"Kidney Transplantation: New Trends in Immunosuppression"

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'ACTIVELY ACQUIRED TOLERANCE' OF FOREIGN CELLS

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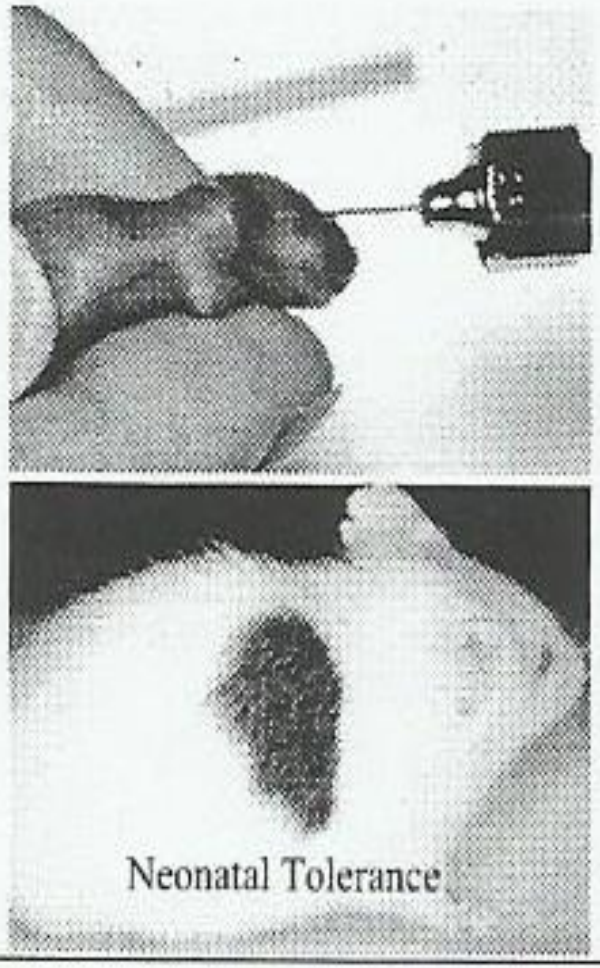
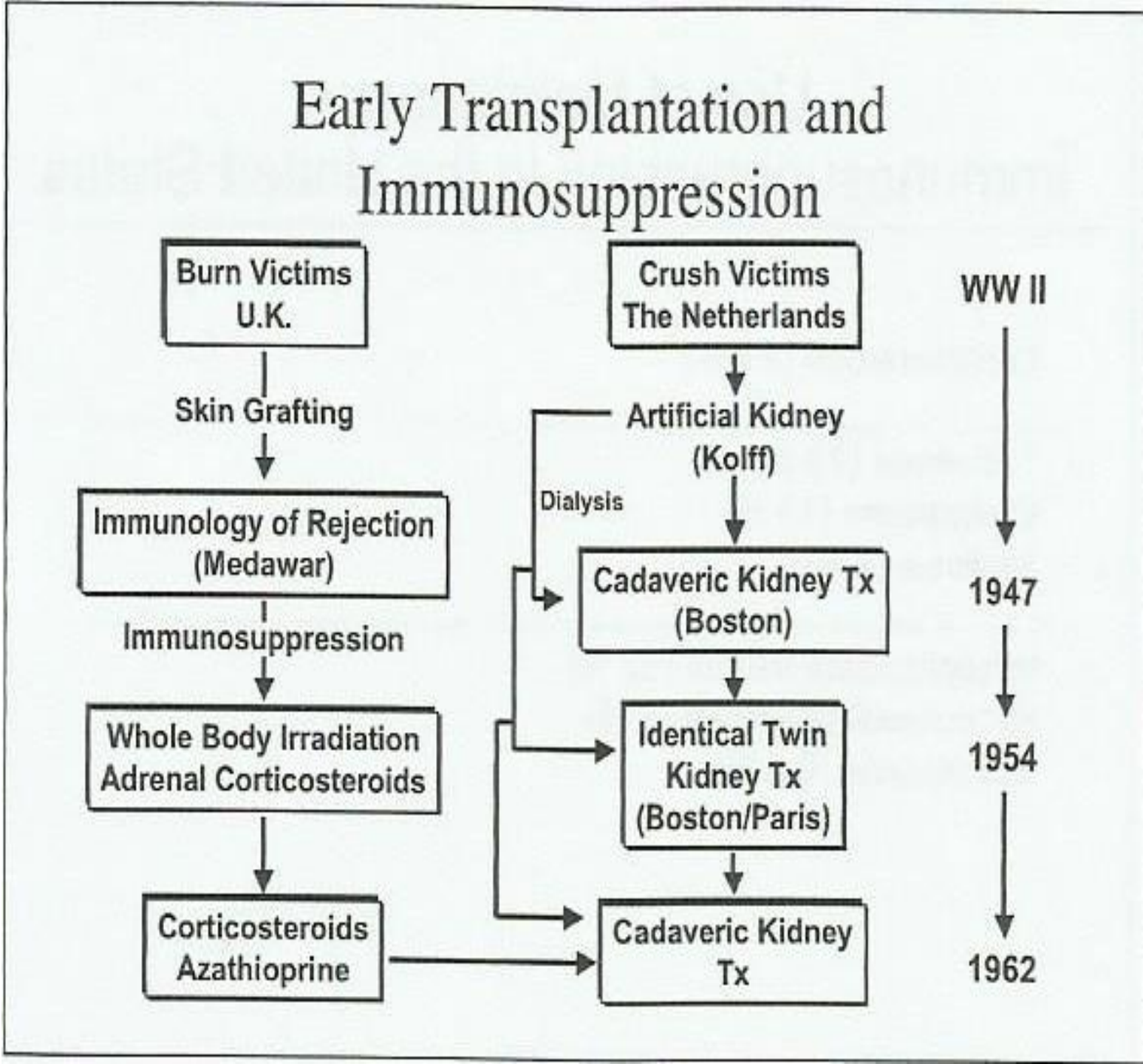


Neonatal Tolerance

The Promise >50 years later:

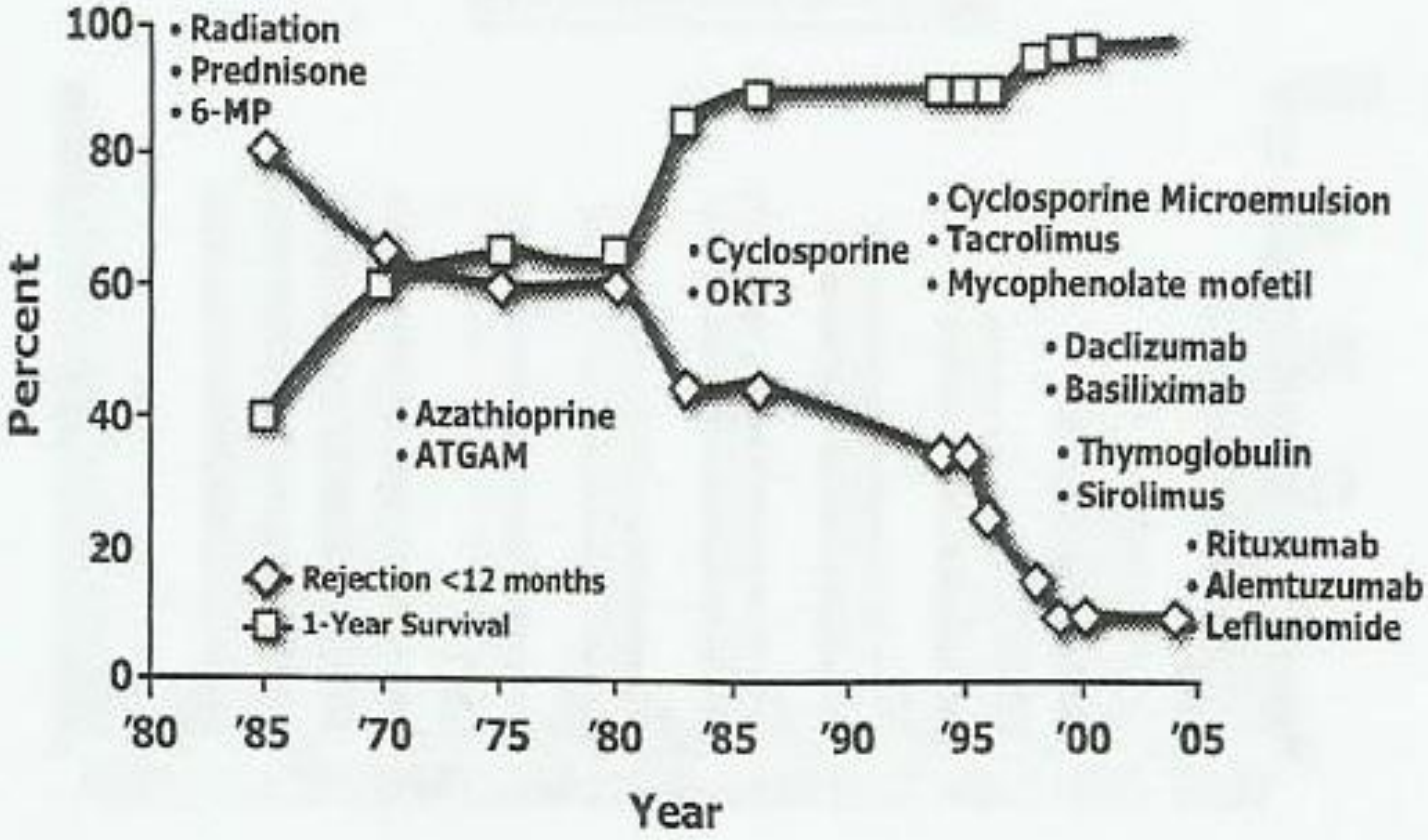
- Indefinite graft survival
- No immunosuppression
- No drug-related side effects
- No chronic rejection?
- Impact on organ shortage?


Early Transplantation and Immunosuppression
Burn Victims U.K.
Skin Grafting
Immunology of Rejection (Medawar)
Immunosuppression
Whole Body Irradiation Adrenal Corticosteroids
Corticosteroids Azathioprine
Crush Victims The Netherlands
Artificial Kidney (Kolff)
Dialysis
Cadaveric Kidney Tx (Boston)
Identical Twin Kidney Tx (Boston/Paris)
Cadaveric Kidney Tx
WW II
1947
1954
1962

Immunosuppression Timeline

- **1906**: first attempted human tx w/ pig kidney
- **1954**: first kidney tx w/ prolonged survival done between identical twins
- **1958**: total body irradiation
- **1959**: 6 - mercaptopurine (6-MP)
- **1961**: azathioprine
- **1965**: corticosteroids used, multidrug regimens initiated
- **1967**: antilymphocyte sera **1969**: mycophenolic acid developed
- **1976**: cyclosporine A (cyclosporine) developed
- **1980**: OKT3 developed
- **1983**: cyclosporine receives FDA approval
- **1987**: tacrolimus developed
- **1989**: sirolimus developed
- **1994**: tacrolimus receives FDA approval
- **1995**: mycophenolate mofetil receives FDA approval
- **1997**: antithymocyte globulin receives FDA approval
- **2001**: sirolimus receives FDA approval
- **2004**: enteric coated mycophenolic acid receives FDA approval

Introduction of immunosuppressants (US)



Adapted from Zand MS. *Semin Dial.* 2005;18:511-519.

Maintenance

- Prednisone
- Cyclosporine
- Tacrolimus
- Azathioprine
- Mycopheolate
- Sirolimus

Special Teams

- Rituximab
- IVIg
- Plasmapheresis
- Leflunamide

Use of Maintenance Immunosuppression in the United States

Corticosteroids (74 %)

Tacrolimus (79 %)
Cyclosporine (15 %)
Sirolimus (9 %)

Mycophenolate mofetil (82 %)
Mycophenolate sodium (5 %)
Azathioprine (0.6 %)

Goals

- Reduce acute rejection
- Reduce nephrotoxicity
- Reduce generalized side effects
- Reduce overimmunosuppression

Host Cell-Mediated Immunologic Reaction Towards the Allograft

- 3-Signal Model
  - Signal 1: HLA recognition
  - Signal 2: Co-Stimulation
  - Signal 3: mToR Pathway

Currently Available Immunossupressive Agents

- Non-depleting proteins:
  - Interleukin-2 receptor antibodies (i.e. humanized / chimeric murine anti-CD25 antibodies)
    - Daclizumab (Zenapax®)
    - Basiliximab (Simulect®)
- Depleting proteins:
  - Antilymphocyte antibodies.
    - Murine monoclonal anti-CD3 antibody
      - OKT3
    - Polyclonal antibodies
      - Equine-derived antithymocyte globulin (ATGAM®)
      - Rabbit-derived antithymocyte globulin (Thymoglobulin®)
- Immunophilin-Binding Agents
  - Cyclosporine (Sandimmune® / Neoral®)
  - Tacrolimus (Prograf®)
- Inhibitors of T-cell Proliferation
  - Azathioprine (Imuran®)
  - Mycophenolate mofetil (CellCept®)
  - Enteric-Coated Mycophenolic Acid (myfortic®)
- Mammalian Target of Rapamycin Inhibitor
  - Sirolimus (Rapamune®)
- Non-specific immunosuppressants
  - Corticosteroids

Induction Therapy

- **What is induction therapy?**
  - use of potent immunosuppressive agents in the critical early post-transplant period.

- **What are the goals of induction therapy?**
  - to decrease the incidence of acute rejection in the immediate post-transplant period; and
  - to possibly allow lower overall intensity of early maintenance immunosuppressive regimen (i.e. delayed onset of calcineurin inhibitor initiation).

Types of Induction Therapies

- Non-depleting proteins:
  - Interleukin-2 receptor antibodies (i.e. humanized / chimeric murine anti-CD25 antibodies)
    - Daclizumab (Zenapax®)
    - Basiliximab (Simulect®)
- Depleting proteins:
  - Antilymphocyte antibodies.
    - Murine monoclonal anti-CD3 antibody
      - OKT3
    - Polyclonal antibodies
      - Equine-derived antithymocyte globulin (ATGAM®)
      - Rabbit-derived antithymocyte globulin (Thymoglobulin®)

Maintenance Medications

- Immunophilin-Binding Agents (aka Calcineurin Inhibitors)
  - Cyclosporine (Sandimmune® / Neoral®)
  - Tacrolimus (Prograf®)
- Inhibitors of T-cell Proliferation
  - Azathioprine (Imuran®)
  - Mycophenolate mofetil (CellCept®)
  - Enteric-Coated Mycophenolic Acid (Myfortic®)
- Mammalian Target of Rapamycin Inhibitor
  - Sirolimus (Rapamune®)
- Non-specific immunosuppressants
  - Corticosteroids

Cyclosporine

- Use: prevention of acute rejection.

- MOA:
  1. CyA forms a complex w/ cyclophilin (cytoplasmic receptor protein).
  2. The CyA-cyclophilin complex binds to and inhibits calcineurin phosphatase.
  3. Calcineurin inhibition prevents the nuclear factor of activated T-cells (NF-AT) from entering the nucleus.
  4. This results in a reduction in several cytokines genes that promote T-cell activation, including...
     - Interleukin-2 (IL-2)
     - IL-4
     - Interferon-gamma (INF-γ)
     - Tumor Necrosis Factor-alpha (TNF-α)

Tacrolimus

- MOA:
  1. FK506 forms a complex w/ FKBP12.
  2. FK506-FKBP12 complex binds to and inhibits calcineurin phosphatase.
  3. Calcineurin inhibition prevents the nuclear factor of activated T-cells (NF-AT) from entering the nucleus.
  4. This results in a reduction in several cytokines genes that promote T-cell activation, including...
     - Interleukin-2 (IL-2)
     - IL-4
     - Interferon-gamma (INF-γ)
     - Tumor Necrosis Factor-alpha (TNF-α)

Inhibitors of T-cell Proliferation

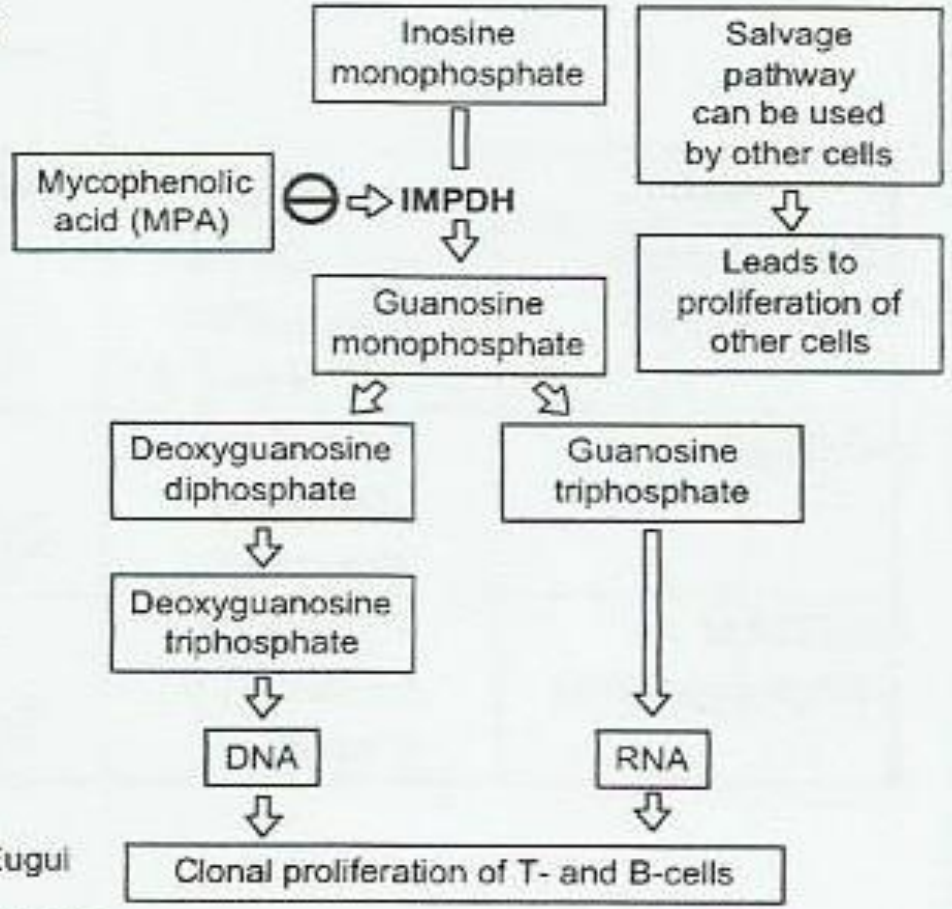
Azathioprine (AZA, Imuran®)

- Use: prevention of acute rejection.

- MOA:
  1. AZA is a prodrug of 6-MP.
  2. 6-MP is incorporated into DNA where it inhibits purine synthesis and prevents the formation of RNA.
     - Inhibits gene replication and subsequent activation of T-cells.

MPA Inhibits the *De Novo* Pathway of Purine Biosynthesis

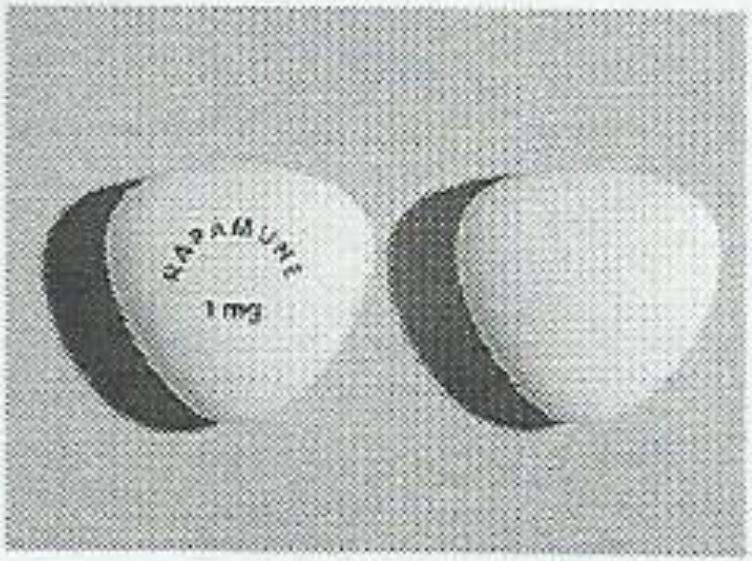
- Lymphocytes rely on *de novo* synthesis of purines for clonal expansion*†‡
- MPA inhibits IMPDH, which effectively blocks clonal B- and T-cell expansion*†
- MPA preferentially targets lymphocytes because other cells have the ability to employ salvage pathways for nucleotide synthesis*
- MPA is also thought to inhibit antibody production and generation of cytotoxic T-cells, as well as downregulate the expression of adhesion molecules on lymphocytes.



*Halloran PF. *Clin Transplant*. 1996;10:118-123; Eugui EM et al. *Ann NY Acad Sci*. 1993;685:309-329.
†Mele TS et al. *Immunopharmacology*. 2000;47:215-245.
‡Allison AC et al. *Clin Transplant*. 1996;10:77-84.

Mammalian Target of Rapamycin Inhibitor

Sirolimus (RAPA, rapamycin, Rapamune®)



- Use: prevention of acute rejection.
- MOA:
  1. Binds w/ FK binding protein.
  2. This complex interacts with the Target of Rapamycin (ToR).
  3. Impairs the ability of IL-2 to trigger T-cells to enter cell division.

Non-Specific Immunosuppressants

Corticosteroids

- Use: prevention and treatment of acute rejection episodes.

- MOA:
- The exact MOA is still not fully understood. Some believe…
  - High dose: > 100 mg of prednisone equivalents.
    - MOA = directly toxic to T cells
  - Low dose: ≤ 100 mg of prednisone equivalents.
    - nonspecific immunosuppressive agents - inhibit IL-1, IL-2, IL-3, IL-6, IL-15, TNF-alpha and INF-gamma at low doses.
      - Decreased activation of T cells.

Non-Specific Immunosuppressants
Corticosteroids

- What we do know:
  - Blockade of Cytokine Gene Expression
    - ↓ T-cell and APC cytokine expression
      - Bind to heat shock protein → translocates to nucleus → binds to GRE → inhibits transcription of cytokine genes → inhibition of IL-1, IL-2, IL-3, IL-6, INF-γ, and TNF-α
    - ↓ cytokine-receptor expression
  - Nonspecific Effects
    - Antiinflammatory effects

Steroid Withdrawal/Avoidance: Why?

- Diabetes
- Hyperlipidemia
- Bone disease
- Cataract formation
- Weight gain
- Patient quality-of-life (skin changes, edema, neurological/psychological effects)

Midtvedt K, et al, JASN, 15, 2004, 3233

Vanrenterghem Y et al, Transplantation, 70, 2000, 1352

Opelz G et al, Am J Transplant 2005; 5: 720

Rogers CC et al, Transplantation, 80, 2005, 26

"Early" steroid withdrawal (within 7 days from transplant) may provide acceptable outcomes

- U of Minnesota Protocol, 1999-2005:
- 589 transplant patients, up to 5-year follow up of prednisone-free maintenance immunosuppression

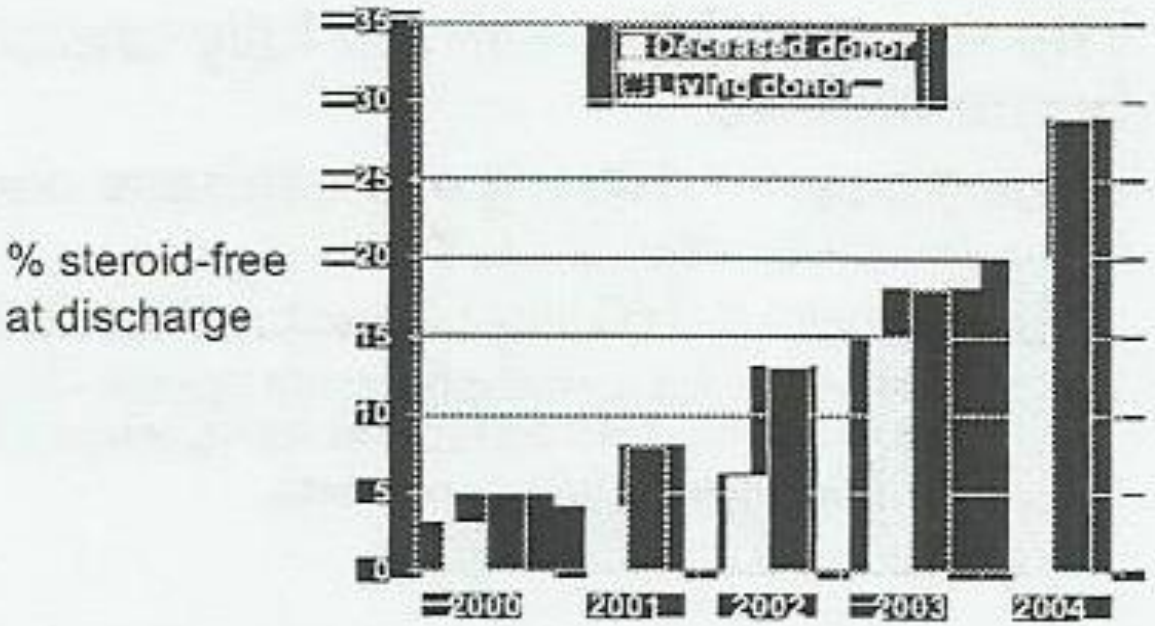
- **Rabbit anti-thymocyte globulin : 1.25 to 1.5 mg/kg x 5, first dose intra-operatively**

- **Steroids given for a total of 5 days:**
  - **Methylprednisone 500mg intraoperatively**
  - **prednisone 1mg/kg on POD#1**
  - **0.5 mg/kg on days 2 and 3**
  - **0.25 mg/kg on days 4 and 5**
- **Maintenance immunosuppression: Cyclosporine or Tacrolimus, MMF or SRL**

Matas AJ, Am J Transplant 2005 (5): 2473

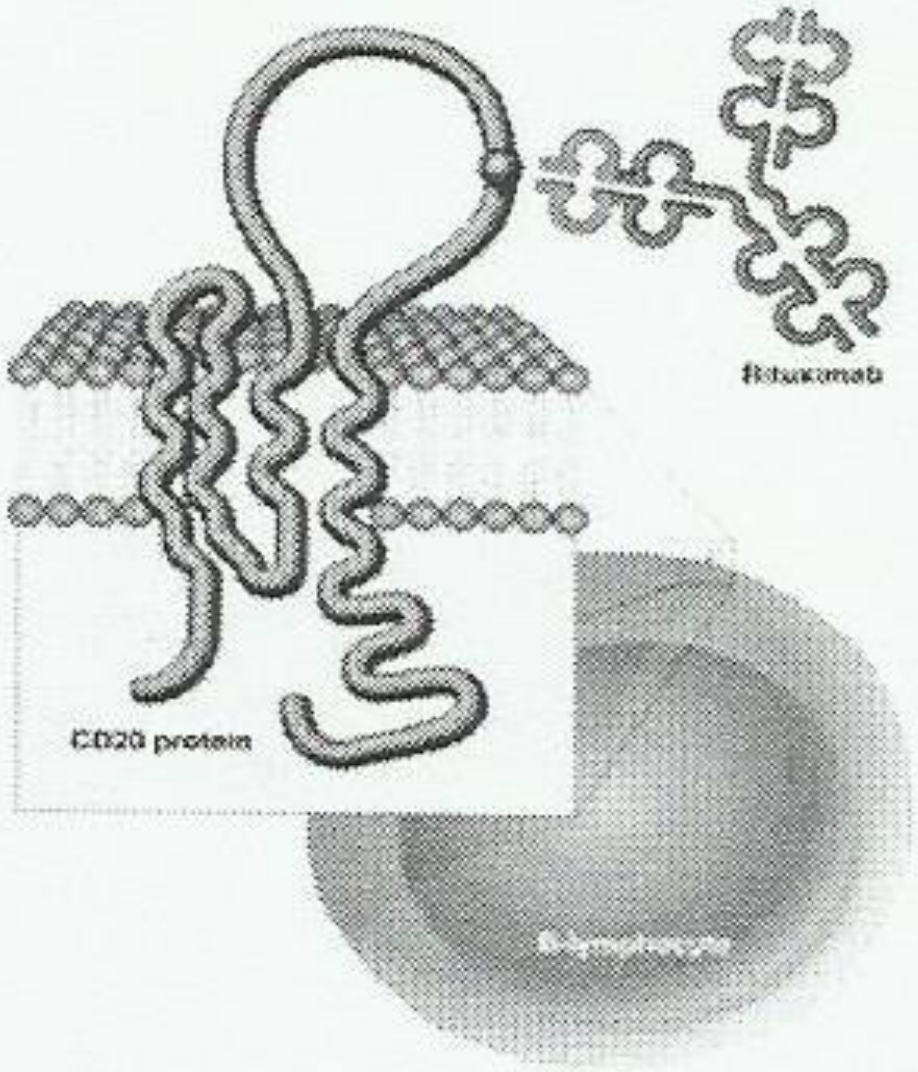
Steroid use in solid organ transplant has declined significantly

Organ	At Discharge	At 1 year
Kidney	77%	68%
Liver	80%	41%
Heart	92%	68%
Lung	97%	95%



H.-U. Meier-Kriesche et al, Am J Transplant 2006; 6: 1111

Rituximab



Pescovitz, M. D.
Rituximab, an Anti-CD20 Monoclonal Antibody: History and Mechanism of Action.
American Journal of Transplantation 6 (5p1), 859-866.

How does Rituximab work?

- Rituximab may be acting as a nonspecific intravenous immunoglobulin (Ivlg)
- Rituximab may deplete specific anti-donor antibody
- Rituximab may be acting by eliminating B cells and interfering with antigen presenting capabilities

Summary

- Approach to immunosuppression has not changed
- Decreased acute rejection episodes
- Newer agents and increased use of induction therapy have allowed development of avoidance/minimization strategies
- Acute rejection has become a less important outcome in studies of newer drugs