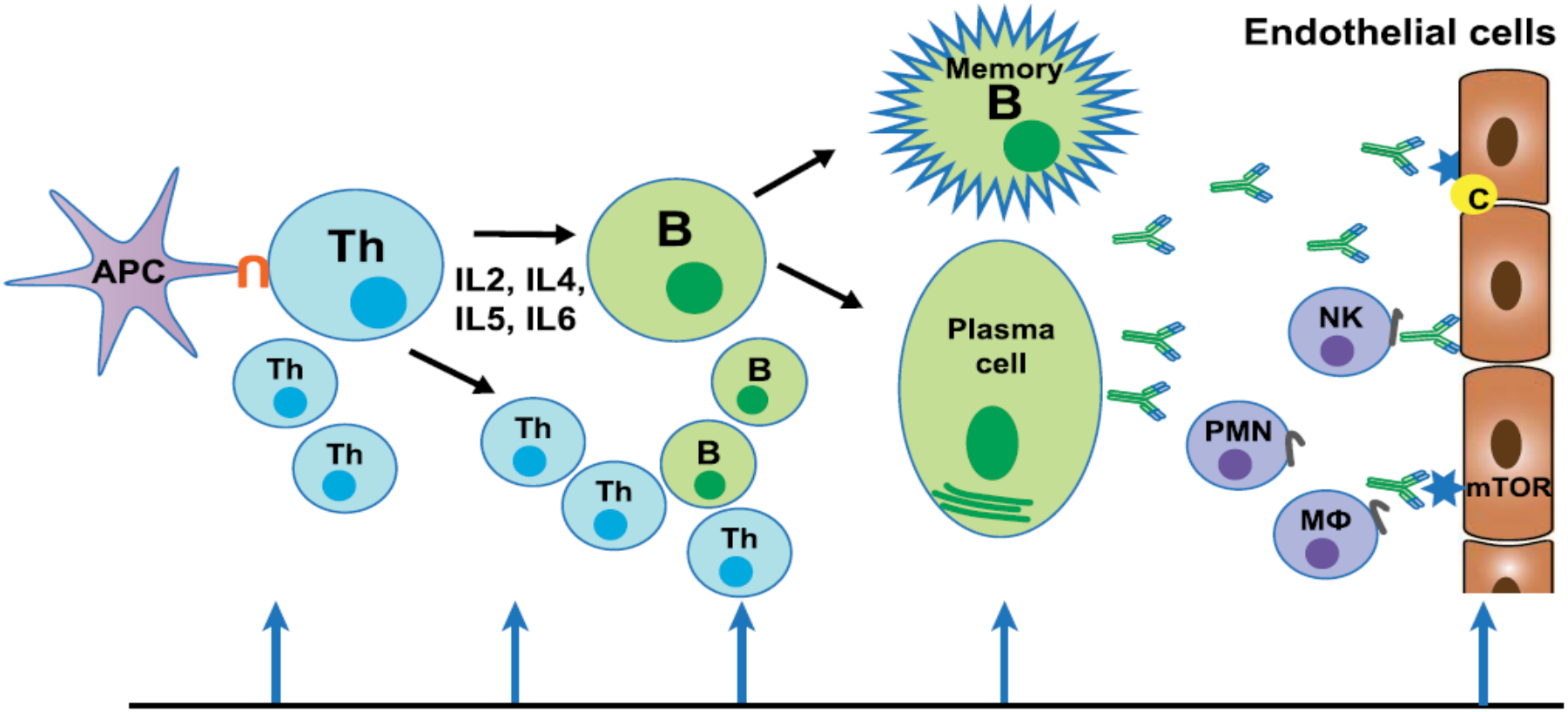
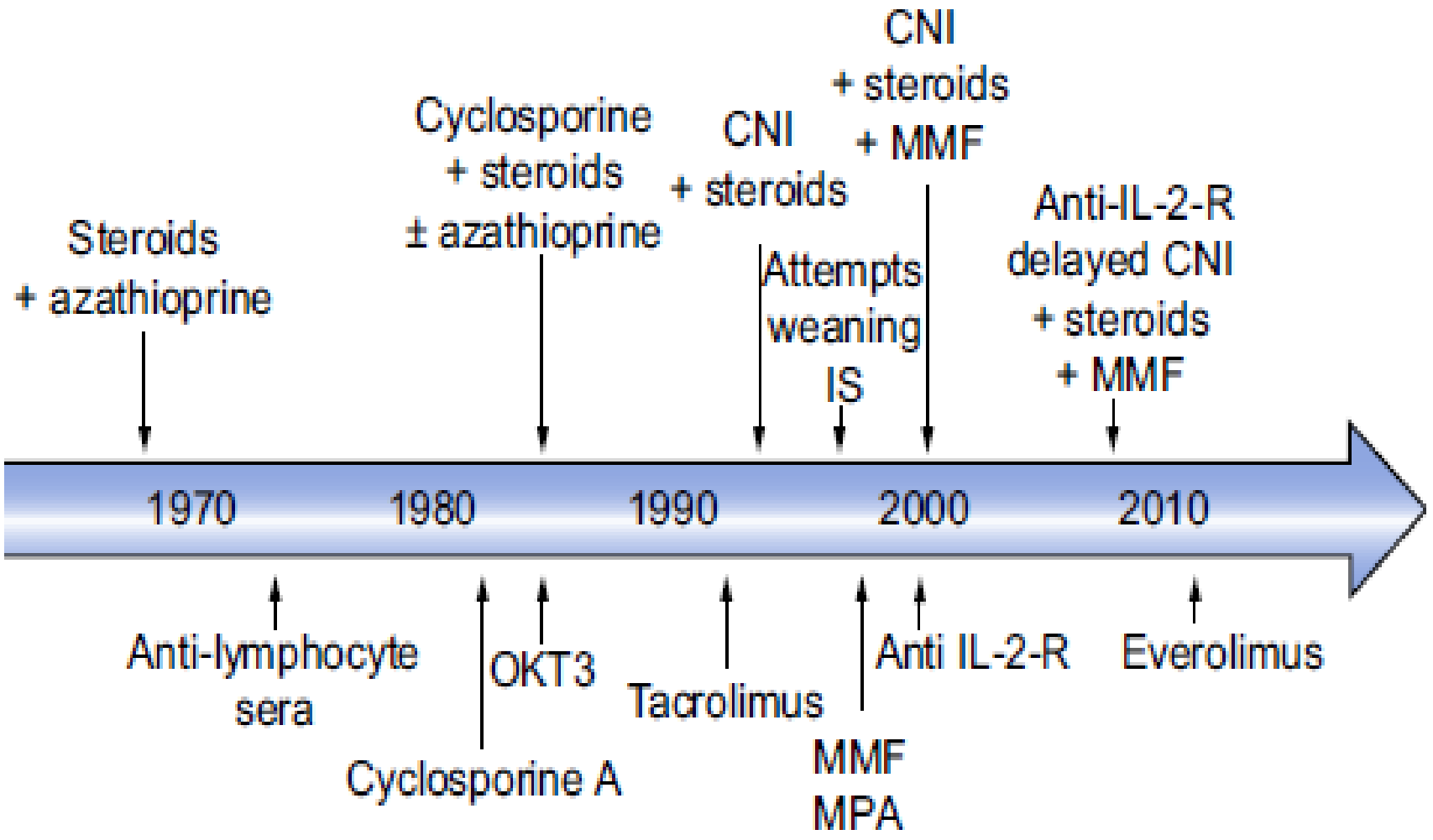
Immunosuppressive strategies in transplantation

Ryszard Grenda

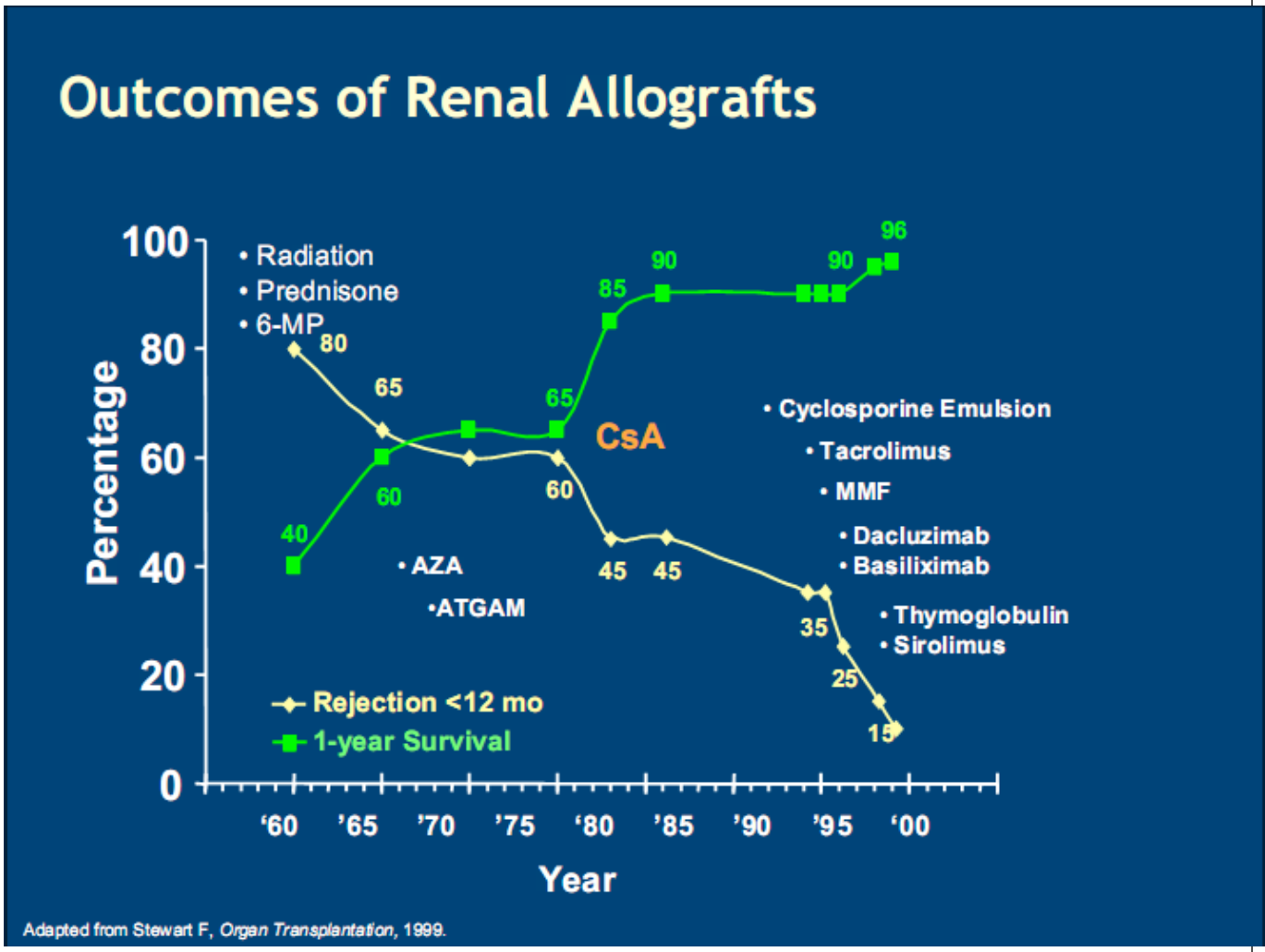
Belatacept	rATG Alemtuzumab	Rituximab Alemtuzumab	Bortezomib
Inhibits costimulation	Depletes T-cells	Depletes B-cells	Depletes plasma cells



Inhibits Th signal	Interferes with T-B interaction	Inhibits proliferation	Inhibits B-cell differentiation & Ig production	Inhibits Ig-mediated endothelial cell signaling and proliferation
CNI mTORi Steroids	**CNI Steroids**	**MPA (T&B) mTORi (T&B)**	**mTORi**	**mTORi**

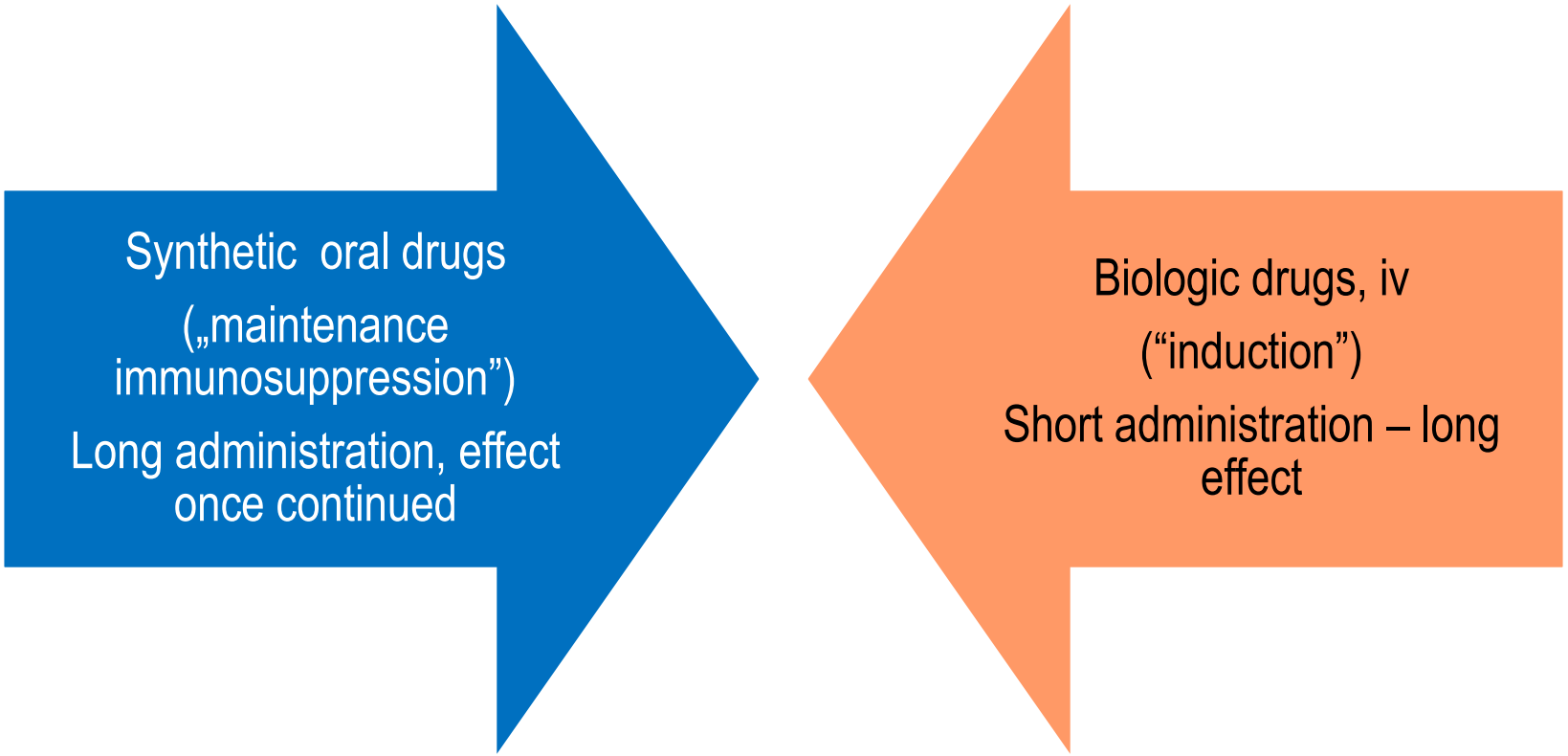

Steroids
+ azathioprine
Cyclosporine
+ steroids
± azathioprine
CNI
+ steroids
CNI
+ steroids
+ MMF
Attempts
weaning
IS
Anti-IL-2-R
delayed CNI
+ steroids
+ MMF
1970
1980
1990
2000
2010
Anti-lymphocyte
sera
Cyclosporine A
OKT3
Tacrolimus
MMF
MPA
Anti IL-2-R
Everolimus

Roczne przeżycie przeszczepu i ryzyko odrzucania – ostatnie 40 lat

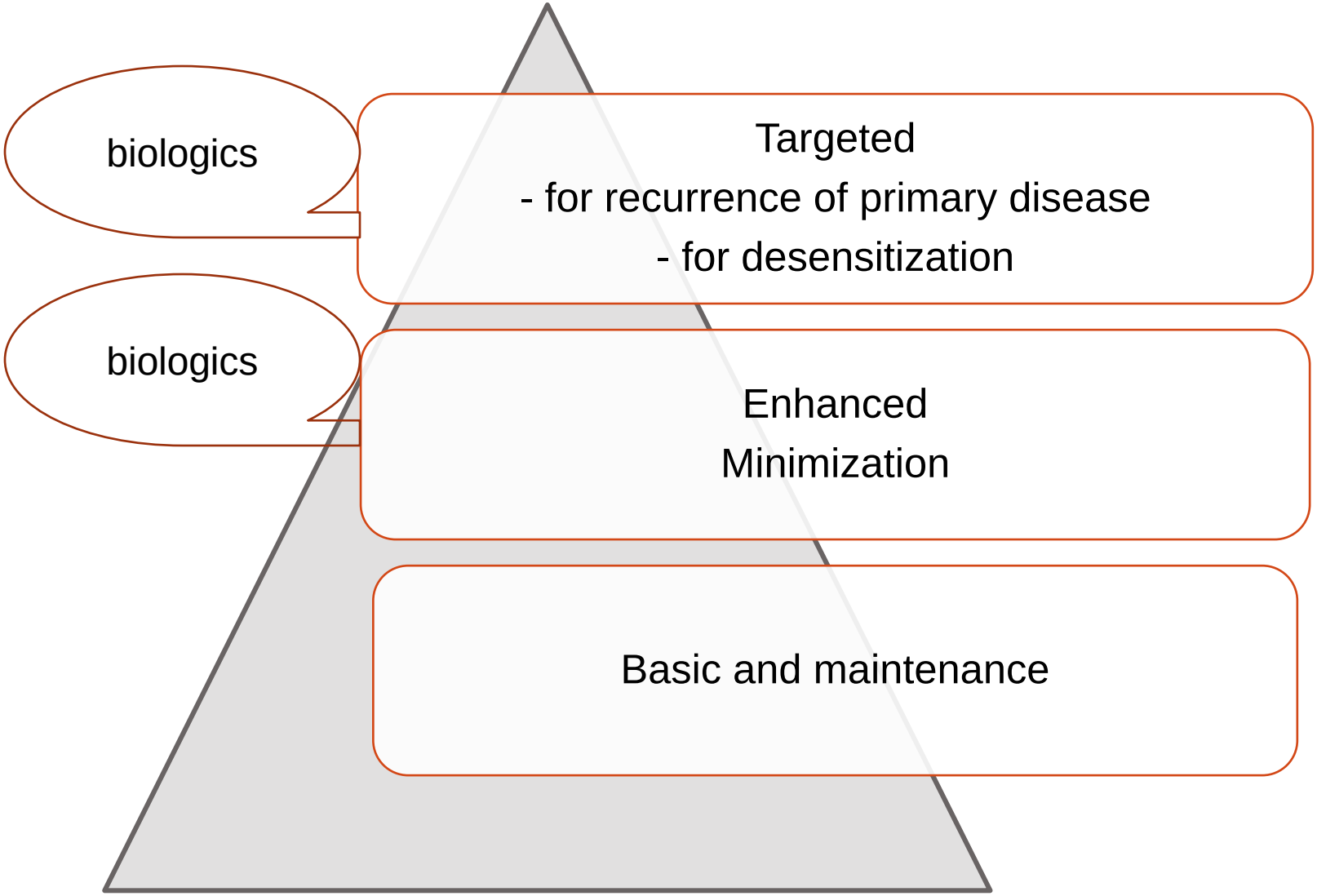


Slide courtesy of Dr. Meier-Kriesche

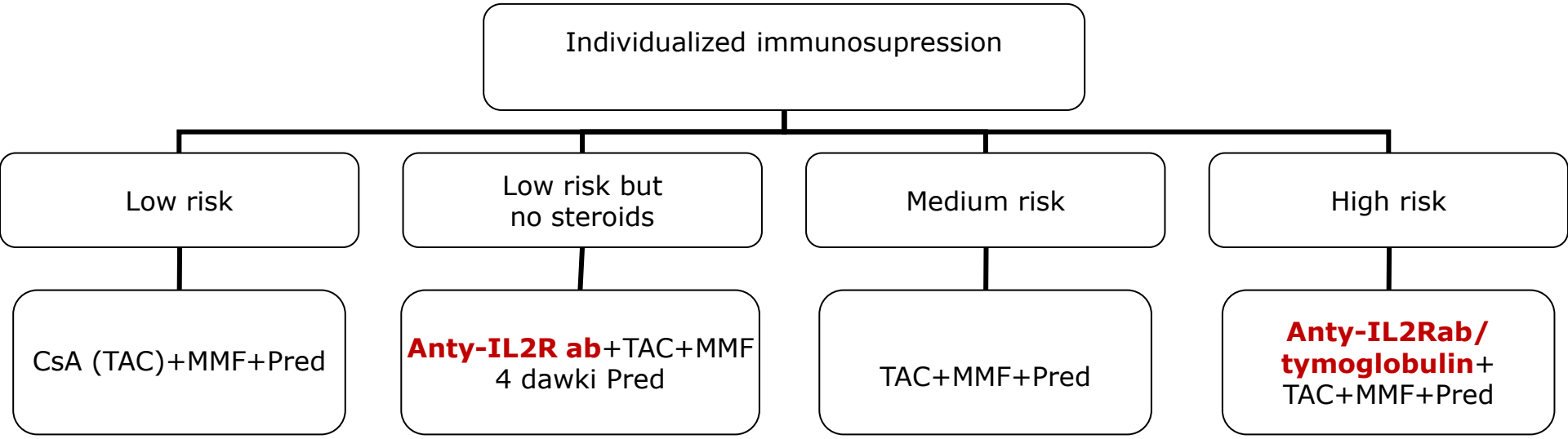
Main group of the immunusuppressives



Main strategies in immunosuppression



Risk stratification & immunosuppression



Distinct risk issue: recurrence of SRNS or aHUS

Drug	Category	Mechanism	Effect
Mycophenolate mofetil	Immunosuppressive (Anti-proliferative)	Inhibitor of inosine monophosphate dehydrogenase (IMPDH)	Decreases proliferation of B and T cells.
Rapamycin (Sirolimus)	Immunosuppressive (Anti-proliferative)	Blocks Cells Cycle at the Junction of G1 and S phase by interacting with intracellular protein, FKBP12 and blocking cell specific kinase TOR (Target of rapamycin)	Decreases proliferation of B cells, T cells, smooth muscles and decreases antibody production
Everolimus	Immunosuppressive (Anti-proliferative)	Same as Rapamycin (Sirolimus)	Same as Rapamycin (Sirolimus)
Leflunomide	Immunosuppressive (Anti-proliferative)	Blocks the action of dihydroorotate dehydrogenase, which is a rate-limiting enzyme in the production of uridine monophosphate (UMP).	Decreases proliferation and differentiation of activated lymphocytes
Azithioprine	Immunosuppressive (Anti-proliferative)	Blocks de novo purine synthesis	Blocks T cell activation
Methylprednisolone	Immunosuppressive (Anti-proliferative and anti-inflammatory)	Causes redistribution of T cells and blocks inflammatory pathways	Decreases circulating T cells and inflammatory cytokines (for instance IL-6)
Tacrolimus (FK506)	Immunosuppressive (Anti-proliferative and antibiotic)	Causes decrease in gene expression	Decreases both cell-mediated and humoral immunity

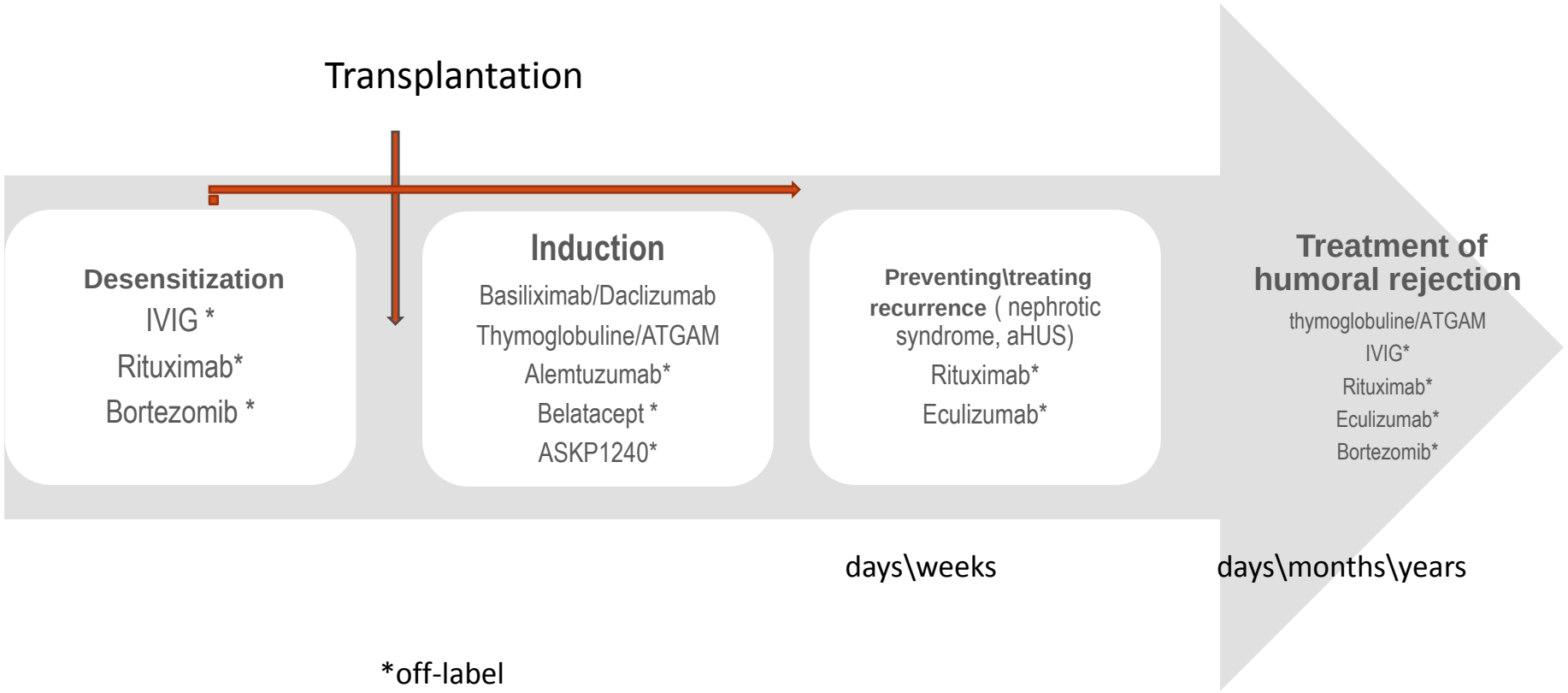
Pediatr Nephrol
DOI 10.1007/s00467-014-2886-4

EDUCATIONAL REVIEW

Biologics in renal transplantation

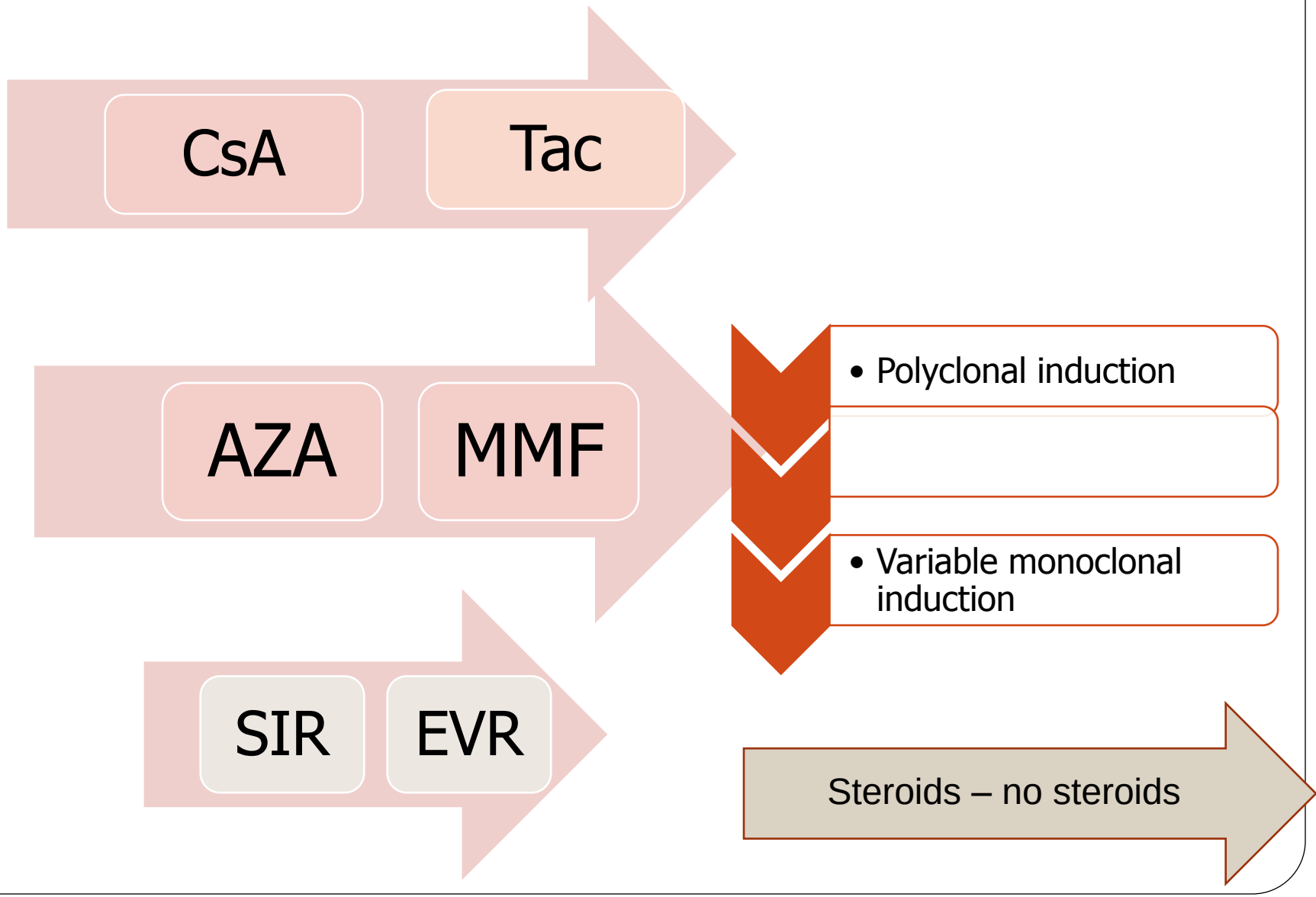
Ryszard Grenda

Timing of biologics use



*off-label

Modification over time



North American Pediatric Renal Trials and Collaborative Studies

PERCENT DRUG UTILIZATION – DAY 30 POST TRANSPLANT
(Patients with functioning grafts)

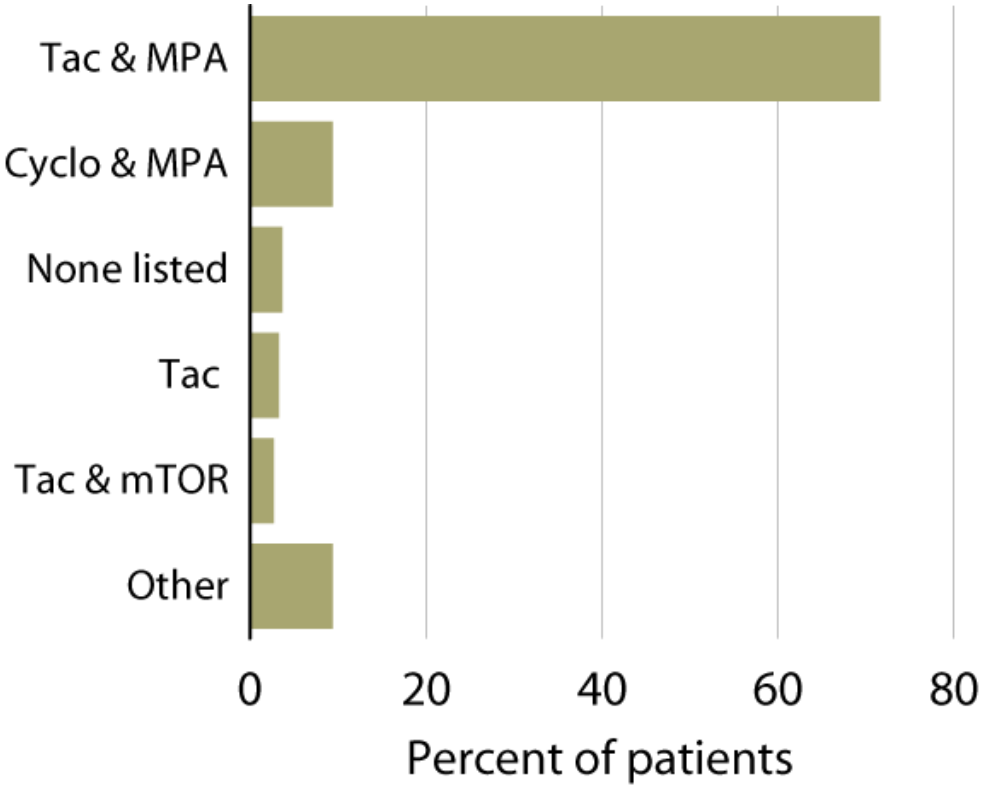
	1996 n=598	1997 n=581	1998 n=534	1999 n=555	2000 n=454	2001 n=511	2002 n=478	2003 n=443	2004 n=434	2005 n=391	2006 n=356	2007 n=315	2008 n=306	2009 n=203
Prednisone ↓	94.8	95.7	94.8	92.6	91.2	86.5	85.2	73.4	68.4	65.7	61.5	56.5	57.2	48.8
Cyclosporine ↓	82.1	78.8	71.7	68.1	57.1	45.4	26.2	15.8	9.2	10.2	4.8	7.6	3.9	1.0
Tacrolimus ↑	3.7	14.8	22.3	24.5	34.4	41.7	58.2	60.1	71.4	68.8	71.9	70.8	73.5	62.1
MMF ↑	9.0	44.8	66.7	66.9	63.9	54.2	57.7	58.5	65.2	71.6	69.4	70.5	69.9	59.6
Azathioprine ↓	49.3	34.4	19.7	16.0	13.7	12.9	2.7	3.8	3.2	1.0	2.0	3.2	3.6	2.5
Sirolimus ↑ ↓	0.0	0.0	0.2	0.4	7.5	21.7	25.5	18.3	12.2	6.1	6.7	2.2	2.3	0.5

North American Pediatric Renal Trials and Collaborative Studies

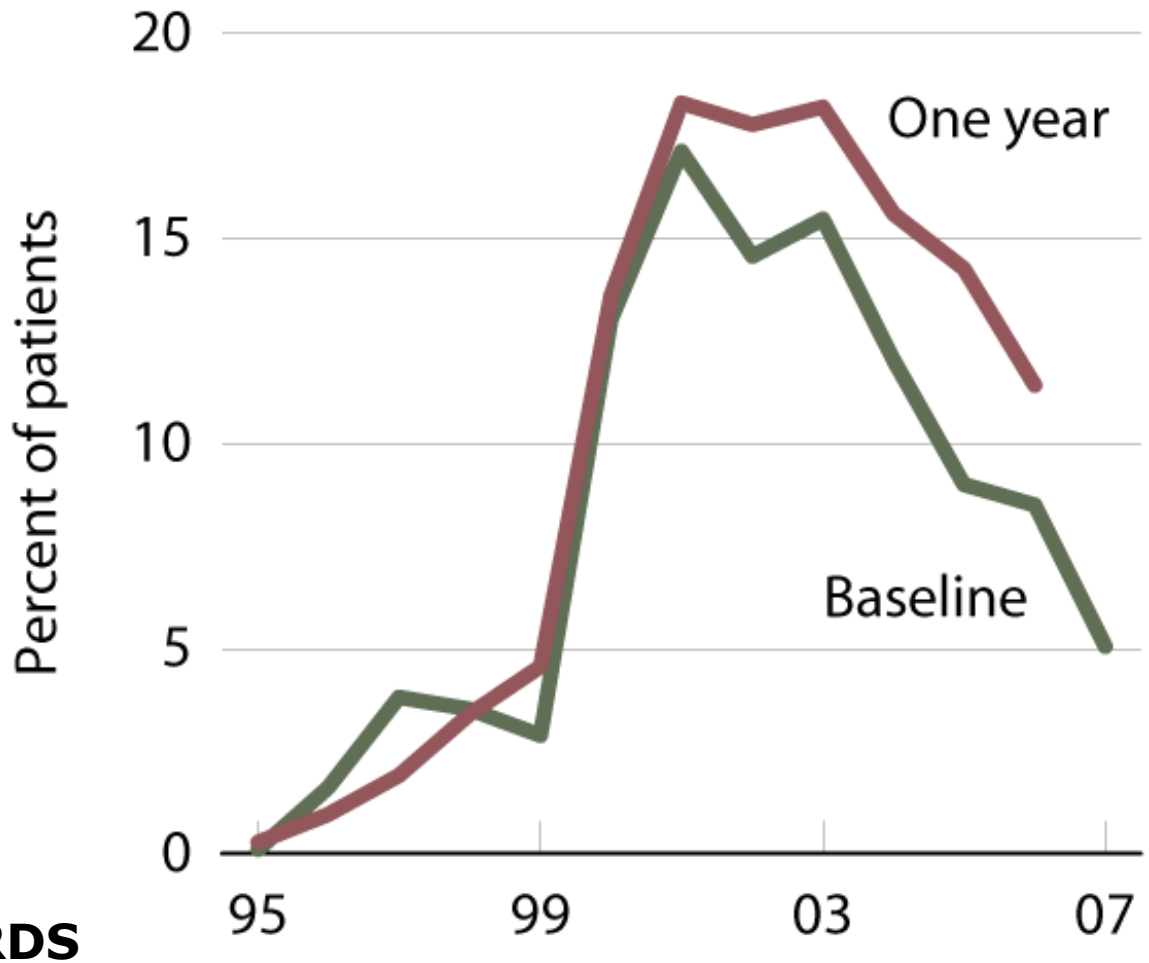
PERCENT DRUG UTILIZATION - POST TRANSPLANT
(Patients with functioning grafts)

	Transplant Era 1996-2002				Transplant Era 2003-2010			
	30 days	1 year	3 years	5 years	30 days	1 year	3 years	5 years
Prednisone/CsA/MMF	33.6	35.3	28.4	21.8	6.6	6.9	7.1	6.2
Prednisone/CsA/Aza	20.5	15.8	12.7	8.1	0.7	0.4	0.4	0.4
Prednisone/Csa	11.2	5.1	4.4	4.9	1.7	1.1	0.7	2.1
Prednisone /TAC/MMF	17.8	22.5	26.6	31.3	56.2	52.1	45.6	40.9
Prednisone /TAC/Aza	2.2	4.5	6.1	6.6	2.1	2.4	2.6	3.7
Prednisone /TAC	7.7	9.2	10.9	11.6	6.2	10.1	11.2	9.9
TAC/MMF	0.6	1.5	2.3	3.5	14.8	12.2	12.8	14.9
Other combination	6.4	6.2	8.6	12.3	11.9	14.8	19.7	21.9

Most common immunosuppression regimens at time of transplant: 2005–2007
USRDS 2009

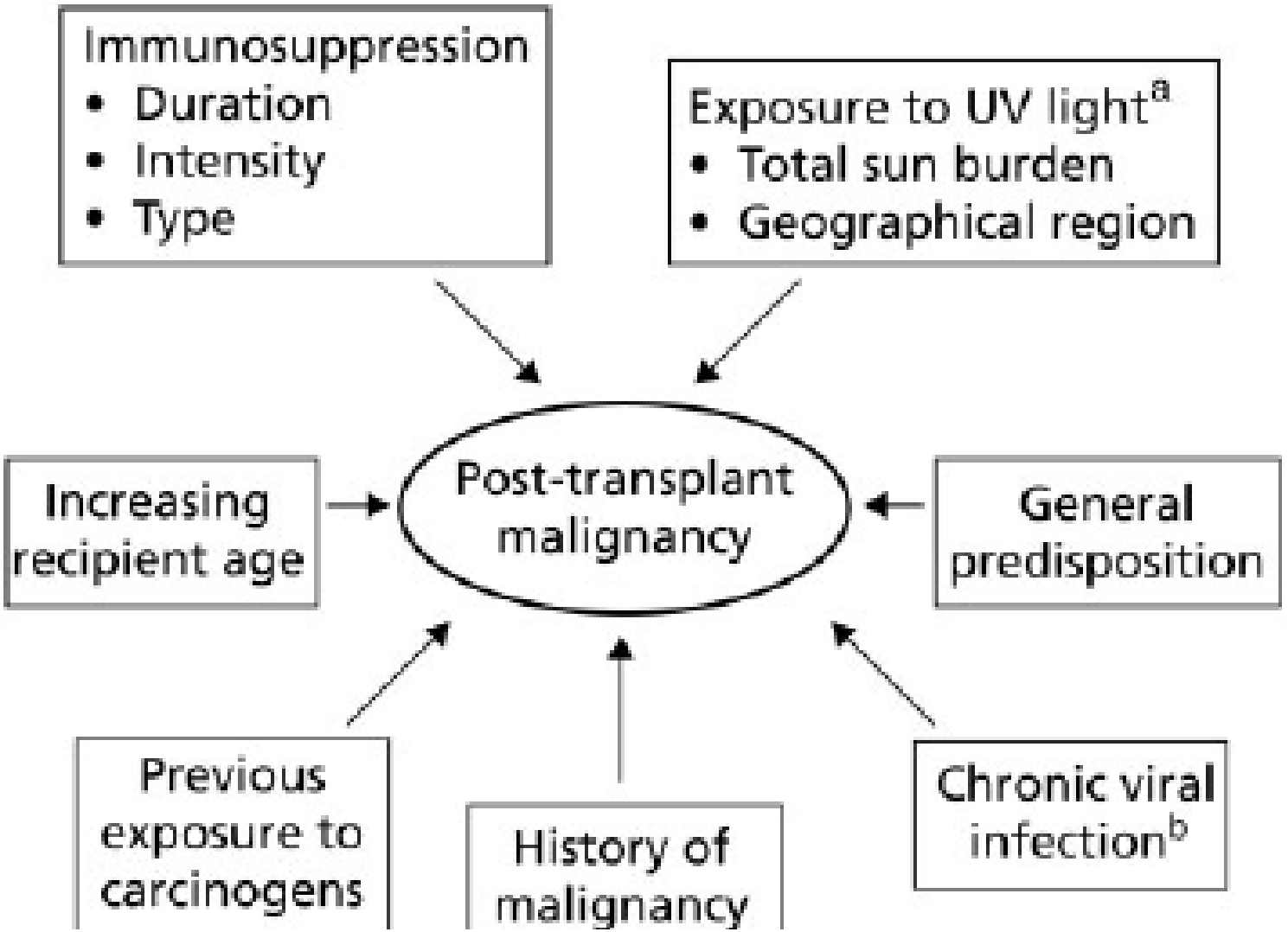


mTOR inhibitor use



USRDS 2009

Immunosuppression vs risk of malignancy



Disassociation Between Risk of Graft Loss and Risk of Non-Hodgkin Lymphoma With Induction Agents in Renal Transplant Recipients

(*Transplantation* 2006;81: 1227–1233)

Gerhard Opelz, Cord Naujokat, Volker Daniel, Peter Terness, and Bernd Döhler

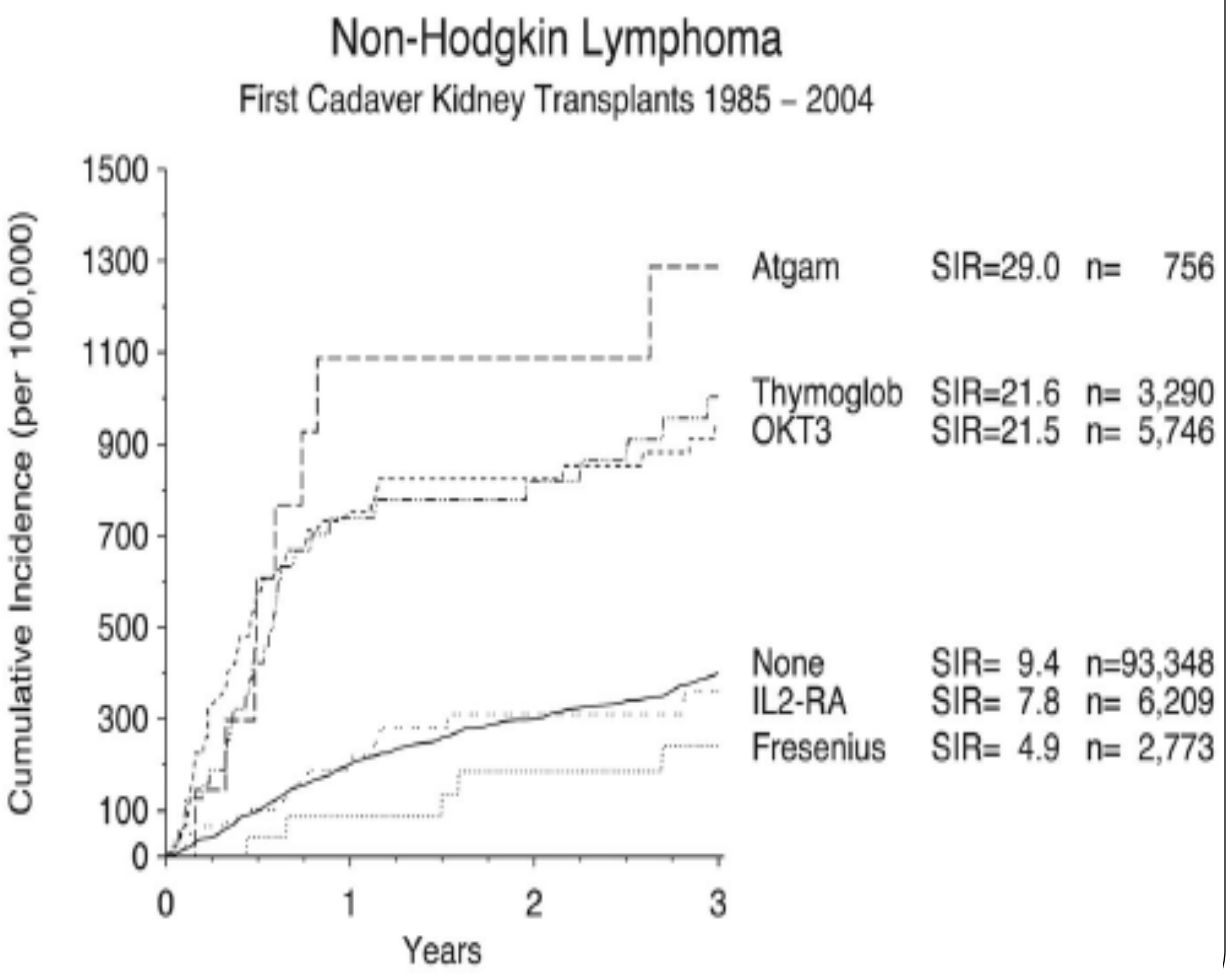


FIGURE 3. Cumulative incidence of non-Hodgkin lymphoma (NHL) after renal transplantation from a deceased donor according to type of induction therapy for patients receiving a transplant during 1985 to 2004. Standardized incidence ratio (SIR) values compare the observed risk of lymphoma versus the estimated risk in the nontransplant control population matched for age, sex, and geographical origin.

Epidemiology of Pretransplant EBV and CMV Serostatus in Relation to Posttransplant Non-Hodgkin Lymphoma

(*Transplantation* 2009;88: 962–967)

Gerhard Opelz, Volker Daniel, Cord Naujokat, and Bernd Döhler

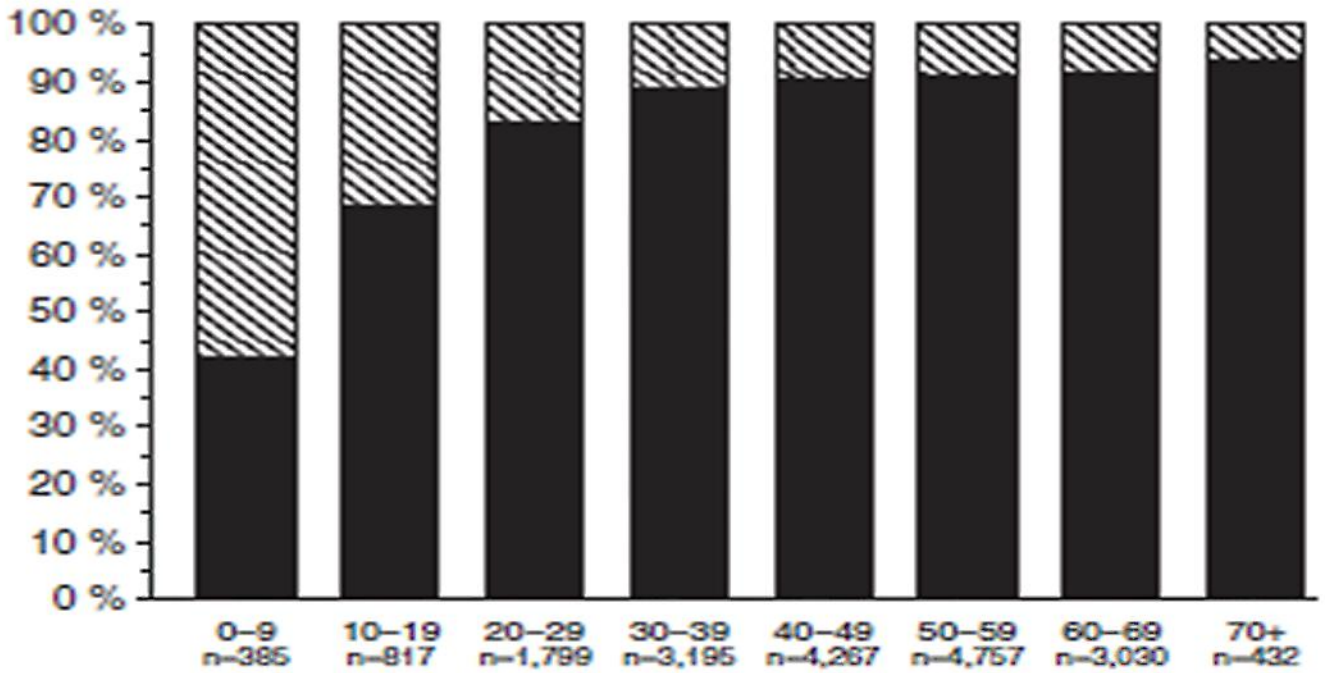
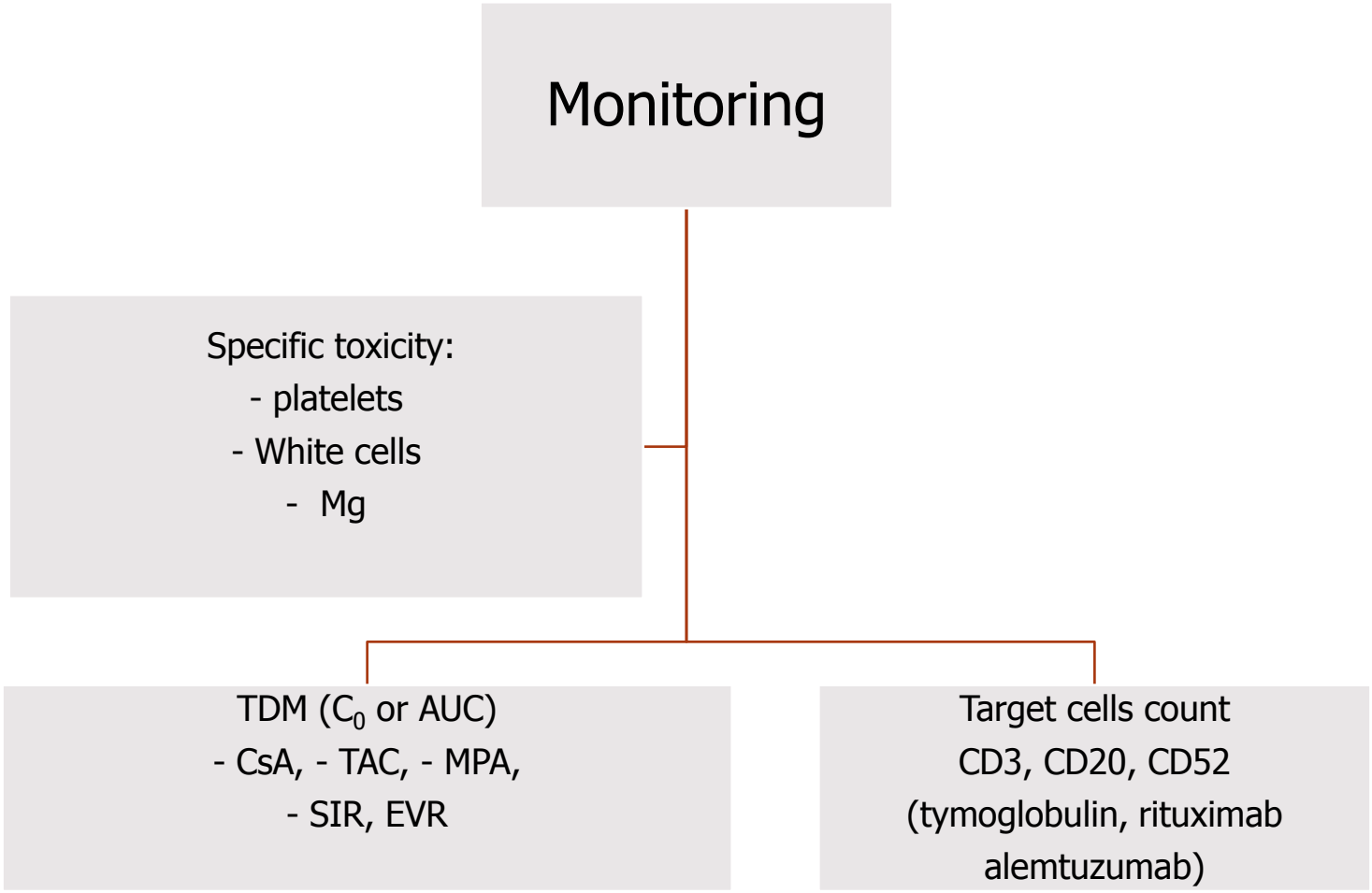
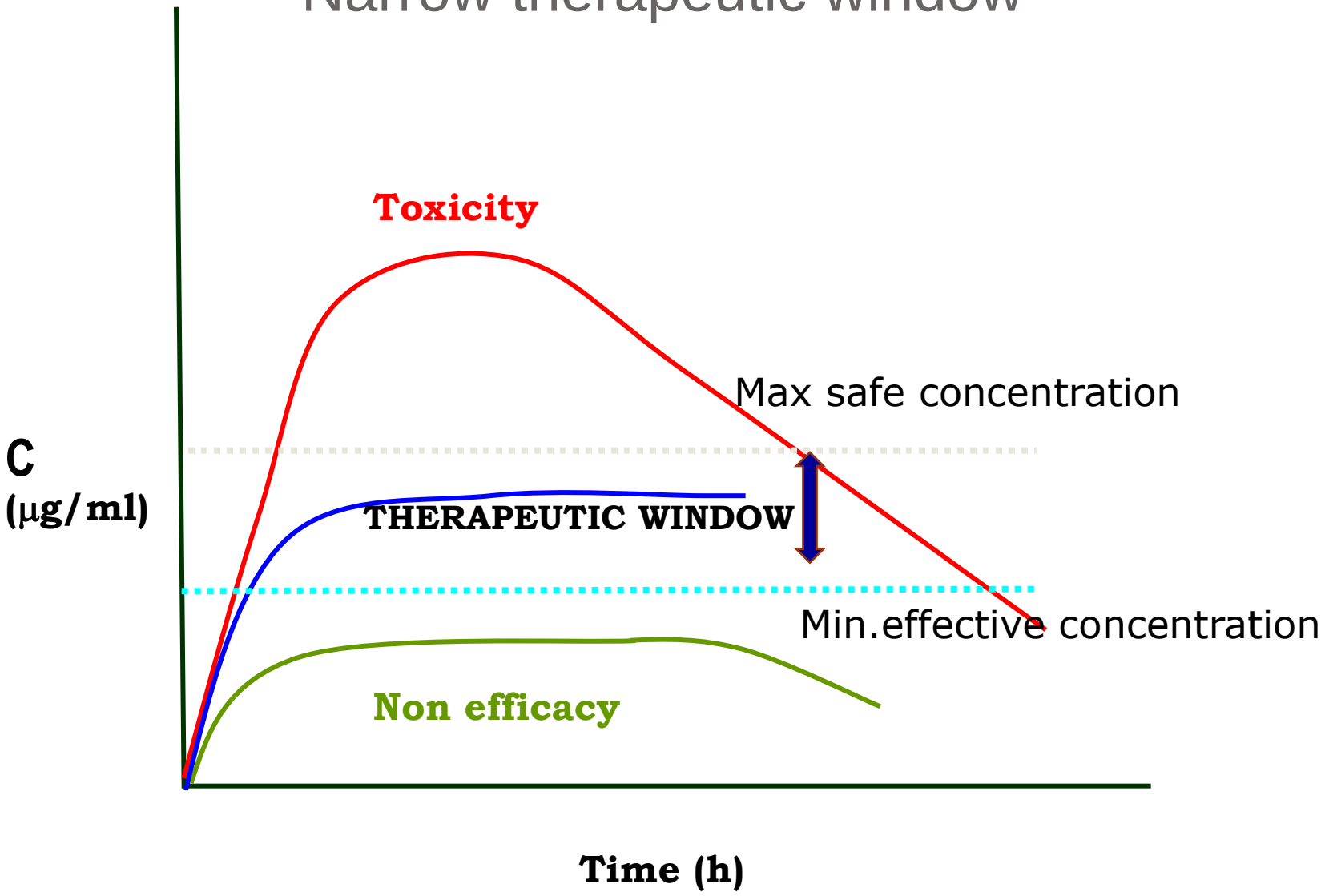


FIGURE 1. Proportion of pretransplant recipient Epstein-Barr virus (EBV) serostatus by recipient age (log-rank $P<0.001$). Recipients of kidney transplants were analyzed.

Monitoring


Monitoring
Specific toxicity:
- platelets
- White cells
- Mg
TDM (C_0 or AUC)
- CsA, - TAC, - MPA,
- SIR, EVR
Target cells count
CD3, CD20, CD52
(tymoglobulin, rituximab
alemtuzumab)

Narrow therapeutic window



Pharmacokinetcs

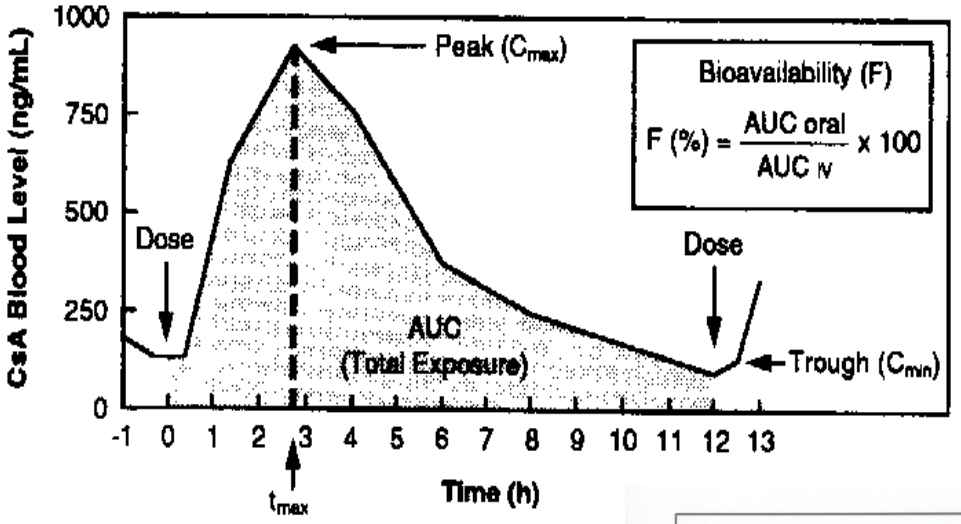
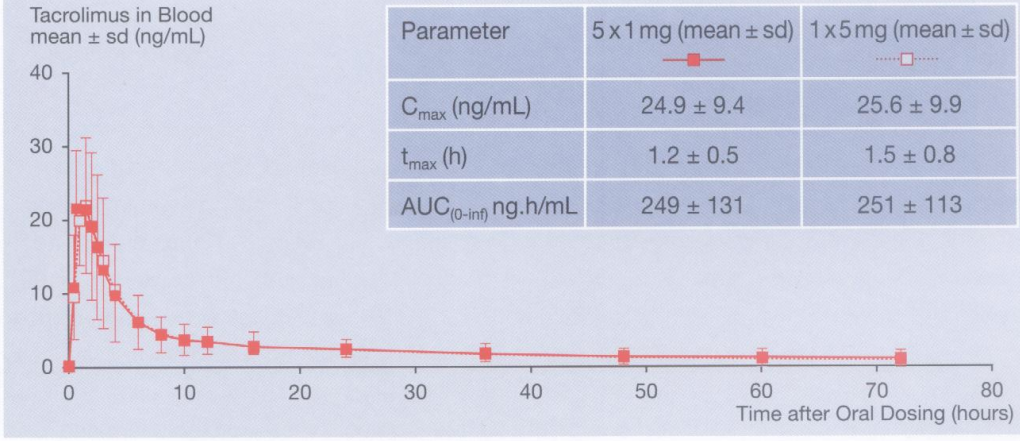


Figure 2

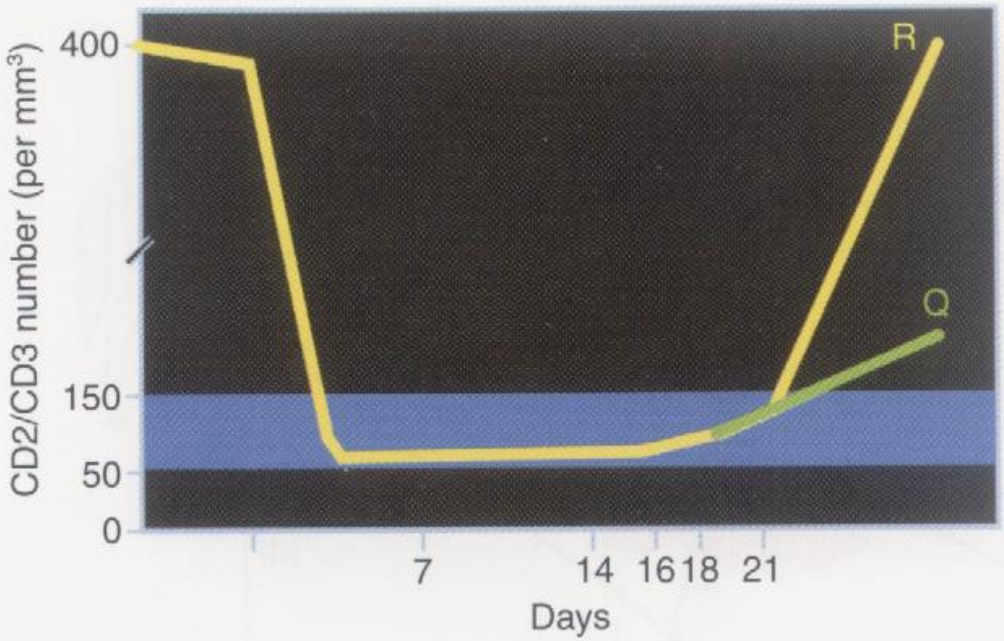
Mean Absorption Profile of Tacrolimus (n = 29) – Marketed Formulations.

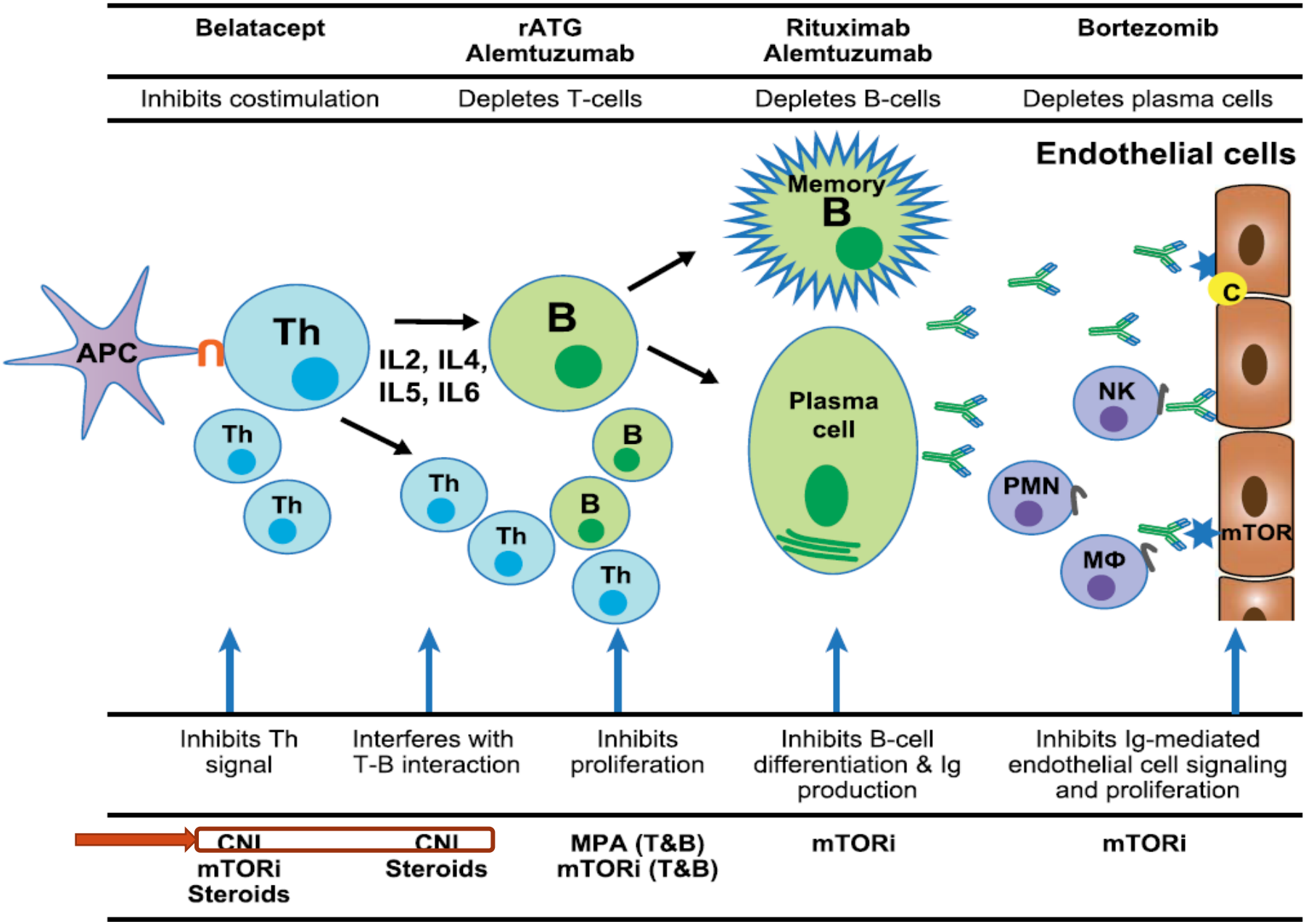


Parameter	5 x 1 mg (mean ± sd)	1 x 5 mg (mean ± sd)
C_{max} (ng/mL)	24.9 ± 9.4	25.6 ± 9.9
t_{max} (h)	1.2 ± 0.5	1.5 ± 0.8
$AUC_{(0\text{-inf})}$ ng.h/mL	249 ± 131	251 ± 113

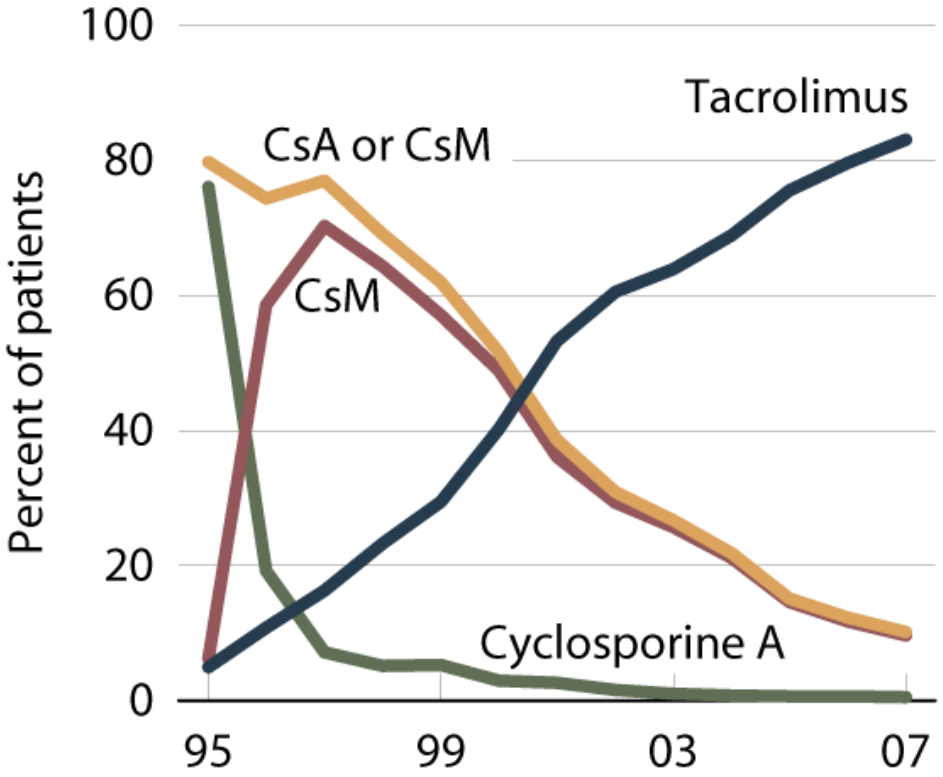
Ref.: Bekersky et al., 1999a

CD3 monitoring (thymoglobulin)




Belatacept
rATG
Alemtuzumab
Rituximab
Alemtuzumab
Bortezomib
Inhibits costimulation
Depletes T-cells
Depletes B-cells
Depletes plasma cells
Endothelial cells
Memory B
APC
Th
IL2, IL4, IL5, IL6
B
Plasma cell
C
NK
PMN
MΦ
mTOR
Inhibits Th signal
Interferes with T-B interaction
Inhibits proliferation
Inhibits B-cell differentiation & Ig production
Inhibits Ig-mediated endothelial cell signaling and proliferation
CNI
mTORi
Steroids
CNI
Steroids
MPA (T&B)
mTORi (T&B)
mTORi
mTORi

Why > Tac than CsA?



USRDS 2009

Pediatr Transplantation 2005: 9: 498–503

Pediatric Transplantation
DOI: 10.1111/j.1399-3046.2005.00334.x

Four-year data after pediatric renal transplantation: A randomized trial of tacrolimus vs. cyclosporin microemulsion

Guido Filler, Nicholas J. A. Webb, David V. Milford, Alan R. Watson, Jutta Gellermann, Gunnar Tyden, Ryszard Grenda, Karel Vondrak, David Hughes, Gisela Offner, Martin Griebel, Inge B. Brekke, Mary McGraw, Egon Balzar, Styrbjörn Friman and Richard Trompeter

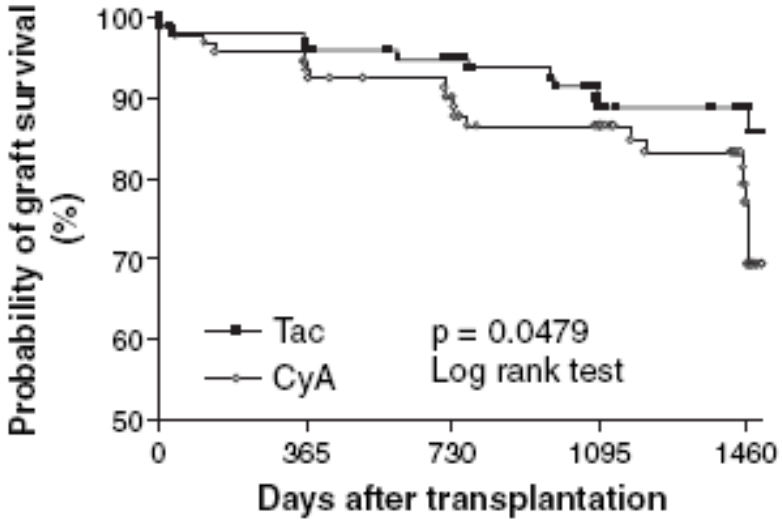


Fig. 2. Actuarial graft survival at 4 yr (intention to treat analysis). Tac, tacrolimus; CyA, cyclosporin microemulsion.

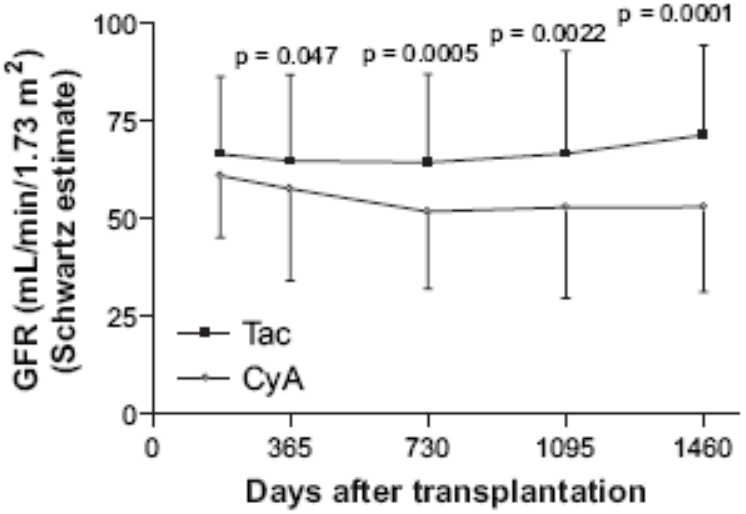
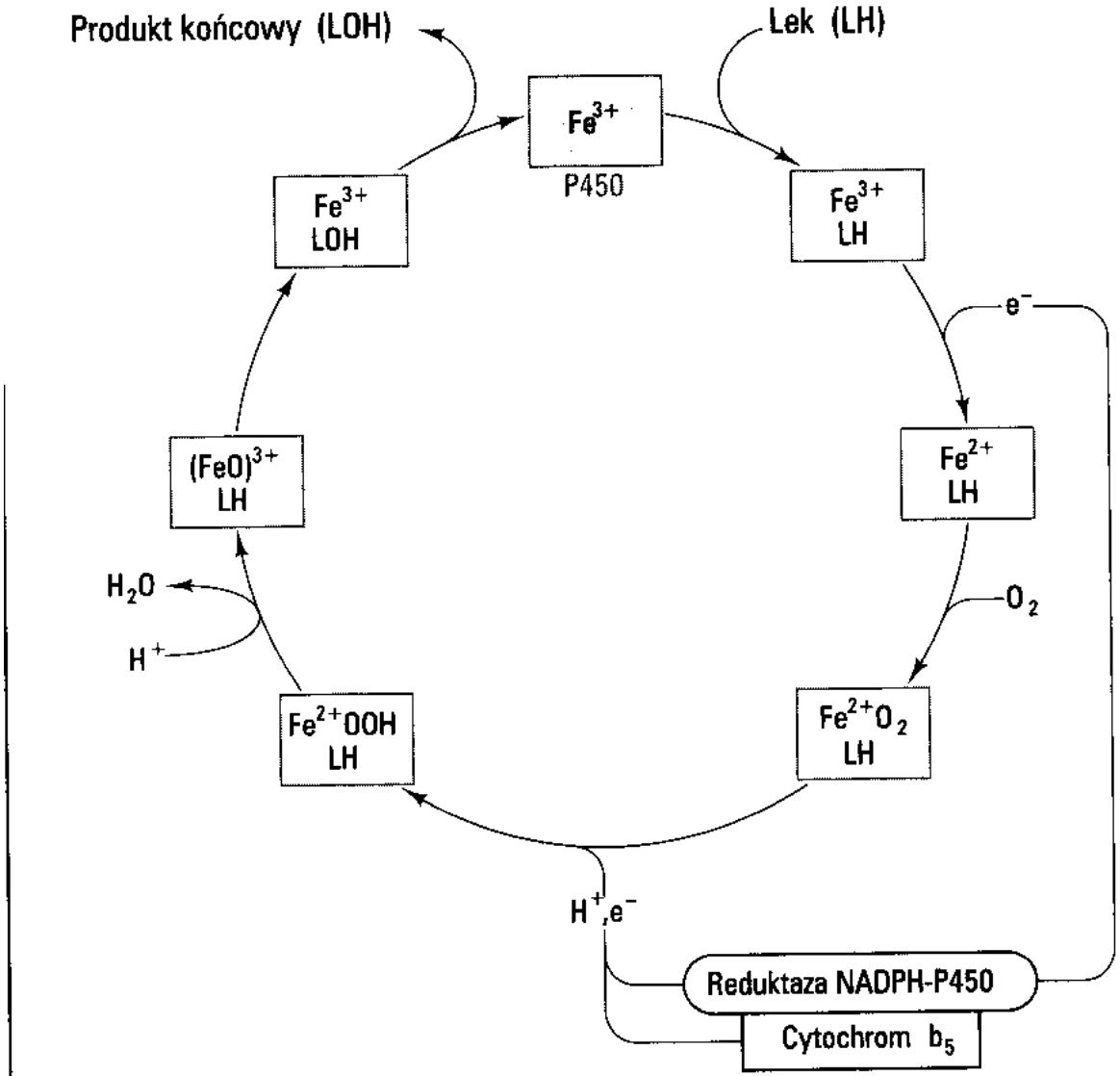
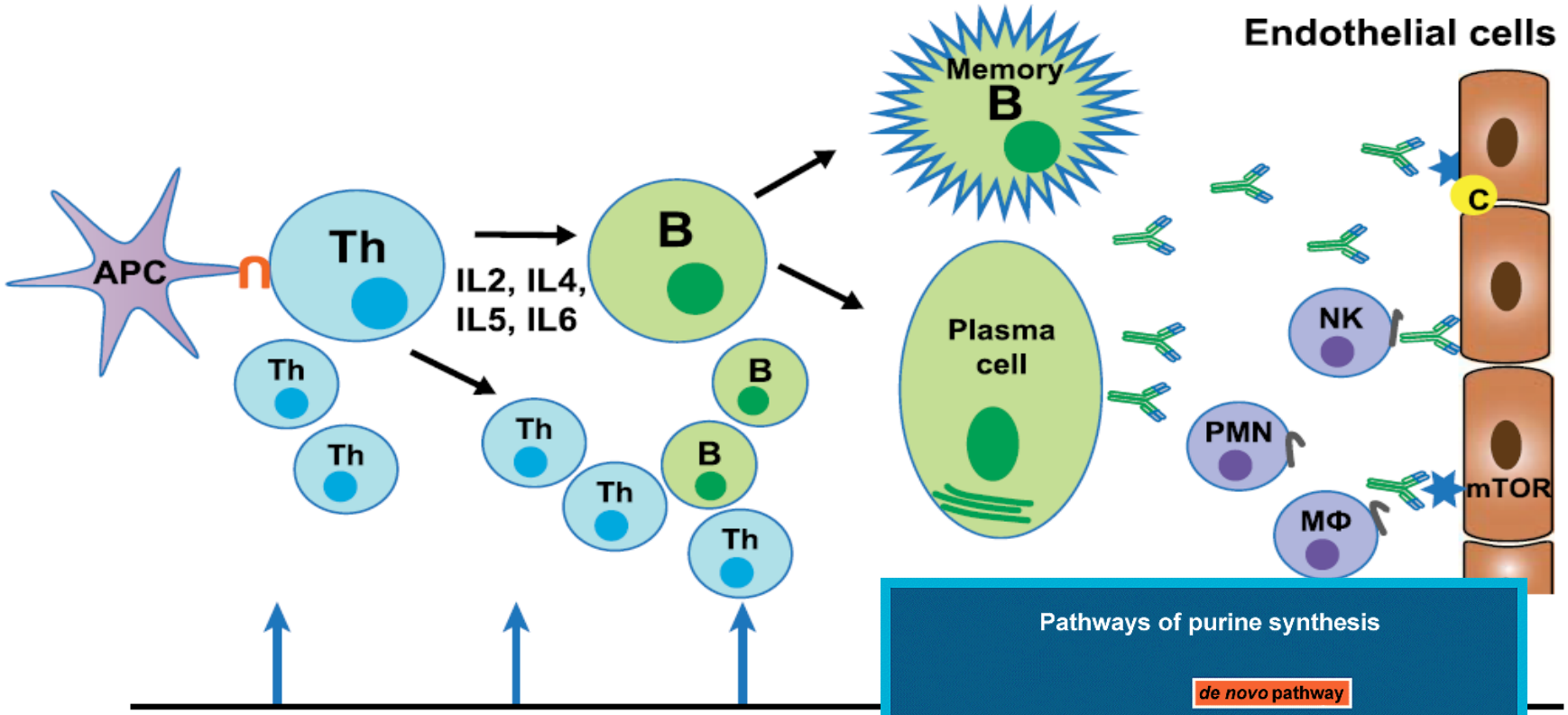


Fig. 4. Mean glomerular filtration rate ±1 s.d. Tac, tacrolimus; CyA, cyclosporin microemulsion.

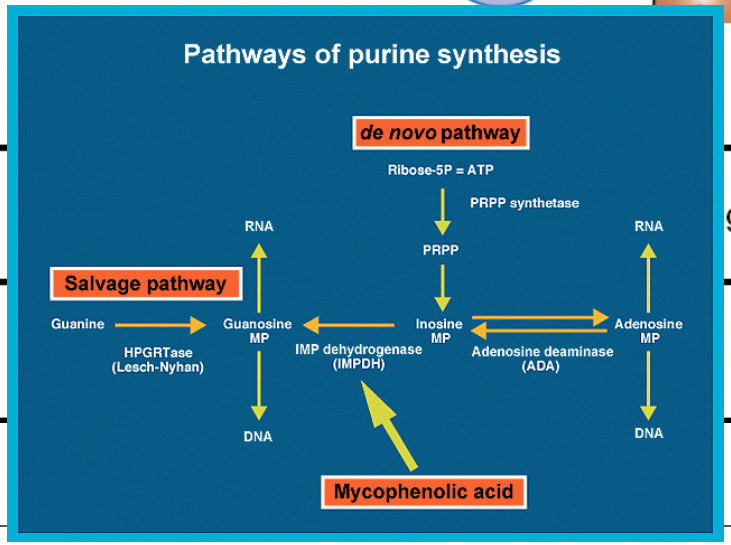
Cytochrom P450

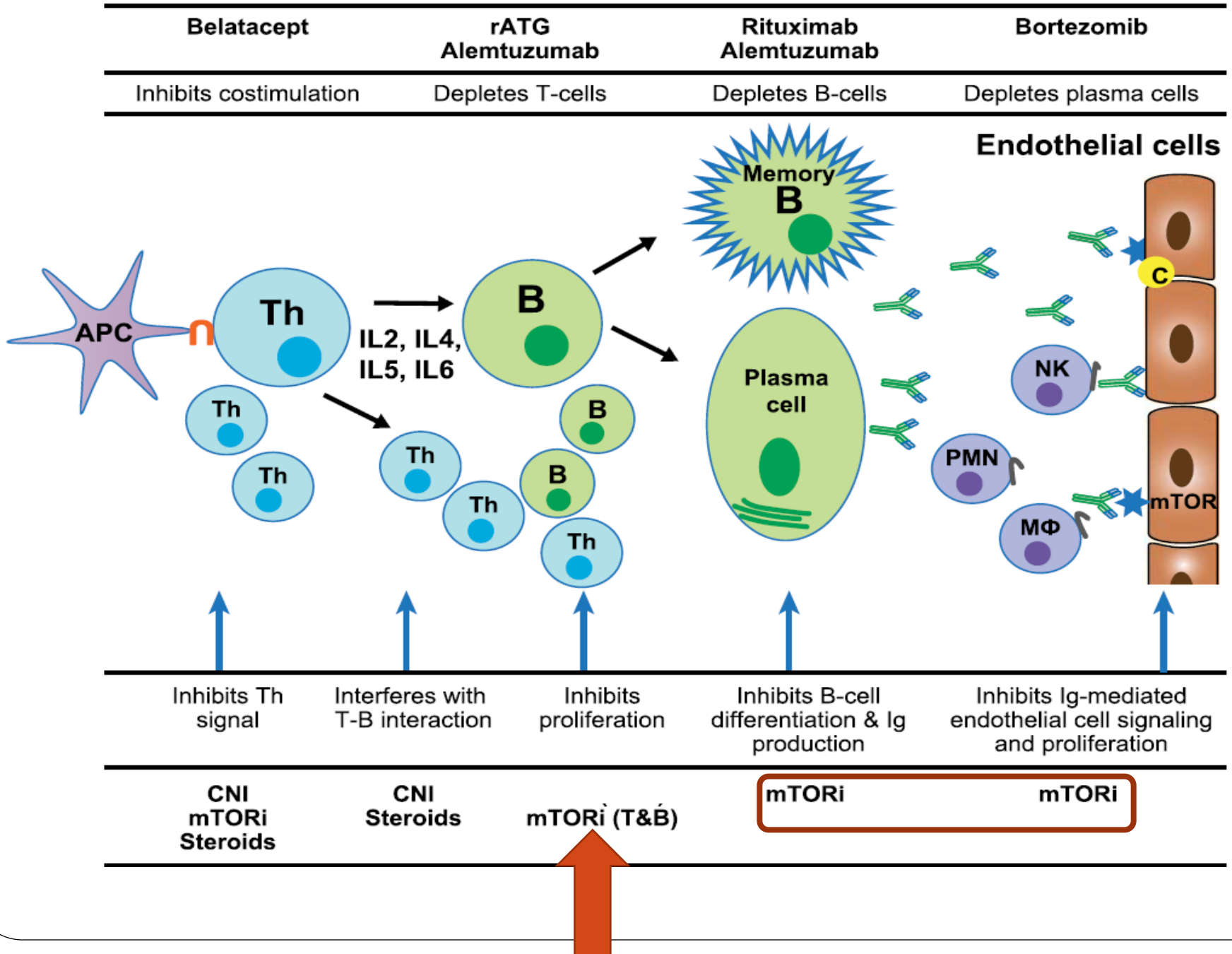


Belatacept	rATG Alemtuzumab	Rituximab Alemtuzumab	Bortezomib
Inhibits costimulation	Depletes T-cells	Depletes B-cells	Depletes plasma cells



CNI mTORi Steroids	CNI Steroids	→ MPA (T&B) mTORi (T&B)




Belatacept
rATG
Alemtuzumab
Rituximab
Alemtuzumab
Bortezomib
Inhibits costimulation
Depletes T-cells
Depletes B-cells
Depletes plasma cells
Endothelial cells
Memory B
APC
Th
IL2, IL4, IL5, IL6
B
Plasma cell
C
NK
PMN
MΦ
mTOR
Inhibits Th signal
Interferes with T-B interaction
Inhibits proliferation
Inhibits B-cell differentiation & Ig production
Inhibits Ig-mediated endothelial cell signaling and proliferation
CNI
mTORi
Steroids
CNI
Steroids
mTORi (T&B)
mTORi
mTORi

Sirolimus Therapy after Early Cyclosporine Withdrawal Reduces the Risk for Cancer in Adult Renal Transplantation

Josep M. Campistol,* Josette Eris,† Rainer Oberbauer,‡ Peter Friend,§ Brian Hutchison,‖ José M. Morales,¶ Kerstin Claesson,# Giovanni Stallone,** Graeme Russ,†† Lionel Rostaing,‡‡ Henri Kreis,§§ James T. Burke,‖‖ Yves Brault,‖‖ Joseph A. Scarola,¶¶ and John F. Neylan;¶¶ for the Rapamune Maintenance Regimen Study Group

Table 4. Number (%) of patients with any nonskin malignancy analyzed by on-therapy events and ITT events (5 yr)

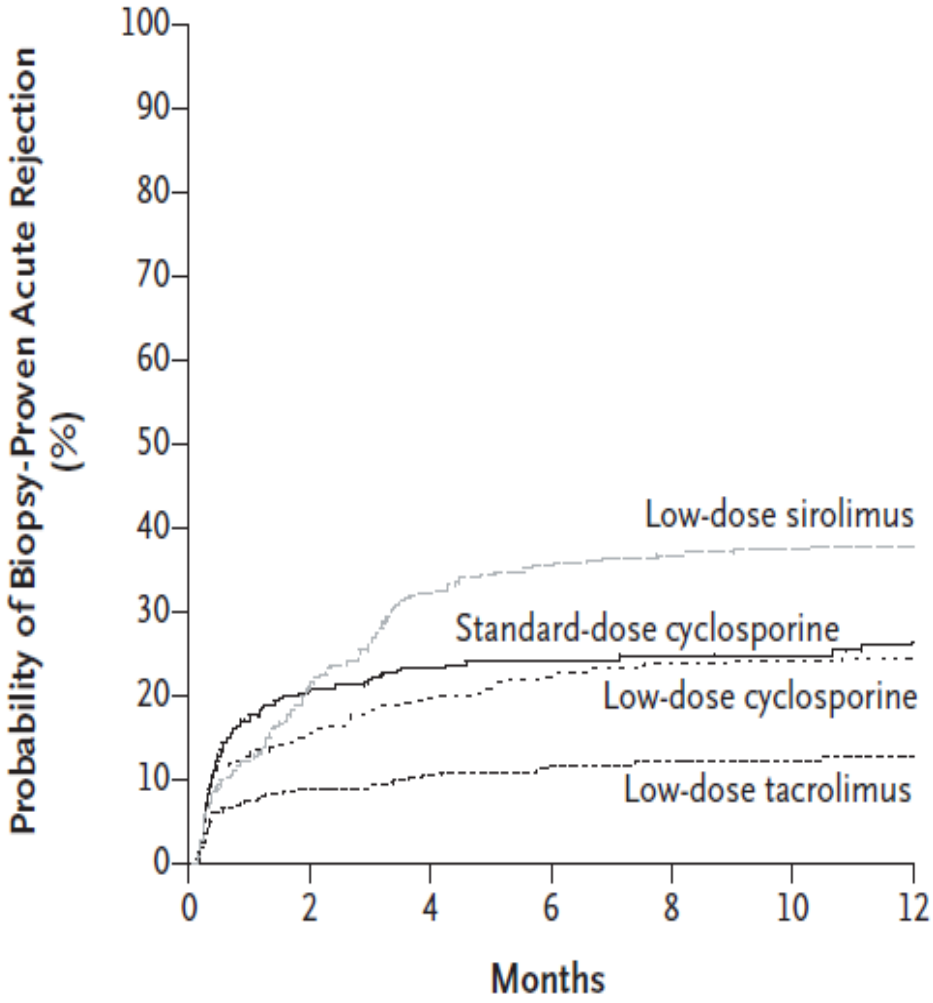
Analyses	SRL-CsA-ST (n = 215)	SRL-ST (n = 215)	P Value
On-therapy			
nonskin malignancies (n [%])	10 (4.65)	4 (1.86)	0.103[c]
time to first malignancy[a] (d; median [95% CI])	638.0 (461 to 1149)	407.5 (242 to 1544)	0.644[d]
malignancy-free survival[b], Kaplan-Meier estimates (%)	92.62	97.36	0.094[d]
ITT			
nonskin malignancies (n [%])	18 (8.37)	8 (3.72)	0.043[c]
time to first malignancy[a] (d; median [95% CI])	668.0 (538 to 1511)	774.5 (267 to 1544)	0.625[d]
malignancy-free survival[b], Kaplan-Meier estimates (%)	90.38	95.99	0.032[d]

The NEW ENGLAND JOURNAL of MEDICINE

ORIGINAL ARTICLE

Reduced Exposure to Calcineurin Inhibitors in Renal Transplantation

Henrik Ekberg, M.D., Ph.D., Helio Tedesco-Silva, M.D., Alper Demirbas, M.D., Štefan Vítko, M.D., Björn Nashan, M.D., Ph.D., Alp Gürkan, M.D., F.A.C.S., Raimund Margreiter, M.D., Christian Hugo, M.D., Josep M. Grinyó, M.D., Ulrich Frei, M.D., Yves Vanrenterghem, M.D., Ph.D., Pierre Daloze, M.D., and Philip F. Halloran, M.D., Ph.D., for the ELITE–Symphony Study*

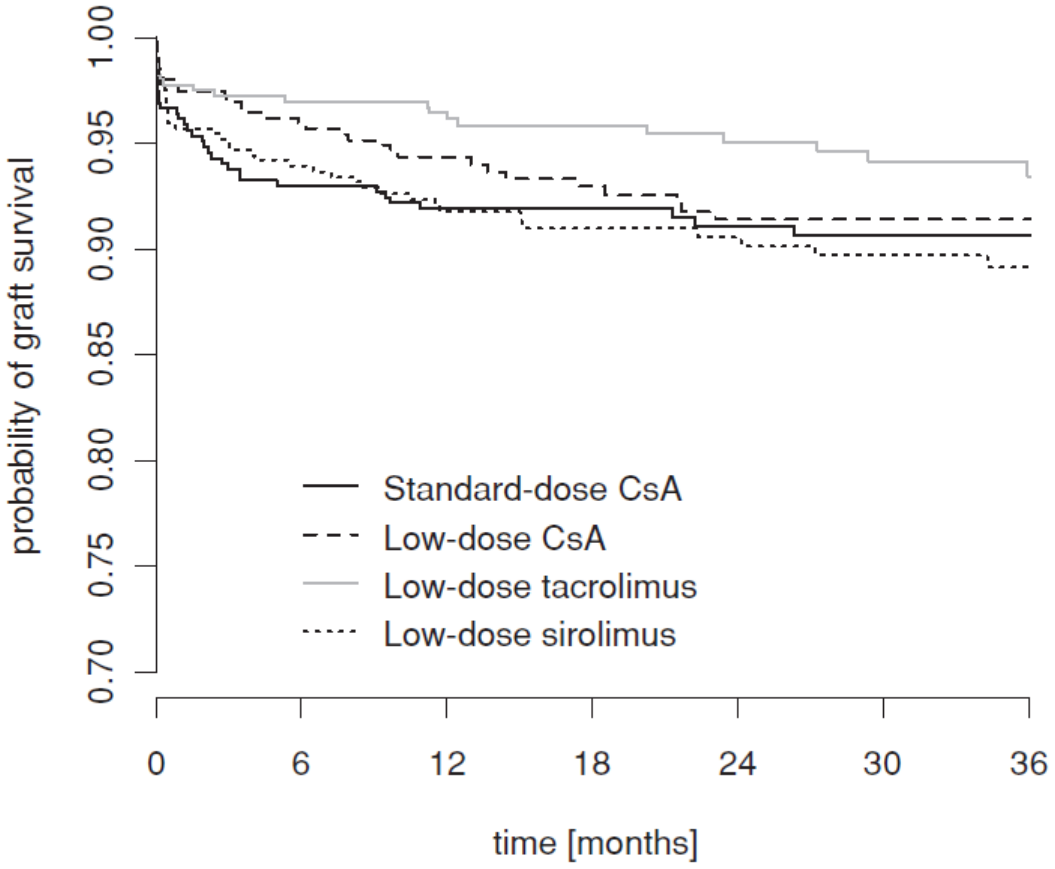


American Journal of Transplantation 2009; 9: 1876–1885
Wiley Periodicals Inc.

doi: 10.1111/j.1600-6143.2009.02726.x

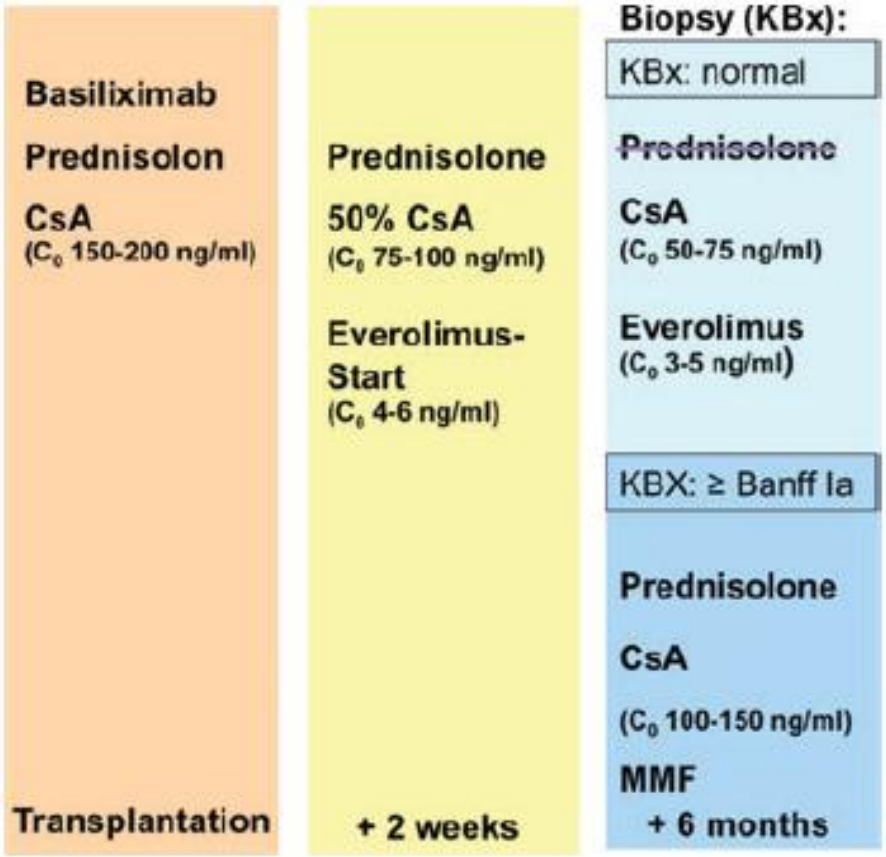
Calcineurin Inhibitor Minimization in the Symphony Study: Observational Results 3 Years after Transplantation

H. Ekberg[a,*], C. Bernasconi[b], H. Tedesco-Silva[c], S. Vítko[d], C. Hugo[e], A. Demirbas[f], R. Reyes Acevedo[g], J. Grinyó[h], U. Frei[i], Y. Vanrenterghem[j], P. Daloze[k] and P. F. Halloran[l]



De novo Therapy with Everolimus, Low-Dose Ciclosporine A, Basiliximab and Steroid Elimination in Pediatric Kidney Transplantation

L. Pape*, G. Offner, M. Kreuzer, K. Froede, J. Drube, N. Kanzelmeyer, J. H. H. Ehrich and T. Ahlenstiel



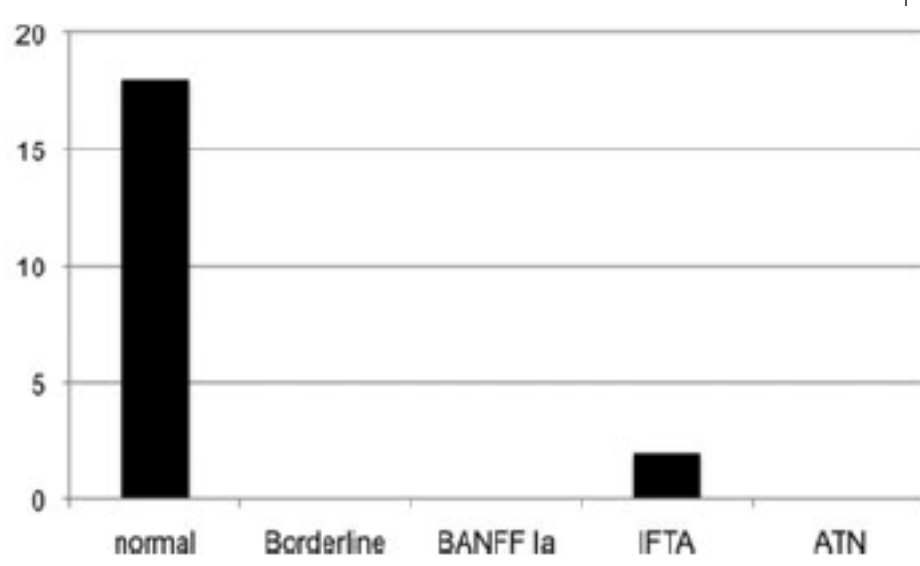
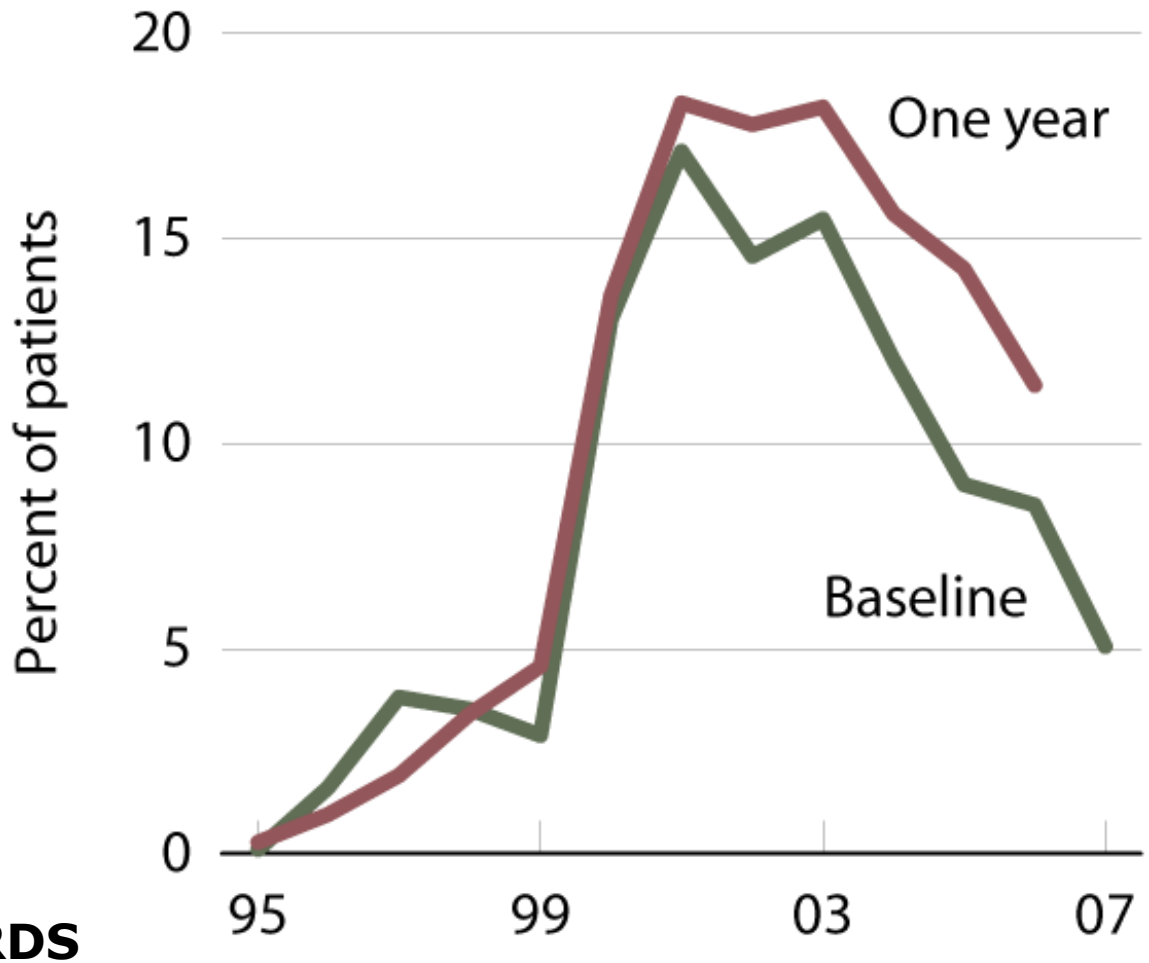


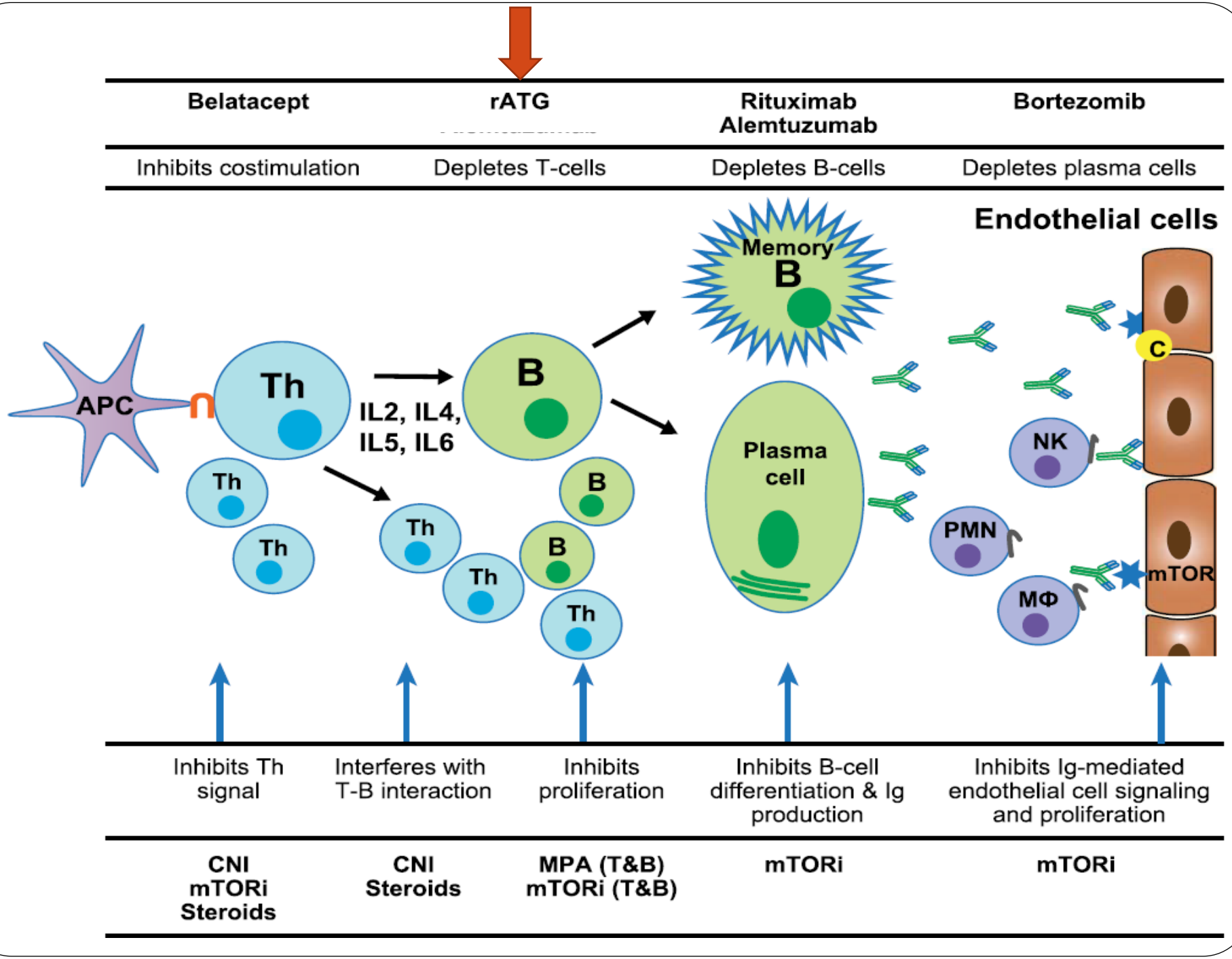
Figure 2: Results of 6 months protocol biopsies (n = 20).

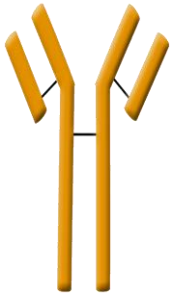
American Journal of Transplantation 2010; 10: 2349–2354
Wiley Periodicals Inc.

mTOR inhibitor use

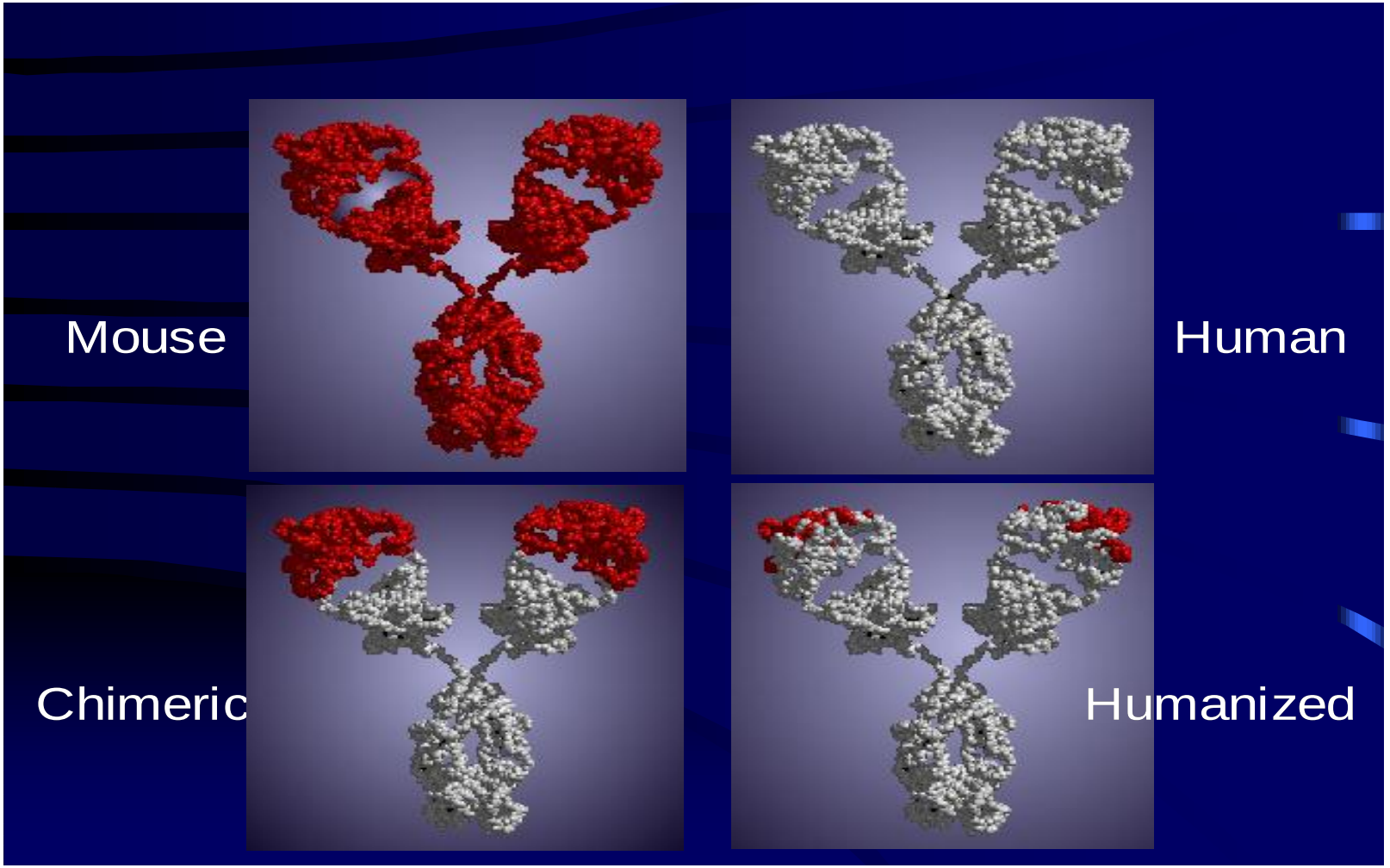


USRDS 2009


Belatacept
rATG
Rituximab
Alemtuzumab
Bortezomib
Inhibits costimulation
Depletes T-cells
Depletes B-cells
Depletes plasma cells
Endothelial cells
Memory B
APC
Th
IL2, IL4, IL5, IL6
B
Plasma cell
NK
PMN
MΦ
C
mTOR
Inhibits Th signal
Interferes with T-B interaction
Inhibits proliferation
Inhibits B-cell differentiation & Ig production
Inhibits Ig-mediated endothelial cell signaling and proliferation
CNI
mTORi
Steroids
CNI
Steroids
MPA (T&B)
mTORi (T&B)
mTORi
mTORi

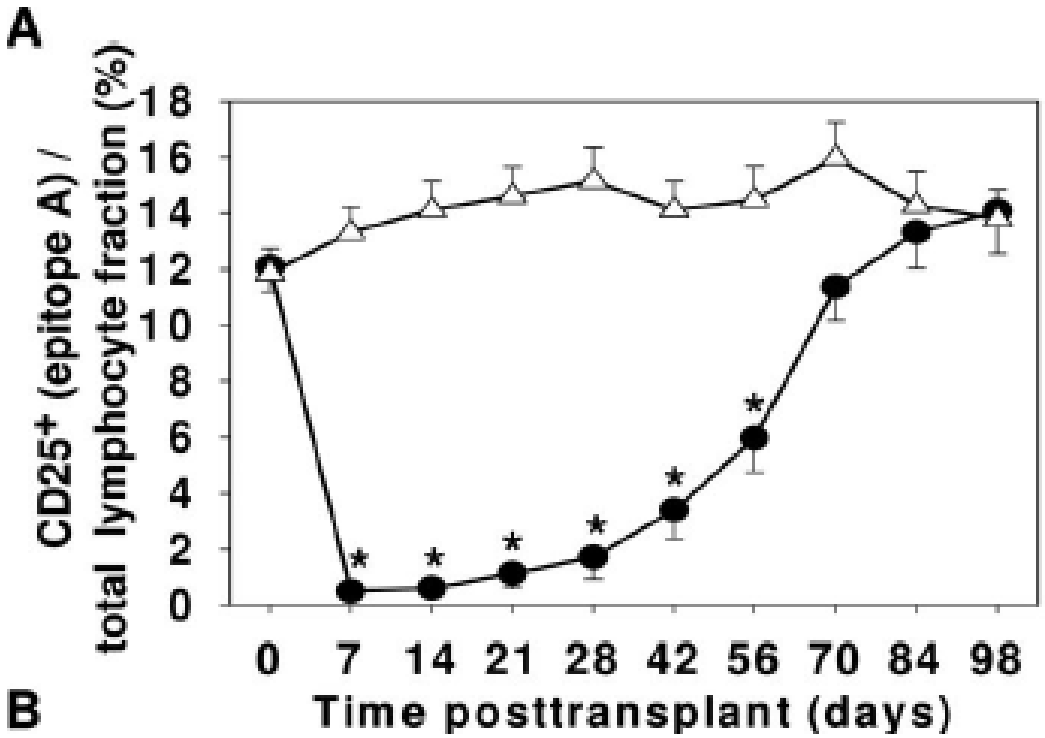
Thymoglo-buline (polyclonal IgG) 	**Target:** T cells: CD3, CD4, CD8, CD58, CD28 and others; -B cells CD5, CD58, CD28, CD152 and others; -APC: HLADR, CD58, -CD80, - CD86, CD40 and others; also: several receptors present on plasma cells, monocytes, dendritic cells, leucocytes and others	**Mechanism:** Blocks several T and B cells receptors, causing cell dysfunction, lysis and long lasting depletion **Duration of effect**: up to 12 months

Antagonists of IL2 Rα - monoclonals



Pharmacokinetics and Immunodynamics of Basiliximab in Pediatric Renal Transplant Recipients on Mycophenolate Mofetil Comedication

Britta Höcker,[1] John M. Kovarik,[2] Volker Daniel,[3] Gerhard Opelz,[3] Henry Fehrenbach,[4] Martin Holder,[5] Bernd Hoppe,[6] Peter Hoyer,[7] Therese C. Jungraithmayr,[8] Sabine Köpf-Shakib,[1] Guido F. Laube,[9] Dirk E. Müller-Wiefel,[10] Gisela Offner,[11] Christian Plank,[12] Monika Schröder,[13] Lutz T. Weber,[1] Lothar B. Zimmerhackl,[8] and Burkhard Tönshoff[1,14]



Transplantation • Volume 86, Number 9, November 15, 2008

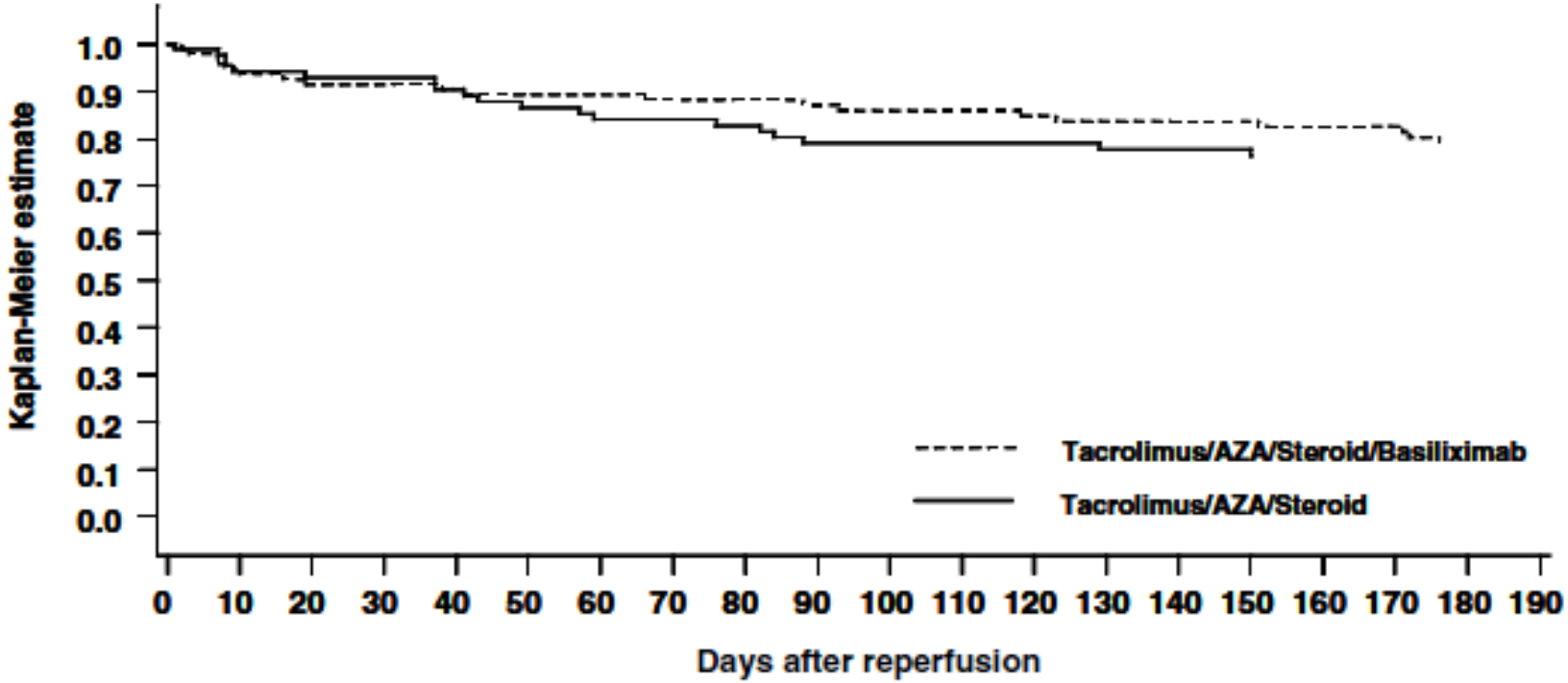
American Journal of Transplantation 2006; 6: 1666–1672
Blackwell Munksgaard

doi: 10.1111/j.1600-6143.2006.01367.x

R. Grenda[a,*], A. Watson[b], K. Vondrak[c], N. J. A. Webb[d], J. Beattie[e], M. Fitzpatrick[f], M. A. Saleem[g], R. Trompeter[h], D. V. Milford[i], N. E. Moghal[j], D. Hughes[k], F. Perner[l], S. Friman[m], R. Van Damme-Lombaerts[n] and F. Janssen[o]

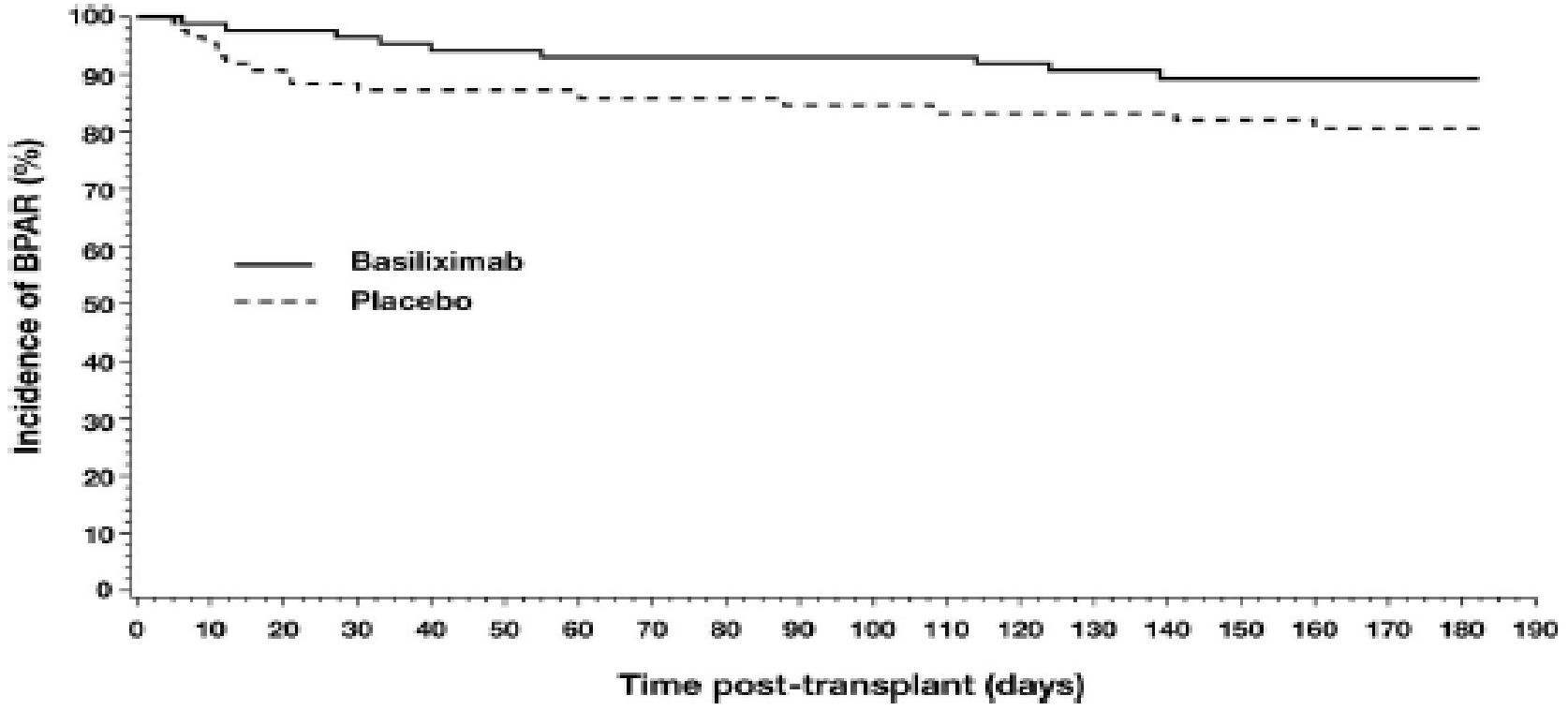
A Prospective, Randomized, Multicenter Trial of Tacrolimus-Based Therapy with or without Basiliximab in Pediatric Renal Transplantation

OVERALL ESTIMATED RATE OF PATIENTS FREE FROM ACUTE REJECTION CONFIRMED BY LOCAL BIOPSY (KAPLAN-MEIER METHOD)

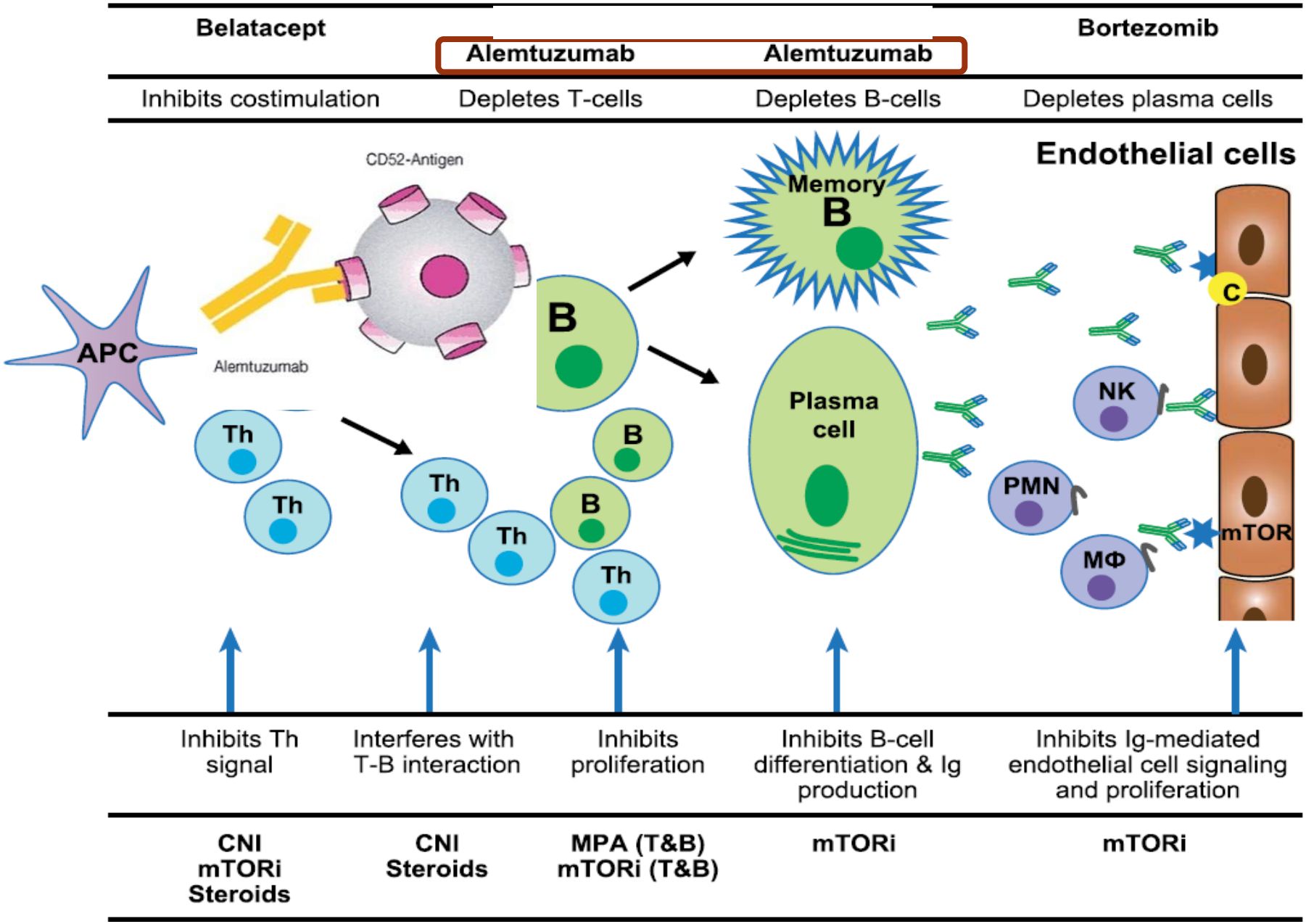


Efficacy and Safety of Basiliximab in Pediatric Renal Transplant Patients Receiving Cyclosporine, Mycophenolate Mofetil, and Steroids

Gisela Offner,[1] Burkhard Toenshoff,[2] Britta Höcker,[2] Manuela Krauss,[3] Monika Bulla,[4] Pierre Cochat,[5] Henry Fehrenbach,[6] Wolfgang Fischer,[3] Michel Foulard,[7] Bernd Hoppe,[8] Peter F. Hoyer,[9] Therese C. Jungraithmayr,[10] Günter Klaus,[11] Kay Latta,[12] Heinz Leichter,[13] Michael J. Mihatsch,[14] Joachim Misselwitz,[15] Carmen Montoya,[16] Dirk E. Müller-Wiefel,[17] Thomas J. Neuhaus,[18] Lars Pape,[1] Uwe Querfeld,[19] Christian Plank,[20] Dieter Schwarke,[21] Simone Wygoda,[22] and Lothar B. Zimmerhackl[10,23]



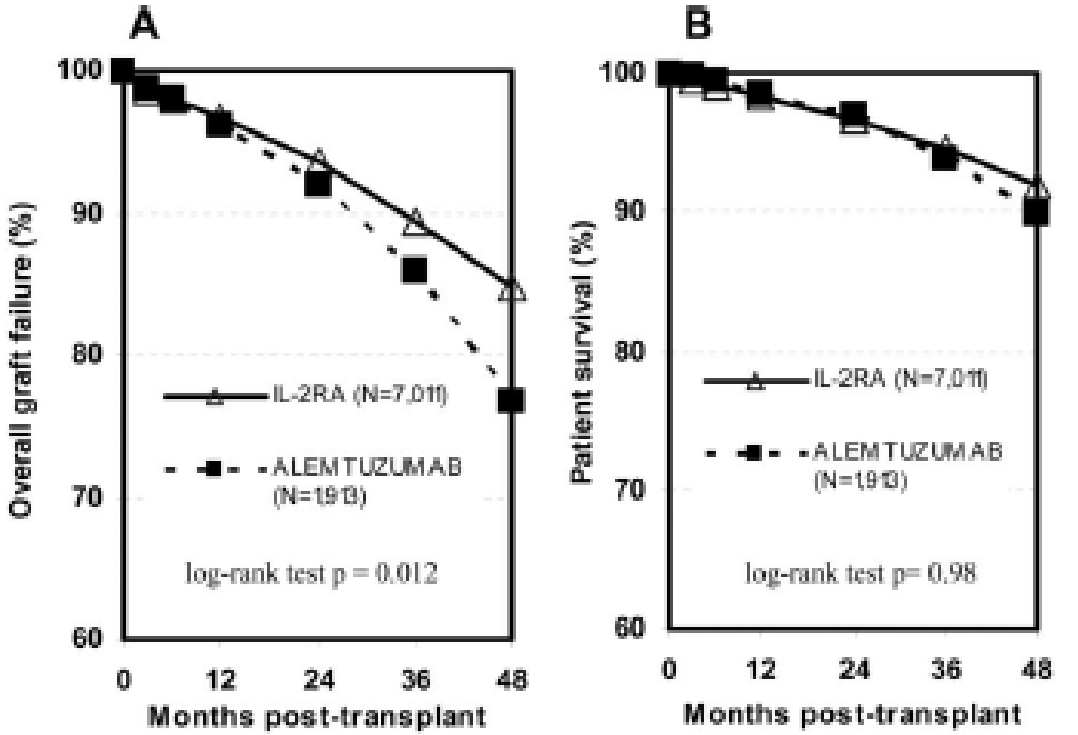
(*Transplantation* 2008;86: 1241–1248)


Belatacept
Alemtuzumab
Alemtuzumab
Bortezomib
Inhibits costimulation
Depletes T-cells
Depletes B-cells
Depletes plasma cells
Endothelial cells
CD52-Antigen
Memory B
APC
Alemtuzumab
B
Plasma cell
Th
Th
Th
Th
B
B
Th
C
NK
PMN
MΦ
mTOR
Inhibits Th signal
Interferes with T-B interaction
Inhibits proliferation
Inhibits B-cell differentiation & Ig production
Inhibits Ig-mediated endothelial cell signaling and proliferation
CNI
mTORi
Steroids
CNI
Steroids
MPA (T&B)
mTORi (T&B)
mTORi
mTORi

Alemtuzumab Versus Interleukin-2 Receptor Antibodies Induction in Living Donor Kidney Transplantation

(*Transplantation* 2009;88: 904–910)

Marcelo S. Sampaio,[1,2] Aditya Kadiyala,[1] Jagbir Gill,[3] and Suphamai Bunnapradist[1,4]



Number at risk (0, 12, 24, 36 and 48 months)

IL-2	7,011	5173	3325	1602	354
Alem	1913	1268	652	193	38

7,011	5250	3408	1664	364
1913	1295	682	207	39

ANTILYMPHOID ANTIBODY PRECONDITIONING AND TACROLIMUS MONOTHERAPY FOR PEDIATRIC KIDNEY TRANSPLANTATION

RON SHAPIRO, MD, DEMETRIUS ELLIS, MD, HENKIE P. TAN, MD, PHD, MICHAEL L. MORITZ, MD, AMIT BASU, MD, ABHAY N. VATS, MD, AKHTAR S. KHAN, MD, EDWARD A. GRAY, BS, ADRIANNA ZEEVI, PHD, CORDE MCFEATERS, RN, BSN, GERRI JAMES, RN, CCTC, MARY JO GROSSO, RN, MSN, AMADEO MARCOS, MD, AND THOMAS E. STARZL, MD, PHD

(J Pediatr 2006;148:813-8)

Table II. Results in the 16 patients with functioning grafts*

	All (n 16)	ATG (n 7)	Alemtuzumab (n 9)
Follow-up months	22 ± 4.9	26 ± 2.8	18 ± 2.6
Creatinine	0.85 ± 0.35	0.96 ± 0.30	0.77 ± 0.38
Creatinine clearance	90.8 ± 22.1	75.6 ± 12.5	102.5 ± 21.0
Spaced dose weaning	14 (88%)	5 (71%)	9 (100%)
Months to spaced dosing	11.1 ± 3.5	11.7 ± 3.8	9.9 ± 2.3
Months since spaced dosing	10.5 ± 5.1	14.3 ± 5.4	8.4 ± 3.6
Received post-transplant prednisone	3†	2†	1‡
Acute rejection	1 (6%)	1 (14%)	0
Delayed graft function	0	0	0
Patients biopsied	6 (38%)	3 (43%)	3 (33%)
PTLD	0	0	0
CMV	0	0	0
Polyoma (BK) virus	0	0	0
Post-transplant diabetes	2 (13%)‡	0	2 (22%)‡
Autoimmune hemolytic anemia	2 (13%)	1 (14%)	1 (11%)

Pediatric Living Donor Kidney Transplantation Under Alemtuzumab Pretreatment and Tacrolimus Monotherapy: 4-Year Experience

Henkie P. Tan, Joseph Donaldson, Demetrius Ellis, Michael L. Moritz, Amit Basu, Claire Morgan, Abhay N. Vats, Elif Erkan, and Ron Shapiro

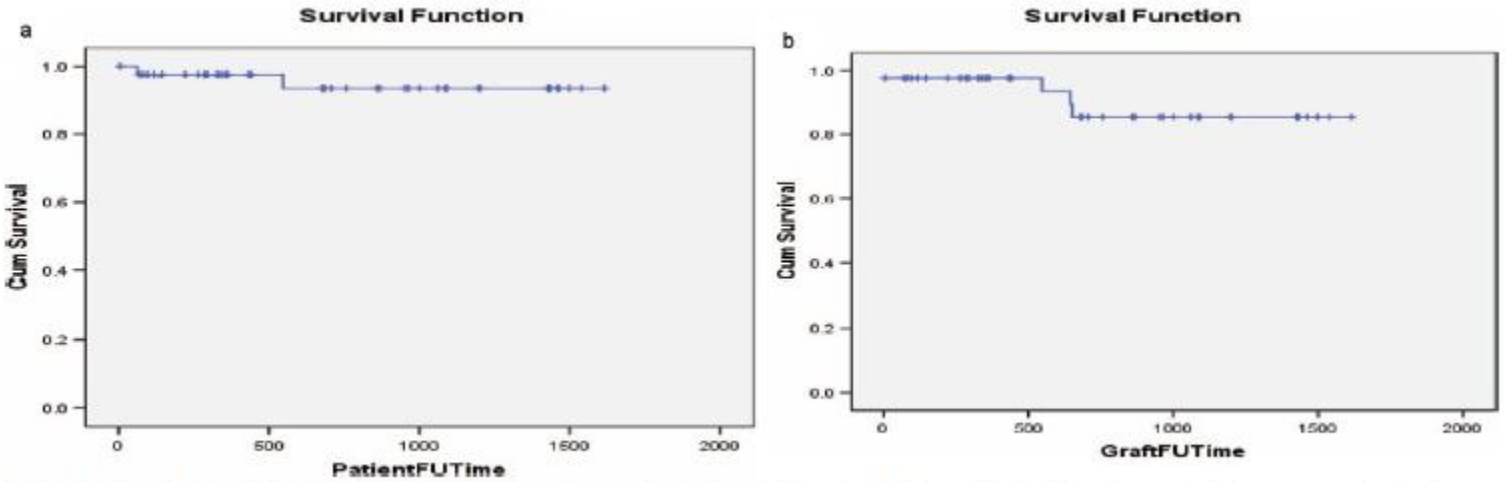


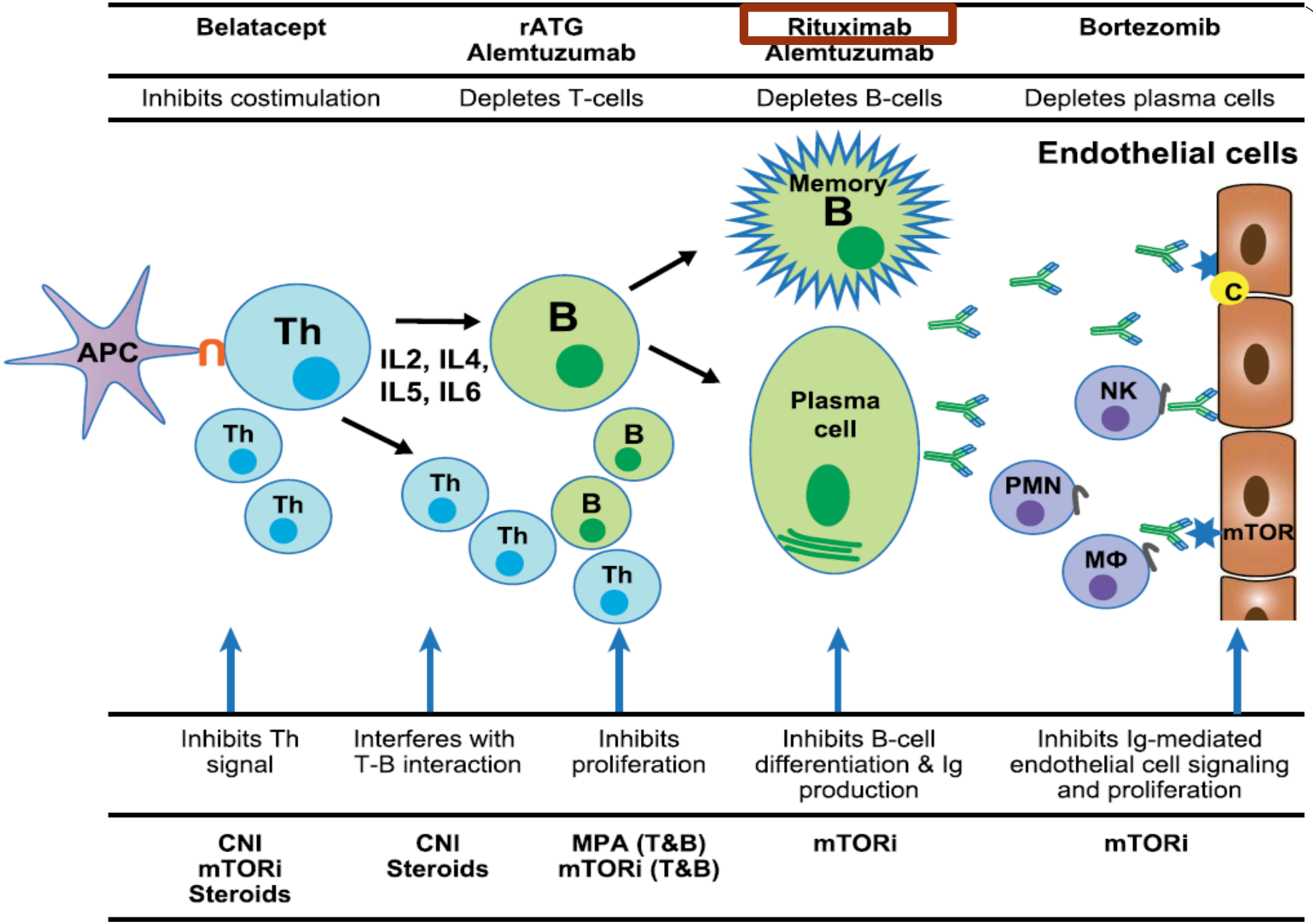
FIGURE 1. Actuarial (a) patient and (b) graft survival of recipients of 42 pediatric live-donor kidney transplantation.

TABLE 3. Mean tacrolimus trough levels

	All recipients	Weaned recipients
At 1 yr	4.4±3.5	3.3±3.1
At 2 yr	3.2±2.6	ND
At 3 yr	3.7±2.0	3.5±1.9
At 4 yr	ND	ND

ND, nondetectable (<3 ng/dL).

(Transplantation 2008;86: 1725–1731)


Belatacept
rATG
Alemtuzumab
Rituximab
Alemtuzumab
Bortezomib
Inhibits costimulation
Depletes T-cells
Depletes B-cells
Depletes plasma cells
Endothelial cells
Memory B
APC
Th
IL2, IL4, IL5, IL6
B
Plasma cell
C
NK
PMN
MΦ
mTOR
Inhibits Th signal
Interferes with T-B interaction
Inhibits proliferation
Inhibits B-cell differentiation & Ig production
Inhibits Ig-mediated endothelial cell signaling and proliferation
CNI
mTORi
Steroids
CNI
Steroids
MPA (T&B)
mTORi (T&B)
mTORi
mTORi

Clin Transplant 2005: 19: 137–140 DOI: 10.1111/j.1399-0012.2004.00292.x

Clinical Transplantation

Morufu Alausa[a], Urias Almagro[b], Nauman Siddiqi[a], Ron Zuiderweg[a], Radhika Medipalli[a] and Sundaram Hariharan[a]

Refractory acute kidney transplant rejection with CD20 graft infiltrates and successful therapy with rituximab

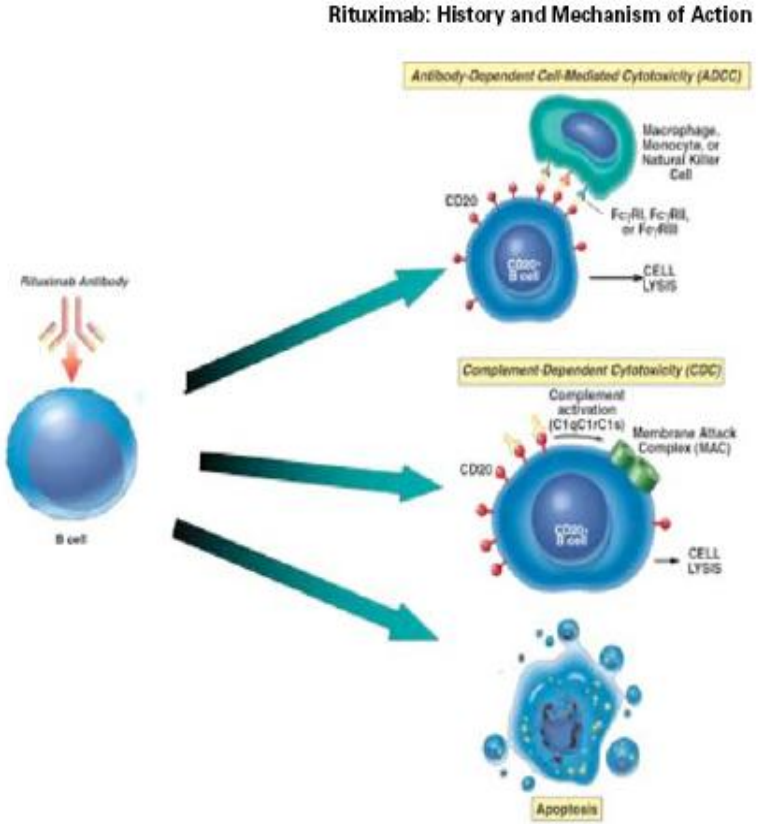


Figure 3. There are three postulated mechanisms of action of rituximab for B-cell depletion. These are complement-mediated cytotoxicity, antibody-dependent cell-mediated cytotoxicity and induction of apoptosis. *In vivo*, most likely the first mechanisms are dominant and the primary mechanism might depend on the specific anatomic location of the cell.

The NEW ENGLAND JOURNAL of MEDICINE

ORIGINAL ARTICLE

Rituximab and Intravenous Immune Globulin for Desensitization during Renal Transplantation

Ashley A. Vo, Pharm.D., Marina Lukovsky, Pharm.D., Mieko Toyoda, Ph.D., Jennifer Wang, M.D., Nancy L. Reinsmoen, Ph.D., Chih-Hung Lai, Ph.D., Alice Peng, M.D., Rafael Villicana, M.D., and Stanley C. Jordan, M.D.

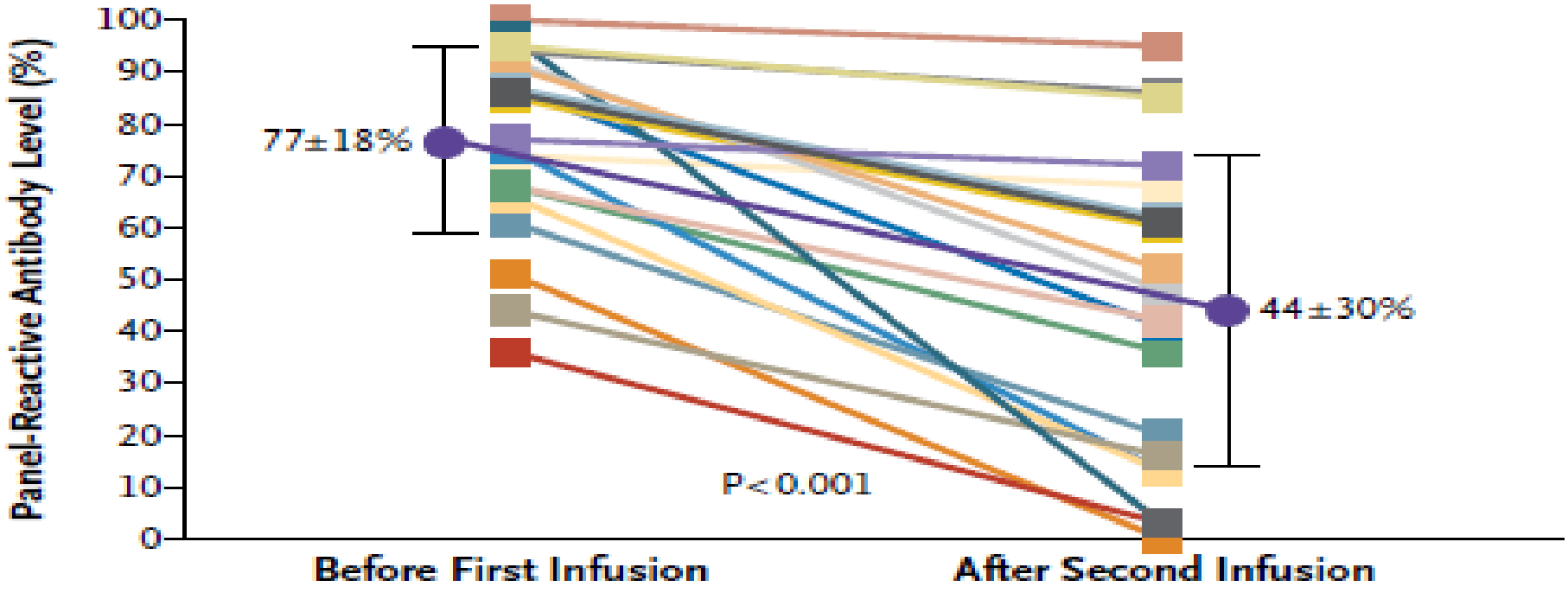
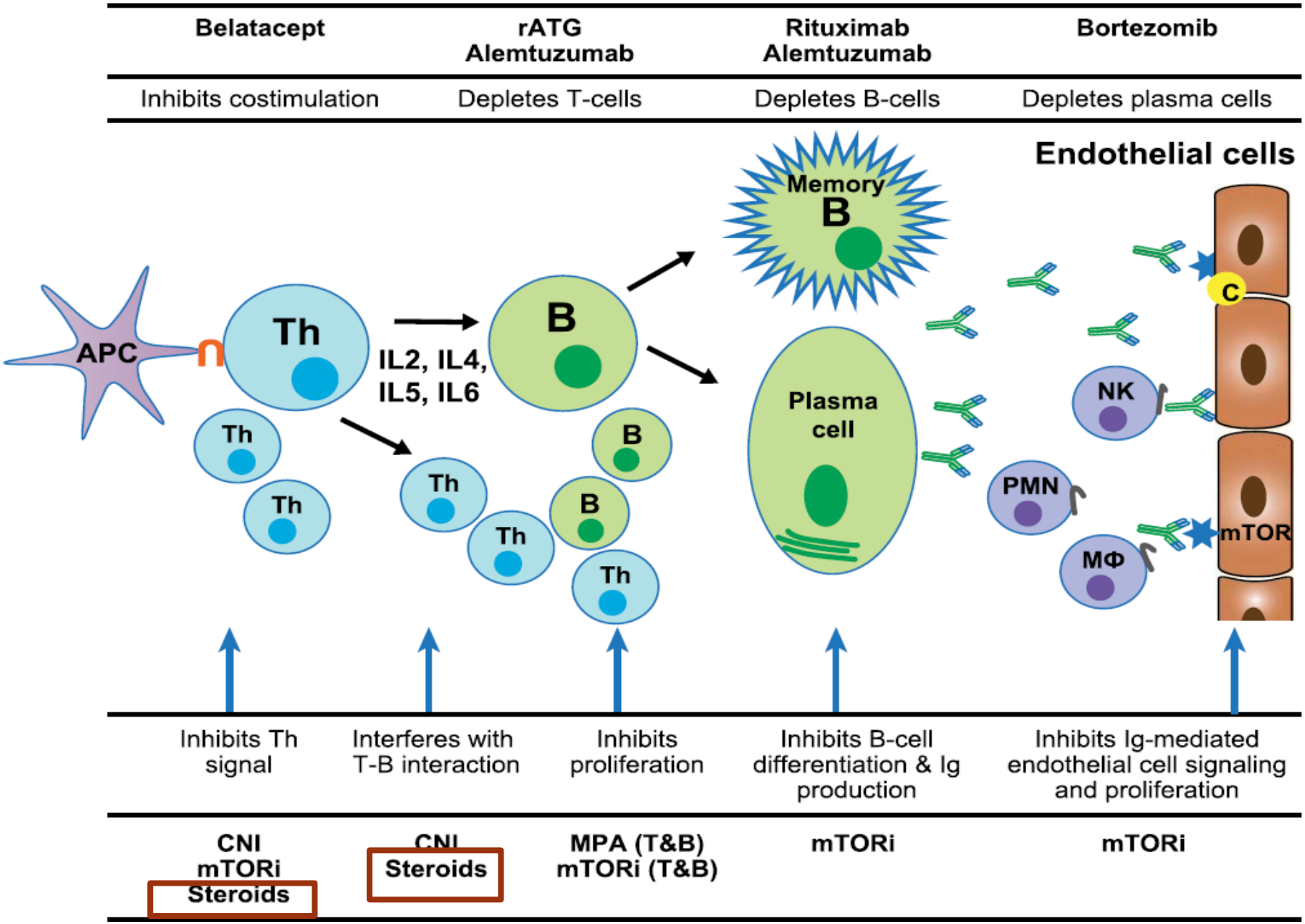


Figure 1. Panel-Reactive Antibody Levels in the 20 Study Patients.

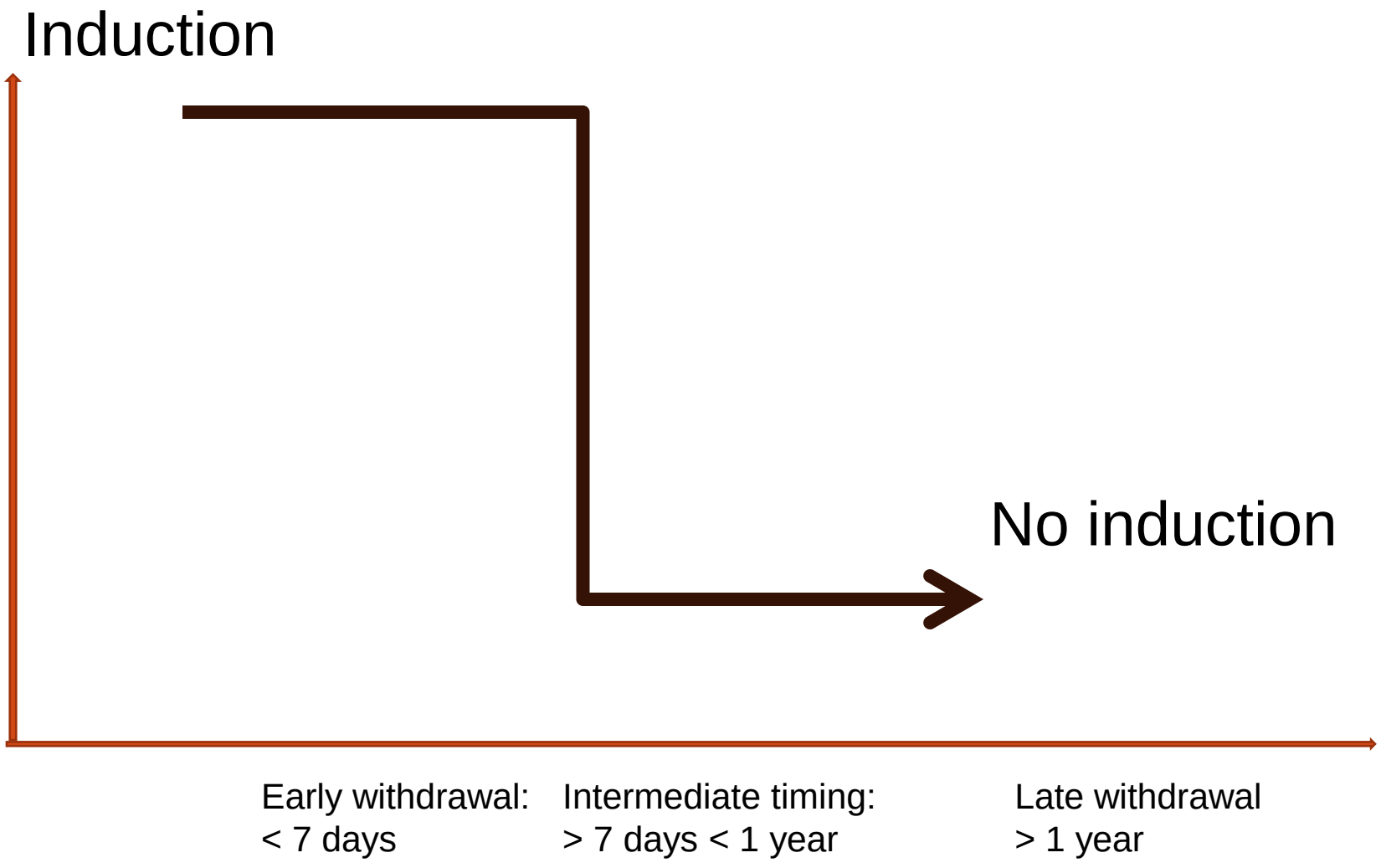

Belatacept
rATG
Alemtuzumab
Rituximab
Alemtuzumab
Bortezomib
Inhibits costimulation
Depletes T-cells
Depletes B-cells
Depletes plasma cells
Endothelial cells
Memory
B
APC
Th
IL2, IL4,
IL5, IL6
B
Plasma
cell
C
NK
PMN
MΦ
mTOR
Inhibits Th
signal
Interferes with
T-B interaction
Inhibits
proliferation
Inhibits B-cell
differentiation & Ig
production
Inhibits Ig-mediated
endothelial cell signaling
and proliferation
CNI
mTORi
Steroids
CNI
Steroids
MPA (T&B)
mTORi (T&B)
mTORi
mTORi

Expected benefits and disadvantages from steroid withdrawal in children

Expected benefits & avoidance of specific drugs	Potential disadvantages & risks
Improved glucose metabolism (less PTDM; **no insulin**/ oral drugs)	Higher rate of acute rejection ?
Better lipid profile (**no statins**)	Inferior graft function ?
Better control of hypertension (less or **no hypotensives)**	Poor long-term graft survival ?
Better growth (**no growth hormone)**	Higher *de novo* DSA production?
Better (preserved?) bone mineral density	
Less cosmetic defects	

Policies aimed to minimize steroid-related comorbidities

Management policy	Criterion
Late withdrawal	Safe post-transplant clinical course over time (**no rejection; stable GFR**) or protocol biopsy (**no rejection**)
Complete avoidance Early withdrawal	Pre-defined pre- transplant entry criteria (**mainly low immunologic risk**)

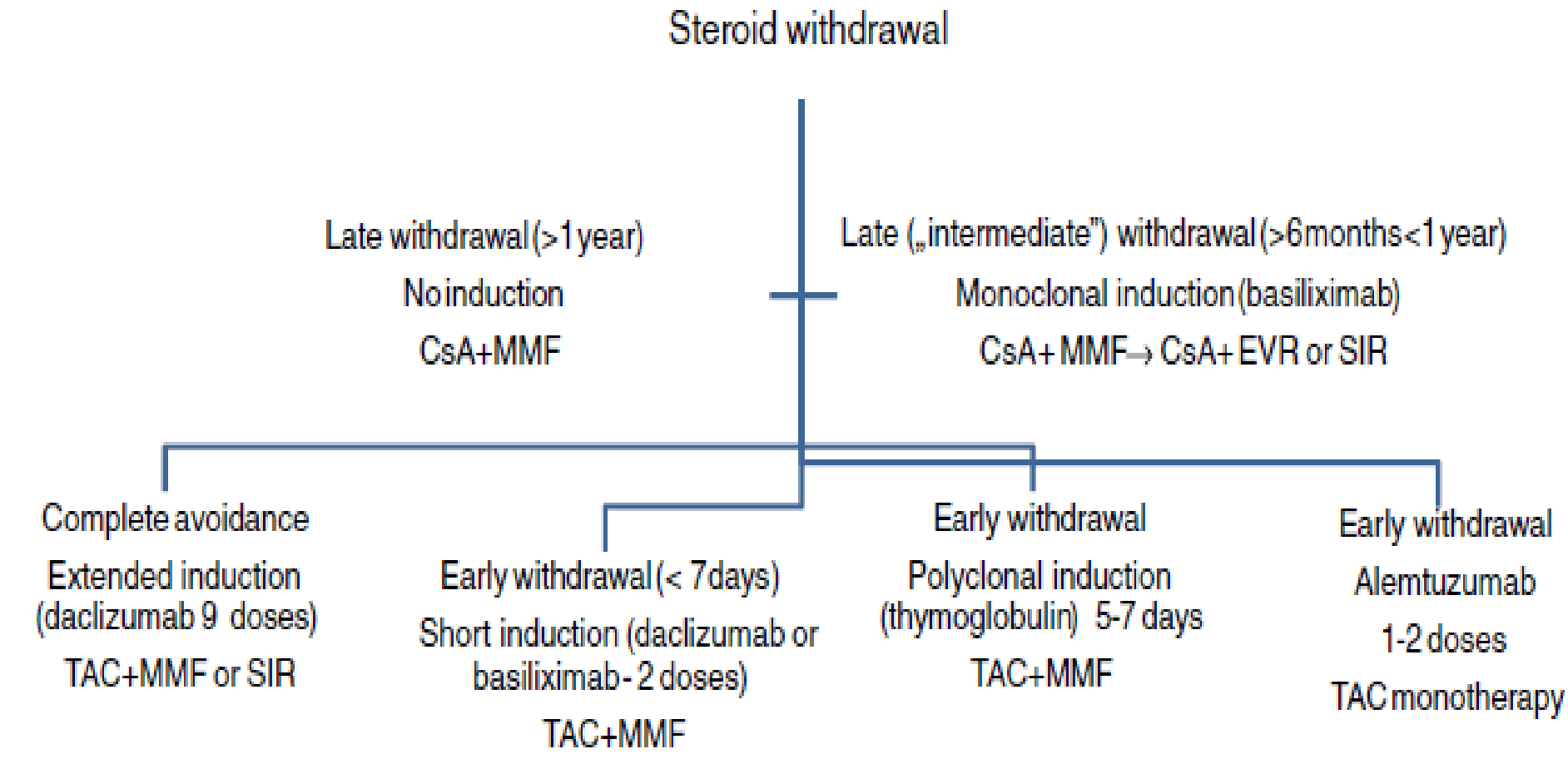

Induction
No induction
Early withdrawal:
< 7 days
Intermediate timing:
> 7 days < 1 year
Late withdrawal
> 1 year

Pediatr Nephrol (2013) 28:2107–2112
DOI 10.1007/s00467-012-2391-6

EDUCATIONAL REVIEW

Steroid withdrawal in renal transplantation

Ryszard Grenda



Steroid minimization

- Effective and safe in low risk patients
- Pre-pubertal childred gain growth acceleration
- All patients gain other clinical advantages: better control of lipidemia, glycaemia, blood pressure and absence of cosmetic disfigurement
- High risk patients: minor experience, polyclonal depelting induction required

American Journal of Transplantation 2015; 15: 2203–2210
Wiley Periodicals Inc.

doi: 10.1111/ajt.13270

Brief Communication

Clinical Practice of Steroid Avoidance in Pediatric Kidney Transplantation

E. Nehus[1,2,*], C. Liu[3], D. K. Hooper[1,2,4], M. Macaluso[2,3] and M.-O. Kim[2,3]

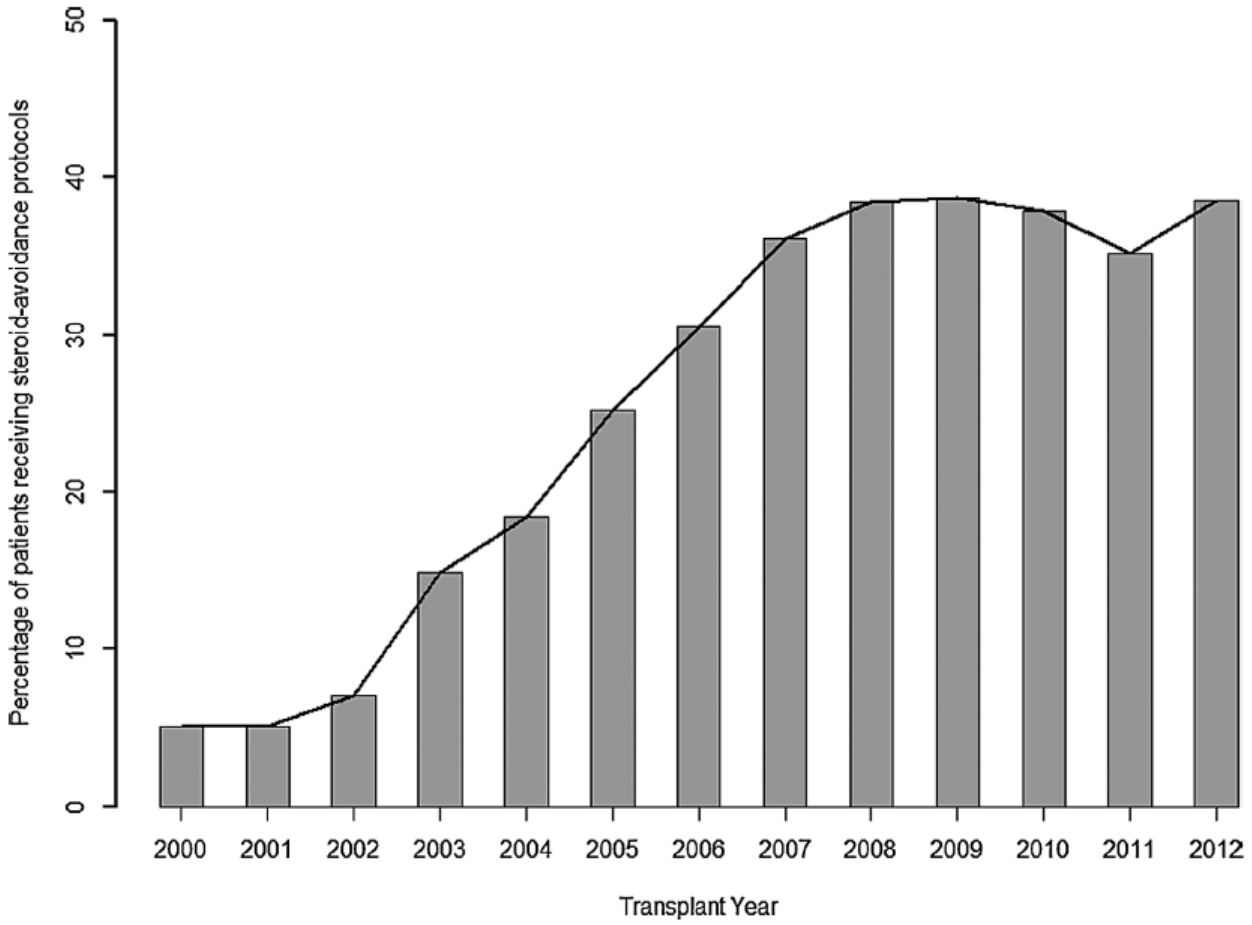
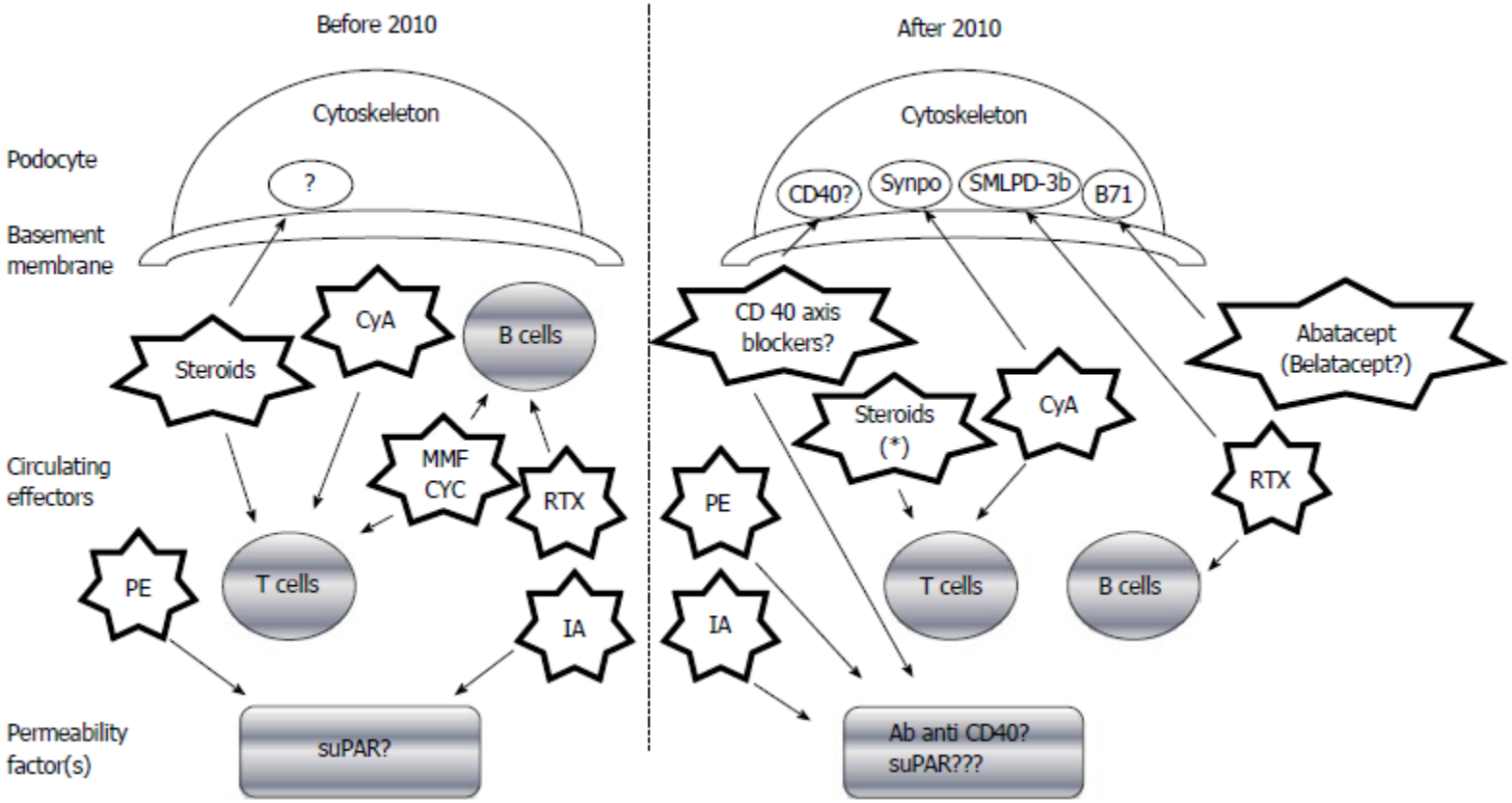


Figure 1: Percentage of patients treated with steroid avoidance by transplant year.

Treatment on NS recurrence



Use of Rituximab in Focal Glomerulosclerosis Relapses After Renal Transplantation

Luca Dello Strologo,[1,5] Isabella Guzzo,[1] Chiara Laurenzi,[1] Marina Vivarelli,[1] Angelica Parodi,[2] Giancarlo Barbano,[2] Roberta Camilla,[3] Floriana Scozzola,[4] Alessandro Amore,[3] Fabrizio Ginevri,[2] and Luisa Murer[4]

(*Transplantation* 2009;88: 417–420)

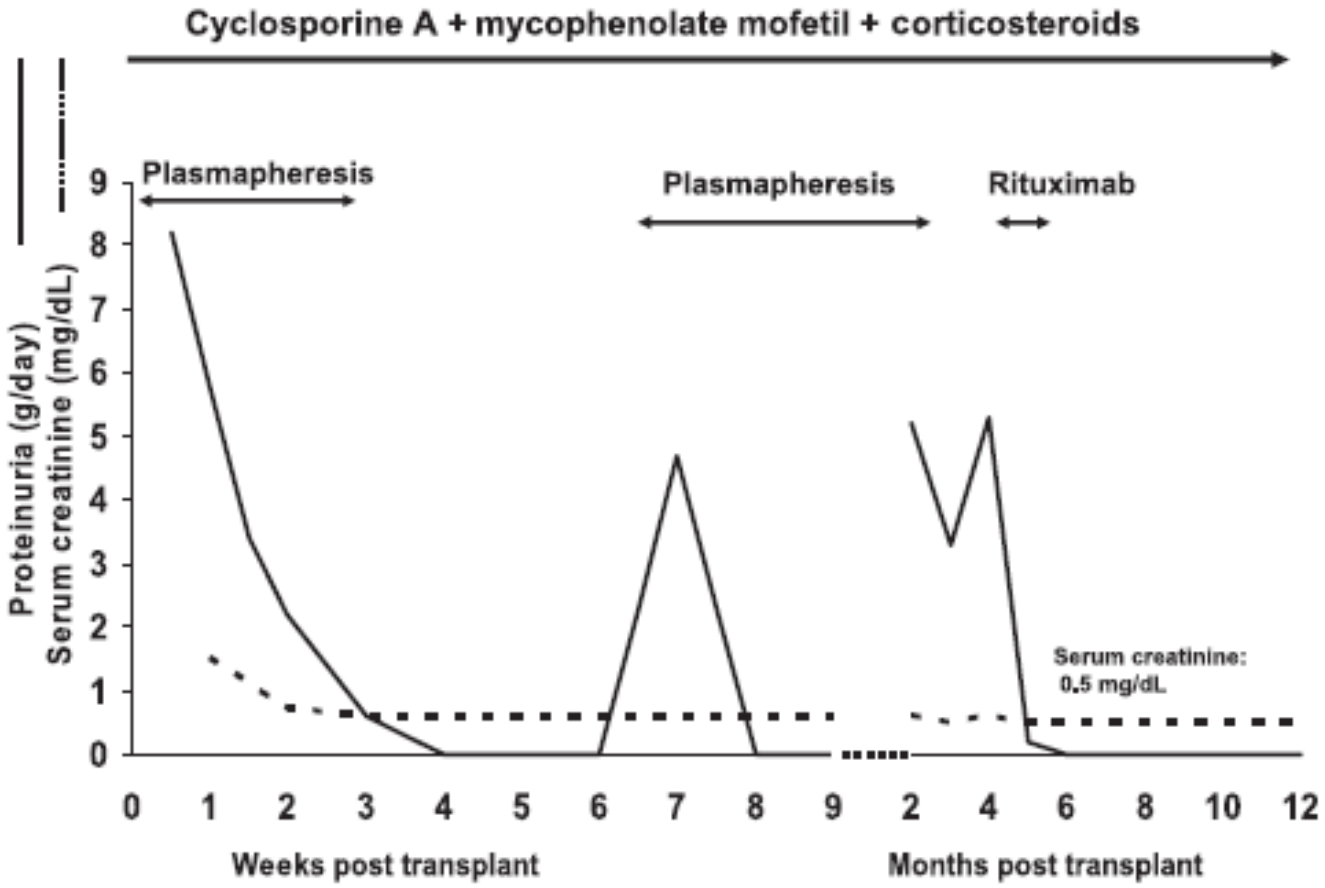
TABLE 1. Clinical characteristics of the patients

	Case 1	Case 2	Case 3	Case 4	Case 5	Case 6
Age at onset of FSGS (yr)	2.1	3.6	14	2	4.2	5
Age at transplant (yr)	9.4	24.1	26.9	13.4	7.3	12.4
Posttransplant follow-up before relapse (mo)	117.1	0.3	12.6	2.8	0.03	0.03
Glomeruli with global sclerosis pretreatment (%)	NA	5	0	0	0	0
Glomeruli with focal sclerosis pretreatment (%)	NA	32,5	0	15	0	15
Numbers of glomeruli in the specimen	—	40	14	13	14	18
Pretransplant HLA donor antibodies	Negative	Negative	Negative	Negative	Negative	Negative
Delay between relapse and PE (d)	2	867	30	4	1	42
Number of PE sessions	16	17	29	66	10	10
Delay between relapse and rituximab (d)	32	1086	167	242	11	64
Number of rituximab infusions (initial)	2	1	2	2	2	4
GFR before treatment with PE (mL/min/1.73 m^2)	65	116	37	105	10	60
GFR post-rituximab (mL/min/1.73 m^2)	107	110	120	172	105	27
Serum albumin before PE (g/dL)	1.4	3	3.7	3.2	2.4	2.6
Serum albumin post-rituximab (g/dL)	4.1	2.9	3.2	3.2	3.9	2.1
Urine protein over creatinine ratio before PE	17	2	3	7.1	9.5	17
Urine protein over creatinine ratio at start of rituximab	7.2	2.7	2.5	9.7	6.2	17
Urine protein over creatinine ratio post-rituximab	0.1	1.3	0.2	2.3	0	35
Response	Complete	Partial	Complete	Partial	Complete	Failure
Time to response (mo)	2	5	4	7	<1	—

Long-term effect of rituximab in maintaining remission of recurrent and plasmapheresis-dependent nephrotic syndrome post-renal transplantation

Pediatric Transplantation

Ryszard Grenda[1], Wioletta Jarmużek[1], Barbara Piątosa[2] and Jacek Rubik[1]



Eur J Pediatr (2016) 175:1133–1137
DOI 10.1007/s00431-016-2747-1

ORIGINAL ARTICLE

Rituximab is not a "magic drug" in post-transplant recurrence of nephrotic syndrome

Ryszard Grenda[1] · Wioletta Jarmużek[1] · Jacek Rubik[1] · Barbara Piątosa[2] · Sylwester Prokurat[1]

Table 1 Clinical chacteristics and treatment course of five children with post-transplant recurrence of nephrotic syndrome

Patient no.	Age at diagnosis of NS (years), gender renal biopsy	Age at transplantation (years) origin of the graft	Timing of NS recurrence post-transplant (days)	Treatment day of rituximab introduction after transplantation	Duration of B CD19 depletion (months)/correlation of number of B CD_{19} cells to clinical effect	Clinical effects renal graft biopsy	SAE
1	2, male FSGS	5.5 deceased donor	1	PF + CsA + MMF + MP + rituximab 4 × 375 mg/m^2 day 133	4 Yes	Complete remission (7 years of follow-up) MCNS	No
2	2, female MCNS	5 deceased donor	1	PF + CsA + MMF + MP + rituximab 4 × 375 mg/m^2 + galactose day 25	3 No	Failure; graft removed 7 months later FSGS	No
3	2, female MesPGN (NPHS2 gene mutation-single heterozygous mutation; p.R229Q)	10 living-related donor	1	PF + CsA + MMF + MP + rituximab 4 × 375 mg/m^2 day 15	2 Yes	Complete remission (5 years of follow-up) FSGS	No
4	6, female FSGS	12 deceased donor	1	PF + CsA + MMF + MP + rituximab 2 × 375 mg/m^2 day 21	7 no	Partial remission; graft removed 2.5 years later FSGS	Relapsing severe infections
5	6, male MesPGN	10 deceased donor	2	PF + CsA + MMF + MP + rituximab 4 × 375 mg/m^2 day 15	4 no	Partial remission MPGN	RALI (fatal)

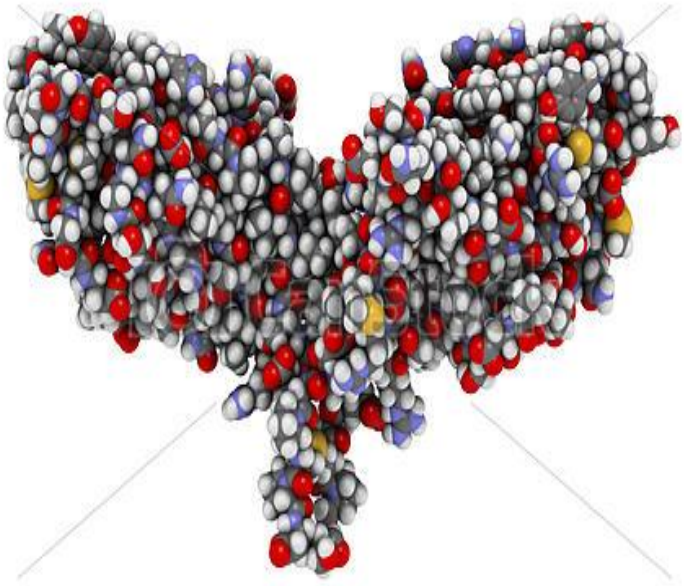
MesPGN mesangial-proliferative glomerulonephritis, *FSGS* focal segmental glomerulosclerosis, *MCNS* minimal change nephrotic syndrome, *NPHS2* podocine, *CsA* cyclosporine A, *MMF* mycophenolate mofetil, *MP* methylprednisolone, *PF* plasmapheresis, *SAE* serious adverse events, *RALI* rituximab-related acute lung injury

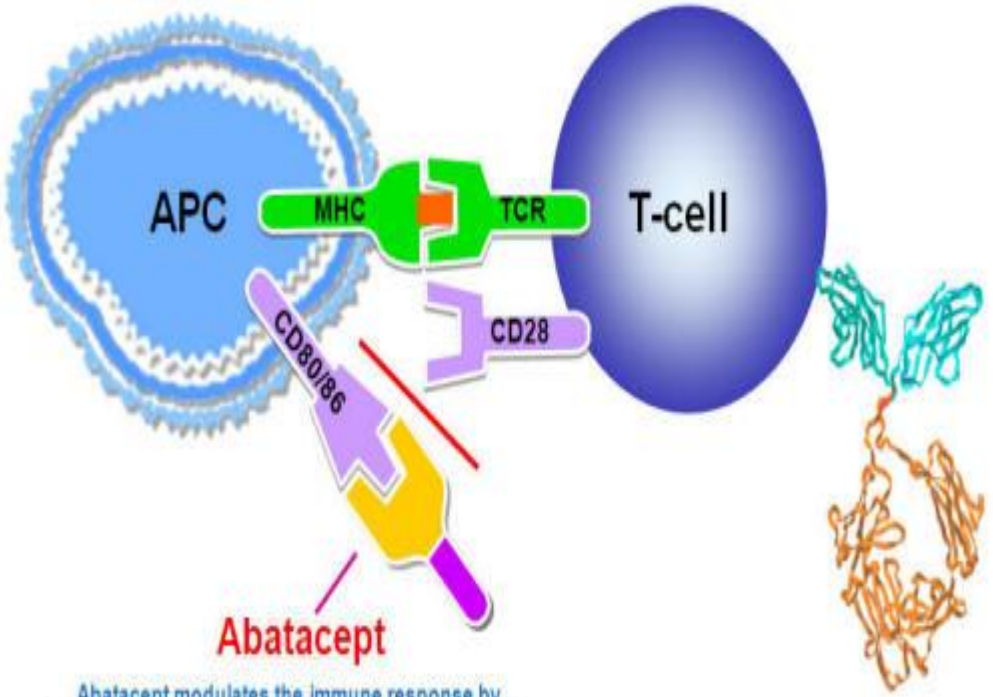
Abatacept in B7-1–Positive Proteinuric Kidney Disease

N ENGL J MED 369;25 NEJM.ORG DECEMBER 19, 2013

Chih-Chuan Yu, M.Sc., Alessia Fornoni, M.D., Ph.D., Astrid Weins, M.D., Ph.D., Samy Hakroush, M.D., Dony Maiguel, Ph.D., Junichiro Sageshima, M.D., Linda Chen, M.D., Gaetano Ciancio, M.D., Mohd. Hafeez Faridi, Ph.D., Daniel Behr, Kirk N. Campbell, M.D., Jer-Ming Chang, M.D., Hung-Chun Chen, M.D., Jun Oh, M.D., Christian Faul, Ph.D., M. Amin Arnaout, M.D., Paolo Fiorina, M.D., Ph.D., Vineet Gupta, Ph.D., Anna Greka, M.D., Ph.D., George W. Burke III, M.D., and Peter Mundel, M.D.

Recombinant fusion protein (CTLA-4) combined with Fc fragment of human IgG1





Abatacept modulates the immune response by binding to CD80/CD86 on an antigen-presenting cell (APC), such as a dendritic cell, thus preventing costimulatory binding of CD28 on naive T cells and attenuating T-cell activation.

Table 1. Characteristics of Five Patients with Focal Segmental Glomerulosclerosis (FSGS).

Variable	Patient 1	Patient 2	Patient 3	Patient 4	Patient 5
Age and sex	28-yr-old woman	19-yr-old woman	14-yr-old boy	7-yr-old boy	27-yr-old woman
Kidney donor	Living related donor; earlier transplant from a living related donor failed owing to recurrent FSGS	Cadaveric donor; earlier transplant from a living related donor failed owing to recurrent FSGS	Living related donor	Cadaveric donor	No donor (native kidney)
Induction immunosuppression	Daclizumab (1 mg/kg, two doses), antithymocyte globulin (1 mg/kg, five doses), rituximab (375 mg/m^2, one dose)	Daclizumab (1 mg/kg, two doses), antithymocyte globulin (1 mg/kg, five doses), rituximab (375 mg/m^2, one dose)	Antithymocyte globulin (1 mg/kg, five doses), basiliximab (10 mg/kg, two doses), rituximab (375 mg/m^2, one dose)	Antithymocyte globulin (1 mg/kg, five doses), basiliximab (10 mg/kg, two doses), rituximab (375 mg/m^2, one dose)	
Maintenance immunosuppression	Tacrolimus (target serum level, 5–7 ng/ml), mycophenolate mofetil (500 mg twice daily), glucocorticoids	Tacrolimus (target serum level, 5–7 ng/ml), mycophenolate mofetil (500 mg twice daily), glucocorticoids	Tacrolimus (target serum level, 5–7 ng/ml), mycophenolate mofetil (125–250 mg twice daily), glucocorticoids	Tacrolimus (target serum level, 5–7 ng/ml), mycophenolate mofetil (125–250 mg twice daily), glucocorticoids	
Treatment for FSGS before abatacept therapy	Plasmapheresis	Plasmapheresis	Plasmapheresis	Plasmapheresis	Prednisone, cyclosporine, tacrolimus
Abatacept therapy	Single dose (10 mg/kg)	Single dose (10 mg/kg)	Two doses (10 mg/kg)	Two doses (10 mg/kg)	10 mg/kg on days 1, 15, and 30 and monthly thereafter
Most recent laboratory test results*	48-mo follow-up (February 2013): serum albumin, 3.4 g/dl; serum creatinine, 1.3 mg/dl; urinary protein-to-creatinine ratio, 0.50	36-mo follow-up (February 2013): serum albumin, 3.8 g/dl; serum creatinine, 0.7 mg/dl; urinary protein-to-creatinine ratio, 0.41	12-mo follow-up (February 2013): serum albumin, 4.0 g/dl; serum creatinine, 0.9 mg/dl; urinary protein-to-creatinine ratio, 0.08	10-mo follow-up (March 2013): serum albumin, 4.3 g/dl; serum creatinine, 0.3 mg/dl; urinary protein-to-creatinine ratio, 0.05	12-mo follow-up (October 2013): serum albumin, 3.8 g/dl; serum creatinine, 0.4 mg/dl; urinary protein-to-creatinine ratio, 0.50

* To convert values for creatinine to micromoles per liter, multiply by 88.4. A urinary protein-to-creatinine ratio of less than 0.15 is considered normal.

We treated five patients with abatacept[3]; nephrotic-range proteinuria resolved in all four patients with rituximab-resistant recurrent FSGS and in one patient with glucocorticoid-resistant primary FSGS.

Update on the treatment of focal segmental glomerulosclerosis in renal transplantation

Maria Messina, Ester Gallo, Alberto Mella, Fabiola Pagani, Luigi Biancone

World J Transplant 2016 March 24; 6(1): 54-68

Alachkar *et al*[104]	Abatacept (1 dose; 10 mg/kg) in patient 1; belatacept (3 doses 10 mg/kg or continuative treatment) in patients 2-5	5 patients (≥ 18 yr)	No response	
Garin *et al*[105]	Abatacept (1 or 2 doses; 10 mg/kg) or belatacept (16 doses 5 mg/kg)	5 patients (2/5 < 18 yr with minimal change in disease or FSGS on native kidneys; 3/5 with FSGS recurrence (1/3 < 18 yr, 2/3 ≥ 18 yr)	Partial response in minimal change disease patient; no response in primary FSGS patient; partial remission in 1/3 with FSGS recurrence (abatacept treated); no response in 2/3 (abatacept/ belatacept treated respectively)	Patients 1, 2 and 4 received 2 abatacept doses: patient 3 received 1 abatacept dose; patient 5 was treated with belatacept
Alkandari *et al*[106]	Abatacept (3 doses; 10 mg/kg)	1 patient (< 18 yr)	No response	
Grellier *et al*[107]	Belatacept (days 1, 15, 30 and monthly thereafter, 5 mg/kg)	5 patients (≥ 18 yr)	Partial response in 2/5; no response in 3/5 (no worsening in proteinuria values pre- and post-belatacept therapy in 1/3)	

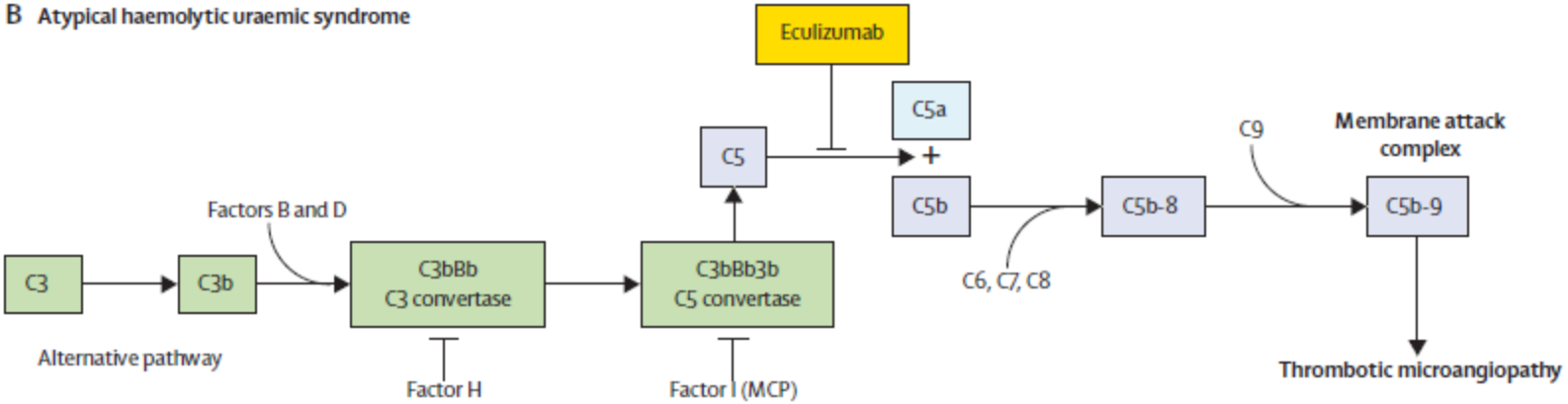
Use of Rituximab in Focal Glomerulosclerosis Relapses After Renal Transplantation

Luca Dello Strologo,[1,5] Isabella Guzzo,[1] Chiara Laurenzi,[1] Marina Vivarelli,[1] Angelica Parodi,[2] Giancarlo Barbano,[2] Roberta Camilla,[3] Floriana Scozzola,[4] Alessandro Amore,[3] Fabrizio Ginevri,[2] and Luisa Murer[4]

(*Transplantation* 2009;88: 417–420)

TABLE 1. Clinical characteristics of the patients

	Case 1	Case 2	Case 3	Case 4	Case 5	Case 6
Age at onset of FSGS (yr)	2.1	3.6	14	2	4.2	5
Age at transplant (yr)	9.4	24.1	26.9	13.4	7.3	12.4
Posttransplant follow-up before relapse (mo)	117.1	0.3	12.6	2.8	0.03	0.03
Glomeruli with global sclerosis pretreatment (%)	NA	5	0	0	0	0
Glomeruli with focal sclerosis pretreatment (%)	NA	32,5	0	15	0	15
Numbers of glomeruli in the specimen	—	40	14	13	14	18
Pretransplant HLA donor antibodies	Negative	Negative	Negative	Negative	Negative	Negative
Delay between relapse and PE (d)	2	867	30	4	1	42
Number of PE sessions	16	17	29	66	10	10
Delay between relapse and rituximab (d)	32	1086	167	242	11	64
Number of rituximab infusions (initial)	2	1	2	2	2	4
GFR before treatment with PE (mL/min/1.73 m^2)	65	116	37	105	10	60
GFR post-rituximab (mL/min/1.73 m^2)	107	110	120	172	105	27
Serum albumin before PE (g/dL)	1.4	3	3.7	3.2	2.4	2.6
Serum albumin post-rituximab (g/dL)	4.1	2.9	3.2	3.2	3.9	2.1
Urine protein over creatinine ratio before PE	17	2	3	7.1	9.5	17
Urine protein over creatinine ratio at start of rituximab	7.2	2.7	2.5	9.7	6.2	17
Urine protein over creatinine ratio post-rituximab	0.1	1.3	0.2	2.3	0	35
Response	Complete	Partial	Complete	Partial	Complete	Failure
Time to response (mo)	2	5	4	7	<1	—



Gene or subgroup	Frequency in aHUS	Minimal age at onset		Risk of death or ESRD at 1st episode or within < 1 y	Risk of relapses	Risk of recurrence after renal transplantation
		Children	Adults			
CFH	20-30%	Birth	any age	50-70%	50%	75-90%
CFI	4 -10%	Birth	any age	50%	10-30%	45-80%
MCP	5 -15%	> 1 y	any age	0-6%	70-90%	< 20%
C3	2 -10%	7 m	any age	60%	50%	40-70%
CFB	1-4%	1 m	any age	50%	3/3 not in ESRD	100%
THBD	3 -5%	6 m	rare	50%	30%	1 patient
Anti-CFH Ab	6%	Mostly 7-11 y		30-40%	40-60%	Yes if high Ab titer

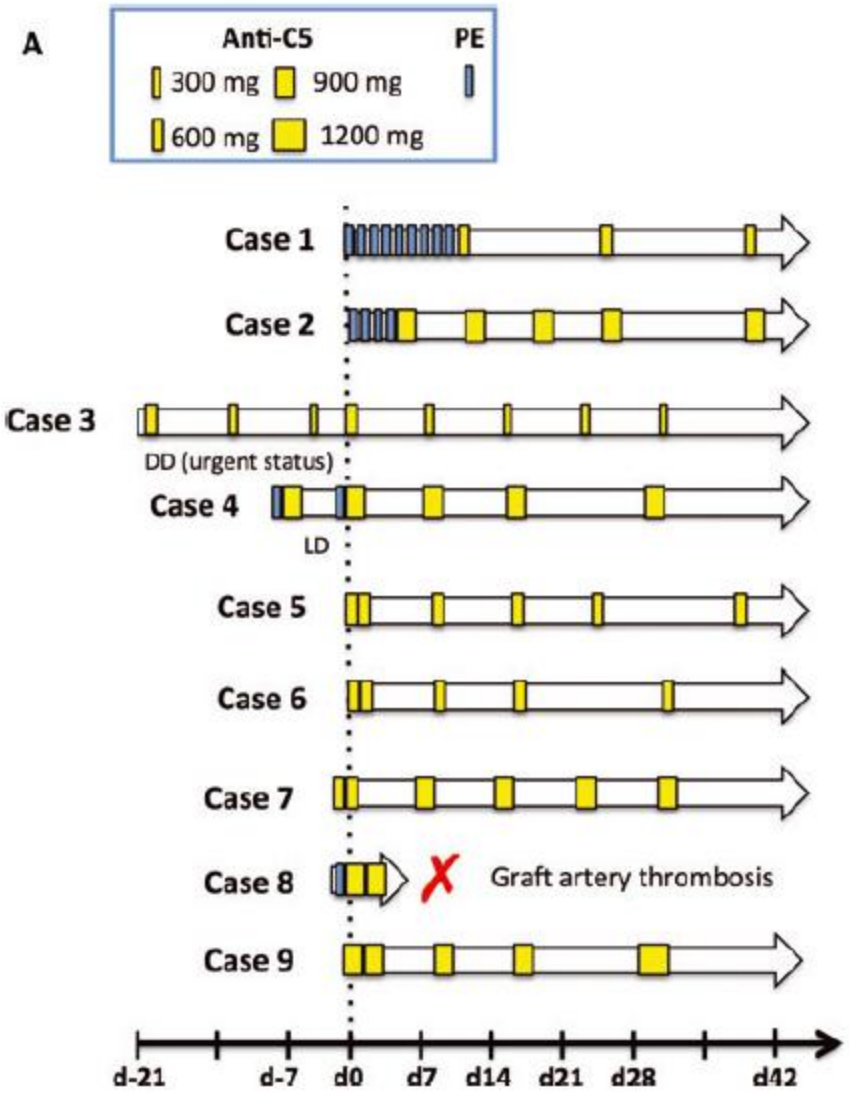
Eculizumab for Atypical Hemolytic Uremic Syndrome Recurrence in Renal Transplantation

American Journal of Transplantation 2012; 12: 3337–3354
Wiley Periodicals Inc.

J. Zuber[a,*], M. Le Quintrec[b], S. Krid[c], C. Bertoye[d], V. Gueutin[e], A. Lahoche[f], N. Heyne[g], G. Ardissino[h], V. Chatelet[i], L.-H. Noël[d], M. Hourmant[j], P. Niaudet[c], V. Frémeaux-Bacchi[k], E. Rondeau[l], C. Legendre[a], and C. Loirat[m] for the French Study Group for Atypical HUS

Outcome of renal transplantation performed in patients given prophylactic anti-C5

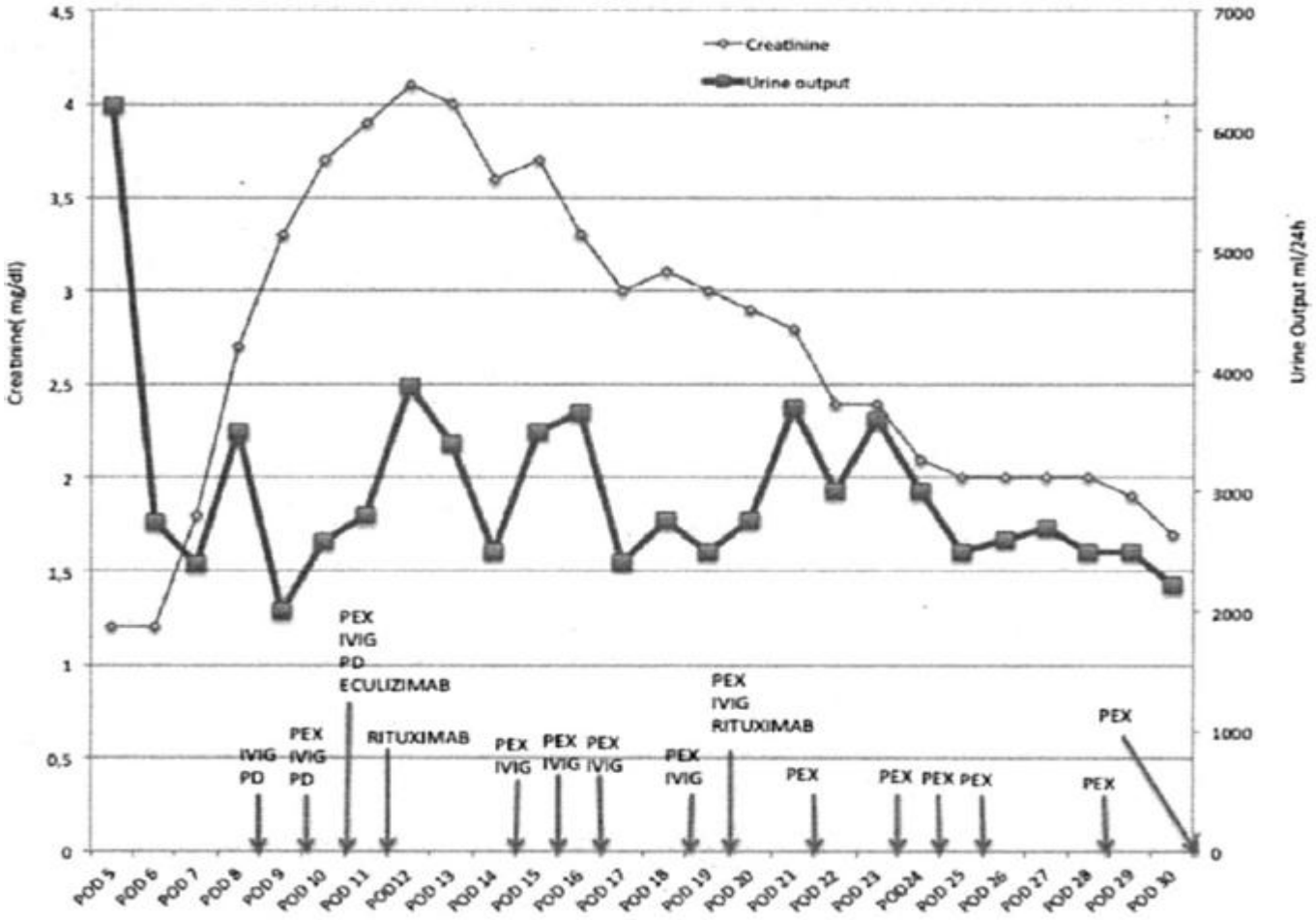
Of the nine patients treated preemptively with eculizumab, eight experienced a successful recurrence-free posttransplant course after a median follow-up of 14.5 months (range, 2–39)



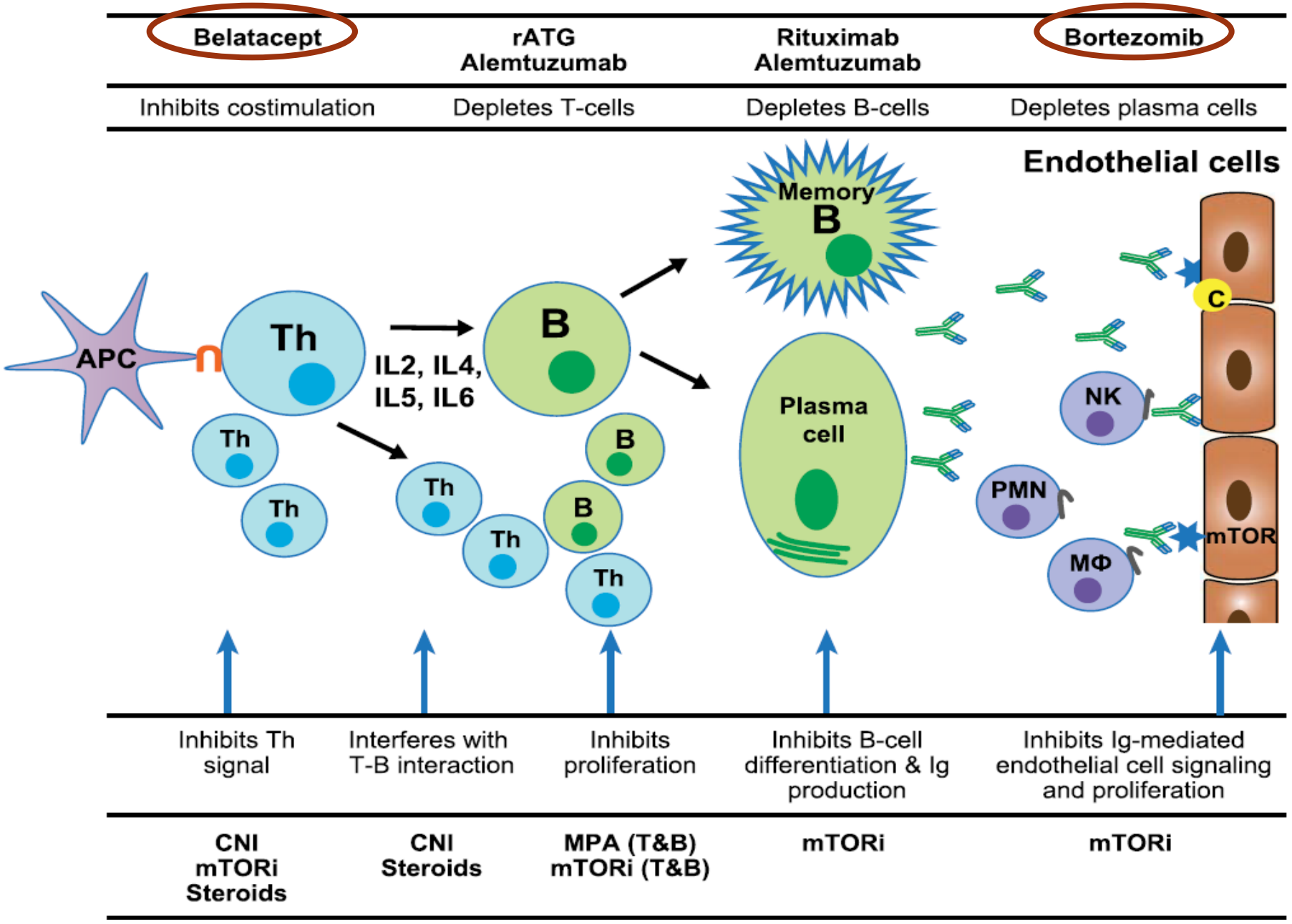
Eculizumab Treatment of Acute Antibody-Mediated Rejection in Renal Transplantation: Case Reports

Transplantation Proceedings, 44, 2690–2694 (2012)

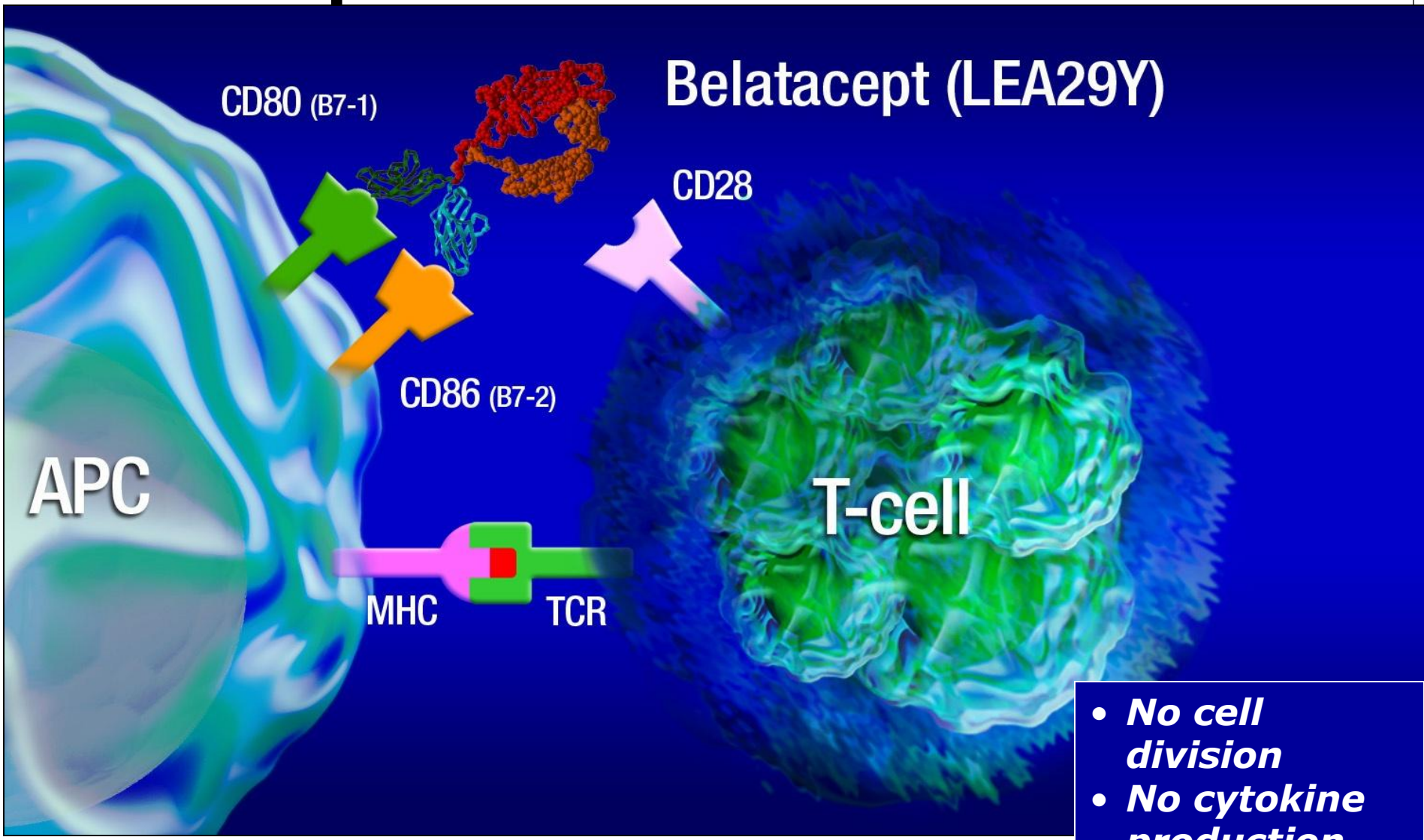
F. González-Roncero, M. Suñer, G. Bernal, V. Cabello, M. Toro, P. Pereira, and M. Angel Gentil



Any news in immunosuppression?


Belatacept
rATG
Alemtuzumab
Rituximab
Alemtuzumab
Bortezomib
Inhibits costimulation
Depletes T-cells
Depletes B-cells
Depletes plasma cells
Endothelial cells
Memory B
APC
Th
IL2, IL4, IL5, IL6
B
Plasma cell
C
NK
PMN
MΦ
mTOR
Inhibits Th signal
Interferes with T-B interaction
Inhibits proliferation
Inhibits B-cell differentiation & Ig production
Inhibits Ig-mediated endothelial cell signaling and proliferation
CNI
mTORi
Steroids
CNI
Steroids
MPA (T&B)
mTORi (T&B)
mTORi
mTORi

Belatacept

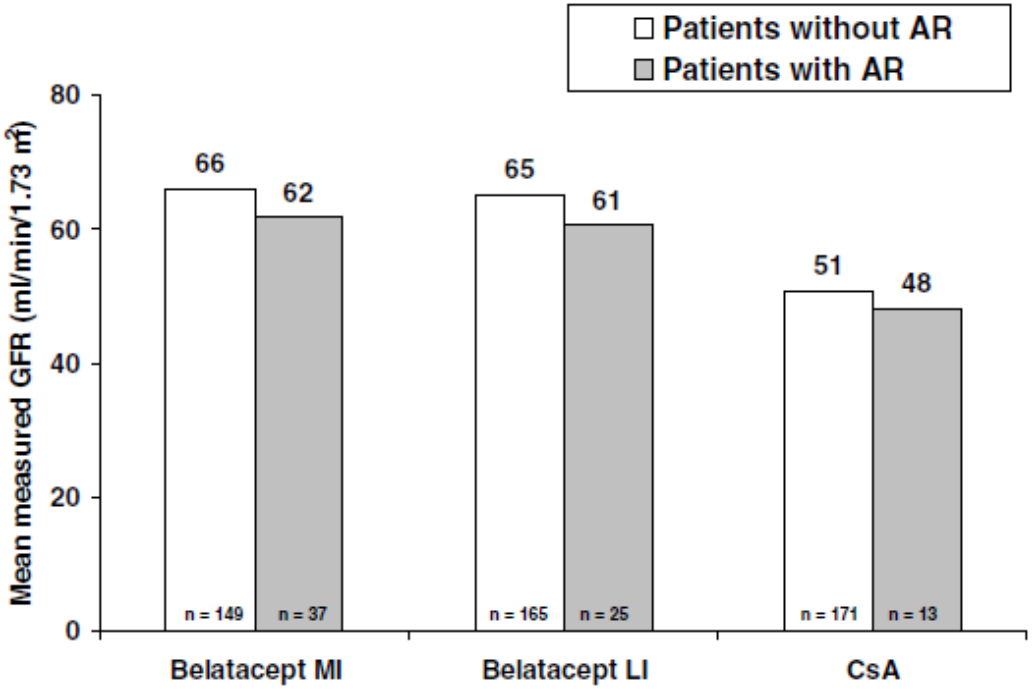


- ***No cell division***
- ***No cytokine production***
- ***Anergy***

American Journal of Transplantation 2010; 10: 535–546
Wiley Periodicals Inc.

F. Vincenti[a,*], B. Charpentier[b], Y. Vanrenterghem[c], L. Rostaing[d], B. Bresnahan[e], P. Darji[f], P. Massari[g], G. A. Mondragon-Ramirez[h], M. Agarwal[i], G. Di Russo[i], C.-S. Lin[i], P. Garg[i] and C. P. Larsen[j]

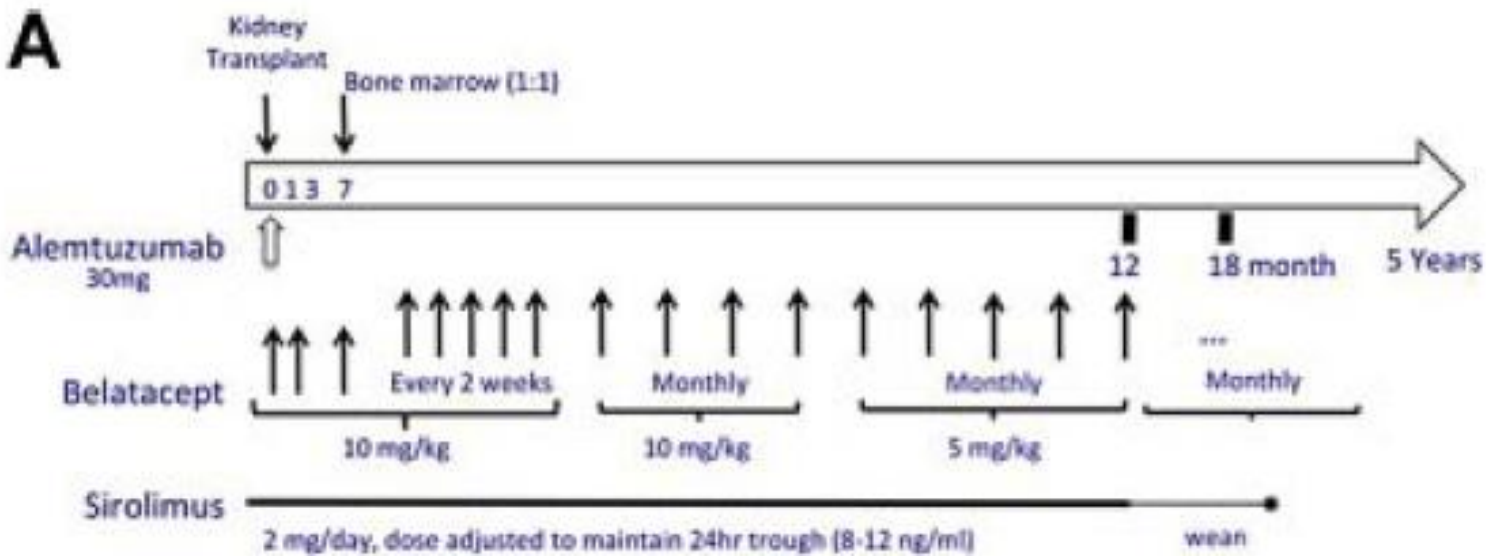
A Phase III Study of Belatacept-based Immunosuppression Regimens versus Cyclosporine in Renal Transplant Recipients (BENEFIT Study)



Renal Transplantation Using Belatacept Without Maintenance Steroids or Calcineurin Inhibitors

A. D. Kirk*, A. Guasch, H. Xu, J. Cheeseman, S. I. Mead, A. Ghali, A. K. Mehta, D. Wu, H. Gebel, R. Bray, J. Horan, L. S. Kean, C. P. Larsen and T. C. Pearson

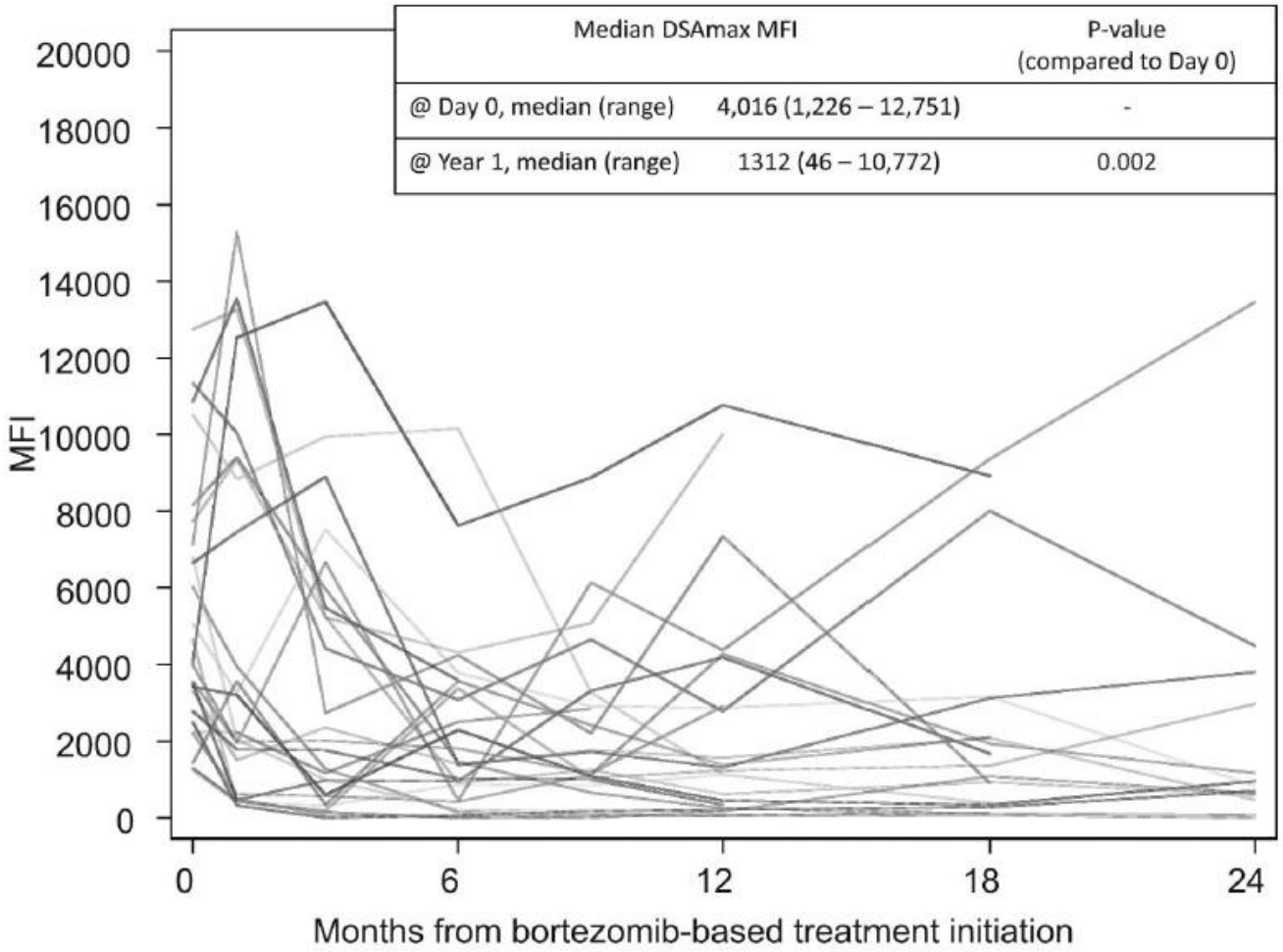
American Journal of Transplantation 2014; Wiley Periodicals Inc.



Durability of Antibody Removal Following Proteasome Inhibitor-Based Therapy

(*Transplantation* 2012;93: 572–577)

Matthew J. Everly,[1] Paul I. Terasaki,[2] and Hargovind L. Trivedi[3]



Transplantation. 2012 February 15; 93(3): 319–324.

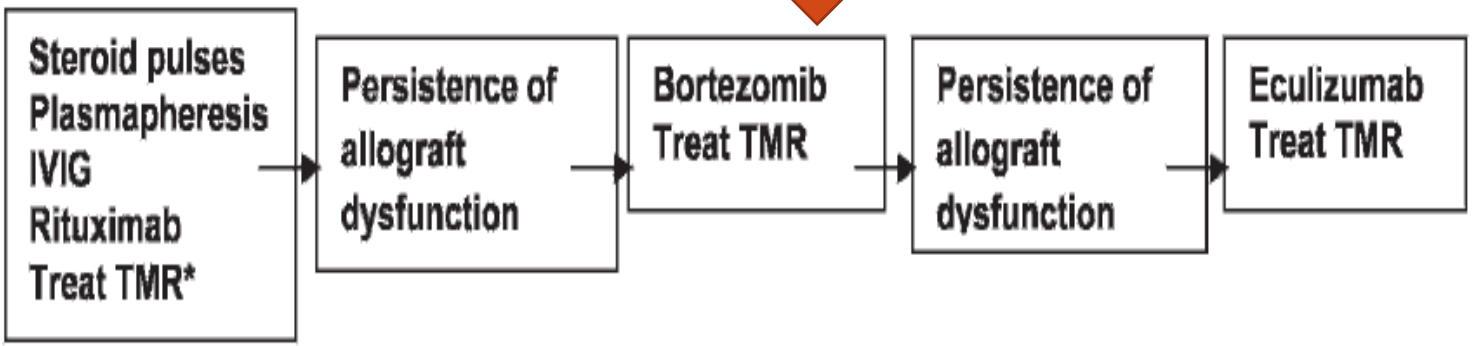
Rapid Reduction in Donor-Specific Anti-Human Leukocyte Antigen Antibodies and Reversal of Antibody-Mediated Rejection With Bortezomib in Pediatric Heart Transplant Patients

William Robert Morrow[1], **Elizabeth A. Frazier**[1], **William T. Mahle**[2], **Terry O. Harville**[1], **Sherry E. Pye**[1], **Kenneth R. Knecht**[1,6], **Emily L. Howard**[1], **R. Neal Smith**[3], **Robert L. Saylors**[1], **Xiomara Garcia**[1], **Robert D.B. Jaquiss**[4], and **E. Steve Woodle**[5]

Medication protocol

Pretreatment	Rituximab	375 mg/m^2 IV
Day1, 4, 7, 11	Plasmapheresis	
	Methylprednisolone	5 mg/kg (max 100 mg)
	Bortezomib	1.3 mg/m^2 IV
Day14–16	Plasmapheresis	
Day 18	PRA, T-/B-cell subsets	
Follow-up after 30 Days	PRA, T-/B-cell subsets	

SUGGESTED ALGORITHM FOR MANAGEMENT OF AMR



*TMR –T-cell-mediated rejection

Treatment

Steroids

If needed anti-thymocyte globulin

Maintenance drugs

Tacrolimus

Mycophenolate mofetil

Table 1 - Target Antigens in Antibody-mediated Rejection of Renal Transplants in Children.

Target Antigen	Antigen Subgroup
Major HLA[1] Antigens	
	Class I
	Class II
Minor HLA[1] Antigens	
	MICA[2]
	MICB[3]
Non-HLA[1] Antigens	
	Angiotensin II type I receptor
	Endothelial and monocyte antigens
	Vimentin
	Agrin
	Percalan
	Collagen types 4 and 6
	Myosin
ABO Blood Group Antigens	

Pediatr Nephrol
DOI 10.1007/s00467-014-2886-4

EDUCATIONAL REVIEW

Biologics in renal transplantation

Ryszard Grenda

„not inferior/ promising"

Table 4 Clinical experience with novel drugs (still being investigated) in adult transplant populations

Agent	Major reports	Clinical indication; treated populations	Efficacy; other benefits	Safety; specific caution
Belatacept	RCTs: BENEFIT study BENEFIT EXT study	Induction: adults (n=445; in two treatment arms); adults (n=102)	Not inferior to CNI-based triple regimen. Better metabolic profile compared to CNI	High risk of PTLD (CNS specific); strongly contraindicated in EBV-naïve patients
Tasocitinib (tofacitinib)	RCT	Induction: adults (n=40, in two treatment arms)	Not inferior to CNI-based triple regimen	High rate of viral infection Dyslipidemia
ASKP1240	RCT	Induction: overall 38 (3 treatment arms)	Not inferior to CNI-based triple regimen	Significant rate of infections
Bortezomib	Case series	Desensitization: treatment of antibody-mediated rejection; largest series n=70)	Promising	Anemia; peripheral neuropathy

Table 1 Novel therapeutic agents for kidney transplantation

Medication (generic/ trade name)	Mechanism of action	Potential use in kidney transplant (clinical trial reference)
Tocilizumab (Actemra®)	Soluble and membrane-bound IL-6 receptor antagonist	• Desensitization (NCT01594424) • Treatment of antibody-mediated rejection
Belimumab (Benlysta®)	Prevents B-lymphocyte stimulator protein from stimulating B-cell activation and differentiation	• Desensitization (NCT01025193, terminated) • Prevention of kidney transplant rejection (NCT01536379)
C1 esterase inhibitor (Berinert®)	C1 inhibitor inactivates both C1r and C1s of the complement pathway	• Prevention of antibody-mediated rejection (NCT01134510) • Delayed graft function and ischemic reperfusion injury (NCT02134314)
C5 inhibitor (Eculizumab®)	C5 inhibitor preventing cleavage to C5a and C5b preventing formation of C5b-9, terminal complement complex	• Desensitization (NCT01567085) • Delayed graft function and ischemic reperfusion injury (NCT01756508, NCT0919346) • Kidney Transplantation in Catastrophic Antiphospholipid Antibody Syndrome (NCT01029587) • Antibody-mediated rejection (NCT01327573, NCT02113891)
IgG Endopeptidase	Cleavage of all four classes of Human IgG	• Desensitization (NCT 02224820)

Overview on current and future strategies to optimize immunosuppression

Objective	Potential strategies	Current challenges
Development of targeted immunosuppressive regimens	Small molecules, antibodies or fusion proteins directed against molecules involved in T cell activation, or targeting specific immune cell subsets (e.g., anti-CD40, anti-CD28, anti-CD20, anti-IL-12, anti-CD2, bortezomid)	• The relatively small patient population, increased costs of clinical trials, and lack of clinically relevant short-term endpoints prevent systematic investigation of new reagents in transplantation

Summary

- The major strategy in post-transplant immunosuppression is stratification of risk and individualized selection of protocol

- Whatever protocol is used – must be monitored

- Future: - minimization of steroid and CNI exposure, with use of induction and EVR; - targeted use of additional innovative drugs, aimed to specific molecules and enzymes, limited to pre-selected patients

Case 1

14-years old boy, CKD 5, HD for 3 years, first deceased-donor transplantation. HLA mismatch 4. Protocol?

a. CsA+MMF+Pred
b. Anti-IL2R ab+CsA+MMF+Pred
c. TAC+MMF+Pred
d. Thymoglobulin+TAC+MMF+Pred

Case 2

16-years old girl, lost the first graft 6-months ago, kidney removed, sensitized (high DSA, MFI > 8000). Now – living-related transplantation, HLA haplotype (3 mismatches). Protocol?

a. Anti-IL2R ab+TAC+MMF +Pred > 7 days (then stopped)
b. TAC+MMF+Pred
c. Thymoglobulin+TAC+MMF+Pred
d. Anti-IL2R ab+CsA+MMF+Pred

Case 3

4-years-old girl, PD for 1 year, first deceased-donor transplant, 2 mismatches in HLA. Protocol?

a. TAC+MMF+Pred
b. Anti-IL2R ab+TAC+MMF+Pred <7 days (then stopped)
c. Thymoglobulin+TAC+MMF+Pred
d. Anti- IL2R ab+TAC+MMF+Pred

Case 4

The 5-years old boy, PD for 1 year, aHUS (genetic form, CFH mutation confirmed).

First, deceased-donor transplantation, well-matched (1 HLA mismatch). Protocol?

a. Thymoglobulin+TAC+MMF+Pred
b. SIR+MMF+Pred
c. Anti-IL2R+TAC+MMF+Pred
d. TAC+MMF+Pred + eculizumab (2-weekly dosing)

Case 5

7-years old boy, PD for 1 year, first graft lost to recurrence of SRNS. Now – deceased donor- second transplant. HLA mismatch – 2. Protocol?

a. TAC+MMF+Pred
b. Thymoglobulin+TAC+MMF+Pred
c. CsA+MMF+Pred + rituximab (once proteinuria present)
d. Anti-IL2R ab+TAC+MMF+Pred