Udruženje ljekara za nefrologiju , dijalizu
i transplantaciju bubrega u Bosni i Hercegovini

Imunosupresivni protokoli u transplantaciji bubrega

Neum, 3 - 5. novembar 2006.

Senaid Trnačević

Imunosupresivni lijekovi - protokoli

Nova homeostaza organizma i presađenog organa

- spriječe naglo odbacivanje grafta
- toleranicja grafta i organizma
- liječenje akutnih odbacivanja
- da su netoksični

Preživljavanje i primaoca i grafta

Risk factors for graft survival
42,000 cadaveric renal transplant recipients: 1992–1998

Variable	Rel. Risk (95% CI)	*P* Value
Donor age (years)		
55–64	1.24 (1.08 – 1.42)	0.002
> 65	1.45 (1.31 - 1.80)	<0.001
Donor hypertension > 10 a	1.17 (1.02 – 1.34)	0.03
Donor DM > 10 a	0.73 (0.45 - 1.20)	0.22
Acute renal failure	1.99 (1.91 – 2.08)	<0.001
Recipient age (per decade)	1.08 (1.06 – 1.10)	<0.001
PRA > 30%	1.21 (1.21 – 1.35)	<0.001
Acute rej. < 6 months	1.32 (1.26 – 1.39)	<0.001

DM = diabetes mellitus

Ojo *et al. JASN* 2001;12:589–97

Immunosuppression: Evolution in Practice and Trends, 1994-2005

Overview

This chapter presents an organ-by-organ review of immunosuppression use over the last 10 years. New to this year's report is a wealth of data on immunosuppressive regimens that include more than one drug; in previous years, use of drugs was reported individually.

In response to concerns about the adverse effects associated with steroid-based regimen increases, many transplant recipients are being taken off corticosteroids as a maintenance therapy (steroid withdrawal) or not being given it in the first place (steroid avoidance).

Razmatra se pregled imunosupresije unazad 10 godina. Zbog steroidnih nus efekata, razmatra se isključivanje steroida iz terapije održavanja ili da se uopšte ne daju već na početku.

Structure protocols

- Pre-transplant (Don‘ts)
- Peri-transplant
- First ½ Year
- Long term

Immunosuppressive Drug Names in OPTN/SRTR Data

General Class	Generic Name	Brand Name
Corticosteroids	-prednisone -methylprednisolone -dexamethasone	-Orasone, Deltasone -Solu-Medrol, A-methaPred, Medrol -Decadron
Calcineurin inhibitors	-tacrolimus (or FK-506) -cyclosporine (also cyclosporin A, CsA)	-Prograf -Sandimmune, Neoral, manufacturers of generic cyclosporine include SangStat (SangCya)*, Abbott (Gengraf), Apotex, Bedford Eon Labs, Geneva, Ivax Pharms, Novex, Morton Grove, and Pliva
Antimetabolites	-azathioprine (or AZA) -cyclophosphamide -mycophenolate mofetil (or RS61443) -mycophenolic sodium (also ERL, mycophenolate acid) -methotrexate -leflunomide (or LFL)***	-Imuran -Cytoxan, Neosar -CellCept -Myfortic -Rheumatrex, Trexall -Arava
Polyclonal antibodies	-antithymocyte globulin (rabbit) -antithymocyte globulin (equine) -Nashville rabbit antithymocyte globulin/serum (NRATG/NRATS) -antilymphocyte globulin (ALG)	-Thymoglobulin -ATGAM
Anti-CD3 monoclonal antibodies	-muromonab-CD3	-Orthoclone OKT3
Anti-CD52 monoclonal antibodies	-alemtuzumab***	-Campath-1H
Anti-IL-2 receptor monoclonal antibodies	-basiliximab -daclizumab	-Simulect -Zenapax
TOR inhibitors	-sirolimus (or rapamycin) -everolimus (or RAD0001)**	-Rapamune -Certican (Phase III Trial)
Other	-FTY720**	-(Phase III Trial)

Note: For some immunosuppressants, the original data collection forms list brand names instead of generic names. As in the SRTR database, the figures in this chapter follow the terms on the data collection forms. However, the text refers to the drugs by their generic names when there exist no additional generic alternatives.

* Currently withdrawn from the market

** Currently only for investigational use

*** off label use

Immunsuppression:

Standard Schema:

Prä OP: 1) Sandimmun 5mg/kgKG p.o. (Neoral)
2) Cellcept 1g p.o.

intraOP: Fortecortin 40 mg i.v. (500mg Urbasona-bolusi)

postOP: (12h after 1st application)
Sandimmun 5mg/kgKG p.o.
Cellcept 1g p.o.

Following Therapy per day:
Sandimmun 2 x tgl (C2 Spiegel 1300-1700 ng/ml)
Cellcept 2 x 1 g
Fortecortin Taper (32 mg, 24mg, 16mg, 8 mg, 4 mg)

Immunsuppression: Group A

Standard Schema:

Prä OP: 1) Prograf 0,8mg/kgKG p.o.
2) Cellcept 500 mg p.o.

intraOP: Fortecortin 40 mg i.v.

postOP: (12h after 1st application)
Prograf 0,7mg/kgKG p.o.
Cellcept 500 mg p.o.

Following Therapy per day:
Prograf 2 x tgl (Co levels: 10-15 ng/ml)
Cellcept 2 x 500 m g
Fortecortin Taper (32 mg, 24mg, 16mg, 8 mg, 4 mg)

Immunsuppression: Group B

Standard Schema:

Prä OP: 1) Certican/Rapamune 4mg
2) Cellcept 500 mg p.o.

intraOP: Fortecortin 40 mg i.v.

postOP: (12h after 1st application)

Cellcept 500 mg p.o.

Following Therapy per day:
Certican/Rapamune 3 mg 1x tgl (Co levels: 8-12 ng/ml)
Cellcept 2 x 500 m g
Fortecortin Taper (32 mg, 24mg, 16mg, 8 mg, 4 mg)

Immunsuppression:
Sensitized PRA40-80 (latest)

Prä OP: 1) Sandimmun 5mg/kgKG p.o.
2) Cellcept 1g p.o.
1 Amp. Dibondrin+2,5g Novalgin+4mg Fortecortin beforeATG
3) **Thymoglobuline 2mg/kgKG (max. 7 Fl.)**

intraOP: Fortecortin 40 mg i.v.

postOP: (12 h after 1st application)
Sandimmun 5mg/kgKG p.o.
Cellcept 1g p.o.
Following Therapy: ATG for 10 days
(Leuko <3000 1/2 Dosis, Leuko<2000 ATG Pause
Sandimmun, Cellcept, Fortecortin Taper

Immunsuppression:
Sensitized > 80% latest

IMMUNADSORPTION and AMM PROTOKOLL

Group 1
ATG
Prograf
MMF
Steroide

Group 2
ATG
Sandimmun C2
MMF
Steroide

Immunsuppression: Other studies

Campath - Studiy:	**Campath + FK mono**	
	FK, MMF, Steroide	
Elite-Symphony:		**MMF, CyA(Stand), Steroids**
	Zenapax	**MMF, CyA(low) Steroids**
	Zenapax	**MMF, FK (low) Steroids**
	Zenapax	**MMF, Rapa(low) Steroids**
BMS Studie:	**Simulect, BMS (high), MMF, Steroide**	
	Simulect, BMS (low), MMF, Steroide	
	Simulect, CyA	**MMF, Steroide**
FTY 720	**FTY(high), CyA (low), Steroide**	
	FTY(low), CyA(norm),Steroide	
	MMF	**CyA(norm),Steroide**

Immunsuppression:

Life donation

≤ 3 Mismatches - Standard
≥ 4 Mismatches - additional Simulect® Induction

Immunsuppression:

„Old for Old“ (donor and recipient ≥65a)

Open randomized prospective trial
On safety and efficacy of a Sirolimus based immunosuppression in renal recipients in the ET „Senior Program“

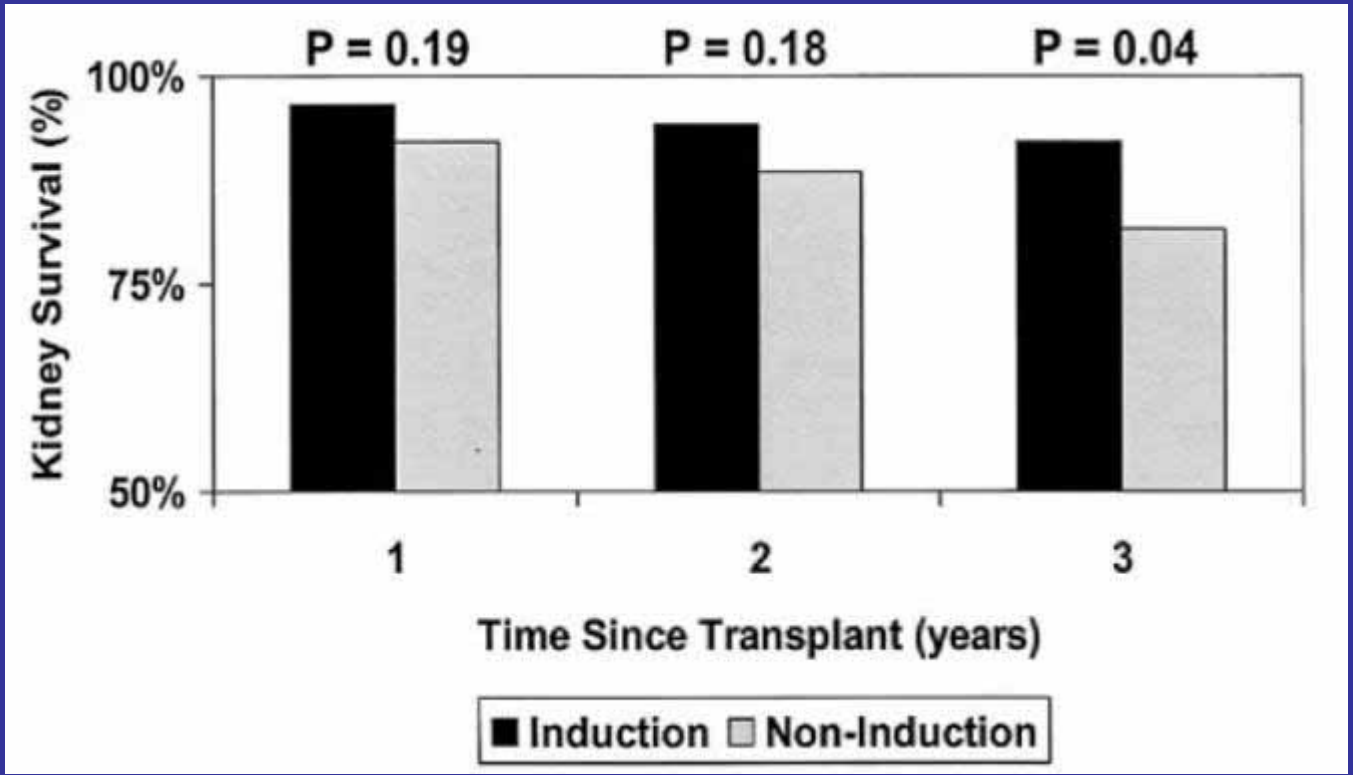
Group 1
Dazlizumab
Sirolimus (10-15ng/ml)
MMF
Steroids

Group 2
Dazlizumab
Sandimmun C2 1000±150 ng/ml
MMF
Steroids

Over the last several years, tacrolimus-mycophenolate mofetil has been the most commonly used discharge regimen for solid-organ transplant recipients, with the exception of intestine and heart recipients. During the same period, the combination of tacrolimus-mycophenolate mofetil was also the most frequently used maintenance regimen at one-year and two-years post-transplant for recipients of most organs.
Antibody-based induction therapy continues to be administered to the majority of kidney and pancreas recipients and to roughly half of intestine and thoracic-organ recipients in 2004.

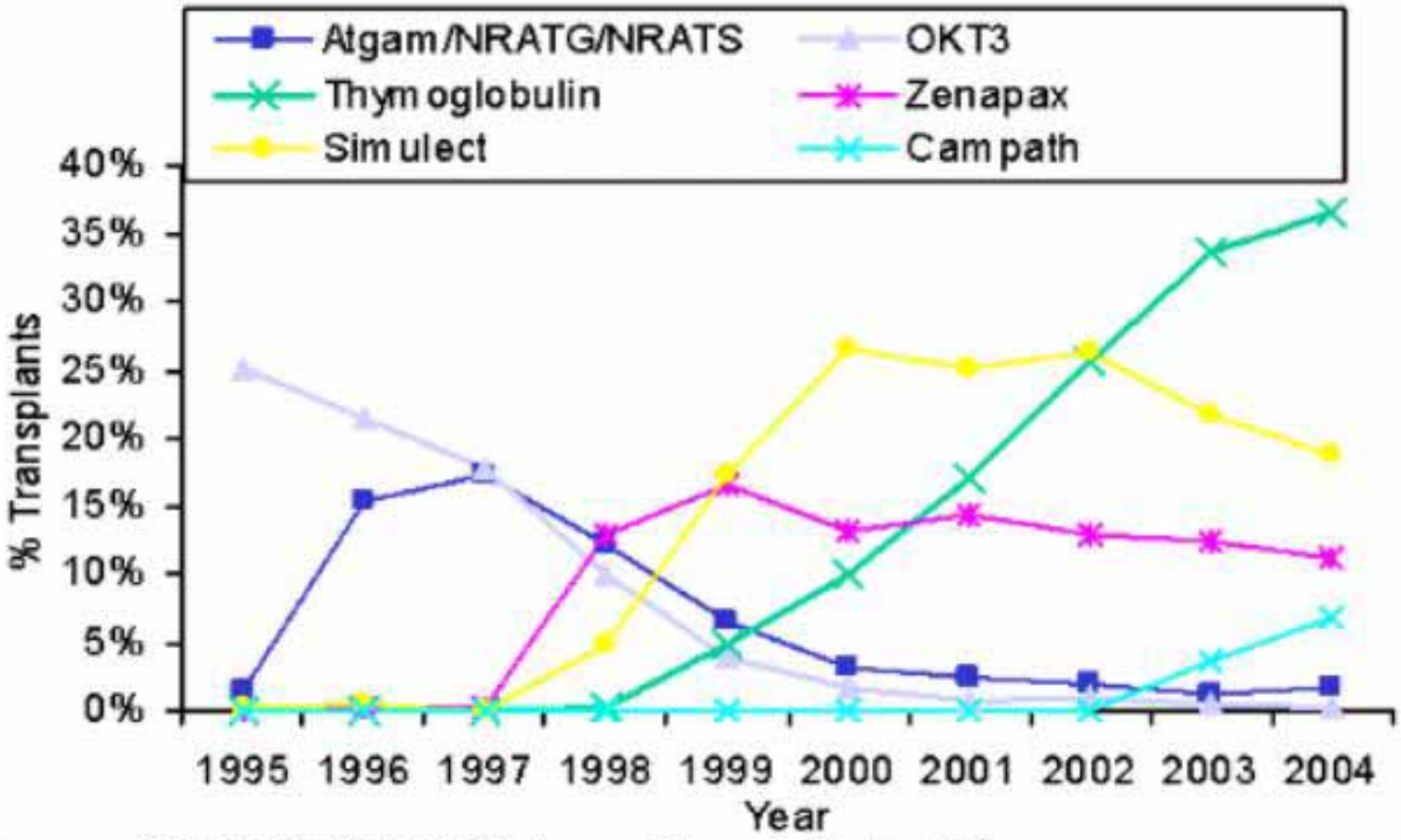
Tokom zadnjih nekoliko godina na otpustu iz bolnice pacijenti imaju takrolimus i Cellcept kao terapijski režim. Indukciona terapija antitijelima se i dalje ordinira većini primalaca bubrega i pankreasa i otprilike pola primalaca crijeva i torakalnih organa.

. Actual kidney survival in induction and noninduction over 3 years.
Methods. A total of 174 SPK transplant recipients were enrolled in a prospective, open-label, multi-center study.
They were randomized to induction (n=87) or non-induction (n=87) groups and followed for 3 years.



Burke G et al. Transplantation: 77(8) 27 April 2004 pp 1269-1275

Figure III-1. Immunosuppression Agents Used for Induction in Kidney Transplantation, 1995-2004



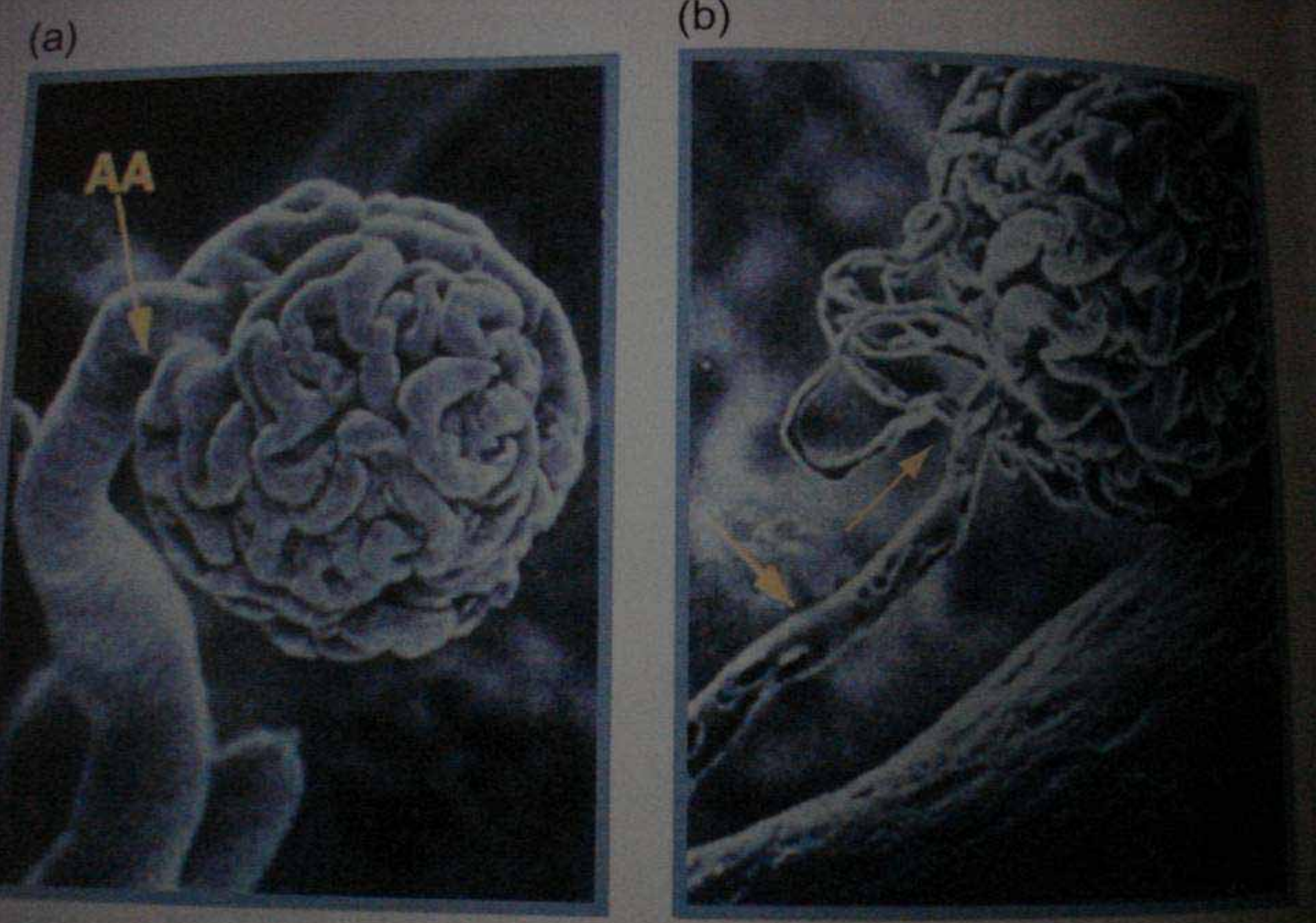
Source: *2005 OPTN/SRTR Annual Report*, Table 5.6a.

Cyclosporin - Neoral

- Prednosti: bolja resorpcija
  bolje iskorištavanje
  lakše uzimanje
  nepostojanje depoa
  manji rizici od akutnog i hroničnog odbacivanja.
- Posebne prednosti su u transplantaciji jetre.

Farmakokinetika u djece

- U djece metabolizam CyS je ubrzan tako da su potrebne veće doze.



gure 9.16. Constriction of the afferent arteriole (AA) in normal (a) versus CsA-treated (b) rat

Doziranje CyS

Vrijeme od transplantacije	Predložena terapijska doza
0 – 2 mjeseca	150-350 ng/ml
2 – 6 mjeseci	100-250 ng/ml
>6 mjeseci	Oko 100 ng/ml

MMF - Cellcept

- Od 1996. u Evropskoj zajednici dio oficijelnog Protokola. Registracija u BiH u martu 2004.
- Inhibira enzim monofosfatdehidrogenazu preko aktivne supstance mikofenoične kiseline, koja smanjuje produkciju gvanozin nukleotida.
- Djeluje selektivno smanjenjem purinskih baza što ima antiproliferativni efekat.

PREDNOSTI CELLCEPTA

- Akutne periode odbacivanja su rijeđe za 60-90 %
- Smanjuje hronicitet za 100% (preživljavanje grafta)
- Smanjuje potrebu za ciklosporinom za 20-30%
- Smanjuje nastanak hipertenzije
- Rijeđe su leukopenije
- Nema toksičnog djelovanjna na jetru
- Jednostavnije doziranje
- Dugotrajna upotreba , odgađanjem hronicitetа odnosno dužim preživljavanjem grafta ga preporučuje kao finansijski pogodnijeg lijeka

Clin Transplant 2003. 17:200-2005

Imunosupresivna terapija održavanja

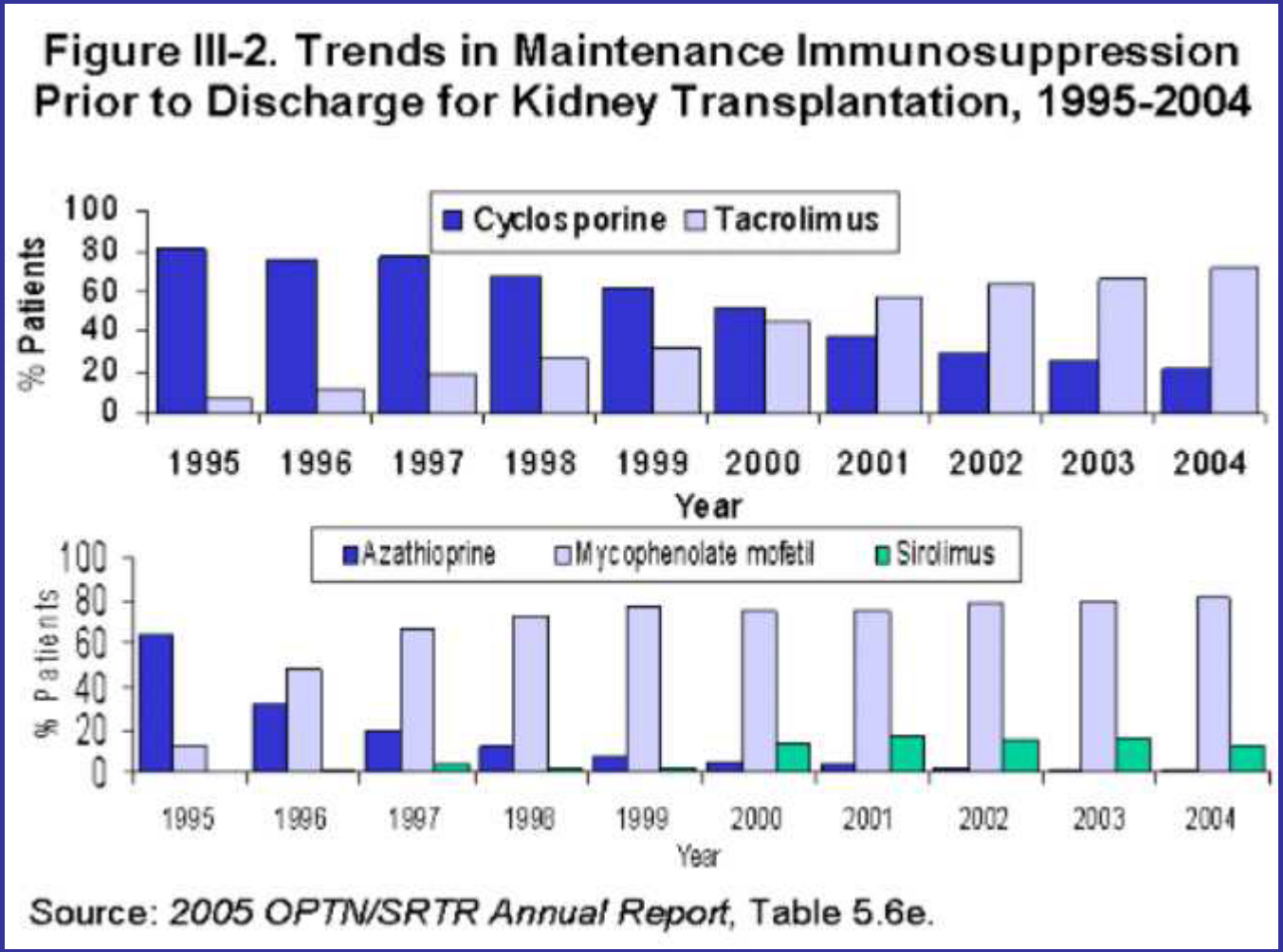
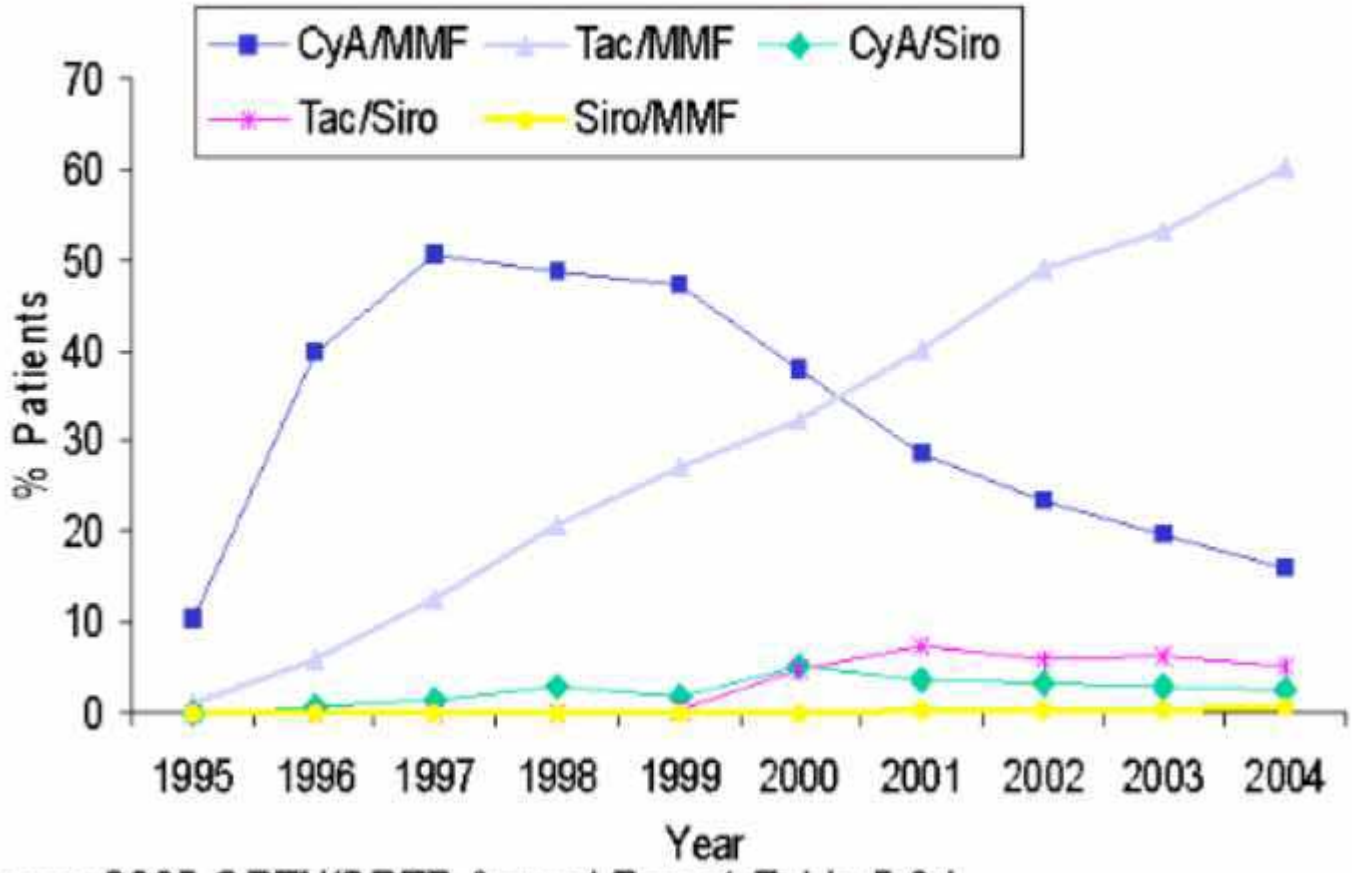
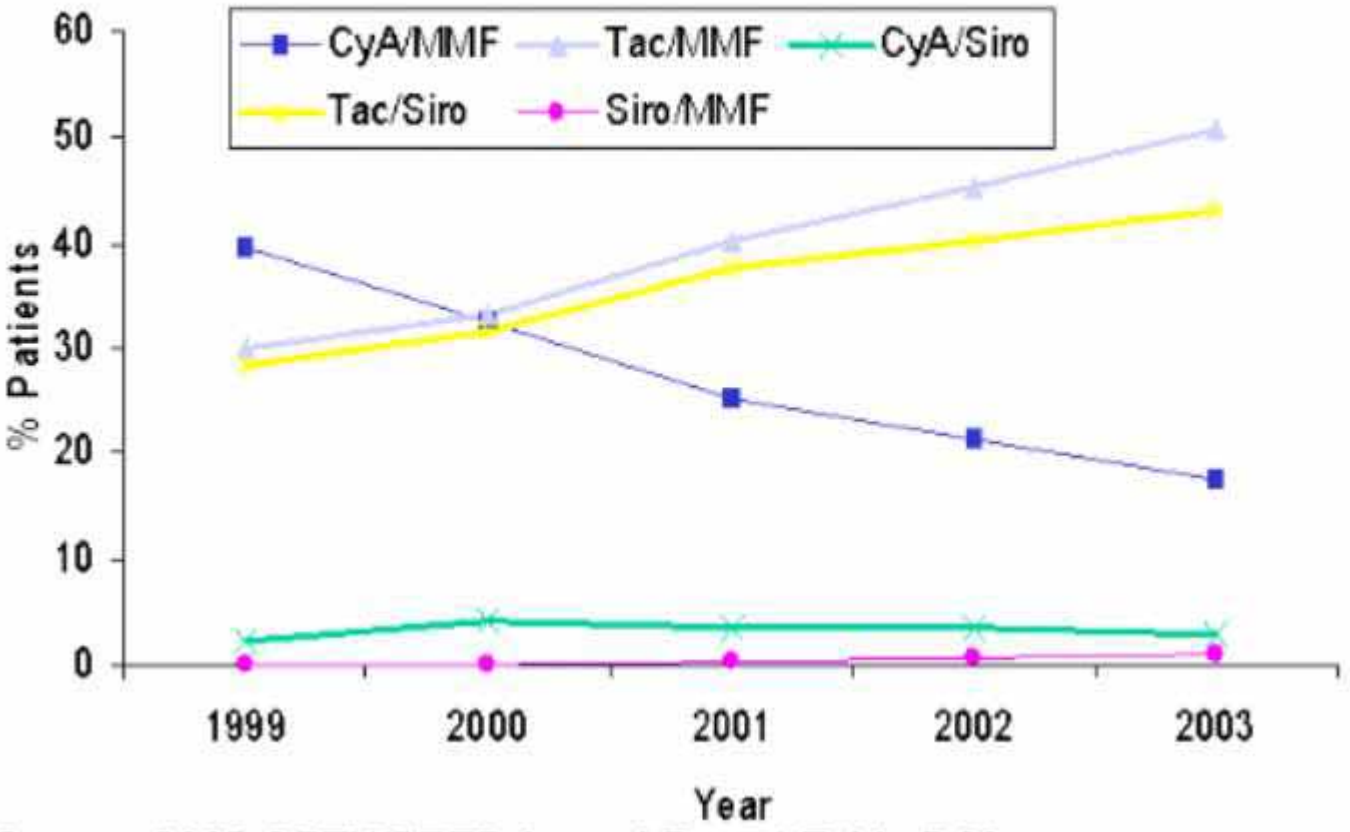


Figure III-3. Trends in Discharge Immunosuppression Regimens for Kidney Transplantation, 1995-2004



Source: *2005 OPTN/SRTR Annual Report*, Table 5.6d.

Figure III-4. Trends in Immunosuppression Maintenance Regimens, One Year Posttransplant for Kidney Transplantation, 1999-2003



Source: *2005 OPTN/SRTR Annual Report*, Table 5.6f.

Steroid Withdrawal and Steroid Avoidance for Kidney Transplantation

Asteroid withdrawal became increasingly established among recipients of a first kidney transplant between 1999 and 2003. In 1999, 4% of patients were taken off steroids by one year following transplantation, compared to 10% in 2003 . At two years a slightly higher proportion of patients who had been on steroids at discharge were no longer receiving them . Steroid withdrawal was slightly more common among living versus deceased donor transplants.

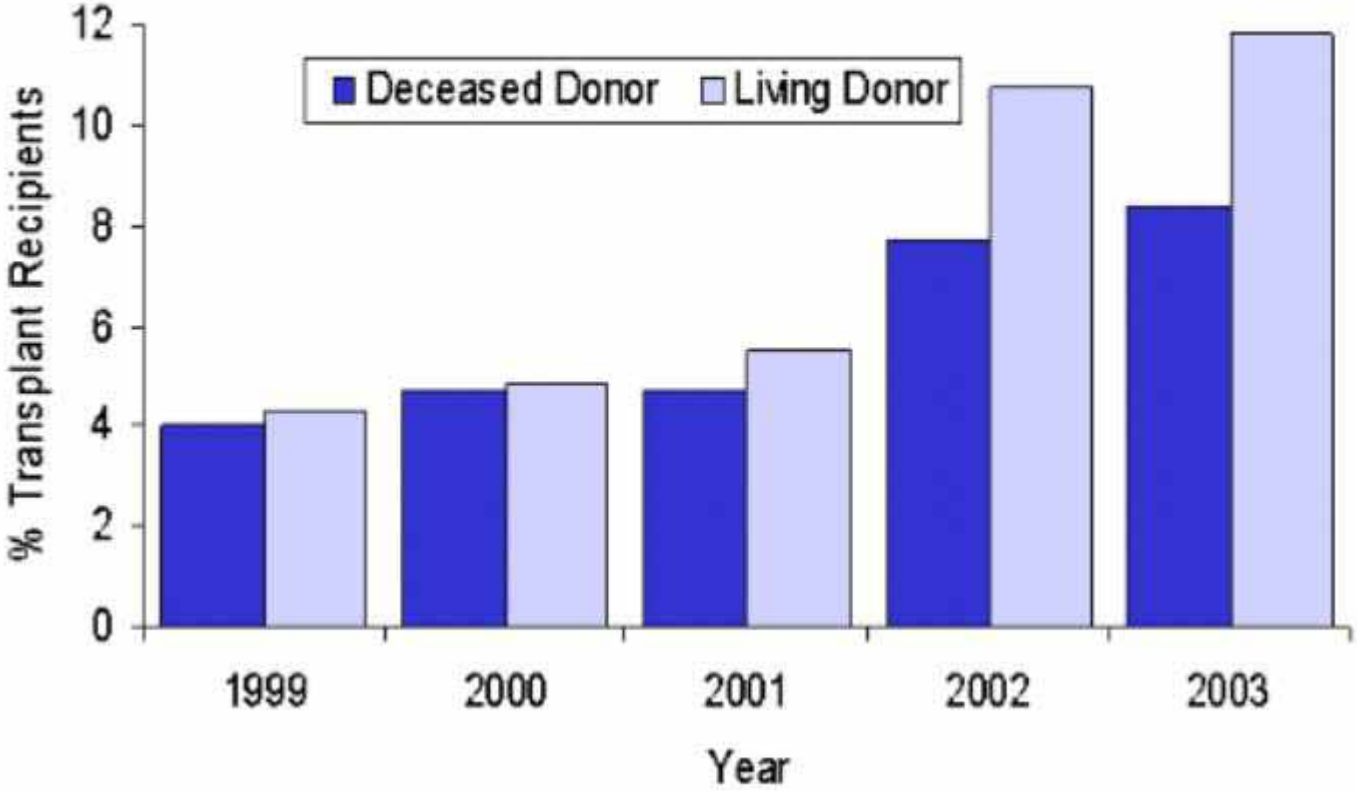
Povlačenje steroida iz postojeće terapije ?
Izbjegavanje ordiniranja steroida uopšte!

Predlaže se samo 6 mjeseci poslije transplantacije upotreba steroida a Kasnije potpuno isključivanje iz terapije

Although corticosteroids are prescribed for the majority of patients, there is an increasing and notable trend toward steroid avoidance and minimization protocols, particularly in abdominal organ transplantation. Since 1999 there has been an increase in steroid withdrawal among first transplant solid organ recipients. There was also a trend toward avoiding the use of steroids altogether (steroid avoidance), as detailed in the organ-specific sections below.
The incidence of acute rejection has declined over the last 10 years, and thus the percentages of patients requiring antirejection treatment have continued to decline. However, there has been an increase in the use of antibody induction for the prophylaxis of acute rejection during the first year following transplantation. This usage ranged from 18% of heart-lung recipients to 77% of pancreas recipients in 2004 This has largely reflected increased utilization of rabbit antithymocyte globulin.

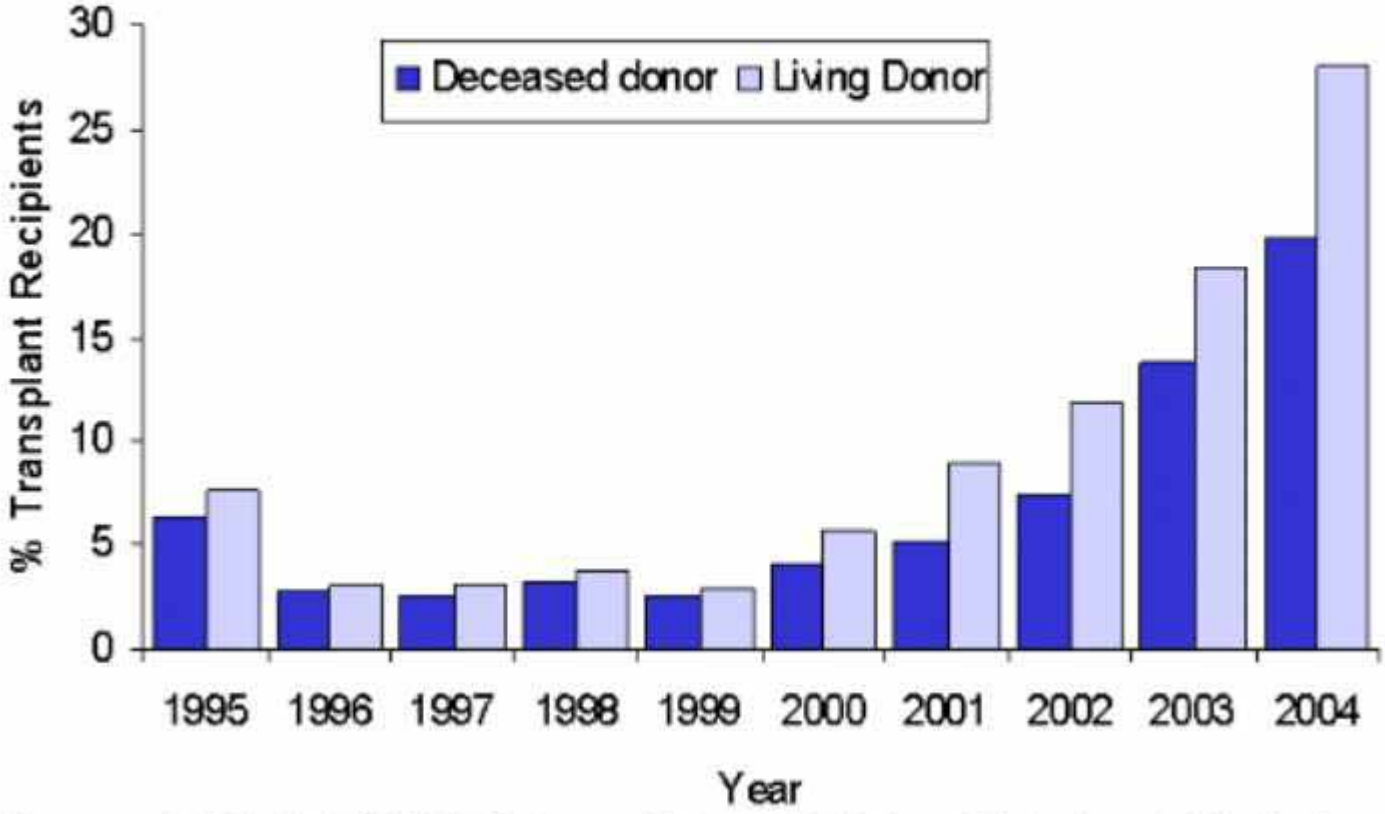
Smanjena upotreba steroida smatra se manje potrebnom jer se upotrebljavanja sve više indukciona terapija u pripremi i postotak akutnih odbacivanja u prvoj godini je značajno manji .

Figure III-5. Steroid Withdrawal Rates at 1 Year Posttransplant for Deceased Donor and Living Donor Kidney Transplants, 1999-2003



Source: *2005 OPTN/SRTR Annual Report*, Tables 15.4a.2 and 15.4b.2.

Figure III-6. Steroid Avoidance Rates for Deceased Donor and Living Donor Kidney Transplants, 1995-2004



Source: *2005 OPTN/SRTR Annual Report*, Tables 15.4a.1 and 15.4b.1.

Maintenance Immunosuppression Before Discharge for Kidney Transplantation

Calcineurin inhibitors were still the cornerstone of immunosuppression in kidney transplantation in 2004: 93% of patients received them as part of their discharge regimen **Tacrolimus is the calcineurin inhibitor of choice and its use continues to grow, with 72% of patients treated with tacrolimus at discharge versus only 21% with cyclosporine.** The use of mycophenolate mofetil, the most frequently used antiproliferative agent, is also still increasing, with 81% of patients discharged on mycophenolate mofetil. Since a peak of 17% in 2001, the use of sirolimus (rapamycin) has declined. In 2004, only 12% of patients were discharged on regimens containing sirolimus.

Rejection:

- If ‚Rejection can firmly be diagnosed on clinical Symptoms:
(Urin Volume↓ Krea, Temperature und Body weight↑
Biopsy not necessary

- In DGF protocoll biopsy between day 4 and 7

- Biopsy ultrasound guided

Therapy

BANFF Kategories:
0: bzw. "borderline": No therapy
1: 3 x 100 mg Fortecortin for 3 days, switch to FK506
2 +3: or Persistence (Re biopsy) ATG Kurs, switch auf FK506

Rejection

	BORDERLINE	BANFF I	BANFF II	
C0 (n= 82)	2,27%	12,5%	7,95%	∑ 20,45%
C2 (n=83)	2,24%	4,49%	7,86%	∑ 12,35%

$P < 0,0044$

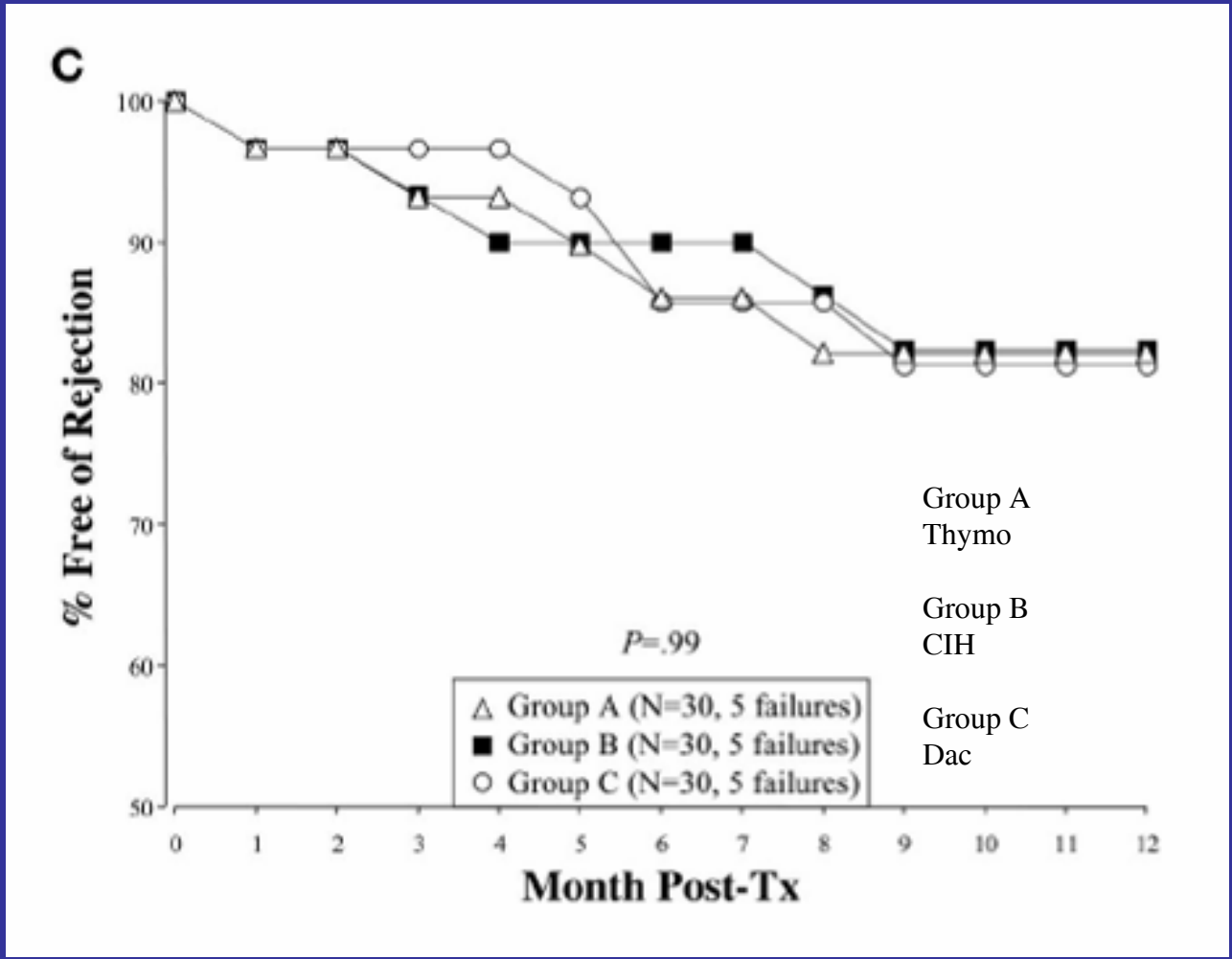
Birsan et al Transplantation 2005 in press

Antirejection Treatment for Kidney Transplantation

The percentage of patients treated for acute rejection has continued to decrease. Only 13% of all patients who received a kidney in 2003 were reported to have been treated for acute rejection during the first year following transplantation The rise in antibody treatment largely reflects increased use of antithymocyte globulin (rabbit) for antirejection (31% of antirejection treatments in 2003, up from 24% in 2002).

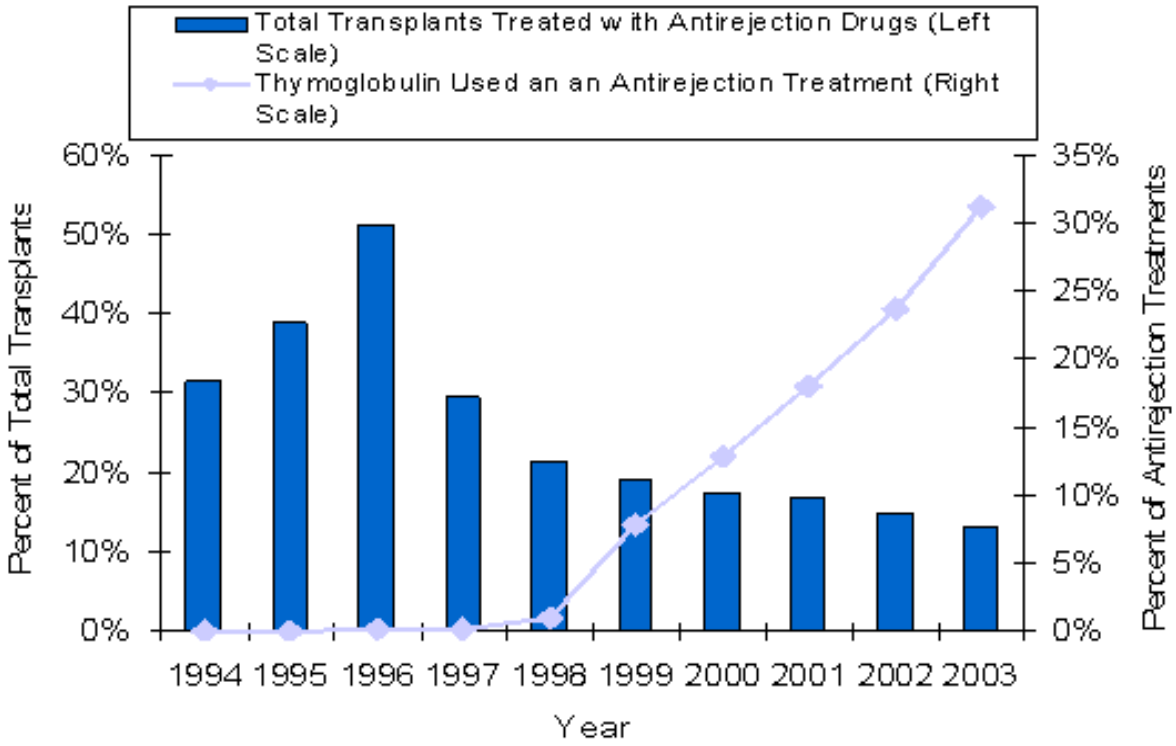
Corticosteroids remain a principal element of rejection treatment even though their use declined slightly. In 2003, 72% of patients requiring antirejection treatment received steroids, down from 80% the previous year.

Biopsiegesicherte Akute Abstoßungen (BCAR)



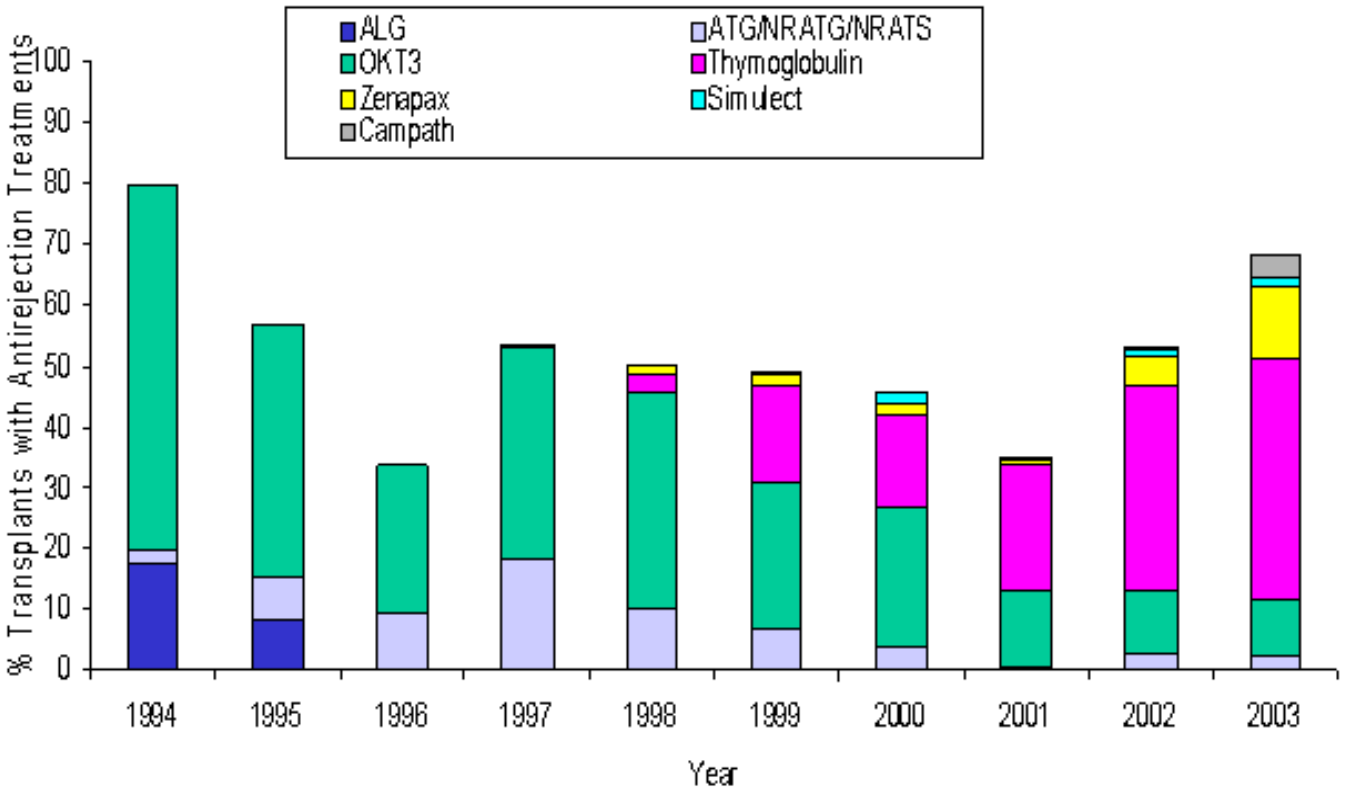
Ciancio G et al. Transplantation: 80: 2005 pp 457-465

Figure III-8. Percentage of Kidney Transplants with Antirejection Treatments and Thymoglobulin Used as an Antirejection Treatment, by Year, 1994-2003



Source: *2005 OPTN/SRTR Annual Report*, Table 5.6i.

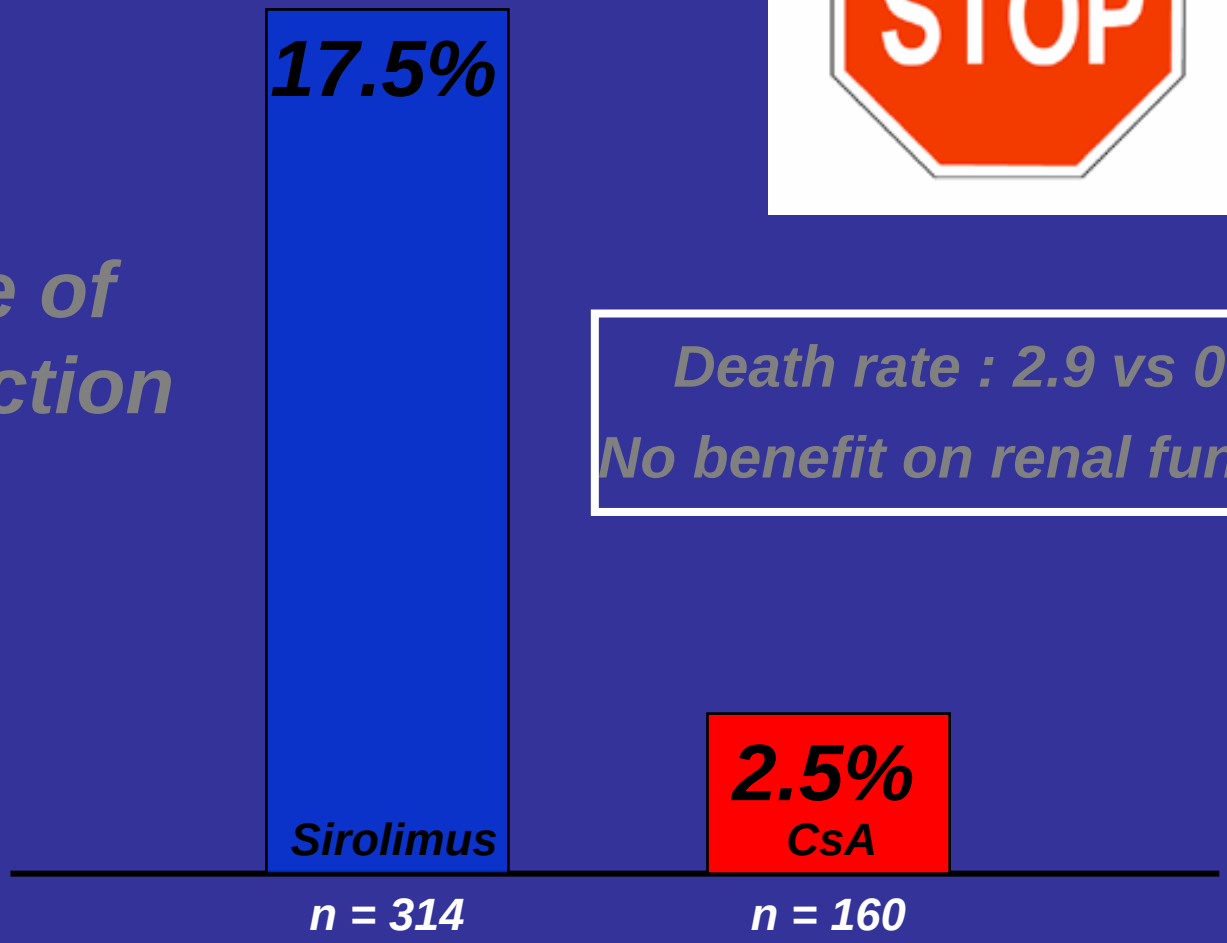
Figure III-15. Trends in Antibody Therapy for Rejection Episodes in First Year Following Simultaneous Kidney-Pancreas Transplantation, 1994-2003



Source: *2005 OPTN/SRTR Annual Report*, Table 8.6i.

Study 318

Incidence of acute rejection



Death rate : 2.9 vs 0.6%

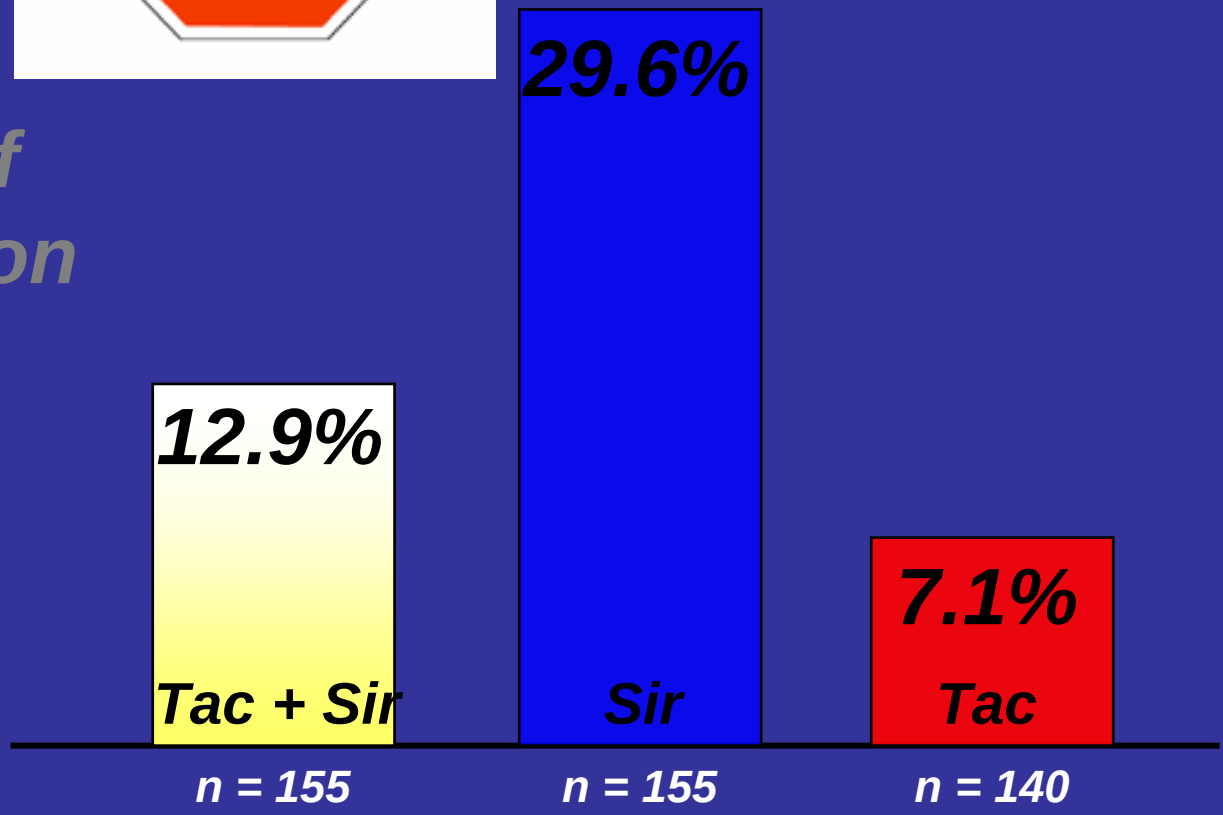
No benefit on renal function

Study Orion

Death rate : 2.6 - 5.2 - 2.9%

No benefit on renal function

Incidence of acute rejection

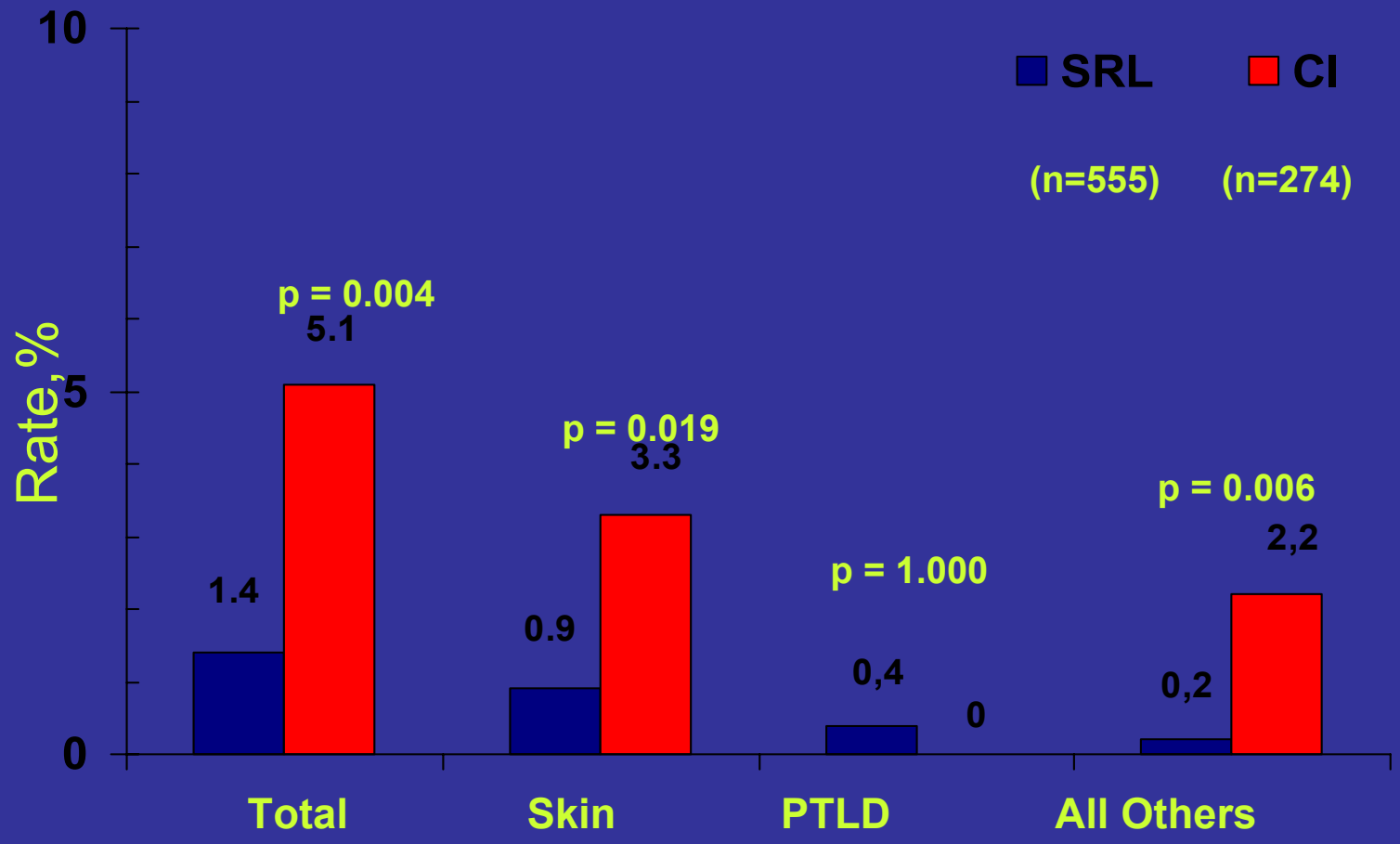


IAS & Rituximab in ABO-incompatible live donor renal transplantation

- 14 recipients (blood groups O, A and B)
  - donors A1, A2, A2B and B
- Specific anti-A/B antibody immunoadsorption (IA)
  - all recipients received 3–6 treatments pre-operatively; 11 received postoperative IA
- Pre-operative anti-CD20 treatment (8 recipients)
- Pre-operative MMF
- Steroids/tacrolimus at transplantation
- Total graft survival 13/14 (observation 2–41 months)
  - one B graft lost; recipient received no anti-CD20
- No significant side-effects of IA

Norden *et al. Xenotransplantation* 2006;13:148–153

Significantly Lower Malignancy Rates



Main Results of Symphony (at 12 months post-Tx)

	GFR [ml/min]* (Cockcroft-Gault)		BPAR (excl. borderline)		Graft Survival (death censored)	
	N	Mean ± SD	N	% of patients	N	% of patients
Normal-dose CsA	388	57.1 ± 25.2	390	25.8	390	91.9
Low-dose CsA	398	59.4 ± 25.1	399	24.0	399	94.3
Low-dose TAC	399	65.4 ± 27.1	401	12.3	401	96.4
Low-dose SRL	399	56.7 ± 26.9	399	37.2	399	91.7

Patient survival was comparable between all groups (96.5 – 98.2%)

ITT population *GFR: with imputation 10ml/min and LOCF (last observation carried forward)

Ekberg H et al WTC 2006

Maintenance Immunosuppression One and Two Years Following Kidney Transplantation

Tacrolimus-mycophenolate mofetil is also the most frequently used maintenance immunosuppression combination at one and two years following transplantation, and its prevalence for maintenance use has increased in recent years *[* **At one year after transplantation in 2003, 51% of patients were receiving tacrolimus-mycophenolate mofetil, 17% were receiving cyclosporine-mycophenolate mofetil, 8% tacrolimus-sirolimus, and 1% sirolimus-mycophenolate mofetil** .Both the tacrolimus-sirolimus and the sirolimus-mycophenolate mofetil regimens were more prevalent at one and two years after transplant than at discharge, indicating a significant switch toward these combinations after transplant. Surprisingly, at one year about 7% and at two years about 2% of patients were receiving tacrolimus alone, compared to about 4% at discharge. All of these percentages refer to medication regimens regardless of steroids, meaning that most of the patients were on steroids in addition to the indicated regimens.

Tacrolimus versus ciclosporin as primary immunosuppression for kidney transplant recipients: meta-analysis and meta-regression of randomised trial data

Angela C Webster, Rebecca C Woodroffe, Rod S Taylor, Jeremy R Chapman, Jonathan C Craig

What is already known on this topic

Both tacrolimus and ciclosporin improve graft survival, but tacrolimus reduces acute rejection in kidney transplant recipients more than ciclosporin does

---

Tacrolimus is associated with more diabetes and neurotoxicity but less hypertension, dyslipidaemia, and cosmetic side effects than ciclosporin

What this study adds

Tacrolimus improves graft survival compared with ciclosporin, with a 44% reduction in graft loss (censored for death) within six months after transplantation

---

Tacrolimus doubles risk of new diabetes mellitus requiring insulin compared with ciclosporin

---

Graft survival is maximised and risk of diabetes minimised when tacrolimus target concentrations are < 10 ng/ml over the first year after transplantation.

Webster A *et al. BMJ* 2005,331:810-821

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PROSPECTIVE, RANDOMIZED TRIAL OF THE EFFECT OF ANTIBODY INDUCTION IN SIMULTANEOUS PANCREAS AND KIDNEY TRANSPLANTATION: THREE-YEAR RESULTS[1]

George W. Burke III,[2,22] Dixon B. Kaufman,[3] J. Michael Millis,[4] A. Osama Gaber,[5] Christopher P. Johnson,[6] David E. R. Sutherland,[7] Jeffrey D. Punch,[8] Barry D. Kahan,[9] Eugene Schweitzer,[10] Alan Langnas,[11] James Perkins,[12] John Scandling,[13] Waldo Concepcion,[14] Mark D. Stegall,[15] James A. Schulak,[16] Paul F. Gores,[17] Enrico Benedetti,[18] Gabriel Danovitch,[19] Alice K. Henning,[20] Marilyn R. Bartucci,[21] Sarah Smith,[21] and William E. Fitzsimmons[21]

Background. Historically, antibody induction has been used because of the higher immunologic risk of graft loss or rejection observed in simultaneous pancreas and kidney (SPK) transplantation compared with kidney transplantation alone. This trial was designed to assess the effect of antibody induction in SPK transplant recipients receiving tacrolimus, mycophenolate mofetil, and corticosteroids. Induction agents included T-cell–depleting and interleukin-2 receptor antibodies.

Methods. A total of 174 SPK transplant recipients were enrolled in a prospective, open-label, multicenter study. They were randomized to induction (n=87) or non-induction (n=87) groups and followed for 3 years.

Results. At 3 years, actual patient (94.3% and 89.7%) and pancreas (75.9% and 75.9%) survivals were similar between the induction and non-induction groups, respectively. Actual kidney survival was similar at 1 and 2 years, but at 3 years, it was significantly better in the induction group compared with the non-induction group (92% vs. 81.6%; P=0.04). At 3 years, median serum creatinine and hemoglobin A1C were similar between the induction and non-induction groups (1.26 mg/dL and 1.20 mg/dL, 5.4% and 5.5%, respectively). Three-year cumulative incidence of biopsy-confirmed, treated acute kidney rejection in the induction and non-induction groups was 19.5% and 27.5% (P=0.14), respectively, with odds 4.6 times greater in African Americans regardless of treatment (P=0.004). Significantly higher rates of cytomegalovirus (CMV) viremia and CMV syndrome occurred in those receiving T-cell–depleting antibody induction (26.1%) when compared with those receiving anti-interleukin-2 receptor antibodies (2%) and non-induction (8.1%) (P<0.0001).

Conclusions. Tacrolimus, mycophenolate mofetil, and corticosteroids resulted in excellent safety and efficacy in SPK transplant recipients. Actual 3-year kidney survival was significantly better in the induction group; however, CMV viremia and CMV syndrome rates were significantly higher in the T-cell–depleting antibody group. African Americans demonstrated a significantly greater risk of acute rejection despite antibody induction. Decisions regarding the use of induction therapy must weigh the risk of kidney graft loss or rejection against the risk of infection.

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[1] Poster presentation at the American Transplant Congress, May 2003.

[2] Department of Surgery, University of Miami, Miami, Florida.

[3] Transplant Division, Feinberg School of Medicine at Northwestern University, Chicago, Illinois.

[4] Department of Surgery, University of Chicago, Chicago, Illinois.

[5] Department of Surgery, University of Tennessee at Memphis, Memphis, Tennessee.

[6] Department of Surgery, Medical College of Wisconsin, Milwaukee, Wisconsin.

[7] Department of Surgery, University of Minnesota, Minneapolis, Minnesota.

[8] Department of General Surgery, University of Michigan Medical Center, Ann Arbor, Michigan.

[9] Department of Surgery, University of Texas, Houston, Texas.

[10] Department of Surgery, University of Maryland, Baltimore, Maryland.

[11] Department of Surgery, University of Nebraska, Omaha, Nebraska.

[12] Department of Surgery, University of Washington, Seattle, Washington.

[13] Kidney Transplant Program, Stanford University, Stanford, California.

[14] Department of Surgery, Loma Linda University, Loma Linda, California.

[15] Department of Surgery, Mayo Clinic, Rochester, Minnesota.

[16] Department of Surgery, University Hospitals of Cleveland,

OVERVIEW

Alemtuzumab (Campath-1H): A Systematic Review in Organ Transplantation

Peter J. Morris,[1] and Neil K. Russell[1,2]

Alemtuzumab (Campath-1H) is a powerful antilymphocyte antibody that produces profound and long-lasting lymphopenia. It is being used with increasing frequency for induction in organ transplantation, with the aim of allowing steroid-free and/or calcineurin-free/sparing maintenance immunosuppressive protocols. Despite a considerable experience with this agent, mostly in kidney transplantation, there are only two relatively small randomized controlled trials available, and therefore the level of evidence for its role in transplantation is limited. Nevertheless, it does appear that the incidence of acute rejection is low after induction with alemtuzumab, perhaps if used with a calcineurin inhibitor, and that steroid-free and calcineurin-sparing protocols are possible. Although there is a profound and long-lasting T cell lymphopenia after administration of alemtuzumab, there is no apparent increase in infection, posttransplantation lymphoproliferative disease, or other side effects, other than perhaps autoimmune disease. Whether alemtuzumab is more effective than Thymoglobulin or anti-interleukin 2 receptor antibodies cannot be answered at this time. However from a cost aspect, the use of alemtuzumab for induction compares more than favorably with other lymphocyte-depleting agents. Alemtuzumab is an attractive agent for induction in organ transplantation, but there is a need for more and larger randomized trials with long-term follow-up before its true role can be established, particularly with respect to safety.

Keywords: Alemtuzumab, Campath, Monoclonal antibodies, Rejection

(Transplantation 2006;81: 1361–1367)

Alemtuzumab (Campath-1H; Berlex, Montville, NJ) is a humanized rat monoclonal antibody (rat immunoglobulin [Ig] G2b) directed against the CD52 antigen, which is expressed on all blood mononuclear cells and also on cells lining the male reproductive tract. It is a powerful cytolytic agent and has been used therapeutically in bone marrow transplantation, several autoimmune diseases, and organ transplantation. Although it was first used in organ transplantation in 1998 to prevent rejection and is being used with increasing frequency as induction therapy in many institutions, there is a paucity of good quality evidence that would allow its role in organ transplantation to be established.

For the purposes of this review, we systematically searched the literature with use of Medline, Embase, and the Cochrane Library as well as hand-searching conference proceedings for relevant abstracts published before March 2006. Herein we will briefly discuss the development of the Campath antibodies and the mechanism of action of alemtuzumab, and we will review in some detail the clinical data that are available. Although quite extensive, this is mostly in the form of retrospective reports of noncontrolled studies in the prevention and treatment of rejection across the whole spectrum of organ transplantation, with most of the data arising from the use of alemtuzumab in kidney transplantation. There are only two randomized controlled trials of alemtuzumab in the literature, and only 50 patients in total received this new agent in these trials. Attention is also given to adverse events, especially infection, in view of the profound and long-lasting lymphopenia produced by alemtuzumab.

THE CAMPATH ANTIBODIES AND ALEMTUZUMAB

The first Campath antibodies were created from rat hybridomas in an attempt to produce antibodies that would lyse lymphocytes in the presence of a human complement (*1*). All these antibodies were directed against the same antigen, now known as the CD52 antigen. The first antibody was a rat IgM antibody (Campath-1M) that resulted in only a transient

[1] Centre for Evidence in Transplantation, Royal College of Surgeons of England and London School of Hygiene & Tropical Medicine, University of London, London, UK.

Kidney Transplant Recipients: A Systematic Review and Meta-Analysis of Randomized Trials

Angela C. Webster,[1,2,3] Vincent W. S. Lee,[2] Jeremy R. Chapman,[2] and Jonathan C. Craig[1,3]

Background. Target of rapamycin inhibitors (TOR-I) have a novel mode of action but uncertain clinical role. We performed a systematic review of randomized trials where immunosuppressive regimens containing TOR-I were compared with other regimens as initial therapy for kidney transplant recipients.

Methods. Databases (inception, June 2005) and conference proceedings (1996–2005) were searched. Two independent reviewers assessed trials for eligibility and quality. Results at 1 year, are expressed as relative risk (RR), where values <1 favor TOR-I, or lower dose of TOR-I, and for continuous outcomes are expressed as weighted mean difference (WMD), both expressed with 95% confidence intervals (CI).

Results. Thirty-three trials (142 reports) were included (27 trials of sirolimus, 5 of everolimus, and 1 of head-to-head comparison). When TOR-I replaced calcineurin inhibitors (CNI) (8 trials with 750 participants), there was no difference in acute rejection (RR, 1.03; 95% CI, 0.74–1.44), but serum creatinine was lower (WMD, −18.31 μmol/L; 95% CI, −30.96 to −5.67) and bone marrow more suppressed (leukopenia: RR 2.02; 95% CI, 1.12–3.66; thrombocytopenia: RR, 6.97; 95% CI, 2.97–16.36; and anaemia: RR, 1.67; 95% CI, 1.27–2.20). When TOR-I replaced antimetabolites (11 trials with 3966 participants), acute rejection and cytomegalovirus infection (CMV) were reduced (RR, 0.84; 95% CI, 0.71–0.99; RR, 0.49; 95% CI, 0.37–0.65, respectively), but hypercholesterolemia was increased (RR, 1.65; 95% CI, 1.32–2.06). When low- was compared with high-dose TOR-I, with equal CNI dose (10 trials with 3,175 participants), rejection was increased (RR, 1.23; 95% CI, 1.06–1.43) but calculated glomerular filtration rate (GFR) higher (WMD, 4.27 mL/min; 95% CI, 1.12–7.41), and when lower-dose TOR-I and standard-dose CNI were compared with higher-dose TOR-I and reduced CNI, acute rejection was reduced (RR, 0.67; 95% CI, 0.52–0.88), but calculated GFR was also reduced (WMD, −9.46 mL/min; 95% CI, −12.16 to −6.76). There was no significant difference in mortality, graft loss, or malignancy risk for TOR-I in any comparison.

Conclusions. TOR-I have been evaluated in four different primary immunosuppressive algorithms: as replacement for CNI and antimetabolites, in combination with CNI at low and high doses, and with a variable dose of CNI. Generally, surrogate endpoints for graft survival favor TOR-I (lower risk of acute rejection and higher GFR), and surrogate endpoints for patient outcomes are worsened by TOR-I (bone marrow suppression and lipid disturbance). Long-term hard-endpoint data from methodologically robust randomized trials are still required.

(*Transplantation* 2006;81: 1234–1248)

Webster A *et al. Transplant 2006;81: 1234–1248*

The EliTE- (Efficacy Limiting Toxicity Elimination) Symphony Study

International Council on Harmonization (ICH) guidelines

Open label study with 4 parallel arms:

- **Group A (control -- standard immunosuppression)**
  MMF + normal dose cyclosporine + corticosteroids

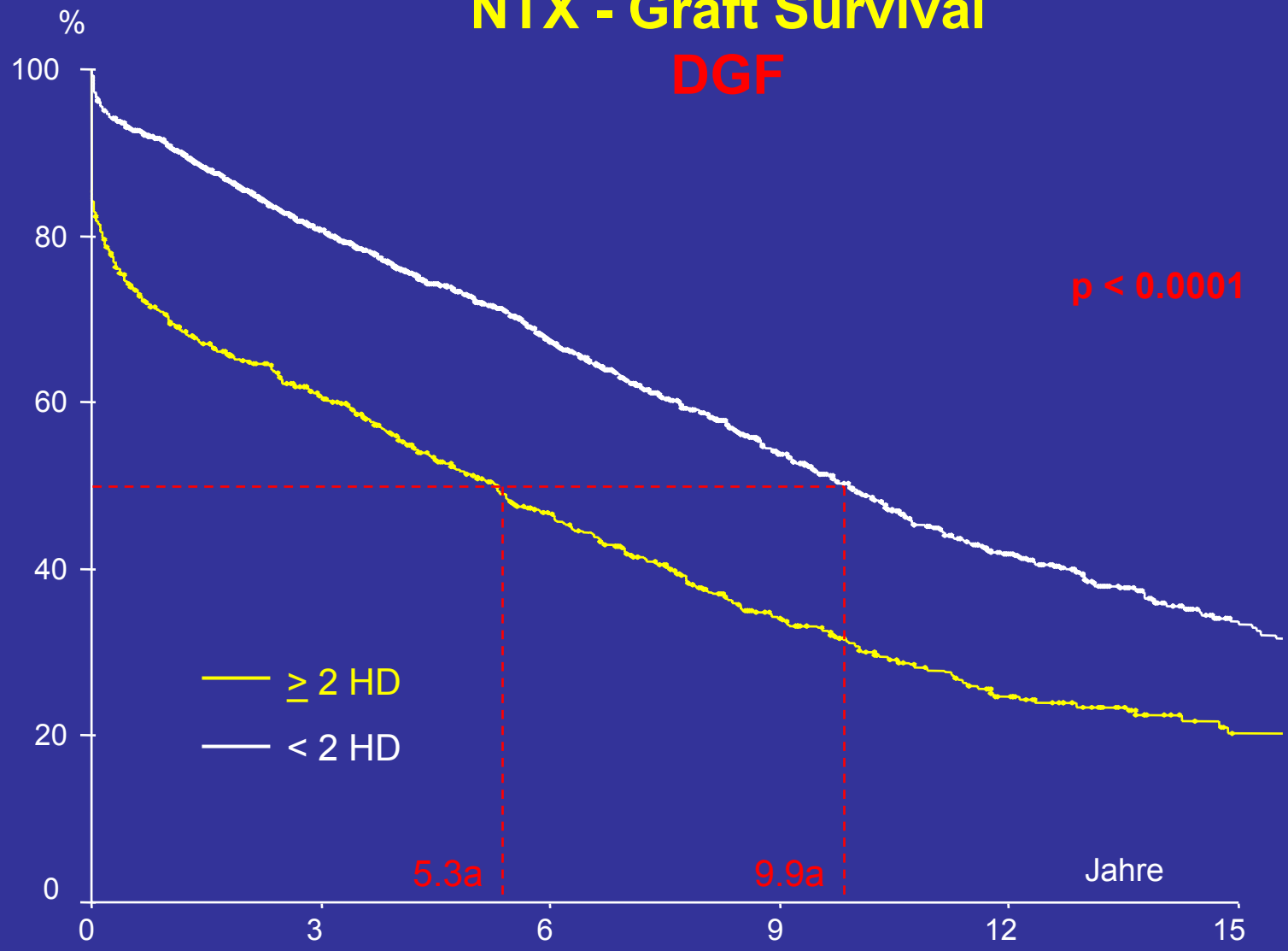
- **Group B**
  daclizumab + MMF + low dose cyclosporine + corticosteroids

- **Group C**
  daclizumab + MMF + low dose tacrolimus + corticosteroids

- **Group D**
  daclizumab + MMF + low dose sirolimus + corticosteroids

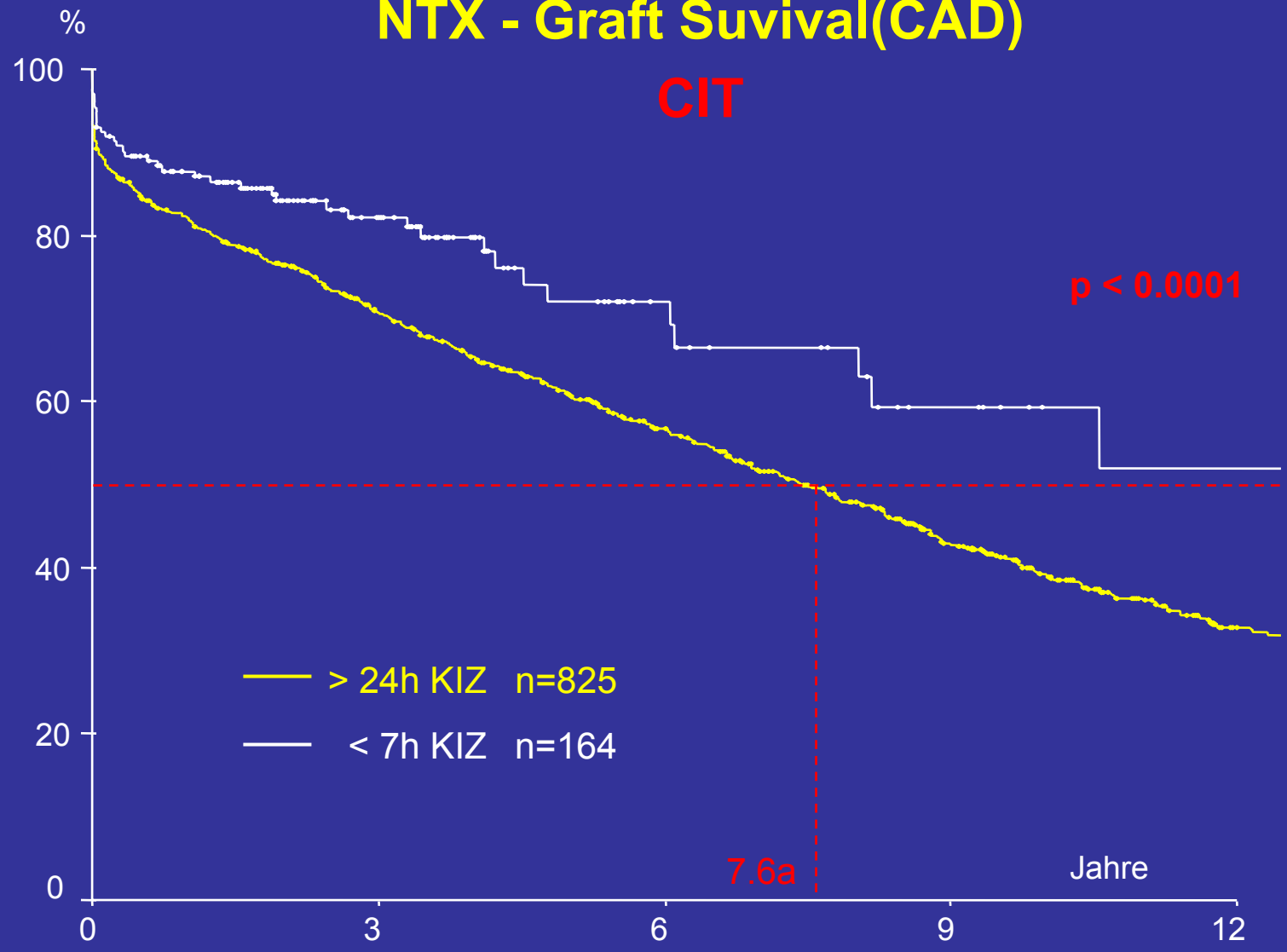
Eckberg H *et al. Am J Transplant* 2006

NTX - Graft Survival
DGF

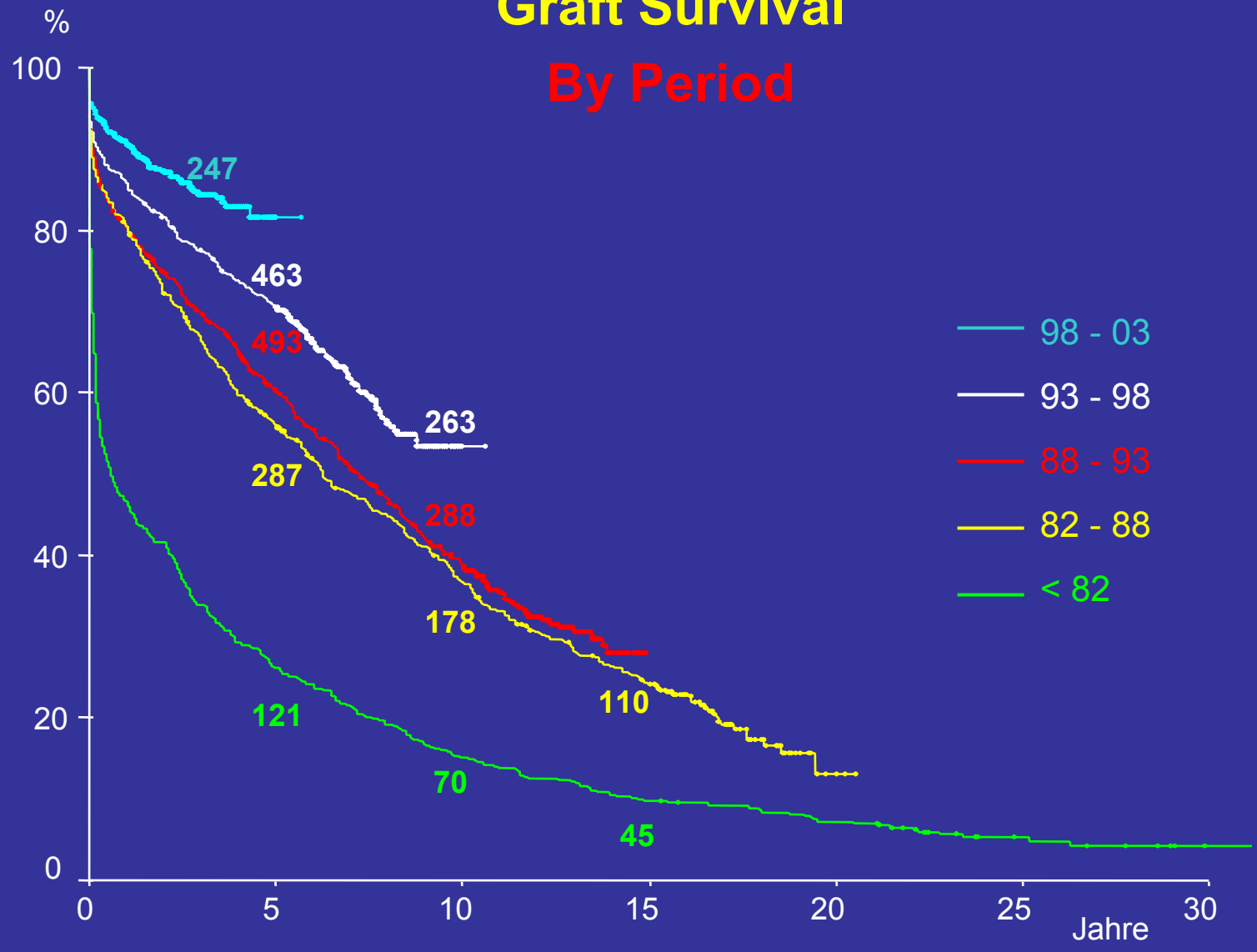


NTX - Graft Suvival(CAD)

CIT



Graft Survival
By Period



Imunosupresivna terapija u Bosni i Hercegovini

- Imamo sve bitnije imunosupresive lijekove
- Tendencija je da ostaje kombinacija CyS A i MMF
- Svi praktičari primjenjuju bar minimalne doze steroida
- MMF je u većini protokola
- MMF i Imuran preživljavanje isto ali su odbacivanja značajno reducirana
- Prograf se sve više preferira (zastupljen) u terapiji
- Nema protokola /ne treba primjenjivati/ sa monoterapijom

Kakav je tumorski efekat imunosupresije ? - oprez u primjeni

Preventivne i redovne sistematske kontrole

Eksperimentalna faza i skora budućnost

SIROLIMUS

CAMPATH

FLY

TOR

Uticaj sponzora je prisutan i agresivan