Better than Google-
Click on Immunosuppression
Renal Transplant

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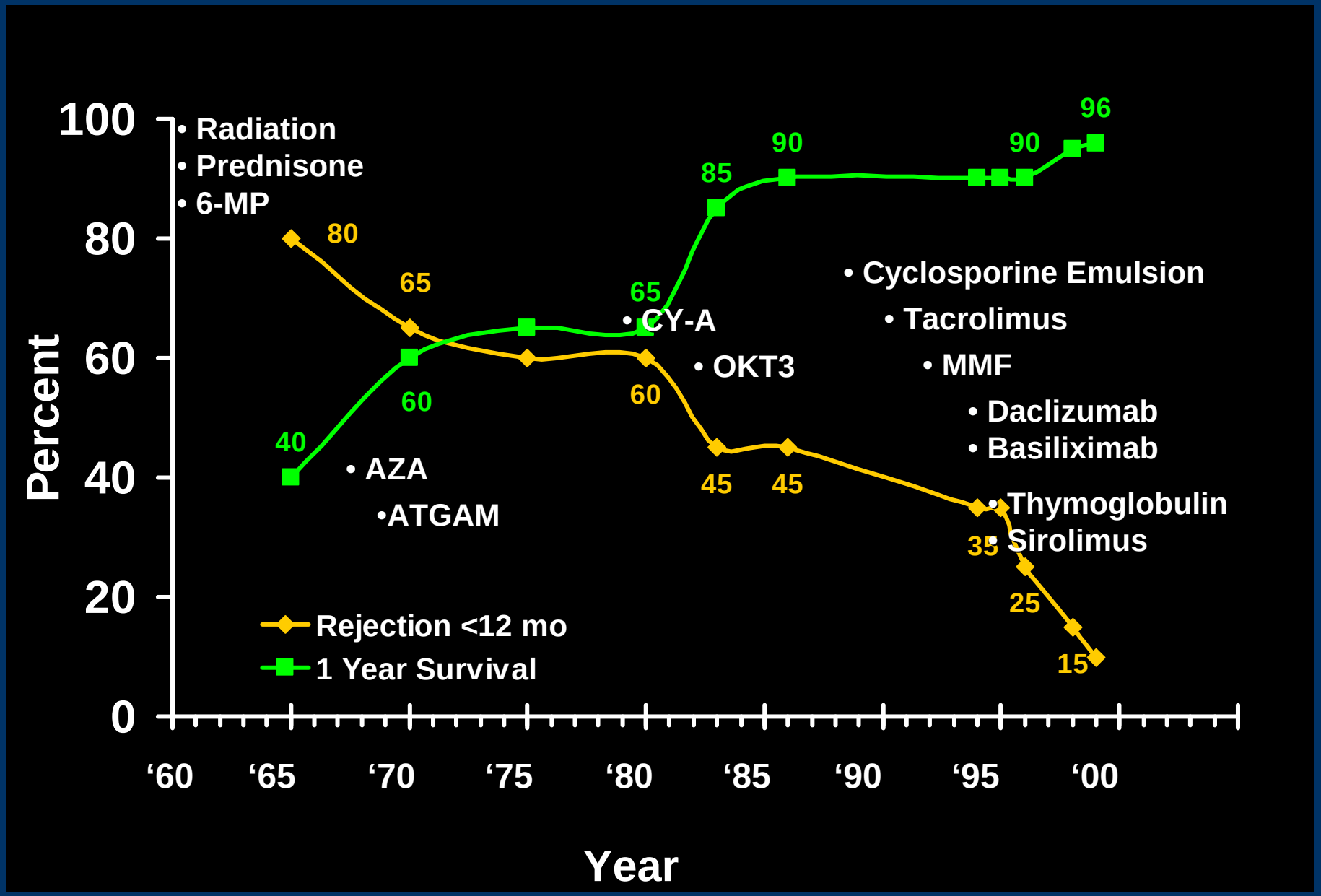
OUTLINE

- History of Immunosuppression
- Trends in Immunosupression
  - FK vs CYA
  - Steroid Minimization
  - CNI Avoidance
  - Sirolimus / Everolimus
- Individualization
- New Agents

HISTORY OF IMMUNOSUPPRESSION

- 1960s — Imuran/Prednisone
- 1970s — Imuran/Prednisone/ALG
- 1980s — Cyclosporine/OKT3
- Early 1990s — Tacrolimus
- mid 1990s — Mycophenolate
- late 1990s — IL2-Receptor Blockers
  Sirolimus / Everolimus
- 2000 — Rituximab /Alemtuzumab
- 2002 — Belatacept / FTY 720

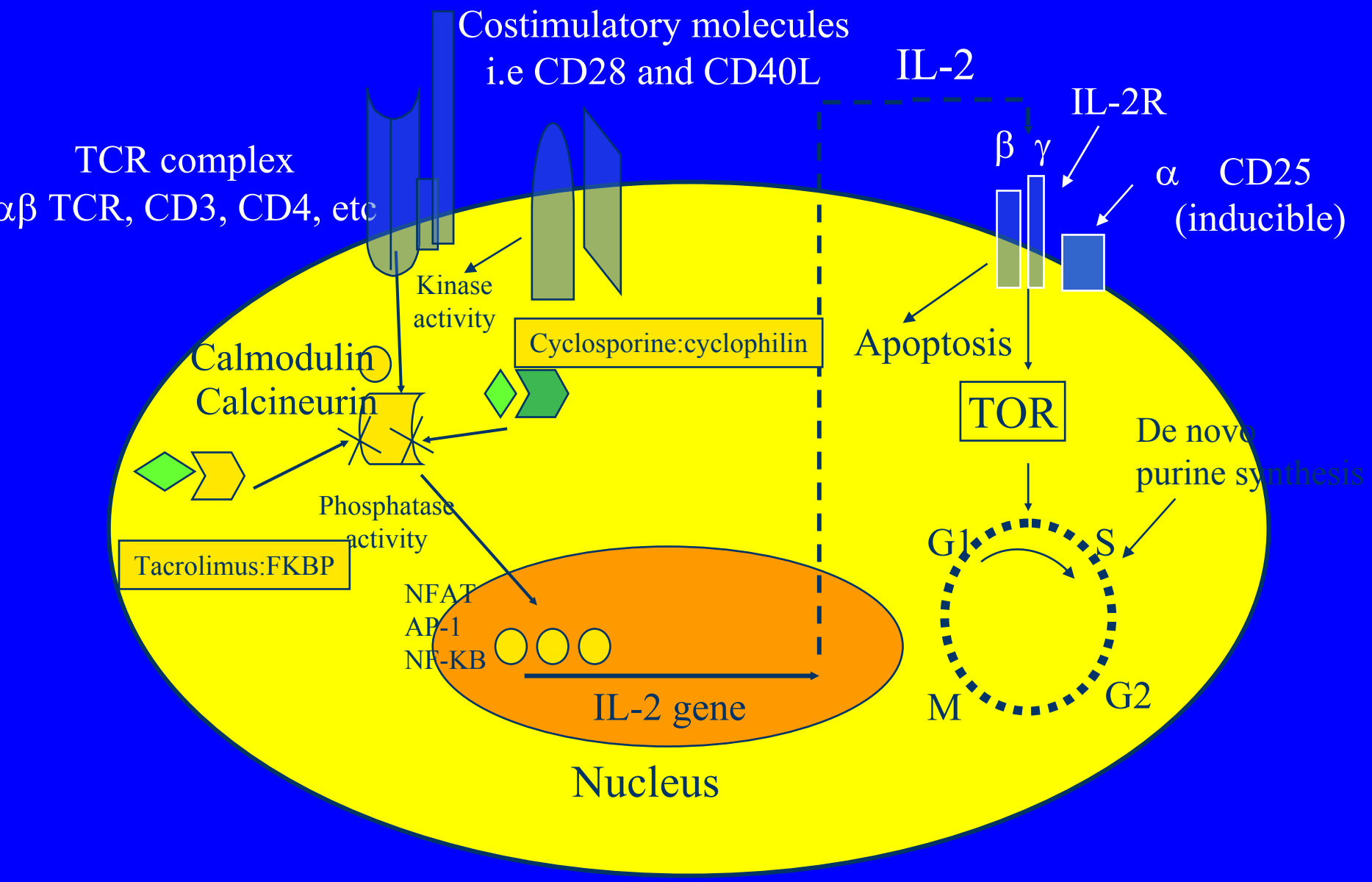
Outcomes of Renal Allografts



Trends in Immunosuppression

- Tacrolimus vs Cyclosporine
- Steroid Minimization
- CNI Avoidance
- Induction

Cyclosporine and Tacrolimus: Calcineurin Inhibitors



CsA vs FK506: side effects

	CsA	FK
nephrotoxicity	+++	+++
hypertension	+++	+++
neurotoxicity (tremor/seizures/convulsions)	+	++
hyperglycemia/diabetes	+/-	++
electrolyte disorders (hypoK/hyperK/hypoMg)	+/-	+

Steroid Minimization

- Withdrawal
- Complete Avoidance
- Periop only
- Early withdrawal

Steroid Withdrawal

- All withdrawal studies have shown higher risk of acute rejection
- Low dose longterm steroid may reduce risk of chronic rejection
- No longterm advantage to late steroid withdrawal versus low dose in terms of the usual steroid complications

Target Groups for Steroid Avoidance

- Previous large exposure
- Children
- Low BMD
- Preexisting atherosclerotic disease
- Risk for hyperglycemia or hyperlipidemia

Immunosuppressive Protocols for Steroid Minimization

- Antibody (anti CD 25, anti CD3, anti CD 52 or ATG)
- CNI or Sirolimus
- Mycophenolate

FREEDOM TRIAL

American Journal of Transplantation 2008; 8: 307–316

- 3 arms
  - no steroid
  - steroid withdrawal by 7 days
  - standard therapy
- Cyclosporine
- Enteric Coated Mycophenolate Sodium
- Simulect

FREEDOM TRIAL

	N	12 month GFR	Acute Rej
no Steroids	111	64.7	31.5%
Steroids to day 7	115	61.6	26.1%
Standard Steroids	109	63.4	14.7%

Freedom – Benefits of Steroid Avoidance

- Less diabetes
- Better Lipids
- Less Weight Gain
- Better BMD

Astellas Steroid Withdrawal Trial

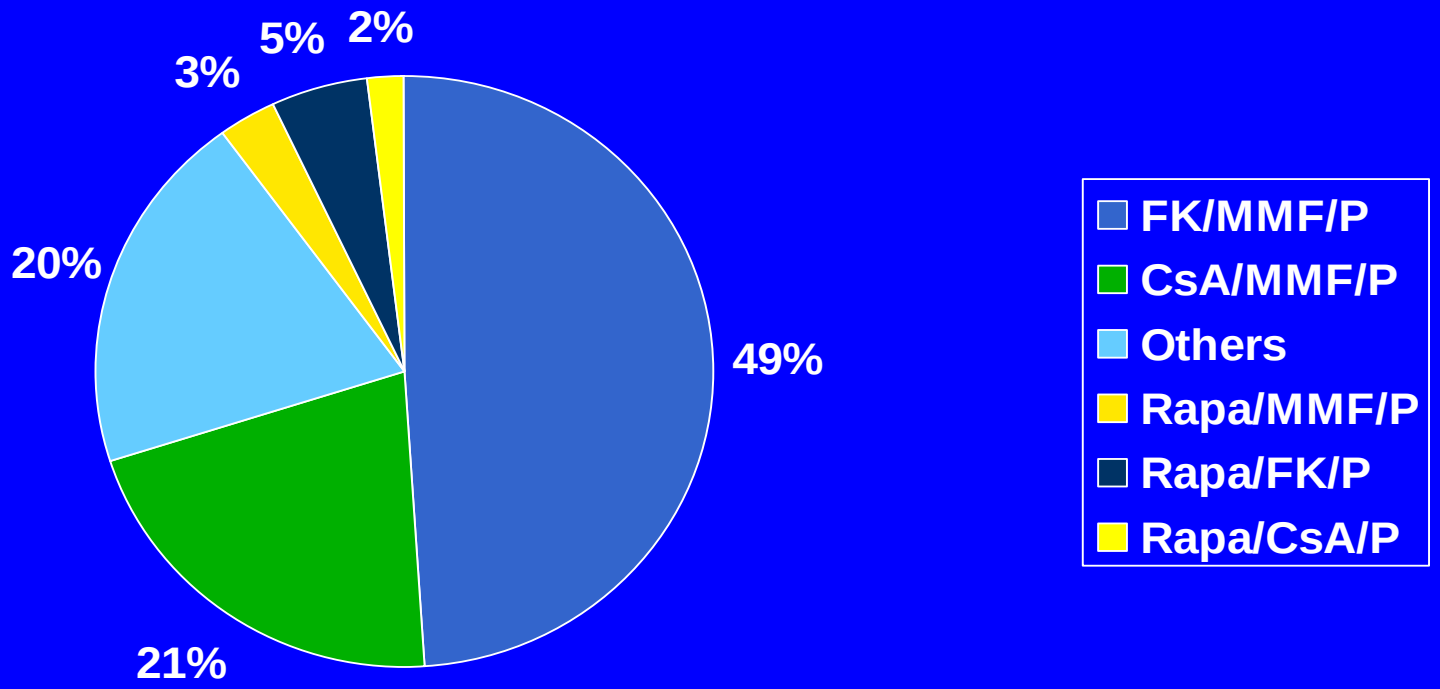
- Multicentre 500 patients
- Double blinded placebo controlled trial
- 7 day steroid withdrawal versus standard therapy
- Tacrolimus, MMF and ATG or IL-2R antibody

Astellas Steroid Withdrawal Trial

- no differences seen at 3 years
- trend to more acute rejection 16.2% vs 9.7%
- no striking differences in “steroid related” complications including diabetes

Can we eliminate calcineurin inhibitors?

US DeNovo Maintenance Regimens for Kidney Transplant Recipients



UNOS: 11/02

Calcineurin Inhibitors Elimination

- Avoidance
  - Sirolimus/MMF
- Withdrawal
  - CYA / Sirolimus
- Sparing

Mycophenolate Mofetil/Sirolimus Compared to Other Common Immunosuppressive Regimens in Kidney Transplantation

American Journal of Transplantation 2007; 7: 586–594

T. R. Srinivas, J. D. Schold, G. Guerra, A. Eagan,
C. M. Bucci and H.-U. Meier-Kriesche

Sirolimus/MMF

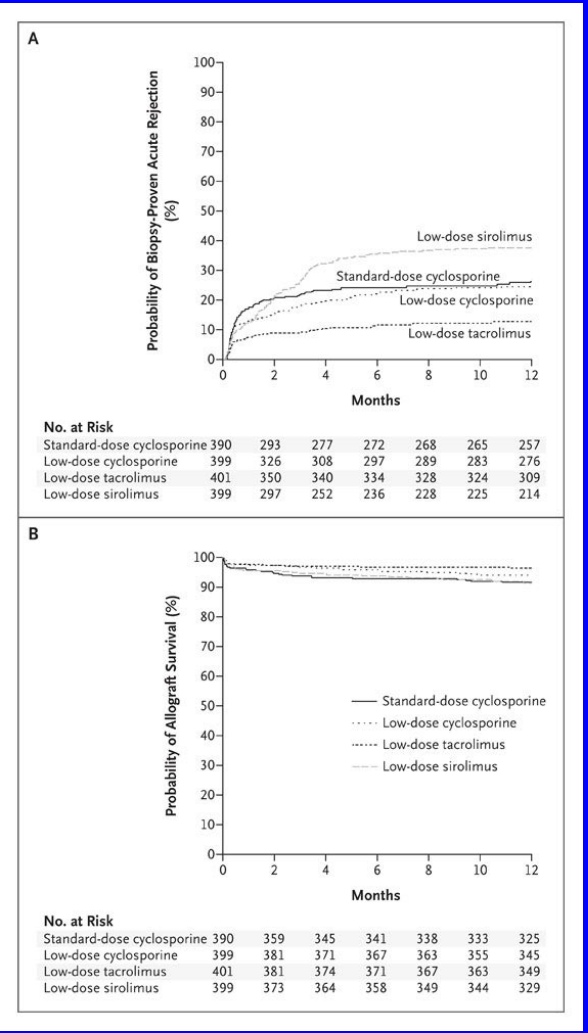
Regimen	Acute Rejection	CI
FK/MMF	ref	-
CSA/MMF	1.16	1.09-1.24
FK/SRL	0.92	0.82-1.03
CYA/SRL	1.01	0.87-1.17
SRL/MMF	1.53	1.33-1.75

Reduced Exposure to Calcineurin Inhibitors in Renal Transplantation The Symphony Trial

Prospective randomized 4 arm trial with 1645 patients enrolled

1. Standard dose CYA, MMF, Steroid
2. Daclizumab, reduced dose Tac, MMF, Steroid
3. Daclizumab, reduced dose CYA, MMF, Steroid
4. Dalizumab, Sirolimus, MMF,Steroid

Cumulative Probability of Biopsy-Proven Acute Rejection (Panel A) and Allograft Survival (Panel B), According to Study Group



Ekberg H et al. N Engl J Med 2007;357:2562-2575

Conclusion

- A regimen of daclizumab, mycophenolate mofetil, and corticosteroids in combination with low-dose tacrolimus may be advantageous for renal function, allograft survival, and acute rejection rates, as compared with regimens containing daclizumab induction plus either low-dose cyclosporine or low-dose sirolimus or with standard-dose cyclosporine without induction

The NEW ENGLAND JOURNAL of MEDICINE

Sirolimus and Everolimus

Pros

- Not nephrotoxic
- Once daily dosing
- Can be used without CNI's but not early
- ? anti neoplastic characteristics
- ? Anti atherosclerotic

Cons

- Delayed wound healing
- Hyperlipidemias
- Proteinuria
- Brochiolitis Obliterans
- Expense
- Drug monitoring

RATIONALE FOR INDIVIDUALIZING IMMUNOSUPPRESSION

Too Much

- Cardiovascular Disease
- Infection
- Neoplasia
- Nephrotoxicity

Too Little

- Allograft Rejection

INDIVIDUALIZING IMMUNOSUPPRESSION BASED ON IMMUNOLOGIC RISK

PRE-TRANSPLANT IMMUNOMODULATION

INDUCTION ANTIBODY THERAPY

TRIPLE THERAPY MAINTENANCE

MINIMIZATION PROTOCOLS

HIGH RISK

- HIGHLY SENSITIZED
- NON-PRIMARY TRANSPLANT
- AFRICAN AMERICAN/HISPANIC ETHNICITY
- CADAVERIC DONOR SOURCE
- POOR HLA MATCH

LOW RISK

- NONSENSITIZED
- ASIAN/CAUCASIAN ETHNICITY
- THE ELDERLY
- LIVING DONOR SOURCE
- GOOD HLA MATCH

Immunosuppression: Long-Term Side Effects that Enhance Cardiovascular Risk

	CsA	Tac	SRL	Ster	MMF
Hypertension	++	+	∅	++	∅
Hyperglycemia	+	++	∅	+++	∅
Renal insufficiency	++	++	∅	∅	∅
Hyperlipidemia	++	+	+++	++	∅

CsA = cyclosporine; Tac = tacrolimus; SRL = sirolimus; Ster = corticosteroids; MMF = mycophenolate m
+++ = severe; + = mild; ++ = moderate; ∅ = none;

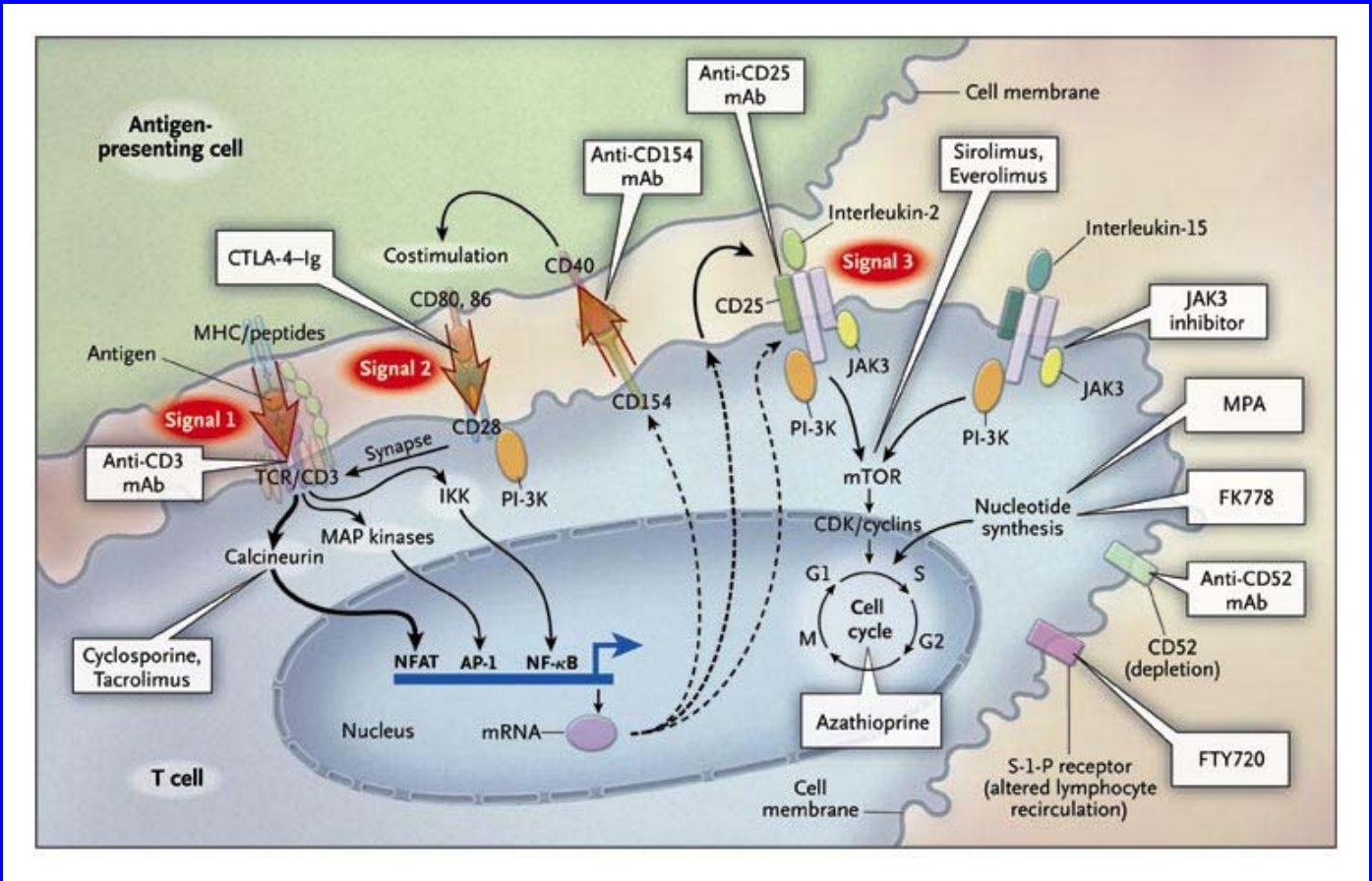
Current Immunosuppressive Low Risk Protocol

- Basilixumab 20mg. Day 0 and 4
- MMF 1 gram bid
- CNI
- Periopertive Steroids

New Agents

- FTY 720
- Alemtuzumab
- Belatacept
- Efalizumab
- Rituximab
- FK 778
- ISA 247
- AEB071
- CP690550

Individual Immunosuppressive Drugs and Sites of Action in the Three-Signal Model



Halloran, P. F. N Engl J Med 2004;351:2715-2729

Target Antigens

Immune Response Antigens		Adhesion & Cell Trafficking	Heterogeneous Pathways
CD1a	CD28*	CD6	CD2
CD3/TCR	CD30	CD11a/CD18 (LFA-1)	CD5
CD4	CD32	CD44	CD11b
CD6	CD40	CD49/CD29 (VLA-4)	CD29
CD7	CD80*	CD50 (ICAM-3)	CD38
CD8	CD86	CD51/61	CD40
CD16	CD152 (CTLA-4)	CD54 (ICAM-1)	CD45
CD19	HLA class I	CD56*	CD52
CD20*	HLA DR	CD58 (LFA-3)	CD95
CD25*	β2-M	LPAM-1(α4β7)	CD126
		CD102 (ICAM-2)	CD138
		CD195 (CCR5)	
		CD197 (CCR7)	
		CD184 (CXCR4)	

FTY720

- Novel immunosuppressant which is a spingosine 1-phosphate receptor agonist (S1P)
- S1P receptor agonists induce sequestration of lymphocytes in secondary lymphatic tissue
- Several phase 1/2 studies have shown efficacy
- Phase 3 trial discontinued early because of toxicity
- Is this another way of inducing lymphocyte depletion?

Alemtuzumab

- Humanized anti - CD 52 IgG1 monoclonal antibody.
- Complement fixing so cytotoxic and lymphodepleting
- Profoundly depletes T cells and to a lessr extent
- B cells, natural killer cells and monocytes

Alemtuzumab

- Unlike other agents discussed alemtuzumab is not approved for use in kidney transplantation
- Despite this in 2006 10% of US transplant centres used it as an induction agent.
- Proposed advantages:
  - Tolerogenic
  - CNI sparing
  - Steroid sparing
  - Less expensive
- Absolute lack of controlled trials (more than 400 reports less than 5 randomized prospective)

Published Effects Of Alemtuzumab

	Yes	No	Possible
Toletrance Induction			
Alone		X	
With DSG		X	
Near Tolerance			
With CYA		X	
Effective with Non-CNI			
Sirolimus alone		X	
Sirolimus / MMF		X	
MMF alone		X	
Effective with CNI			
steroid sparing	X		
CNI sparing	X		
Effective to Treat Rejection			X

Belatacept

- Selective costimulation blocker
- Binds surface costimulatory ligands CD 80 and CD 86 of APC
- Interferes with signal 2 by preventing interaction with CD 28 the costimulatory surface receptor of the T cell

Incidence of Primary and Secondary Efficacy End Points

Table 2. Incidence of Primary and Secondary Efficacy End Points.

End Point	Intensive Belatacept (N=74)	Less-Intensive Belatacept (N=71)	Cyclosporine (N=73)
Primary efficacy end point			
Clinically suspected and biopsy-proven acute rejection at 6 mo — no. (%)	5 (7)	4 (6)	6 (8)
Absolute difference in rate from cyclosporine group — percentage points (exact 95% CI)*	−1.5 (−11.3 to 8.3)	−2.6 (−12.3 to 6.7)	—
Secondary efficacy end points			
Mild acute rejection (grade IA) — no. (%)	2 (3)	0	1 (1)
Mild acute rejection (grade IB) — no. (%)	0	0	1 (1)
Moderate acute rejection (grade IIA) — no. (%)	2 (3)	3 (4)	2 (3)
Moderate acute rejection (grade IIB) — no. (%)	1 (1)	1 (1)	2 (3)
Subclinical rejection — no. (%)	7 (9)	14 (20)	8 (11)
Treated episode of subclinical rejection — no. (%)	6 (8)	11 (15)	5 (7)

* CI denotes confidence interval.

Vincenti, F. et al. N Engl J Med 2005;353:770-781

Efalizumab Humanized anti CD-11a

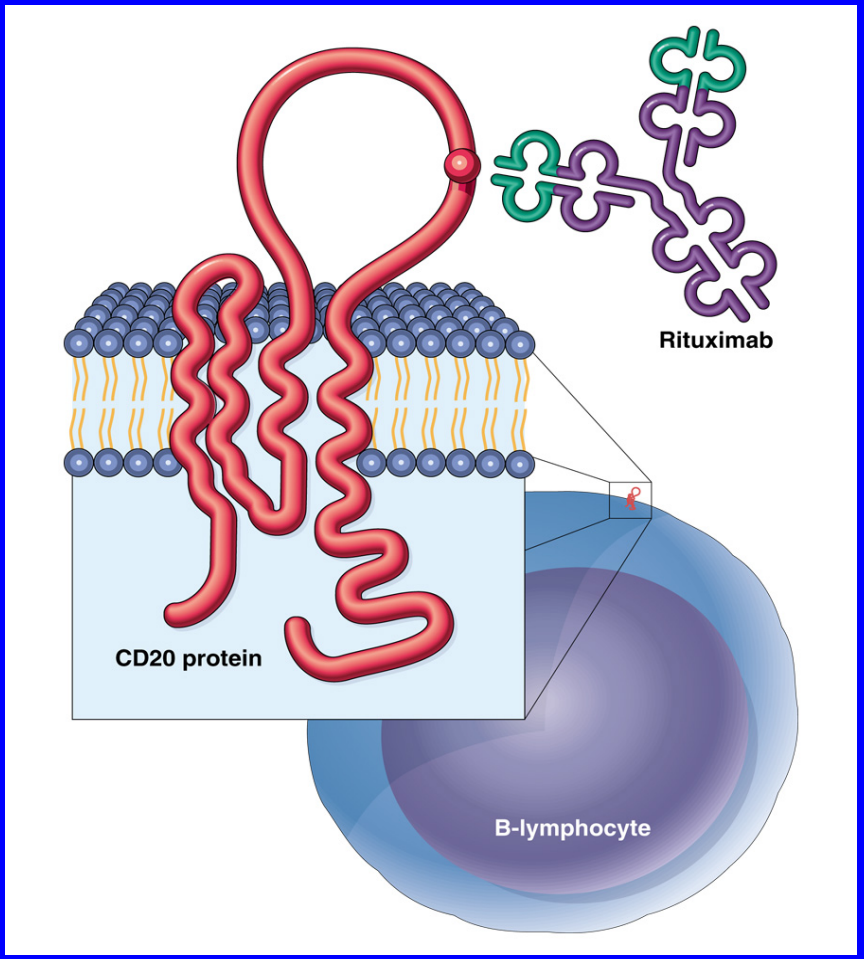
- Humanized monoclonal against the alpha chain of the LFA-1 molecule
- LFA-1 is a classic adhesion molecule
- Member of the heterodimeric B2 integrin family LFA-1
- plays a role in stabilizing the immune synapse of the TCR-MHC complex
- Participates in costimulation

Efalizumab Humanized anti CD-11a

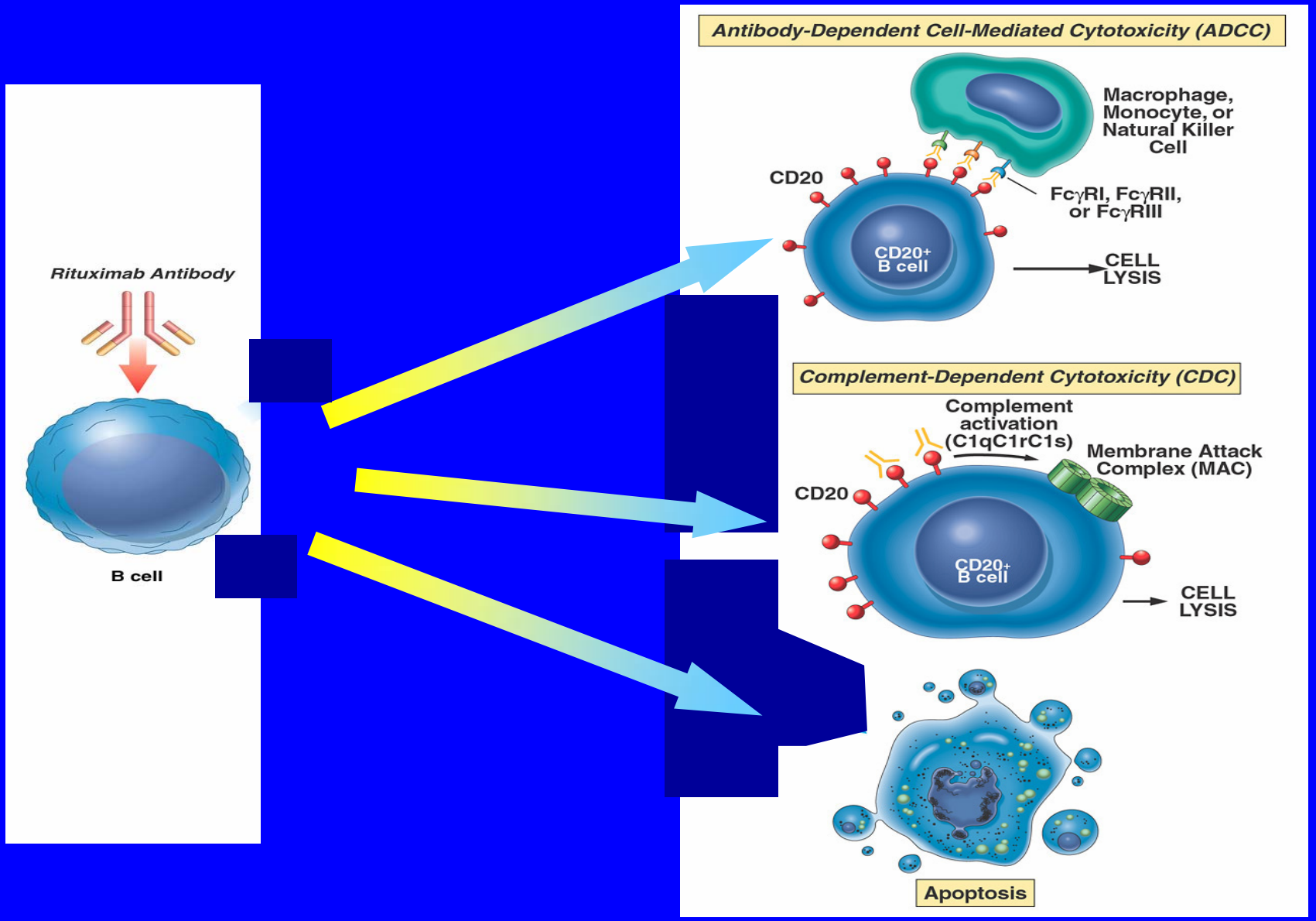
- In phase III studies in moderate to-severe psoriasis efalizumab, administered by subcutaneous injection, was found to be safe, well tolerated and effective
- This was a Phase 1 / 2 study in renal transplant
- 38 patients
- Weekly sc administration
- 3 cases of PTLPD

Rituximab: B-cell Depletion

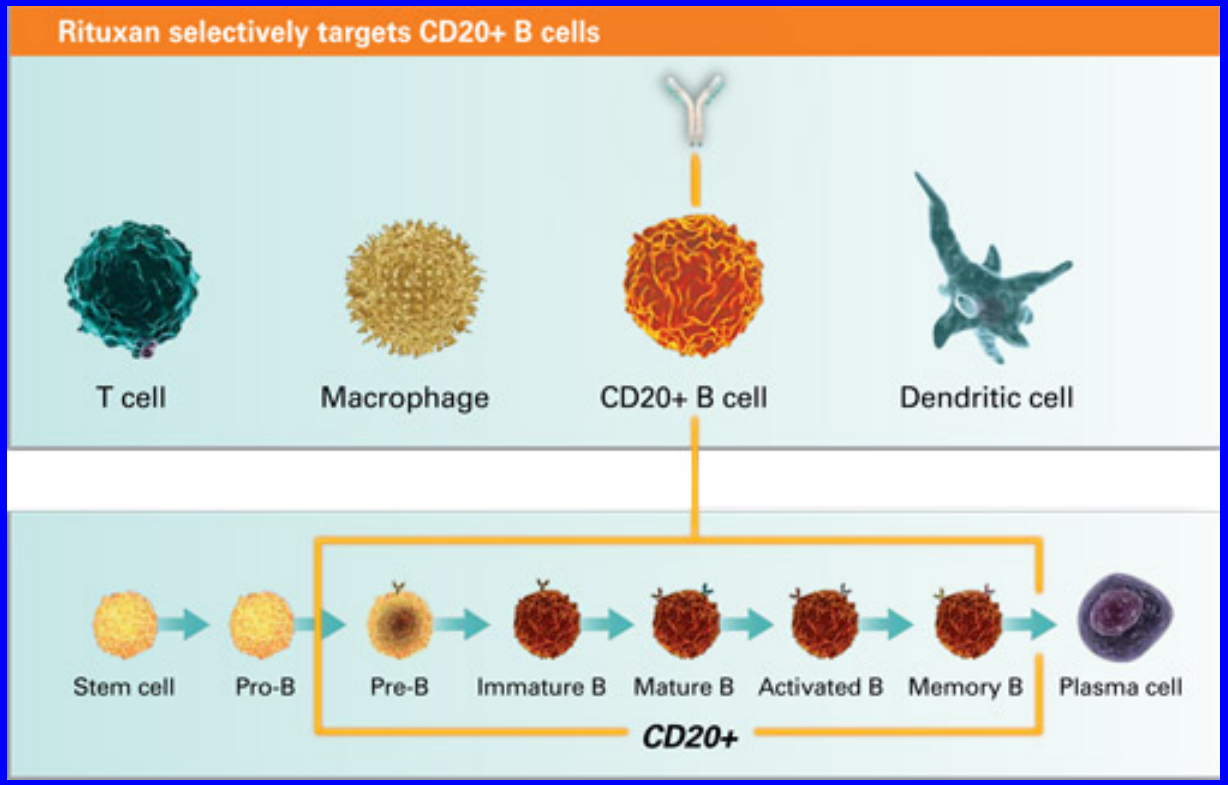
- **Genetically engineered chimeric murine/human monoclonal antibody**
  - Variable light- and heavy-chain regions from murine anti-CD20 antibody IDEC-2B8
  - Human IgGk constant regions
- **First monoclonal antibody to be approved by the FDA for treatment of cancer**



Rituximab: Mechanisms of Action



Rituximab – only targets peripheral CD20 positive B cells



FK 778

- analogue of the active metabolite of leflunomide

ISA 247

- An isomeric cyclosporine A analog mixture
- may be a more potent immunosuppressive agent than cyclosporine and less nephrotoxic
- There is an ongoing phase IIIb study of ISA247 versus tacrolimus

AEB071

- AEB071 is an oral protein kinase C inhibitor that inhibits T cell activation
- Phase 2 clinical kidney transplant trials are ongoing.

CP690550

- JAK 3 inhibitor
- Currently in phase II study

Examples of Current and Experimental Immunosuppressive Drug Protocols

Table 4. Examples of Current and Experimental Immunosuppressive Drug Protocols.

Protocol	Protocol Elements			Comments
	Protein Induction	Preadaptation Maintenance	Postadaptation Maintenance*	
Conventional treatment	Anti-CD25 antibody, polyclonal antithymocyte globulin, or none	Calcineurin inhibitor, mycophenolate mofetil, and prednisone	Calcineurin inhibitor and mycophenolate mofetil; prednisone tapered	Possibly excessive immunosuppression during postadaptation
Conventional treatment with no steroids[95]	Anti-CD25 antibody	Calcineurin inhibitor and mycophenolate mofetil; prednisone only if needed	Calcineurin inhibitor and mycophenolate mofetil; prednisone only if needed	Possible increase in rejection
Conventional treatment with depleting antibodies	Polyclonal antithymocyte globulin	Calcineurin inhibitor, mycophenolate mofetil, and prednisone	Calcineurin inhibitor and mycophenolate mofetil; prednisone tapered	Effects of depletion (e.g., increased incidence of post-transplantation lymphoproliferative disorder), possible late rejection
Sirolimus with cyclosporine withdrawal	Anti-CD25 antibody, polyclonal antithymocyte globulin, or none	Cyclosporine, sirolimus, and prednisone	Sirolimus; prednisone tapered	Early toxicity of cyclosporine–sirolimus combination
Calcineurin-inhibitor avoidance with maintenance sirolimus and mycophenolate mofetil[96,97]	Anti-CD25 antibody, polyclonal antithymocyte globulin, or none	Sirolimus, mycophenolate mofetil, and prednisone	Sirolimus and mycophenolate mofetil; prednisone tapered	Possibly excessive early rejection; no phase 3 trials; possible increase in late rejection
Calcineurin-inhibitor withdrawal with mycophenolate mofetil maintenance[98]	Anti-CD25 antibody, polyclonal antithymocyte globulin, or none	Calcineurin inhibitor, mycophenolate mofetil, and prednisone	Mycophenolate mofetil; prednisone tapered	No phase 3 trials
Alemtuzumab induction[84-86]	Alemtuzumab	Sirolimus, prednisone	Sirolimus; prednisone tapered	Long-term consequences of severe depletion unknown; no controlled trials; possible increase in antibody-mediated rejection
Depletion with minimization of immunosuppressive drugs[99]	Polyclonal antithymocyte globulin	Tacrolimus only if no rejection	Minimal tacrolimus if no rejection	Risk of late rejection as lymphoid system recovers
Maintenance with CTLA-4–Ig and mycophenolate mofetil†	Anti-CD25 antibody	CTLA-4–Ig, mycophenolate mofetil, and prednisone	CTLA-4–Ig, mycophenolate mofetil, and prednisone	Efficacy and safety must be established

* For most protocols, no data are available regarding the relative cost and cost-effectiveness of the treatment and long-term requirements for the administration of prednisone.

† CTLA-4–Ig denotes cytotoxic T-lymphocyte–associated antigen 4 combined with the Fc portion of immunoglobulin G.