody-sensitive	14	4.9%	18	6.6%	
MMF Added	8	2.2%	6	2.2%	
Switch of Cornerstone Immunosuppression	1	0.3%	27	10.0%	*
Refractory Rejection	4	1.4%	9	3.3%	

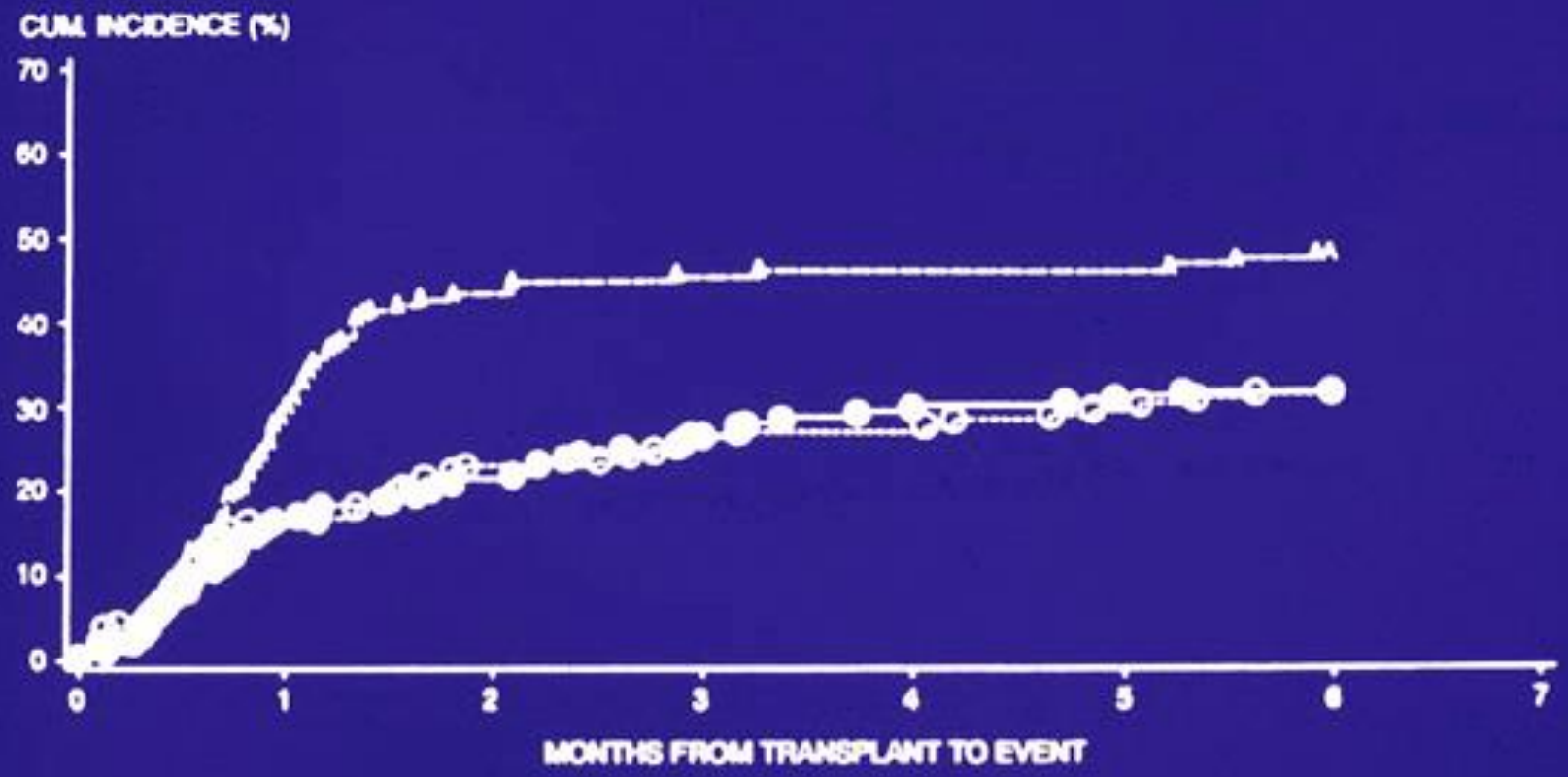
*** p < 0.001**

Tacrolimus (FK506) in Kidney Transplantation

Adverse Events

- Nephrotoxicity
- Neurotoxicity
- Diabetogenicity

Mycophenolate Mofetil (CellCept® - RS61443)

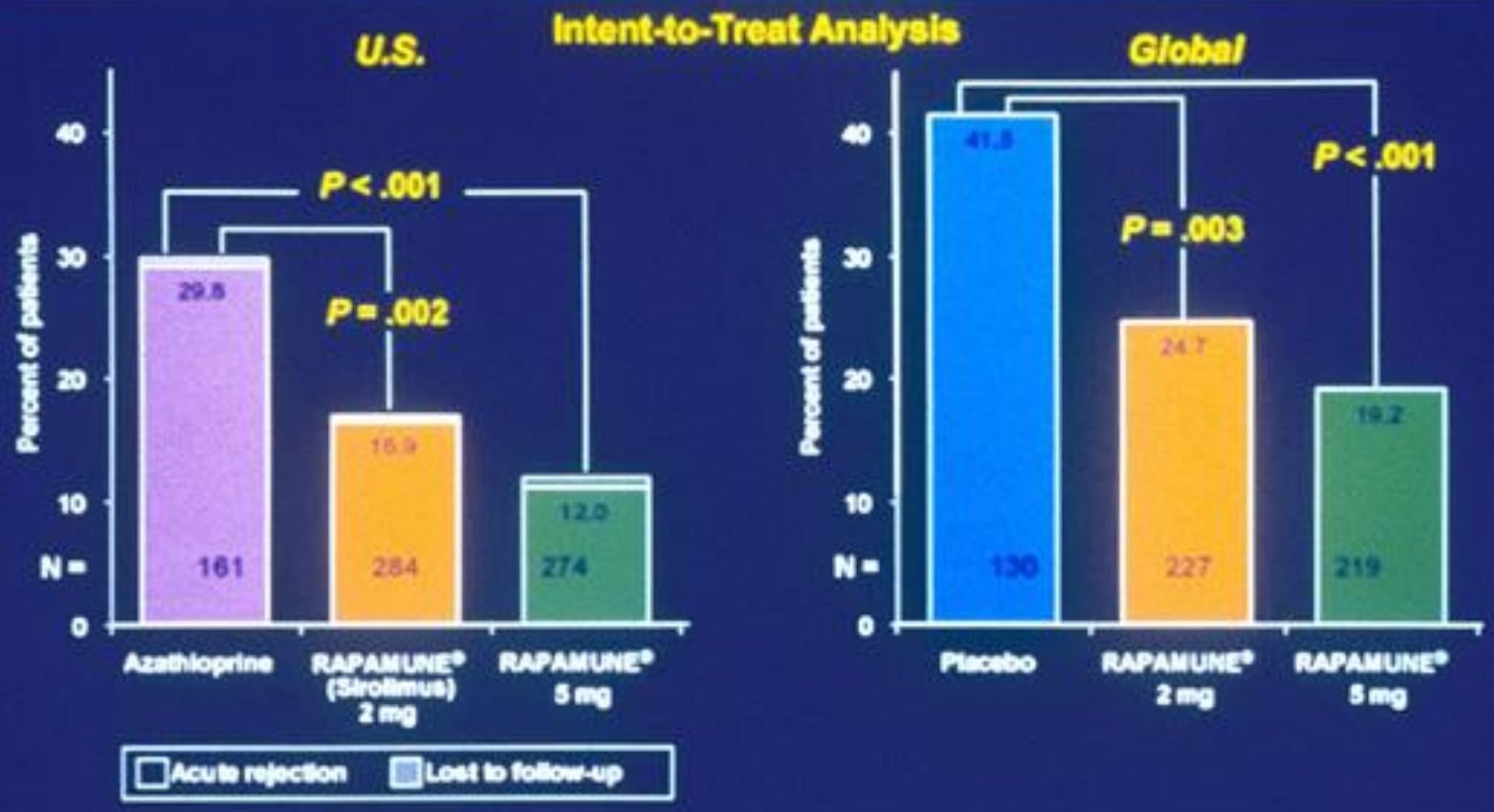

CUM. INCIDENCE (%)
70
60
50
40
30
20
10
0
0
1
2
3
4
5
6
7
MONTHS FROM TRANSPLANT TO EVENT

MMF Toxicity

- Gastrointestinal
- Hematologic

Sirolimus (Rapamycin)

Incidence of First Biopsy-Confirmed Acute Rejection



Sirolimus Toxicity

- Hypercholesterolemia
- Hypertriglyceridemia
- Thrombocytopenia
- Impaired Wound Healing
- Joint Pain

Daclizumab (Zenapax)

Humanized (90% human, 10% mouse)

Induction Agent

Daclizumab

Less Rejection

35% ⟶ 22%

47% ⟶ 28%

Basiliximab (Simulect)

Chimeric (67% human, 33% mouse)

Induction Agent

Basiliximab

Less Rejection

51% ⟶ 35%

51% ⟶ 33%

Thymoglobulin (rabbit anti-thymocyte globulin)

Alemtuzumab (Campath 1H)

Humanized Anti-CD52 Monoclonal Antibody

CD52 – T&B Cells, Monocytes, NK Cells

Maintenance

Cyclosporine → Tacrolimus

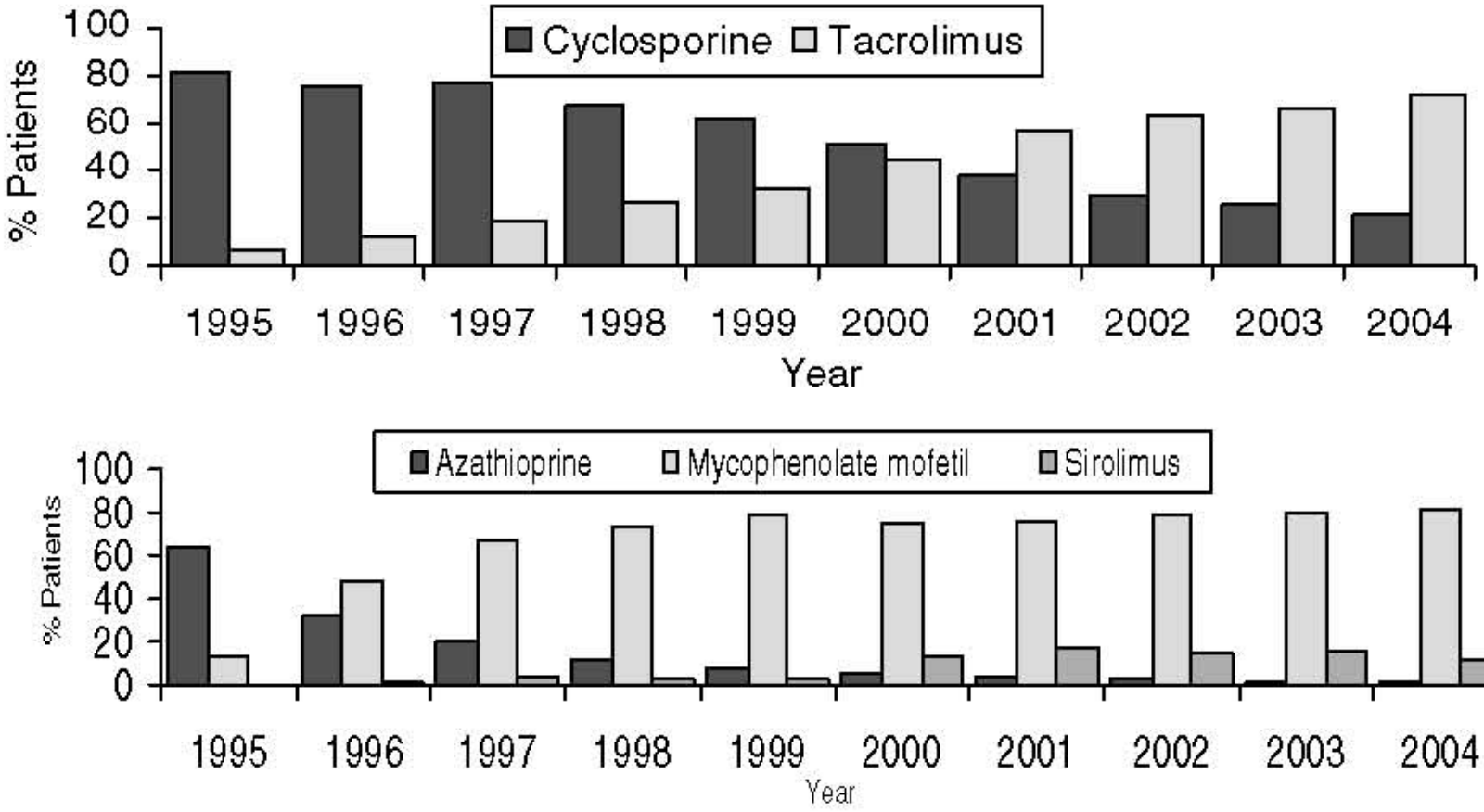
Azathioprine → Mycophenolate

Maintenance

Kidney

- Tacrolimus 79%
- Mycophenolate 87%

Trends in Maintenance Immunosuppression Prior to Discharge for Kidney Transplantation



Sirolimus

Kidney

- At Transplantation 9%
- At 1 Year 18%

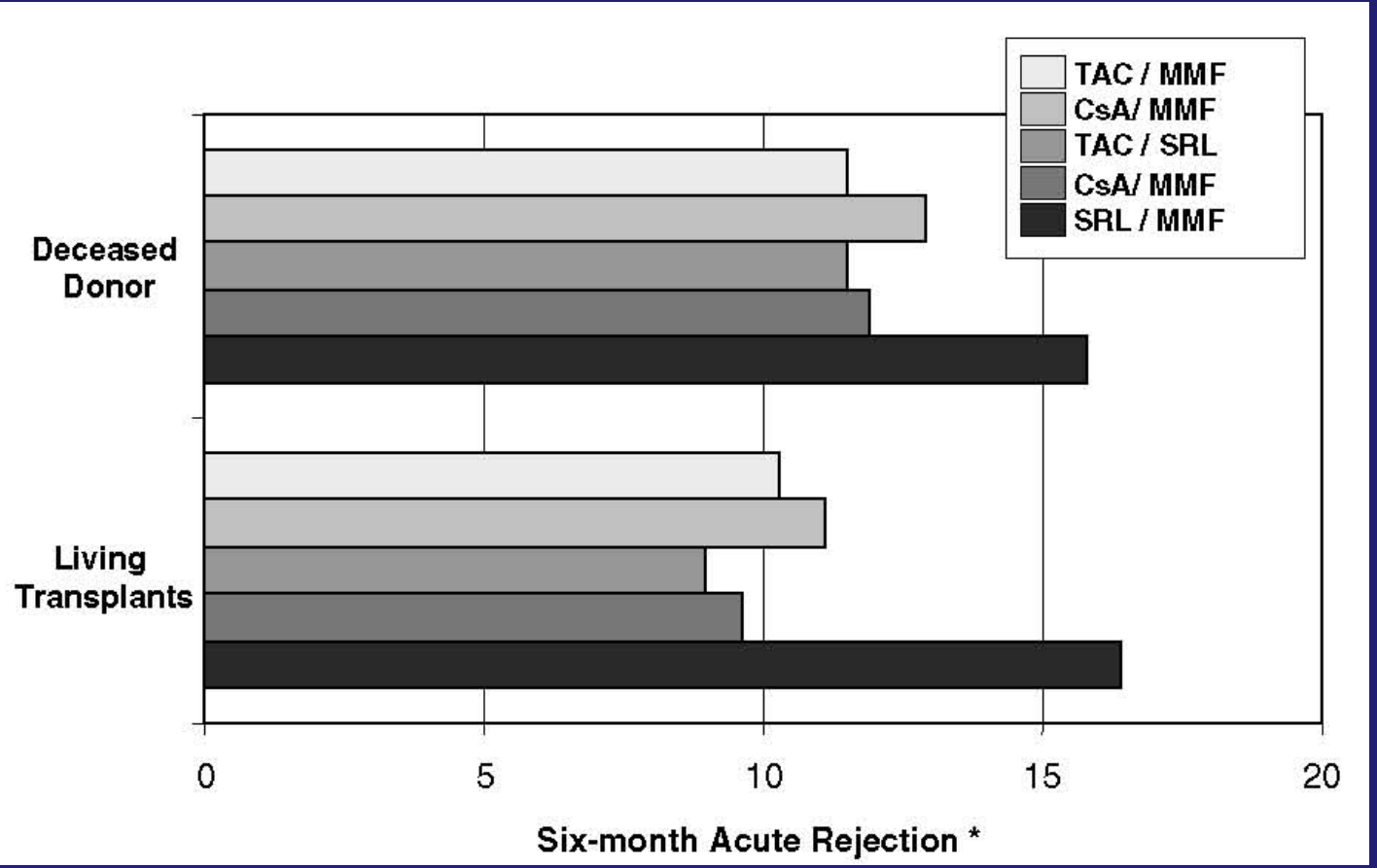
Calcineurin Inhibitor Avoidance - Remains Uncommon

Kidney 6%

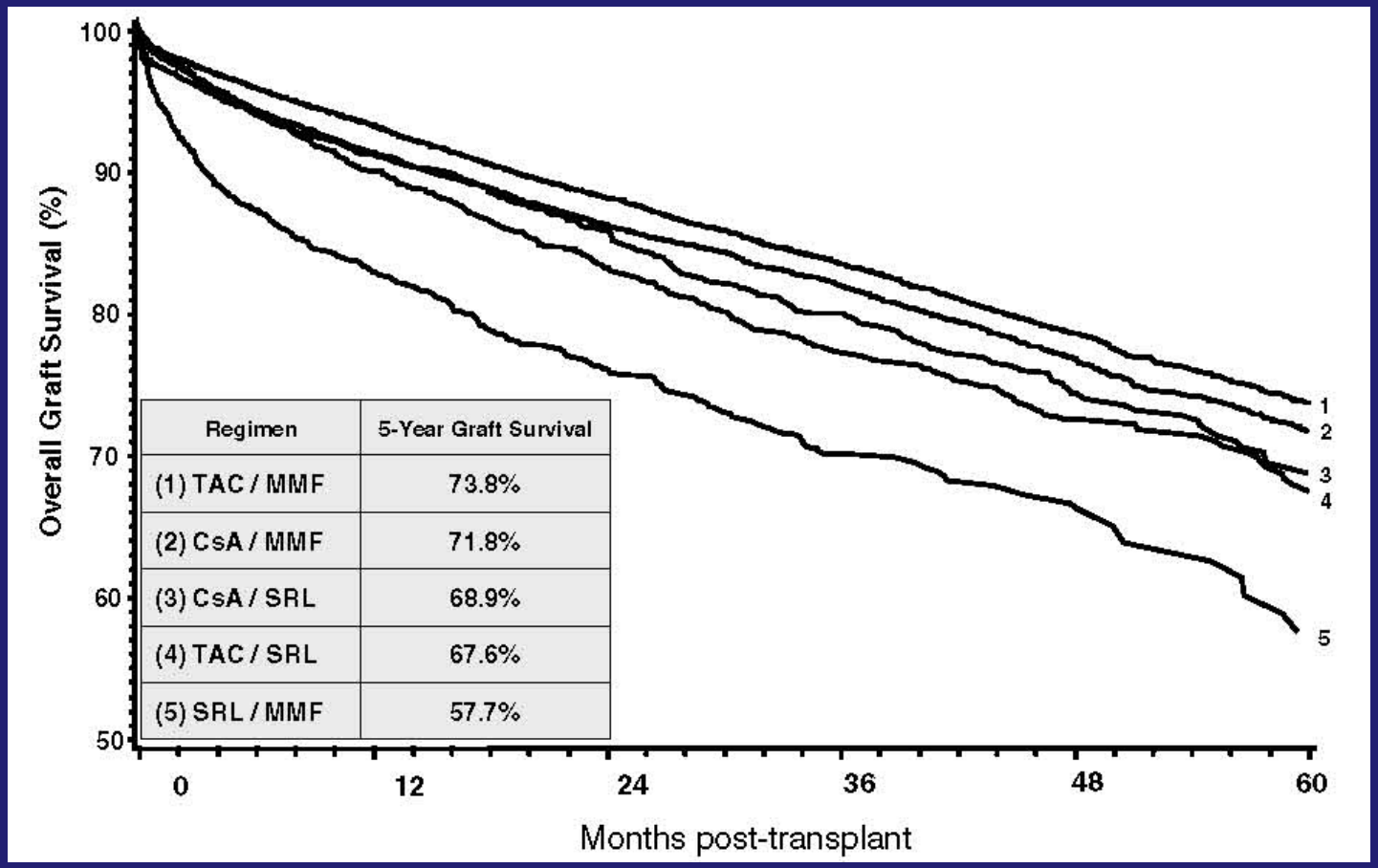
CNI Elimination - Also Uncommon

Kidney 1%

Six-Month Acute Rejection Rates by Immunosuppressive Regimen



Overall Graft Survival by Immunosuppressive Regimen for Deceased Donor Transplant Recipients



Regimen	5-Year Graft Survival
(1) TAC / MMF	73.8%
(2) CsA / MMF	71.8%
(3) CsA / SRL	68.9%
(4) TAC / SRL	67.6%
(5) SRL / MMF	57.7%

Steroid Avoidance / Near Avoidance

Kidney 26%

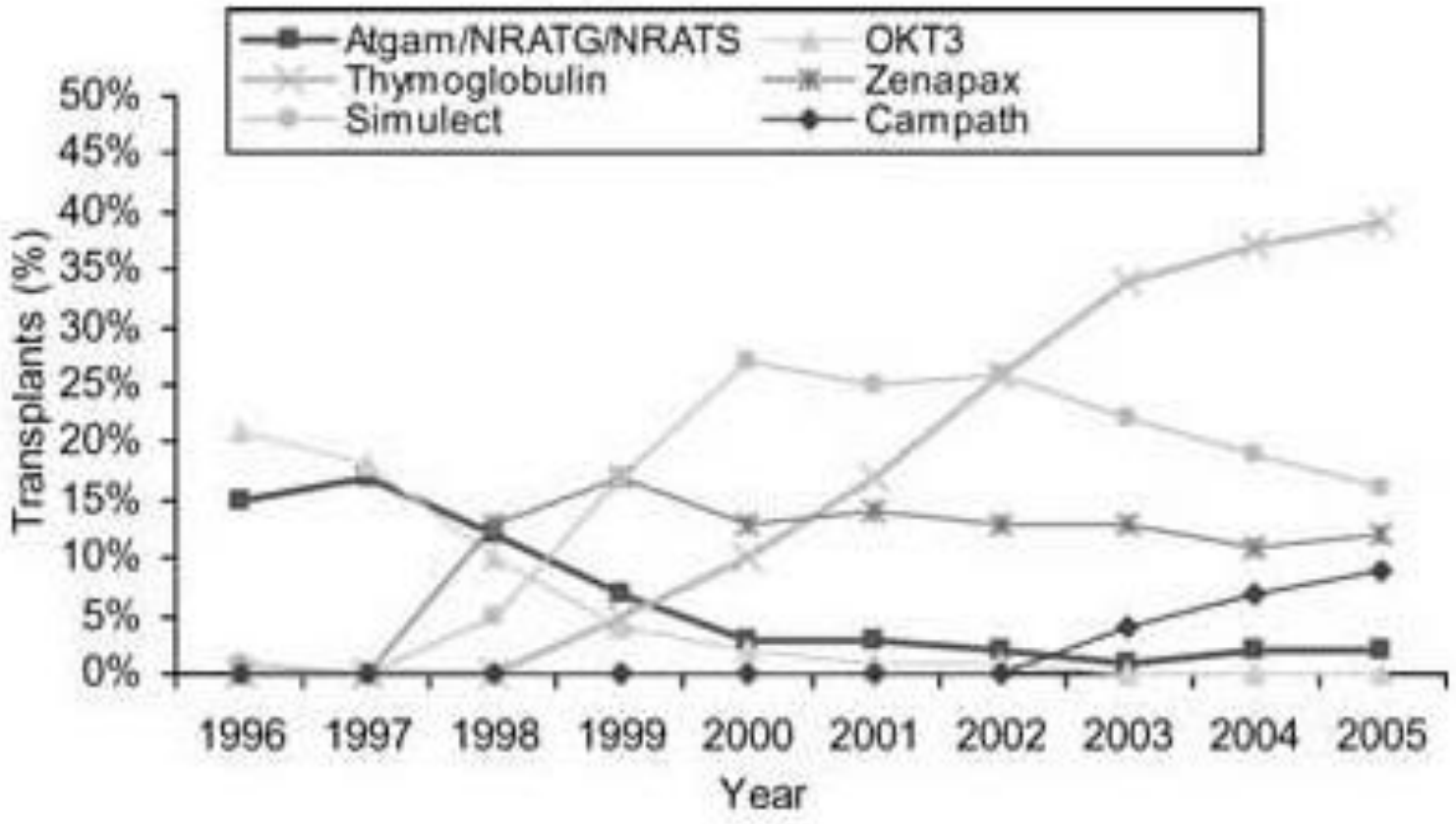
Steroid Withdrawal - Increase Over Time

Kidney 10%

General Trend Toward Increasing use of Antibody Induction

Kidney 74% ⬆

Immunosuppressive Agents Used For Induction in Kidney Transplantation



Acute Rejection – Falling Incidence

Kidney 12%

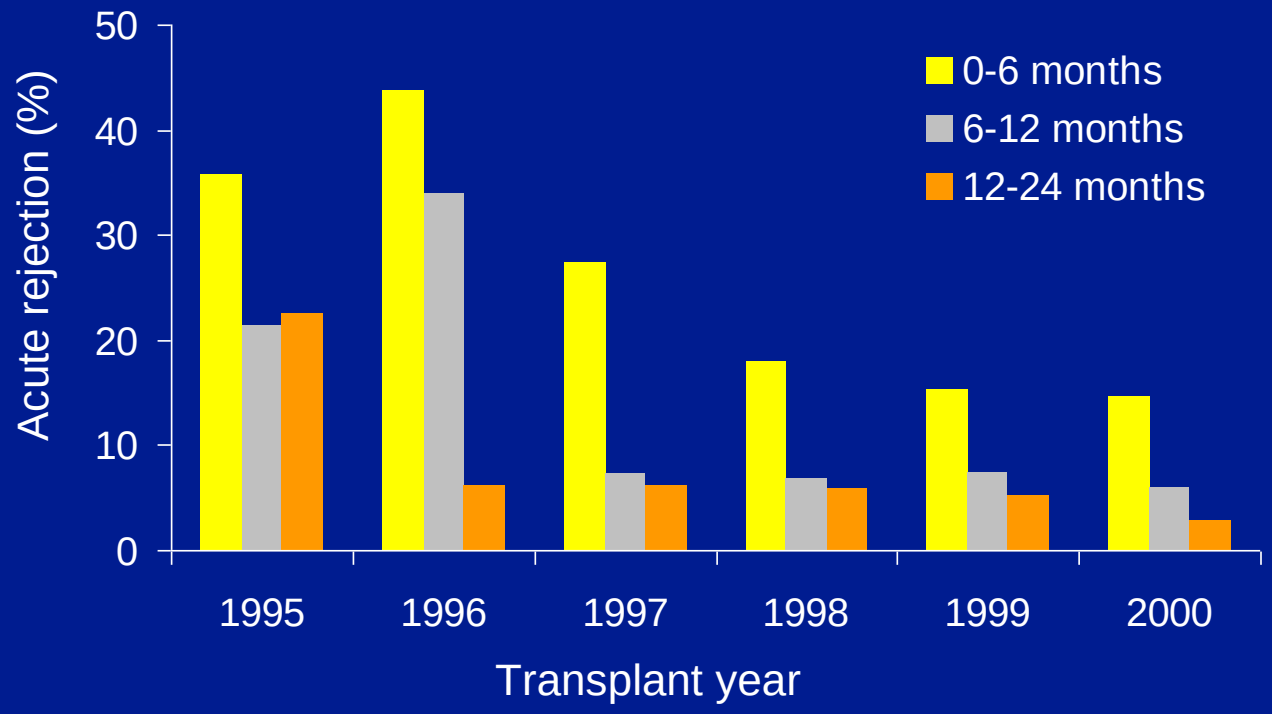
Treatment of Rejection

Kidney

- Steroids 72%
- Antibody 48%

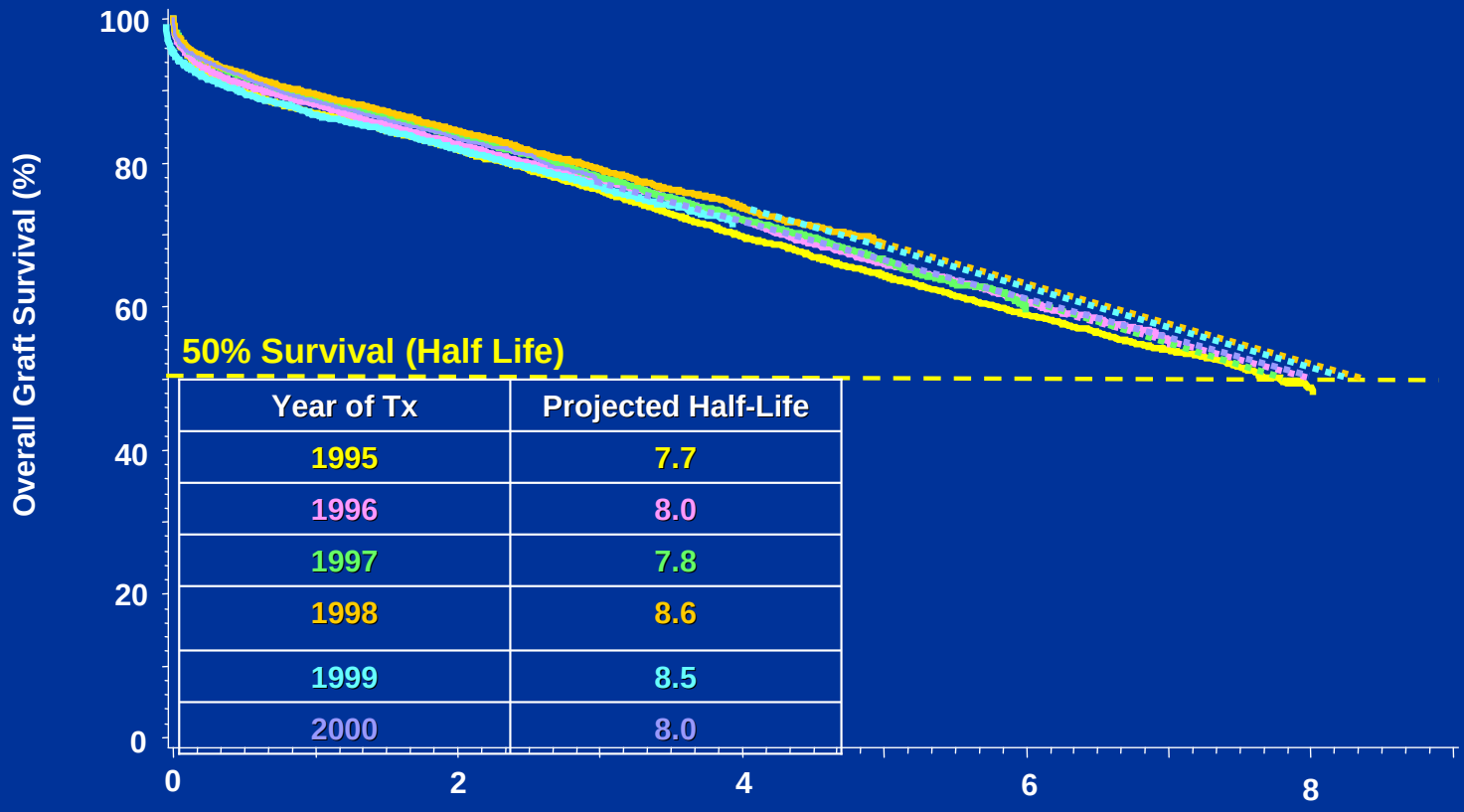
Decreased incidence of AR episodes from 1995 to 2000

Data from the Scientific Registry of Transplant Recipients (SRTR)



Meier-Kriesche HU et al. *Am J Transplant* 2004; 4:378-83.

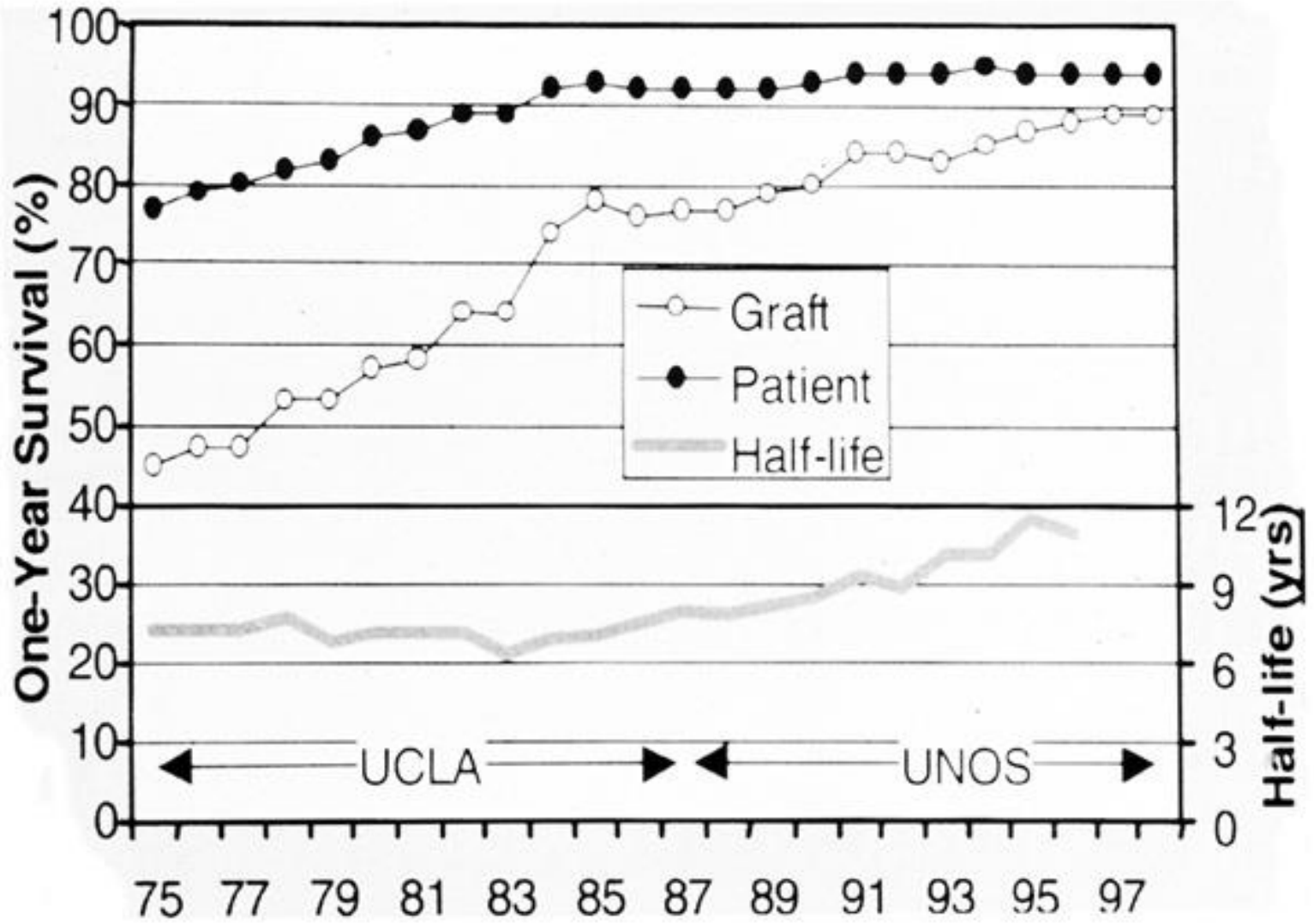
Projected Half Lives: Primary Deceased Donor Transplants 1995-2000



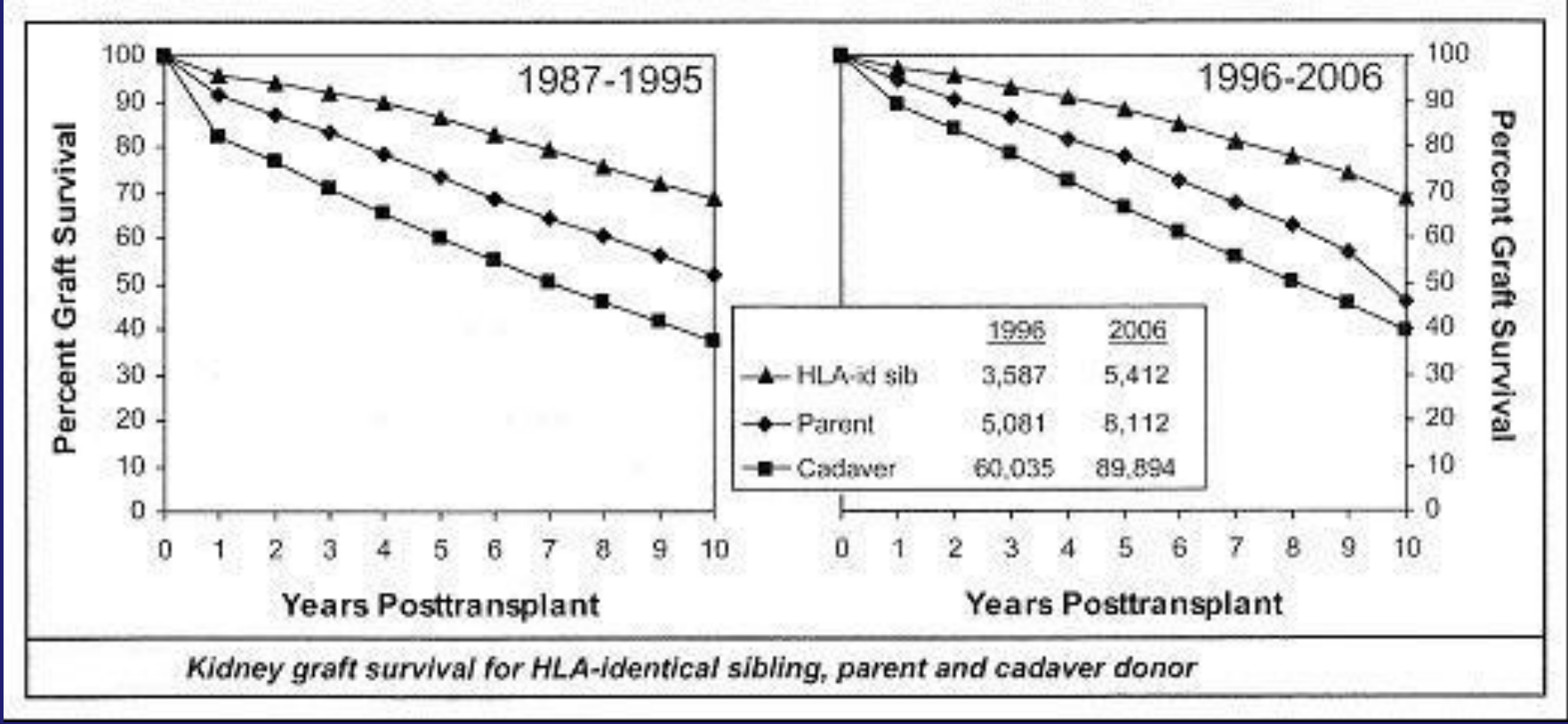
Year of Tx	Projected Half-Life
1995	7.7
1996	8.0
1997	7.8
1998	8.6
1999	8.5
2000	8.0

* Projected from data > 2 year post-tx

Meier-Kriesche et al. *Am J Transplant*. 2004 Mar;4(3)


One-Year Survival (%)
100
90
80
70
60
50
40
30
20
10
0
Graft
Patient
Half-life
UCLA
UNOS
12
9
6
3
0
Half-life (yrs)
75 77 79 81 83 85 87 89 91 93 95 97

Kidney graft survival for HLA-identical sibling, parent and cadaver donor



Kidney graft survival for HLA-identical sibling, parent and cadaver donor

Belatacept

Co- stimulation blocker

Approved 06/2011

2 Large Registration Trials

SCD/LRD – Benefit

ECD – Benefit Ext

- SCD/LRD (Benefit)

Comparable 4 year patient & graft survival

More rejection in Belatacept arms

Better renal function – 25ml/min

7 Years

Better graft survival

in

Bela patients

ECD (Benefit – Ext)

Comparable 4 year Patient & Graft Survival

No Difference in ACR incidence

Better renal function – 11ml/min

Big Problem

PTLD in EBV – Patients

Kirk – Alemtuzumab/Belatacept/Sirolimus

No CNI, No Steroids

Excellent 3 Year Patient, Graft Survival in

LD Transplants

10 Patients weaned off Sirolimus

ASKP 1240 (Anti – CD40)

Phase 1B – dose ranging (only one dose)

Well tolerated, No Cytokine release

Phase 2 trial completed

Tofacitinib

JAK3 Inhibitor

Phase 2 B

(Tofacitinib, Cont'd)

Comparable patient and Graft survival

Comparable rejection

Better renal function

More infection, PTLD

Need for therapeutic Drug Monitoring

?Low Dose (5mg BID vs 10 or 15 mg BID)

Approved for Rheumatoid Arthritis

Bortezomib

Proteasome inhibitor

Targets Plasma cells

Indicated for Multiple Myeloma

Bortezomib, Cont'd

Use in antibody – mediated rejection (AMR)

With pheresis (and rituximab)

Most Effective - Early,
Acute AMR in compliant patients

Less Effective Late

? Role in Chronic AMR

No Randomized Trials

Eculizumab

C5 Inhibitor

Approved for PNH, atypical HUS

Eculizumab cont'd

Prevention / Treatment acute AMR

- Single Center – Mayo Clinic

- Multicenter trial in progress

Eculizumab, Cont'd

Prevention of Recurrent Atypical HUS after Transplantation

Tolerance Induction

Louisville/Northwestern

LD Transplantation

Kidney / Bioengineered stem cell transplantation

Macrochimerism

Immunosuppression withdrawal at 1 year

No GVHD, No Engraftment syndrome

CMX – 001

Oral Cidofovir

Broad Anti-Viral Properties

Potential to Prevent / Treat CMV, BKV,

EBV, Etc.

Not Yet Approved by the FDA

Conclusion

1. Immunosuppressive protocols have evolved over the past 40+ years, as newer, more potent agents have become available.

2. Tacrolimus has largely replaced cyclosporine as the calcineurin inhibitor of choice.

3. Mycophenolate has largely replaced azathioprine as the antimetabolite of choice.

4. The use of sirolimus remains relatively low, although the percentage of patients receiving it increases over the first year after transplantation. Registry data suggest that sirolimus as a primary immunosuppressive agent is associated with inferior outcomes when compared with tacrolimus or cyclosporine.

5. There has been a gradual increase in steroid avoidance/near avoidance in kidney transplantation, although it remains < 30%. Steroid withdrawal has also increased over time, but is still carried out in a minority of patients.

6. Antibody Induction has become increasingly common in Kidney Transplantation.

7. The incidence of rejection has declined over time. Steroids still remain the first line therapy for rejection.

8. In spite of a falling incidence of acute rejection, allograft half lives have not improved. This suggests that complacency in our approach to immunosuppression may not be entirely justified.

9. Belatacept is a recently approved costimulation blockade agent that is associated with better renal function but more early rejection, and cannot be used in EBV negative patients.

10. ASKP 1240 is a human anti-CD40 Monoclonal antibody. It has just finished phase 2 testing.

11. Tofacitinib is a JAK3 inhibitor that will not enter phase III studies for transplantation. It is effective and not nephrotoxic but associated with infectious complications and PTLD.

12. Bortezomib is a proteasome inhibitor that seems to have some efficacy in treating AMR.

13. Eculizumab is a C5 inhibitor that may be effective at preventing/treating AMR and recurrent atypical HUS.

14. A new tolerance induction protocol combining kidney and stem cell transplantation has shown early promising results.

15. CMX – 001 May be the next important anti-viral agent.